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# The increasing mortality burden of liver disease among opioid-dependent people: cohort study

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## ABSTRACT

**Aims** Hepatitis C (HCV) infection is highly prevalent among injection drug users (IDUs) and likely to cause significant mortality over time, but little research attention has focused upon the magnitude of this risk, particularly among ageing users. This study examined trends over time in mortality attributed to liver disease, and in particular contrasting this with other more commonly studied causes of death [acquired immune deficiency syndrome (AIDS), suicide and overdose] among an ageing cohort of heroin-dependent people in Australia. **Design** Data linkage study of methadone treatment entrants with the National Deaths Index. **Setting** A cohort entering methadone treatment for heroin dependence in New South Wales, Australia, 1980–85. **Participants** A total of 2489 people entering methadone treatment for heroin dependence and 54 847 person-years (PY) of follow-up. **Measurements** Linkage of data on all methadone entrants between 1980 and 1985 with data from the Australian National Deaths Index, linked using probabilistic record linkage software. **Findings** There were 8.2 deaths per 1000 PY [95% confidence interval (CI) 7.5–9.0], with standardized mortality ratios (SMRs) of 4.6 (95% CI 4.2–5.0). Almost one in five (17%) of deaths were from underlying liver-related causes, most commonly viral hepatitis. The overall mortality rate for any liver cause was 1.4 deaths per 1000 PY (95% CI 1.1–1.7), 17 times higher than to the general population (95% CI 13.4–21.3), with relative elevations more marked for females (SMR 27.9; 95% CI 17.7–41.9) than males (SMR 14.5; 95% CI 10.8–19.0). Liver mortality increased over time, becoming the most common cause of death by the end of follow-up. **Conclusions** Liver disease has become the most common cause of mortality among ageing opioid-dependent people in an ageing Australian cohort. There is an imperative to reduce the long-term risks of HCV and other risks to the liver, including alcohol consumption, which are typically not the major clinical focus for this group.

**Keywords** Cancer, cohort, hepatitis, heroin, mortality.

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## INTRODUCTION

Opioid dependence is associated with highly elevated mortality [1]. Reviews of cohort studies conducted to date suggest that most deaths are accounted for by drug overdose, suicide, acquired immune deficiency syndrome (AIDS) and traumatic deaths [1,2]. The importance of these causes of death varies: mortality in general, and from human immunodeficiency virus (HIV) in particular, is lower in cohorts with low HIV prevalence [1]; HIV varies markedly across countries [3]. If HIV prevalence is reduced or prevented other causes of death, such as liver disease, may become more prominent, particularly as cohorts age.

Opioid-dependent people have a number of risk factors for liver disease, including highly elevated levels of alcohol dependence [4], and even higher levels of hepatitis C (HCV) infection [5,6]. HCV prevalence among Australian injecting drug users (IDUs) ranges between 50 and 75% [7]. Among those who contract HCV, 75–85% develop chronic HCV infection [8–10], leading potentially to cirrhosis, liver failure and hepatocellular carcinoma [11]. The proportion of HCV-infected people developing cirrhosis is 7% at 20 years, and 20% by 40 years [12]. Additional liver stresses such as heavy alcohol intake, liver fibrosis and HIV or hepatitis B coinfection increase the speed of progression to complications [12].

Few studies have followed opioid-dependent people later in life, despite recognition that liver-related mortality will become a prominent cause of morbidity and mortality among ageing IDUs. We followed a cohort of Australian opioid-dependent people entering methadone in New South Wales (NSW), Australia from entrance in 1980–1985 until 2008. Here, HIV prevalence among IDUs has remained low (around 1.5% [3]) and HCV is highly prevalent (currently, over 50% [6,7]). Chronic hepatitis B infection is considerably lower [as hepatitis B surface antigen (HBsAg)], around 2.7–5% [6]).

## METHODS

This was a retrospective cohort study using data linkage with mortality data from the National Death Index (NDI) held by the Australian Institute of Health and Welfare (AIHW), conducted in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting [13]. The cohort included all people approved to receive methadone syrup for the treatment of opioid dependence by the Medical Committee of Pharmaceutical Services, NSW Health between 1980 and 1985; the Committee met quarterly, with the cohort identified through manual searches of their minutes. Identifiers were confirmed through searches of NSW Health electronic records.

These data were forwarded to AIHW for data linkage with the NDI. The NDI contains all death records in Australia since 1980, compiled from the Registers of Births, Deaths and Marriages in each jurisdiction. Records contain identifying information and causes of death classified by International Classification of Diseases (ICD) versions 9 (1980–96) or 10 (1997–present). Data linkage was performed by probabilistic record linkage software by AIHW staff. Variables used for matching included full name, date of birth, sex, date and State of last known contact. Matching was performed in a number of passes, and the matched records were weighted according to the quality of the match. Clerical review to select the best match from each pass was conducted by A.G.; decisions were made using selection criteria provided by AIHW, and alias identities from NSW Health.

De-identified mortality data was forwarded on completion of linkage. Underlying causes were provided for deaths prior to 1997 (ICD-9), and both underlying and contributing for deaths 1997 or later (ICD-10). An underlying cause of death is the disease or injury initiating the train of events leading to death, or the circumstances which produced the fatal injury [14]. Contributing causes of death include all additional morbid conditions, diseases and injuries entered on the death certificate [15]. Only limited methadone/buprenorphine treatment data were available for this cohort, so treatment exposure data was not used.

### Statistical analyses

Analyses were performed using SAS version 9.1, SPSS version 15.0 and Excel 2003. PY of follow-up contributed by each cohort member to different age groups and time-periods were calculated using macros written in SAS. Mortality rates (general and age-specific) were expressed as deaths per 1000 PY. Kaplan–Meier survival analysis was performed to show stratified survival rates.

Unit record data were obtained on all deaths and their causes in NSW, 1980–2006. Standardized mortality ratios (SMRs) were calculated from the ratio of age-specific death rates in the cohort, compared to the NSW population.

Causes of death were grouped into categories of related conditions, based on groupings published previously [16–18]; details of ICD-9 and ICD-10 codes in these categories are available elsewhere [19]. SMRs for particular causes of death were calculated relative to the NSW population.

### Ethics

Ethics approval was received from University of NSW Human Research Ethics Committee, NSW Health Ethics Committee and the AIHW Ethics Committee.

## RESULTS

There were 2654 individuals approved for methadone treatment, 1980–85. Alternate name spellings and names were recorded as 'aliases': 350 participants (14%) had one alias, 73 participants (3%) had two aliases and four (0.2%) had three aliases. A total of 2496 people with full name and date of birth had sufficient information for linkage (including aliases, a total of 3009 names were submitted), completed on 28 August 2008. Seven people were excluded, as the date of death preceded commencement of treatment. The final cohort comprised 2489 participants and 54 847 PY; 1420 were male (57%), 1058 were female (43%) and 11 were listed as both male and female in different aliases ('other', 0.4%). The cohort formation process is shown in Fig. 1.

### Mortality rates

A total of 478 participants were deceased at 28 August 2008, with a mortality rate of 8.2 deaths per 1000 PY (Table 1); sex had a significant impact on survival ($\chi^2$ = 17.99, 2 d.f., $P$ = 0.0001). Participants died at 4.6 times the rate of the general NSW population [95% confidence interval (CI): 4.2–5.0); SMRs were 4.0 for males (95%

CI: 3.5–4.5) and 6.4 for females (95% CI: 5.4–7.5). Death rates increased with age, with the highest elevations in mortality relative to the general population among the youngest age groups (Table 1).

### Underlying (primary) causes of death

A total of 432 participants had an underlying cause of death recorded (Table 2). Of these, 130 (30%) died of drug-induced deaths; 81 (19%) accidental traumatic injury; 75 (17%) liver-related deaths; 60 (14%) cancers; 36 (8%) suicide; 35 (8%) cardiovascular disease; and 23 (5%) alcohol-related deaths. Of drug-induced deaths, 91% were considered accidental, and 84% accidental opioid-induced deaths. These causes are not necessarily mutually exclusive: alcoholic liver disease deaths were counted as both liver deaths and alcohol deaths.

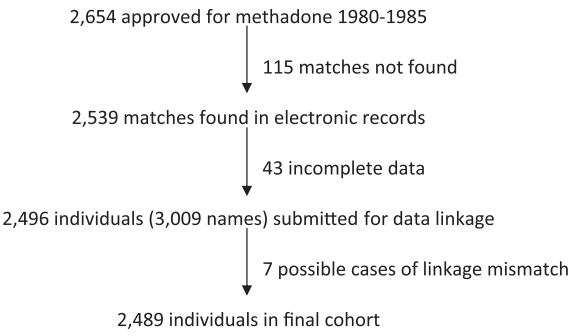



**Figure 1** Cohort formation flowchart

Of the 75 people dying from liver-related causes, 34 (45%) died from viral hepatitis, 25 (33%) from chronic liver disease, 17 (23%) from alcoholic liver disease, 13 (17%) from liver cancer and 11 (15%) from non-alcoholic liver disease. The crude mortality rate (CMR) estimate for any underlying liver cause was 1.4 deaths per 1000 PY (95% CI 1.1–1.7); mortality was elevated 17-fold (95% CI 13.4–21.3) compared to the NSW population, with elevations more marked for females (SMR 27.9; 95% CI 17.7–41.9) than males (SMR 14.5; 95% CI 10.8–19.0).

A clear time trend was evident (Fig. 2). In 1980–84, there were no liver-related deaths. By 2000–04, there were 2.6 underlying liver deaths per 1000 PY (95% CI: 1.7–3.7), levels similar to those for drug-related deaths (2.9 per 1000 PY; 95% CI: 1.9–4.0). In 2005–06, there were five underlying liver deaths per 1000 PY (95% CI: 3.1–7.7), in comparison to 1.9 underlying drug deaths per 1000 PY (95% CI: 0.8–3.8); liver deaths had become the most common cause of death among this group.

For deaths occurring after 1996 ($n = 247$), up to 16 contributing causes of were recorded; 112 deaths (45% of deaths 1997–2006) mentioned liver causes underlying ($n = 64$) or contributing ($n = 102$) to death. In comparison, 23% had opioids coded as underlying or contributing to death.

**Table 1** Mortality according to sex and age group at death (1980–2008).

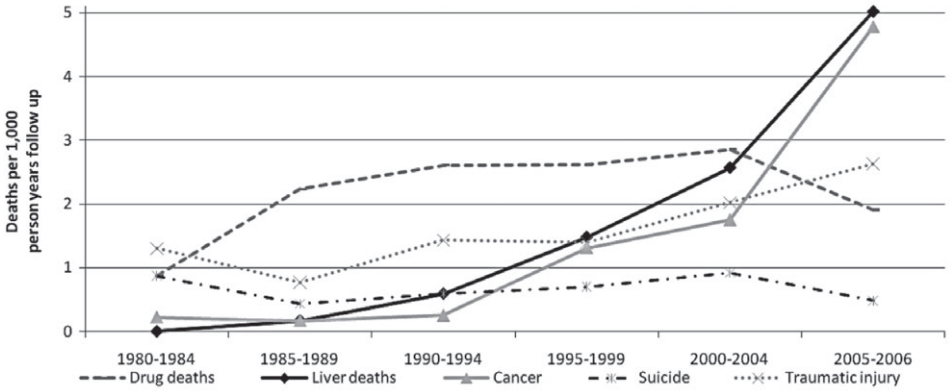
| *Age group (years)* | *Person-years* | *Deaths* | *Crude mortality rate (1980–2008)*[a] | *95% CI* | *Standardized mortality ratio (1980–2006)*[b] | *95% CI* |
|---|---|---|---|---|---|---|
| Males | 32 869 | 315 | 9.6 | 8.6–10.7 | 4.0 | 3.5–4.5* |
| <20 | 14.95 | 0 | 0 | 0.0–6.7 | 0.0 | 0.0–237.0 |
| 20–29 | 4 155.37 | 19 | 4.6 | 2.8–7.1 | 3.7 | 2.2–5.8* |
| 30–39 | 12 286.71 | 79 | 6.4 | 5.1–8.0 | 4.6 | 3.7–5.7* |
| 40–49 | 11 407.58 | 133 | 11.7 | 9.6–13.6 | 4.7 | 3.9–5.5* |
| 50–59 | 4 248.02 | 76 | 17.9 | 14.1–22.4 | 2.8 | 2.1–3.7* |
| 60+ | 218.84 | 4 | 18.3 | 5.0–46.8 | 0.8 | 0.1–2.8 |
| Females | 24 900 | 160 | 6.4 | 5.5–7.5 | 6.4 | 5.4–7.5* |
| <20 | 47.57 | 1 | 21.0 | 0.5–117.1 | 62.1 | 1.6–345.9* |
| 20–29 | 4 617.83 | 25 | 5.4 | 3.5–8.0 | 13.4 | 8.7–19.8* |
| 30–39 | 9 687.15 | 45 | 4.6 | 3.4–6.2 | 7.4 | 5.4–9.9* |
| 40–49 | 7 685.12 | 62 | 8.1 | 6.2–10.1 | 5.7 | 4.4–7.3* |
| 50–59 | 2 074.6 | 20 | 9.6 | 5.9–14.9 | 3.5 | 1.9–5.7* |
| 60+ | 49.45 | 2 | 40.5 | 4.9–146.1 | 11.1 | 1.3–39.9* |
| Total[c] | 58 016 | 478 | 8.2 | 7.5–9.0 | 4.6 | 4.2–5.0* |

*Values are significant at $P \leq 0.05$. [a]The end of the follow-up period was 28 August 2008; all deaths and person-years of observation occurring up until this point were included in crude mortality rate (CMR) estimates. [b]At the date of analysis data were not available to allow the inclusion of deaths and person-years of observation in 2007 and 2008. Standardized mortality ratios (SMRs) in this and all other tables refer to deaths in 1980–06. [c]The total person-years of follow-up and deaths are slightly greater than the addition of male and female totals as there were people of undetermined sex included in the total for person-years of observation and deaths. SMRs were not calculated separately for this group, so deaths and person-years of follow-up are not included in these or other SMR estimates. CI: confidence interval.

**Table 2** Selected underlying causes of death according to sex (deaths 1980–2006).

| *Cause of death* | *Sex* | *Deaths* | *Crude mortality rate* | *Crude mortality rate 95% CI* | *SMR*[b] | *SMR 95% CI* |
|---|---|---|---|---|---|---|
| Drug-induced deaths | | | | | | |
| | All[a] | 130 | 2.38 | 1.99–2.82 | 22.6 | 18.8–26.8[c] |
| | Male | 79 | 2.55 | 2.02–3.17 | 18.3 | 14.5–22.8[c] |
| | Female | 50 | 2.14 | 1.59–2.82 | 36 | 26.7–47.4[c] |
| Accidental traumatic injury | | | | | | |
| | All[a] | 81 | 1.48 | 1.18–1.84 | 14 | 11.1–17.4[c] |
| | Male | 51 | 1.64 | 1.22–2.16 | 11.8 | 8.8–15.5[c] |
| | Female | 29 | 1.24 | 0.83–1.78 | 20.9 | 14.0–29.9[c] |
| All liver deaths | | | | | | |
| | All[a] | 75 | 1.37 | 1.08–1.72 | 17.0 | 13.4–21.3[c] |
| | Male | 52 | 1.68 | 1.25–2.20 | 14.5 | 10.8–19.0[c] |
| | Female | 23 | 0.98 | 0.62–1.47 | 27.9 | 17.7–41.9[c] |
| Viral hepatitis | | | | | | |
| | All[a] | 34 | 0.62 | 0.43–0.87 | 7.7 | 5.3–10.8[c] |
| | Male | 27 | 0.87 | 0.57–1.27 | 7.5 | 5.0–10.9[c] |
| | Female | 7 | 0.30 | 0.12–0.62 | 8.5 | 3.4–17.5[c] |
| Chronic liver disease | | | | | | |
| | All[a] | 25 | 0.46 | 0.30–0.68 | 5.7 | 3.7–8.4[c] |
| | Male | 14 | 0.45 | 0.25–0.76 | 3.9 | 2.1–6.5[c] |
| | Female | 11 | 0.47 | 0.23–0.84 | 13.4 | 6.7–23.9[c] |
| Alcoholic liver disease | | | | | | |
| | All[a] | 17 | 0.31 | 0.18–0.50 | 3.0 | 1.7–4.8[c] |
| | Male | 10 | 0.32 | 0.15–0.59 | 2.3 | 1.1–4.3[c] |
| | Female | 7 | 0.30 | 0.12–0.62 | 5.0 | 2.0–10.4[c] |
| Liver cancer | | | | | | |
| | All[a] | 13 | 0.24 | 0.13–0.41 | 2.3 | 1.2–3.9[c] |
| | Male | 9 | 0.29 | 0.13–0.55 | 2.1 | 1.0–3.9 |
| | Female | 4 | 0.17 | 0.05–0.44 | 2.9 | 0.8–7.4 |
| Non-alcoholic liver disease | | | | | | |
| | All[a] | 11 | 0.20 | 0.10–0.36 | 1.9 | 1.0–3.4 |
| | Male | 6 | 0.19 | 0.07–0.42 | 1.4 | 0.5–3.0 |
| | Female | 5 | 0.21 | 0.07–0.50 | 3.6 | 1.2–8.4[c] |
| Cancer | | | | | | |
| | All[a] | 60 | 1.10 | 0.84–1.41 | 10.3 | 7.9–13.3[c] |
| | Male | 35 | 1.13 | 0.79–1.57 | 8.1 | 5.6–11.2[c] |
| | Female | 24 | 1.03 | 0.66–1.53 | 17.3 | 11.1–25.7[c] |
| Suicide | | | | | | |
| | All[a] | 36 | 0.66 | 0.46–0.91 | 6.3 | 4.4–8.7[c] |
| | Male | 25 | 0.81 | 0.52–1.19 | 5.8 | 3.7–8.5[c] |
| | Female | 11 | 0.47 | 0.23–0.84 | 7.9 | 3.9–14.2[c] |
| Cardiovascular disease | | | | | | |
| | All[a] | 35 | 0.64 | 0.45–0.89 | 6.1 | 4.3–8.5[c] |
| | Male | 23 | 0.74 | 0.47–1.11 | 5.3 | 3.4–8.0[c] |
| | Female | 12 | 0.51 | 0.26–0.90 | 8.6 | 4.5–15.1[c] |
| Alcohol-related deaths | | | | | | |
| | All[a] | 23 | 0.42 | 0.27–0.63 | 4.0 | 2.6–6.0[c] |
| | Male | 14 | 0.45 | 0.25–0.76 | 3.2 | 1.8–5.4[c] |
| | Female | 9 | 0.38 | 0.18–0.73 | 6.5 | 3.0–12.3[c] |
| HIV/AIDS deaths | | | | | | |
| | All[a] | 5 | 0.09 | 0.03–0.21 | 1.1 | 0.4–2.6 |
| | Male | 4 | 0.13 | 0.04–0.33 | 1.1 | 0.3–2.9 |
| | Female | 1 | 0.04 | 0.001–0.24 | 1.2 | 0.0–6.8 |

[a]Includes one 'other' sex subject. [b]Standardized mortality ratios (SMRs) do not include 'other' sex participants. [c]Significant at $P < 0.05$. CI: confidence interval; HIV: human immunodeficiency virus; AIDS: acquired immune deficiency syndrome.




| | 1980-1984 deaths per 1000 PY (95%CI) | 1985-1989 deaths per 1000 PY (95%CI) | 1990-1994 deaths per 1000 PY (95%CI) | 1995-1999 deaths per 1000 PY (95%CI) | 2000-2004 deaths per 1000 PY (95%CI) | 2005-2006 deaths per 1000 PY (95%CI) |
|---|---|---|---|---|---|---|
| **Drug-induced** | 0.87(0.24-2.22) | 2.23(1.46-3.27) | 2.61(1.77-3.71) | 2.62(1.77-3.74) | 2.85(1.93-4.00) | 1.91(0.83-3.77) |
| **Liver-related** | 0.0(0.00-0.02) | 0.17(0.02-0.62) | 0.59(0.24-1.21) | 1.48(0.86-2.38) | 2.57(1.71-3.72) | 5.02(3.11-7.68) |
| **Cancer** | 0.22(0.01-1.21) | 0.17(0.02-0.62) | 0.25(0.05 | 1.31(0.73-2.16) | 1.75(1.05-2.73) | 4.78(2.92-7.39) |
| **Suicide** | 0.87(0.24-2.22) | 0.43(0.14-1.00) | 0.59(0.24-1.21) | 0.7(0.30-1.38) | 0.92(0.44-1.69) | 0.48(0.06-1.73) |
| **Traumatidnjury** | 1.3(0.48-2.83) | 0.77(0.35-1.47) | 1.43(0.83-2.29) | 1.4(0.80-2.27) | 2.02(1.27-3.06) | 2.63(1.31-4.71) |

**Figure 2** Trends across time in deaths per 1000 person-years (PY) for the most common underlying causes of death (participants with death causes recorded, $n = 432$); CI: confidence interval

## DISCUSSION

We examined causes of death among 2480 opioid-dependent people close to 30 years after they entered treatment. The CMR was 8.2 deaths per 1000 PY (95% CI: 7.5–9.0), lower than pooled estimates of 20.9 per 1000 PY (95% CI: 19.0–22.0) [1], similar to other Australian cohorts [20,21]. Mortality was 4.6 times higher than the general NSW population, with this excess particularly pronounced in younger and female participants: females in their 20s were 13.4 times more likely to die as the NSW female population of the same age.

Although much attention is understandably focused on acute forms of harm such as opioid overdose, opioid-dependent people can and do survive long enough to experience harms from slowly developing conditions such as liver disease, especially in populations where HIV infection is low. We found that almost 30 years post-cohort entry, causes of death due to chronic illness such as liver death and cancer became more prevalent, surpassing drug overdose deaths. We have examined and discussed in greater detail elsewhere changes in overdose mortality [20,22] and increasing cancer in a more recent NSW cohort [23], which consider the reasons for elevations and changes in mortality attributable to these causes.

Here, we focus on liver-related mortality. Liver deaths comprised 17% of all underlying causes of death, and 26% of those occurring from 1997 to 2006; 45% of these later deaths had either a contributing or underlying cause of death that was a liver code. The major sources of this liver mortality are to be chronic HCV, chronic liver disease and concurrent heavy alcohol use.

A recent Scottish study suggested that among a cohort of comparatively younger IDUs (median age 31 years), problematic alcohol use may have played a larger role in liver-related hospitalizations and mortality than HCV infection [24]. The current study suggests that this may shift as IDUs age, given the larger number of hepatitis-related deaths compared to alcohol-related liver disease. The majority of the cases of chronic HCV-related advanced liver disease occur after the second decade of HCV infection [12], with the mean period between infection and mortality 20 years for cirrhosis and 29 years for hepatocellular carcinoma (HCC) [10]. Our results demonstrate the slow and increasing onset of fatal liver disease; studies with even longer follow-up would show HCC increases.

AIDS deaths were not elevated significantly in this cohort (SMR 1.1, 95% CI: 0.4–2.6). Although low prevalence of HIV in Australia IDUs is known [25], a later cohort of NSW oral substitution therapy (OST) entrants between 1985 and 2006 *did* have slightly elevated AIDS mortality [20]. The reasons for this difference could be multiple: this cohort entered treatment when HIV awareness campaigns were commencing in the media and when the first needle exchanges began in Sydney, NSW [26]. It is possible that such HIV prevention interventions may have had a stronger impact in this cohort (they are likely to have greater impact when both risk behaviours and HIV prevalence are less common [27]).

### Clinical implications

This study has clear clinical implications. Ageing, HIV-negative, opioid-dependent people die at higher rates

from liver disease than drug overdose, yet many causes of liver disease are both preventable and treatable. Efforts to prevent, treatment and reduce harms related to liver disease are essential, particularly in situations where HIV has been prevented or managed successfully. Although evidence regarding the impact of needle and syringe programmes [28] and other injecting paraphernalia [29] upon prevention of HCV infection is extremely limited, reduction of risk is important, particularly during the period of initiation to injecting, when HCV incidence is highest [11]. Mathematical modelling suggests that HCV treatment remains an under-utilized, yet a potentially effective, strategy for reducing HCV prevalence among IDU populations [30,31] in addition to improving the health of individual patients. Greater attention also needs to be paid to the likely impact of continued heavy drinking among HCV-positive people in this population, and to encouraging development of and participation in HBV inoculation programmes to reduce rates of HCV/HBV coinfection.

### Study limitations

Data linkage relies on clerical review; although this can be subjective, it was minimized by using consistent and documented selection criteria, with the same individual (A.G.) conducting all reviews. The first stage of data linkage clerical review was blinded to the subject's vital status; this was not possible for NDI linkage, as the NDI only holds records of deceased individuals. However, we are confident of a good match, given the similarity in mortality rates with a later NSW cohort [20].

The accuracy of data linkage also relies upon the accuracy of identified personal information, which may be poorly recorded; this was reduced with additional linkage to electronic records. Alias identities may lead to inaccuracies in linkage; prisoners often use small changes in personal information to obtain bail [32]; 17% of this cohort had at least one known alias. None the less, linkage accuracy for NSW prisoners and the NDI has a sensitivity of 88.4% and specificity of 99.7% [32], showing it is still accurate even when aliases are very common.

Finally, given the study design, which relied on routinely collected data, we were not able to specify specific exposures that may have accounted for the increased mortality (for example, patterns of alcohol use, chronic HCV or HBV infection). To that end, we cannot specify the magnitude of risks that these exposures pose. Similarly, we were unable to measure desistance from injecting and/or drug and alcohol use in a time-dynamic way, which meant we were unable to consider potential changes in mortality when such changes occurred, as have been demonstrated in other studies [33]. Prospective cohorts with rich data on behavioural risks are better served to answer such questions.

## CONCLUSIONS

This long-term follow-up study permitted the observation of the dramatic impact of advanced liver disease. Liver-related deaths were 17 times elevated, and attributable primarily to viral hepatitis, chronic liver disease and alcoholic liver disease. Prevention and treatment of HCV infection and other risks to liver function is vital to avoid marked long-term impact on the mortality of opioid-dependent people.

### Declarations of interest

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