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Lower life expectancy among people with an HCV notification: a population-based linkage study

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SUMMARY. Among people with hepatitis C virus (HCV) infection, liver disease-related deaths have risen over the last 20 years. Life expectancy has not been estimated in this population. HCV notifications (mandatory notification of anti-HCV-positive serology since 1991) reported to the New South Wales Health Department from 1992 to 2006 were linked to cause of death data. Abridged life tables were constructed from age-specific mortality rates. Life expectancy from ages 18–70 years for non-drug-related mortality causes was estimated using competing risk methods and compared to the general population of Australia. The cohort comprised 81 644 individuals with an HCV notification, with median follow-up of 7.6 years. Median age at notification was 34 years [interquartile range (IQR) 28–42] and 63% were male. Between 1992 and 2006, 4607 deaths occurred. Median age at liver- and drug-related death among males was 51 (IQR 45–66) and 36 (IQR 31–42) years, respectively, and among females was 63 (IQR 49–74) and 36 (IQR 30–41) years, respectively. In each year of follow-up before 2000, 15–21% of deaths were liver- and 30–39% were drug-related. After 2000, liver-related deaths increased to 20–26% of deaths in each year and drug-related deaths decreased to 13–19%. Excluding drug-related causes of death, life expectancy was lowered by an average of 4.2 (SD ± 1.0) and 5.4 (SD ± 0.7) years for males and females, respectively. Among people with an HCV notification, an increasing proportion of deaths are liver-related. Following removal of drug-related mortality, life expectancy in this population remained considerably lower, compared with the general population.

Keywords: drug-related mortality, HCV treatment, liver-related mortality, people who inject drugs.

INTRODUCTION

Despite two decades of research on the natural history of hepatitis C virus (HCV) infection, uncertainty remains on the individual mortality risk and estimates of life expectancy among people with HCV infection. HCV-related liver disease is generally progressive, accelerated by co-factors, including heavy alcohol intake [1], HIV or hepatitis B virus (HBV) co-infection [2,3], obesity and diabetes [4].

Abbreviations: ABS, Australian Bureau of Statistics; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; IQR, interquartile range; NDD, Notifiable Diseases Database; NHR, National HIV Registry; NSW, New South Wales; PWID, people who inject drugs; RBDM, the NSW Registry of Births, Deaths and Marriages.

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At individual and population levels, risk of HCV mortality from end-stage liver disease depends on a number of factors, such as duration of chronic HCV infection [5], age at HCV acquisition [6] and co-factors for disease progression. Competing causes of death also impact HCV liver disease mortality risk [7], particularly for people who have acquired infection via contaminated blood products and people who inject drugs [8].

The absence of large cohorts with long-term follow-up of people with chronic HCV infection in different settings, together with suboptimal HCV screening in most countries, has limited characterization of HCV disease progression and representative mortality distribution [8]. The mandatory notification of anti-HCV-positive serology since 1991 in Australia [9], alongside high rates of screening of individuals with prior or current HCV risk behaviour [10], has enabled characterization of disease-specific mortality rates and trends [11,12]. Our objectives in this study were to further characterize the distribution and rates of mortality across age groups and notification periods and to estimate life expectancy among people with an HCV notification.

MATERIALS AND METHODS

Data sources

The study population consisted of all people recorded in the New South Wales (NSW) Notifiable Diseases Database (NDD) with a notification of anti-HCV-positive serology between 1 January 1992 and 31 December 2006. Since 1991, state government legislation has mandated reporting of all notifications of hepatitis B virus (HBV) and HCV to the NSW Department of Health (NSW Public Health Act 1991) [9]. Notifications of HCV are made to local health authorities and de-identified information, including age, gender, postcode of residence and year of serology test results are forwarded to the NDD in each state. The vast majority of HCV notifications are received from laboratories where serological screening tests for HCV have been available since 1990. A notifiable HBV case requires detection of HBV surface antigen or HBV DNA. A notifiable HCV case requires detection of anti-HCV antibody or HCV RNA. Personal identifiers were first recorded in the NDD in 1992.

The NSW Registry of Births, Deaths, and Marriages (RBDM) records the date of death for all deaths occurring in NSW. The RBDM supplies the Australian Bureau of Statistics (ABS) with the Medical Certificate of Cause of Death. ABS codes the underlying cause of death according to the International Classification of Diseases (ICD) [13].

In Australia, national surveillance for HIV is coordinated by The Kirby Institute. Notified cases of HIV infection are reported to the National HIV Registry (NHR) on the first occasion of diagnosis. Reporting of HIV has been mandatory in NSW since 1985 and has been nationally administered since 1989 [14]. NHR data sources use a four-letter name code consisting of the first two letters of the first and last name and record gender and date of birth information.

Linkage

Data linkage occurred in two stages. In the first stage, HBV and HCV notifications in the NDD were matched internally to allow identification of cases with an HCV/HBV notification. All notifications were then matched to RBDM death records. In these steps, linkage was performed by probability using full name, gender, date of birth and address by means of ChoiceMaker software [15]. ABS cause of death records were linked deterministically to RBDM death records. In the second stage, to identify individuals with an HCV/HIV notification, data were matched deterministically to notifications from NHR using name code, gender and date of birth. All linkage was performed by the NSW Centre for Health Record Linkage [16].

People with an HBV notification, HCV/HBV, HCV/HIV and HCV/HBV/HIV notification were excluded from analysis. Thus, all analyses are based on people with a notification of anti-HCV-positive serology without evidence of co-infection.

Statistical methods

People who died within 6 months of an HCV notification were not included in any analyses because of the potential for bias towards higher rates of notifications in people with symptomatic advanced liver disease. Consistent with this exclusion, all other people remaining in the study group had their time at risk shortened by 6 months. Underlying causes of death in the ABS mortality data were defined using ICD-9 codes prior to 1 January 1997, and thereafter ICD-10 codes were used. Drug-related deaths were defined according to methods set out by the ABS [17]. This refers to deaths involving dependence disorders due to psychoactive substances, abuse of nondependence producing substance (chapters: ICD-10 mental and behavioural disorders, ICD-9 mental disorders), and poisoning or overdose by exposure to legal or illegal drugs (chapters: ICD-10 external causes, ICD-9 injury and poisoning). Liver-related deaths consisted of deaths by underlying cause of viral hepatitis, sequelae of viral hepatitis (chapters: ICD-10 certain infectious and parasitic diseases, ICD-9 infectious and parasitic diseases), hepatocellular carcinoma (HCC), other causes of primary liver cancer (chapters: ICD-10 and ICD-9 neoplasms) and alcoholic and nonalcoholic liver disease (chapters: ICD-10 and ICD-9 diseases of the digestive system) [18]. Among people with HCV mono-infection, comparability ratios between ICD-9 and ICD-10 coding of drug- and liver-related mortality are very close to 1.0 [19].

The distribution of age at death (all-cause and cause-specific) was described and stratified by gender. Temporal trends in the distribution of liver-, drug- and other-cause-related deaths were described over the 1992–1995 follow-up period and thereafter for each calendar year of follow-up up to 2006. Small numbers of deaths over the 1992–1995 follow-up period were combined to allow meaningful comparison with the rest of the follow-up period. Mortality rates after an HCV notification were estimated using person time methodology, for individuals aged 0–20 years, and thereafter for 5-year age groups up to 70 years. Confidence intervals for mortality rates were estimated by use of a quadratic approximation, on the assumption that recorded deaths follow a Poisson distribution. Person-years at risk were calculated for each person as time from NDD notification date to either date of death or 31 December 2006, if there was no death recorded. The cumulative incidences of liver-, drug- and other-cause-related mortality were calculated within a competing risk framework [20]. Competing risks were defined as competing events (drug- and other-cause-related deaths) whose occurrence prevent or alter the probability of occurrence of the main event under examination (liver-related deaths).

Abridged life tables were constructed from age-specific mortality probabilities to estimate life expectancy from 18 to 70 years of age. These tables describe the mortality experience that hypothetical cohorts of people with an

HCV notification would have had if they were subjected to the mortality in the observed period. Life expectancy at an exact age is the average additional years that will be lived by a person after that age, according to the cross-sectional age-specific mortality rates for all causes during the study period. To estimate the potential association of HCV with life expectancy, only non-drug-related deaths were included in the abridged life tables, using a competing risk methodology [20]. Competing risks were defined as competing events (drug-related deaths) whose occurrence prevent or alter the probability of occurrence of the main event under examination (non-drug-related deaths). Cause-specific mortality probabilities (for non-drug-related deaths) in each age stratum were calculated, taking into account the effect of competing risk and assuming no individual died later than 100 years of age. Mortality probabilities for the open age grouping (≥70 years) could not be meaningfully estimated as the sample size was too small to allow further stratification by age. Therefore, the mortality probabilities in those aged ≥70 years were adjusted using the average relative risk of mortality in the NSW population with an HCV notification to that of the Australian population (hereafter referred to as the general population). Among the NSW study cohort aged <70 years, smoothed mortality probabilities (by including a nonlinear regression line) were used to calculate relative risks of mortality. The average relative risk of mortality was then extrapolated from the 50–70 year age group to the open age group; 1.81 for males and 2.40 for females. We investigated the sensitivity of these estimates by varying the calculation of average relative risk from 60–80 to 70–80 year age groups. We assumed mortality probabilities in the open age group were the same as the average mortality probabilities calculated from extrapolated average relative risks in NSW cohort and mortality probabilities in the general population aged ≥70 years.

Ethics approval for the study was granted by NSW Health, NSW Cancer Council, the Australian Institute of Health and Welfare and the University of New South Wales.

RESULTS

The initial NSW cohort consisted of 128 726 people who had an HCV or HBV notification between 1992 and 2006. Data on 42 480 people with an HBV notification, 3285 people with an HCV/HBV notification, 620 people with an HCV/HIV notification 269 people with an HBV/HIV notification, and 38 people with an HBV/HCV/HIV notification were excluded. Moreover, 390 people with an HCV notification whose gender was unknown were excluded. Overall, 81 644 people with an HCV notification were included in this analysis (Fig. 1). The median year of birth among males and females was 1963 [interquartile range (IQR) 1956–1970] and 1964 (IQR 1957–1972), respectively. The median age at HCV notification among males and females was 35 years (IQR 28–42) and 34 years (IQR 27–41), respectively.

A total of 4607 (6%) people with an HCV notification died during a median follow-up of 7.6 years, comprising 20% (n = 939) liver-related deaths, 24% (n = 1109) drug-related deaths, and 56% (n = 2559) deaths from other causes. Median age at death among males and females was 46 years (IQR 37–59) and 51 years (IQR 40–74), respectively. Among males, median age at all-cause-, liver-, drug- and other-cause-related deaths was 46 years (IQR 37–59), 51 years (IQR 45–66), 36 years (IQR 31–42) and 50 years (IQR 40–70), respectively (Table 1). Among females, median age at all-cause-, liver-, drug- and other-cause-related deaths was 51 years (IQR 40–74), 63 years (IQR 49–74), 36 years (IQR 30–41) and 60 years (IQR 44–78), respectively (Table 1).

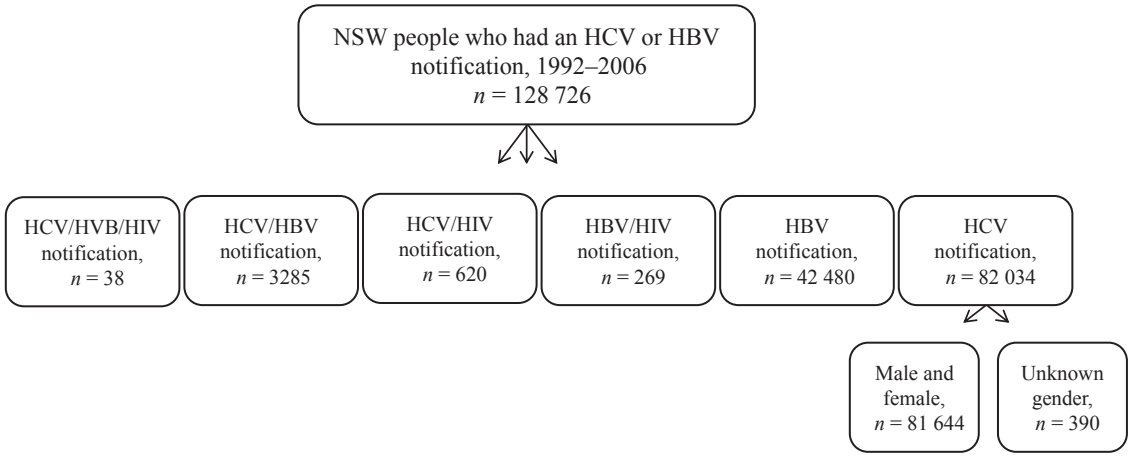

Fig. 1 Distribution of HCV and HBV notifications in NSW, 1992–2006.

Table 1 Distribution of age at death among NSW people with an HCV notification, $n = 81\ 644$

	Number of deaths	Median age at death	Interquartile range (IQR)
All-cause mortality	4607	47	38–66
Male*	3220	46	37–59
Female	1387	51	40–74
Liver-related mortality†	939	53	46–70
Male	665	51	45–66
Female	274	62	49–74
Drug-related mortality‡	1109	36	31–42
Male	845	36	31–42
Female	264	36	30–41
Other-cause mortality	2559	51	41–73
Male	1710	50	40–70
Female	849	60	44–78

*Unknown/other gender is not included in analysis; †defined as any death caused by viral hepatitis, sequelae of viral hepatitis, HCC, non-HCC liver cancer, alcoholic and nonalcoholic liver disease; ‡defined by ABS definition of drug-related deaths.

Over the 1992–1995 period and thereafter in each calendar year up until 2000, liver-, drug- and other-cause-related deaths comprised <21%, 30–39% and 44–51% of the total number of deaths, respectively (Fig. 2). After 2000, the number of liver- and other-cause-related deaths increased to reach 26% and 63% in 2006, respectively. After 2000, the number of drug-related deaths decreased to 13% of all deaths in 2006 (Fig. 2). Over the 1992–1995 period and thereafter in each calendar year up until 2001, median age at liver-related death was between 53 years and 60 years, with the exception of 1998 (median age at death 46 years). After 2001, the median age at liver-related death lowered to 52 years in 2006 (IQR 48–61) (Table 1; Fig. 2). Between 1992 and 1995, the median age at drug- and other-cause-related deaths was 33 years (IQR 28–39) and 52 years (IQR 35–73), respectively. The median age at drug- and other-cause-related deaths remained between 35 to 40 years and 45 to 54 years from 1997 to 2006, respectively (Table 1; Fig. 2).

The study population was followed for a median of 7.6 years (range 0.7–15.0) or a total of 627 821 person-years at risk. Cumulative incidence of drug-related mortality was initially higher than liver-related mortality (Fig. 3). At 12 years following HCV notification, cumulative incidence of liver-related mortality surpassed the cumulative incidence of drug-related mortality (Fig. 3).

For both genders, age-specific rates of all-cause, liver- and other-cause-related mortality increased by age, from 30 years onwards (Fig. 4). However, there were lower numbers of HCV notifications in older age groups among both genders. The crude numbers of liver-related deaths were highest in the 35–39 ($n = 133$), 40–44 ($n = 190$) and 45–49 year ($n = 104$) age groups. Compared with other age-specific mortality rates, rates of drug-related mortality were higher among relatively younger ages for both genders. The rates were elevated from early 20s into early to mid-40s, after which they decreased gradually (Fig. 4). Estimates of life expectancy were undertaken following removal of drug-related mortality.

Among the NSW study cohort, males had consistently shorter life expectancy compared to females (Fig. 5). The life expectancy (after excluding drug-related causes of death) at the median age of HCV notification among NSW males and females (35 and 34 years, respectively) was 39 and 44 years, compared with 45 and 51 years among males and females of the general population, respectively. The life expectancy at a notification age of 50 years among NSW males and females was 27 and 29 years, compared with 31 and 35 years among males and females of the general population, respectively. Compared with males of the general population, life expectancy for males in the NSW study cohort was lowered by an average of 4.2 years (SD $\pm$ 1.0). Compared with females of the general population, life expectancy for females in the NSW study cohort was lowered by an average of 5.4 years (SD $\pm$ 0.7).

DISCUSSION

In this large population-based linkage study, once drug-related deaths were excluded, life expectancy among people with an HCV notification was 4–5 years lower compared with the general population. This study also demonstrates the changing distribution of cause of death among people with an HCV notification in NSW, Australia. Since 2000, concurrent with the HCV cohort ageing and the decreasing number of drug-related deaths, liver-related deaths have steadily increased. These findings build on those from previous NSW linkage studies [11,12] in providing additional data on mortality among people with an HCV notification.

Our analysis demonstrated drug-related death as a major cause of mortality in people with an HCV notification in 1990s. During this decade, heroin was the most commonly injected drug among people who injected drugs regularly in NSW, resulting in an increase in associated harms, including fatal overdoses [10]. Following a wider implementation of harm reduction policies in the late 1990s [21] and the nation-wide reduced availability of heroin from 2001 [22,23], indicators of injecting drug use decreased across the country [24]. Subsequently, there has been a decline in the number of drug-related deaths [21] and young adults initiating injecting drug use [25]. The initial reduction in injecting drug use has been further

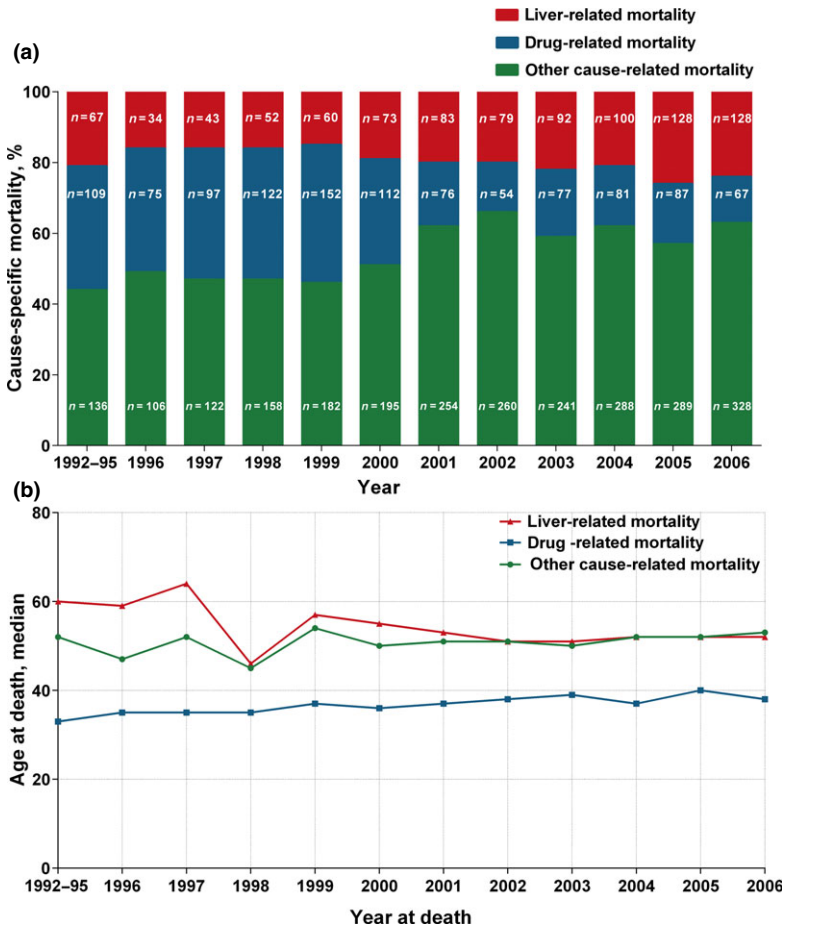

Fig. 2 Temporal trends in the distribution of mortality among NSW people with an HCV notification, by year of follow-up. (a) Cause-specific mortality; (b) median age at cause-specific mortality.

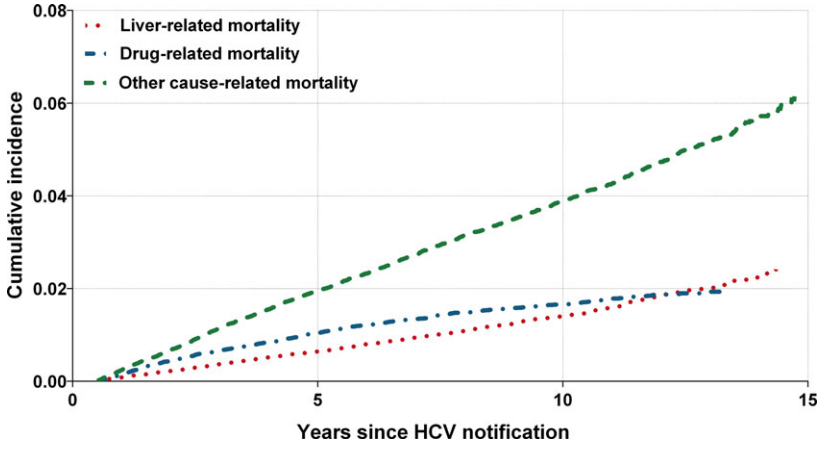

Fig. 3 Cumulative incidence for cause-specific mortality among NSW people with an HCV notification.

enhanced within the population of people with HCV mono-infection through the ageing cohort nature of the population and the resultant impact on drug use patterns.

Declining drug-related mortality among people with an HCV notification in NSW is contrasted by increasing liver-related deaths. Although age-specific liver-related mortality is not increasing [12], expanding HCV prevalence and the ageing cohort nature of the population are leading to a rising burden of liver-related deaths. Low HCV treatment uptake remains another major contributor [8]. It has been suggested that achieving sustained virological response is associated with reduced risk of all-cause mortality, including mortality from non-liver-related causes [26]. High proportions of other-cause-related deaths in this analysis may further reflect on suboptimal HCV treatment uptake and development of liver- and non-liver-related conditions that

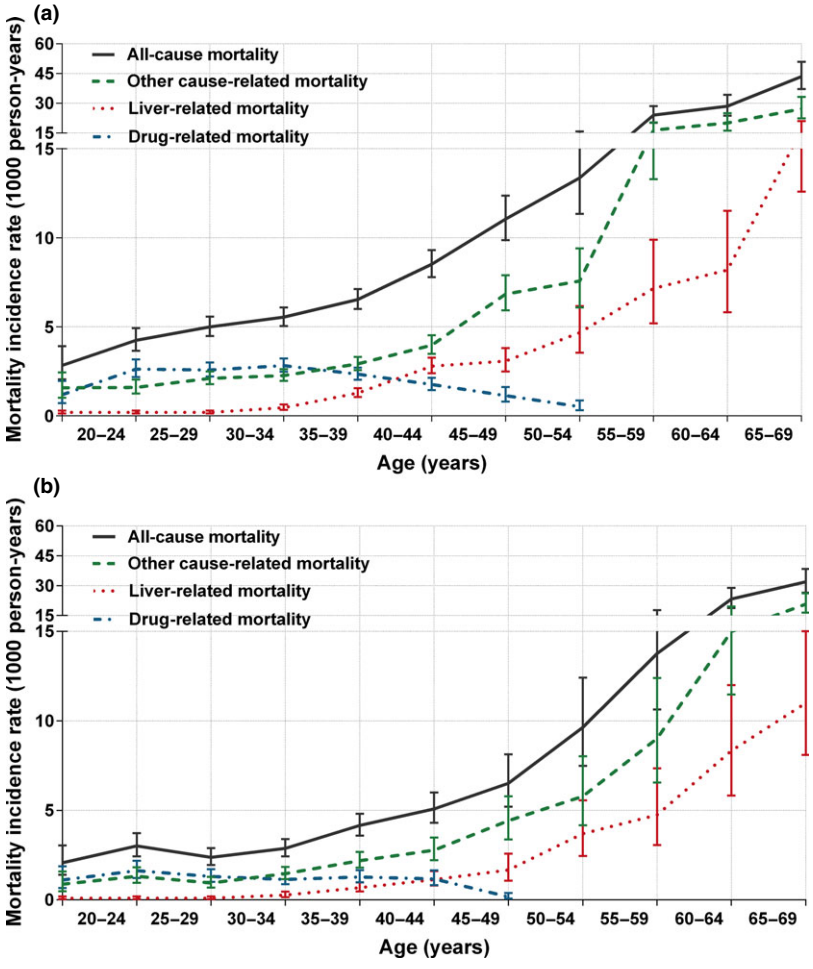

Fig. 4 Incidence of all-cause, other-cause-, liver- and drug-related mortalities, by age group. (a) Males; (b) females.

contribute to high mortality among people with an HCV notification.

There are several limitations in our study. First, HCV notification registries do not collect treatment information; therefore, we could not assess the impact of HCV therapy on liver disease mortality. However, HCV treatment uptake has been low throughout the study period, with only 1–2% of people with chronic infection receiving interferon-based treatment annually [27]. Second, while confirmed HCV notifications are entered to NDD within a short period of time, it is not possible to precisely distinguish between diagnosed and notified cases in each calendar year. Third, as HCV notifications are generally based on anti-HCV-positive serology, many HCV notifications will not have chronic infection, as an estimated 25% of infections spontaneously clear [28] and remain HCV antibody positive. However, inclusion of all anti-HCV antibody-positive notifications should underestimate the liver disease mortality related to chronic HCV infection. Fourth, there may be some uncertainty with respect to the duration of HCV infection, given these data are based on the date of notification (the time of infection among many cases may be unknown).

Fifth, given the absence of lifestyle information in this study, we were also not able to evaluate the potential impact of specific exposures (e.g. alcohol consumption, smoking, drug use) on increased mortality. As such, the direct impact of HCV infection on mortality and decline in life expectancy could not be quantified. Sixth, although an estimated 80–85% of all HCV infections in Australia have been notified [24], lower screening rates in some subpopulations (particularly non-PWID), could affect representativeness. The exclusion of individual cases with death within 6 months of notification should, however, have reduced potential symptomatic-base selection bias. Seventh, the current analysis is among people with an HCV notification until December 2006 which may limit our understanding of more recent changes in mortality trends. However, given the ageing cohort effect and continued low levels of HCV treatment uptake [29], overall mortality trends in this population are not expected to have changed markedly since 2006. Lastly, the accuracy of data linkage relies upon the accuracy of identified personal information, which may be poorly recorded. Alias identities may lead to inaccuracies in linkage. However, another Australian study in prisons, where aliases are common, has estimated that the linkage

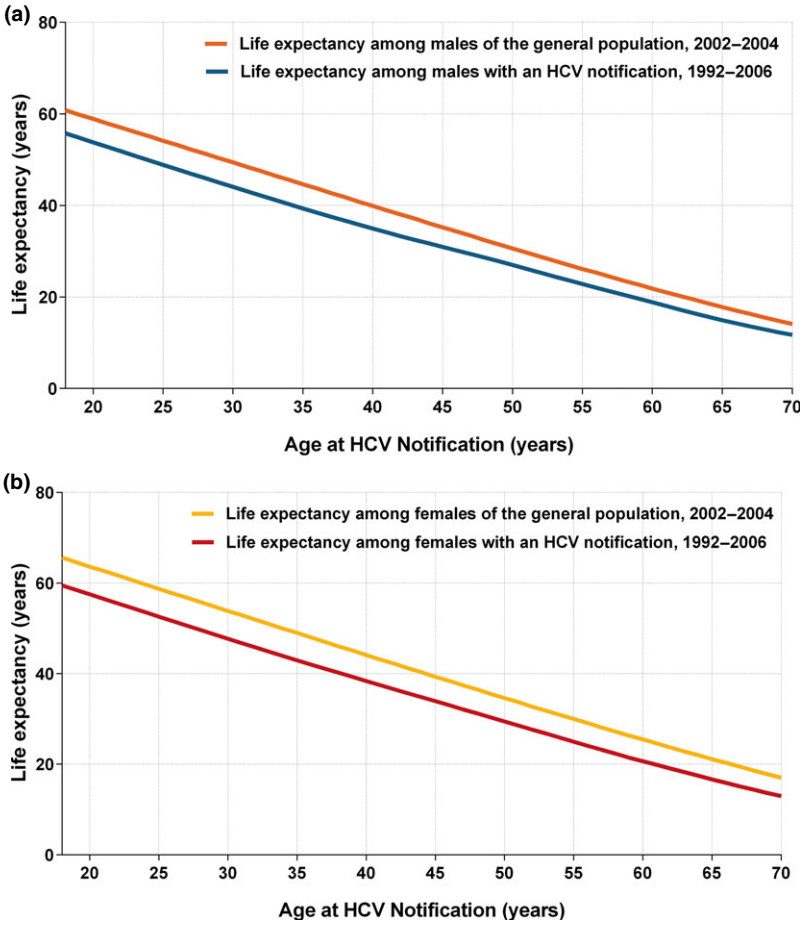

Fig. 5 Life expectancy in NSW cohort compared with general population, excluding drug-related mortality. (a) Males; (b) females.

accuracy for NSW prisoners and the National Death Index has a sensitivity of 88.4% and specificity of 99.7% [30]. There is no reason to believe the accuracy of linkage was lower in this study.

Successful HCV treatment with viral eradication is associated with improved quality of life, liver disease regression and reduction in liver- and all-cause-related mortality [26]. The HCV therapeutic landscape will change markedly over the next decade [31]. Preliminary evidence indicates that interferon-free combination direct acting antiviral regimens should reduce toxicity, shorten treatment durations (from 24–48 weeks to 8–12 weeks), improve dosing schedules, and enhance cure rates [31]. These therapeutic developments will be associated with considerable additional expense, at least during the initial decade of their implementation. Cost-effectiveness analyses will therefore need to incorporate parameters associated with disease progression and lowered life expectancy based on representative population-based cohorts. Often, these parameters have been derived from liver clinic-based studies, which contain selection bias [32].

In summary, among people with an HCV notification, mortality is higher and life expectancy is lower, compared with the general population. As individuals age, major causes of death shift from drug- to liver-related causes. Liver-related deaths are expected to further increase as the cohort is ageing and duration of infection increases. Our findings should facilitate public health strategic planning in response to increasing disease burden among people with HCV infection.

AUTHORS CONTRIBUTIONS

M Alavi contributed to the statistical analysis, interpretation of data and drafting the article; M Law and G Dore contributed to the study conception, design and the interpretation of data; J Grebely contributed to interpretation of data and drafting the article; J Amin contributed to the study design, the acquisition and interpretation of data; S Walter contributed to the acquisition and interpretation of data; HH Thein contributed to the study conception, design and interpretation of data. All authors revised and approved the final version for publication.

FINANCIAL DISCLOSURE

J Grebely is a consultant/advisor for Merck. GJ Dore is a consultant/advisor and has received research grants from

Roche, Merck, Janssen, Gilead, Bristol Myers Squibb and AbbVie. The other authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

ETHICS COMMITTEE APPROVAL

Ethics approval for the study was granted by NSW Health, NSW Cancer Council, the Australian Institute of Health and Welfare and the University of New South Wales.

CONFLICT OF INTEREST

None of the authors has commercial relationships that might pose a conflict of interest in connection with this manuscript.

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ROLE OF THE FUNDING SOURCE

The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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REFERENCES

1 Younossi ZM, Zheng L, Stepanova M, Venkatesan C, Mir HM. Moderate, excessive or heavy alcohol consumption: each is significantly associated with increased mortality in patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2013; 37(7): 703–709.

2 Grebely J, Tyndall MW. Management of HCV and HIV infections among people who inject drugs. *Curr Opin HIV AIDS* 2011; 6(6): 501–507.

3 Gaeta GB, Stornaiuolo G, Precone DF *et al.* Epidemiological and clinical burden of chronic hepatitis B virus/hepatitis C virus infection. A multicenter Italian study. *J Hepatol* 2003; 39(6): 1036–1041.

4 Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol* 2002; 97(9): 2408–2414.

5 Thein H-H, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008; 48(2): 418–431.

6 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; 349(9055): 825–832.

7 Grady B, van den Berg C, van der Helm J *et al.* No impact of hepatitis C virus infection on mortality among drug users during the first decade after seroconversion. *Clin Gastroenterol Hepatol* 2011; 9(9): 786–792.

8 Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? *Semin Liver Dis* 2011; 31(4): 331–339.

9 Notification of Infectious Diseases under the Public Health Act 1991 [Internet]. Department of Health, NSW. 2006. Available at: http://www.health.nsw.gov.au/policies/pd/2006/pdf/PD2006_014.pdf (accessed 30 March 2012).

10 Law MG, Dore GJ, Bath N *et al.* Modelling hepatitis C virus incidence, prevalence and long-term sequelae in Australia, 2001. *Int J Epidemiol* 2003; 32(5): 717–724.

11 Amin J, Law MG, Bartlett M, Kaldor JM, Dore GJ. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. *Lancet* 2006; 368(9539): 938–945.

12 Walter SR, Thein H-H, Amin J *et al.* Trends in mortality after diagnosis of hepatitis B or C infection: 1992-2006. *J Hepatol* 2011; 54(5): 879–886.

13 International Classification of Diseases (ICD) [Internet]. World Health Organization 2012. Available at: http://www.who.int/classifications/icd/en/. (accessed 30 March 2012).

14 McDonald AM, Crofts N, Blumer CE *et al.* The pattern of diagnosed HIV infection in Australia, 1984-1992. *AIDS* 1994; 8(4): 513–519.

15 ChoiceMaker Technologies, Inc. New York, NY 10010. Available at: http://oscmt.sourceforge.net/. (accessed 30 March 2012).

16 The Centre for Health Record Linkage (CHeReL) Available at: http://www.cherel.org.au/. (accessed 30 March 2012).

17 Drug-induced Deaths – A Guide to ABS Causes of Death Data. Cat. No. 4809.0.55.001. Australian Bureau of Statistics: Australian Bureau of Statistics; 2006. Available at: http: //www.abs.gov.au/AUSSTATS/abs@.nsf/0/0AA81AFAFCBB1F8ECA256C0F00038E98?OpenDocument. (accessed 30 March 2012).

18 Mortality Among People who Use Illicit Drugs: A Toolkit for Classifying Major Causes of Death. Technical Report No. 301. [Internet]. National Drug and Alcohol Research Centre, Sydney, Australia. 2009. Available at: http://ndarc.med.unsw.edu.au/sites/ndarc.cms.med.unsw.edu.au/files/ndarc/resources/TR.301.pdf. (accessed 30 March 2012).
19 Anderson RN, Miniño AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. *Natl Vital Stat Rep* 2001; 49(2): 1–32.
20 Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999; 18 (6): 695–706.
21 Degenhardt LJ, Conroy E, Gilmour S, Hall WD. The effect of a reduction in heroin supply on fatal and non-fatal drug overdoses in New South Wales, Australia. *Med J Aust* 2005; 182(1): 20–23.
22 Australian drug Trends 2001. Findings of the Illicit Drug Reporting System (IDRS) [Internet]. 2002. Available at: http://ndarc.med.unsw.edu.au/resource/australian-drug-trends-2001-findings-illicit-drug-reporting-system. (accessed 30 March 2012).
23 Weatherburn D, Jones C, Freeman K, Makkai T. Supply control and harm reduction: lessons from the Australian heroin 'drought'. *Addiction* 2003; 98(1): 83–91.
24 Razali K, Thein HH, Bell J *et al.* Modelling the hepatitis C virus epidemic in Australia. *Drug Alcohol Depend* 2007; 91(2–3): 228–235.
25 Day C, Degenhardt L, Hall W. Changes in the initiation of heroin use after a reduction in heroin supply. *Drug Alcohol Rev* 2006; 25(4): 307–313.
26 Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011; 9(6): 509–516.
27 Grebely J, Bryant J, Hull P *et al.* Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. *J Viral Hepat* 2011; 18(4): e104–e116.
28 Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006; 13(1): 34–41.
29 HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Report 2010. National Centre in HIV Epidemiology and Clinical Research. [Internet]. 2010. Available at: http://www.kirby.unsw.edu.au/surveillance/2010-hiv-viral-hepatitis-sexually-transmissible-infections-australia-annual. (accessed 30 March 2012).
30 Kariminia A, Butler T, Corben S, Kaldor J, Levy M, Law M. Mortality among prisoners: how accurate is the Australian National Death Index? *Aust N Z J Public Health* 2005; 29(6): 572–575.
31 Dore GJ. The changing therapeutic landscape for hepatitis C. *Med J Aust* 2012; 196(10): 629–632.
32 Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. *J Viral Hepat* 2003; 10(4): 285–293.