Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study

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Summary

Background Hepatitis B and hepatitis C virus infections are common causes of death related to liver disease. In this large study, we aimed to investigate all cause mortality of the viruses in a community-based setting.

Methods In the study population, 39 109 people had hepatitis B, 75 834 had hepatitis C, and 2604 had hepatitis B and hepatitis C co-infection, notified to the New South Wales state health department, Australia, between 1990 and 2002. Their data were probabilistically linked to the National Death Index. Standardised mortality ratios for all causes of death were calculated and adjusted for age, sex, and calendar year.

Results The number of deaths identified by the linkage were 1233 (3·2 %) for hepatitis B, 4008 (5·3)% for hepatitis C, and 186 (7·1)% for hepatitis B and C co-infection. Raised risk of liver-related death (standardised mortality ratios 12·2, 95% CI 10·7–13·9; 16·8, 15·4–18·3, and 32·9, 23·1–46·7, for hepatitis B, hepatitis C, and hepatitis B and C co-infected patients, respectively) and drug-induced death (1·4, 1·0–2·0; 19·3, 18·1–20·5; and 24·7, 18·2–33·5, respectively) were detected. In people with hepatitis C, raised risk of dying from drug-related causes was significantly greater than from liver-related causes (p=0·012), with the greatest excess risk in women aged 15–24 years (56·9, 39·2–79·9).

Interpretation All groups had increased risk of liver-related death compared with the standard population, with the greatest excess in people diagnosed with hepatitis B and hepatitis C co-infection. Our data highlight that young people with hepatitis C and with co-infection face a higher mortality risk from continued drug use than from their infection, whereas the main cause of hepatitis B death was liver related.

Introduction

Chronic infection with hepatitis B or hepatitis C viruses are common causes of progressive liver disease, cirrhosis, and hepatocellular carcinoma.[1–4] Co-infection with hepatitis B and hepatitis C further increases risk of liver disease complications.[5] The natural history of hepatitis B and hepatitis C infections has been extensively studied, especially in relation to rates of progression of liver disease.[6,7] However, mortality related to hepatitis B and hepatitis C infection is less well defined. Most mortality-based studies have used selected populations with limited power or have restricted analysis to liver-related causes of death.[8–15]

We know of no one study that systematically examines the risk of all causes of death after hepatitis B or hepatitis C infection in a community-based setting. To provide precise estimates of the risk of death after infection, we investigated the incidence and excess risk of disease-specific and all cause mortality in a population of people diagnosed with hepatitis B and hepatitis C infection in New South Wales (NSW), Australia.

Methods

Data sources

We did a retrospective study, linking notified cases of hepatitis B and hepatitis C infection in NSW to the Australian National Death Index (NDI). Notification to the NSW Health Department Notifiable Diseases Database (NDD) of newly diagnosed hepatitis B and hepatitis C infection has been mandatory for laboratories since 1991.[16] The case definition for hepatitis B notification requires detection of hepatitis B surface antigen or hepatitis B DNA. The case definition for hepatitis C notification requires detection of anti-hepatitis C antibody or hepatitis C RNA. Date of notification, sex, date of birth, last name, first name, postcode of residence, and NDD registration number were extracted from the database for people notified with hepatitis B or hepatitis C infection between Jan 1, 1990, and Dec 31, 2002.

The NDI database contains records of all deaths in Australia since 1980, based on reports from the Registrars of Births, Deaths, and Marriages in each State and Territory. Last name, first name, date of birth (or estimated year of birth), age at death, sex, date of death, ICD 9 (deaths before 1997) and ICD10 (deaths since 1997) classification code for underlying cause of death and NDI registration number were extracted from NDI for all notifications received by the end of 2002.

Linkage procedure

Record linkage between the NDD population and NDI was done in two steps: matching hepatitis B and hepatitis C notifications to identify co-infected cases, and matching NDD notifications to deaths in NDI. Linkage was done probabilistically on the basis of name, date of birth, sex, and place of residence data with Integrity software, version 3·6.[17]

Data linkage was done by NSW Health (NDD hepatitis B–NDD hepatitis C linkage) and the Australian Institute of Health and Welfare (NDD–NDI linkage). All

personal identifiers were removed before the linked data were transferred to the National Centre in HIV Epidemiology and Clinical Research for data analysis.

Statistical analysis

Causes of death in people with hepatitis B and hepatitis C infection were summarised as total counts of linked deaths. People who died within 6 months of hepatitis B or hepatitis C diagnosis were not included in analyses of the incidence of death because of the potential for bias towards higher rates of diagnosis in people with major morbidity. Incidence of death was determined by person-time methods. Person-years at risk were calculated for each person as time from date of NDD notification to either the date of death or Dec 31, 2002. For people with hepatitis B and hepatitis C co-infection, risk time commenced at the later of hepatitis B or hepatitis C notification.

For each cause of death, incidence seen in the study population was compared with the expected incidence derived from NSW population death rates by the calculation of standardised mortality ratios.[18,19] Ratios were adjusted by 5-year age-group, sex, and calendar year of hepatitis notification, with age-group and calendar year treated as time dependent covariates. People with missing information about age or sex on NDD notification were excluded from these analyses. CIs for standardised mortality ratios were estimated by use of a quadratic approximation, on the assumption that recorded deaths follow a Poisson distribution. Poisson regression was used to compare standardised mortality ratios, obtain p values, and test for change in slope. Causes of death were categorised according to ICD10 and corresponding ICD9 chapter headings. For drug related deaths, the Australian Bureau of Statistics classification was used, which included mental and behavioural disorders due to psychoactive substance use, misuse of non-dependence-producing substances, death by accidental, intentional, or undetermined intent, or poisoning or assault by drugs, medicaments, and biologicals.[20]

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.

	Viral hepatitis notification		
	Hepatitis B virus n=39 109	Hepatitis C virus n=75 834	Hepatitis B and C co-infection n=2604
Year of viral hepatitis notification, median (IQR)	1997 (1994–2000)	1997 (1995–2000)	1999 (1996–2002)*
Age at viral hepatitis notification [years], median (IQR)	35 (27–44)	34 (28–41)	35 (29–42)*
Data missing [n], (%)	1507 (4%)†	789 (1%)	13 (<1%)
Males [n], (%)	20 808 (53%)	47 903 (63%)	1932 (74%)
Data missing [n], (%)	772 (2%)	555 (1%)	14 (1%)
Linked deaths‡ [n], (%)	1233 (3%)	4008 (5%)	186 (7%)

*At second infection. †84% received before 1993. ‡Includes deaths within 6 months of hepatitis notification.

Table 1: **Characteristics of people diagnosed with hepatitis B, hepatitis C, or co-infection in NSW 1990–2002**

	Description	Viral hepatitis notification											
		Hepatitis B virus				Hepatitis C virus				Hepatitis B and C co-infection			
		Observed deaths	Rate	SMR	95% CI	Observed deaths	Rate	SMR	95% CI	Observed deaths	Rate	SMR	95% CI
	All cause	896	46·1	1·4	1·3–1·5	3342	92·5	3·1	3·0–3·2	150	141·7	5·6	4·8–6·6
A00-B99	Infection	118	6·1	10·2	8·5–12·2	270	7·5	11·4	10·1–12·8	21	19·8	30·0	19·5–46·0
C00-D48	Neoplasms	326	16·8	1·6	1·5–1·8	518	14·3	1·8	1·6–1·9	24	22·7	3·2	2·2–4·8
D50-D89	Blood/immune	6	0·3	9·3	4·2–20·6	17	0·5	15·1	9·4–24·2	0			
E00-E90	Endocrine	41	2·1	2·3	1·7–3·1	88	2·4	2·9	2·4–3·6	2	1·9	2·7	0·7–10·7
F00-F99	Mental and behavioural	24	1·2	1·3	0·9–2·0	590	16·3	15·0	13·9–16·3	26	24·6	23·6	16·1–34·7
G00-G99	Nervous system	11	0·6	0·7	0·4–1·2	49	1·4	1·6	1·2–2·2	0			
I00-I99	Circulatory system	149	7·7	0·8	0·6–0·9	450	12·5	1·3	1·2–1·5	19	17·9	2·6	1·6–4·0
J00-J99	Respiratory system	27	1·4	0·6	0·4–0·9	84	2·3	1·2	1·0–1·5	2	1·9	1·3	0·3–5·3
K00-K-93	Digestive system	40	2·1	1·8	1·3–2·5	221	6·1	6·0	5·2–6·8	12	11·3	12·1	6·8–21·2
L00-L99	Skin	0				3	0·1	1·7	0·6–5·4	0			
M00-M99	Musculoskeletal	4	0·2	1·4	0·5–3·6	13	0·4	2·6	1·5–4·5	0			
N00-N99	Genitourinary	17	0·9	2·1	1·3–3·4	41	1·1	2·7	2·0–3·7	3	2·8	10·6	3·4–32·7
O00-Q99	Pregnancy/perinatal/ congenital	6	0·3	1·9	0·9–4·3	10	0·3	1·6	0·9–3·0	0			
R00-R99†	Other	4	0·2	2·0	0·8–5·4	38	1·1	9·5	6·9–13·0	1	0·9	9·1	1·3–64·8
V00-Y98	External	123	6·3	1·5	1·3–1·8	950	26·3	5·5	5·2–5·9	40	37·8	7·2	5·3–9·8

Rate reported per 10 000 person years. SMR=standardised mortality ratio, adjusted for age, sex, and calendar year. Death, rate, and SMR calculated only including hepatitis cases where death occurred at least 6 months after hepatitis diagnosis and information about age at diagnosis and sex were available. *For deaths before 1997, corresponding ICD9 codes were used. †Includes deaths with no cause specified.

Table 2: **Causes of death in people diagnosed with hepatitis B, hepatitis C, or hepatitis B and C co-infection in NSW 1990–2002 by ICD-10 code***

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 120 815 hepatitis B and hepatitis C infections were notified to the NDD from 1990 to 2002. The data linkage processes identified 664 duplicate records and 2604 people with both hepatitis C and hepatitis B notifications to give a final study population of 117 547. From this population, three groups were defined on the basis of hepatitis B and hepatitis C infection status (table 1). The three groups were similar in their median year and age at NDD notification; the hepatitis B and hepatitis C co-infected group had a higher proportion of men. The number of deaths identified in the study population were 1233 (3·2%) for hepatitis B, 4008 (5·3%) for hepatitis C and 186 (7·1%) for hepatitis B and hepatitis C co-infection. The most frequently reported causes of death were neoplasms for hepatitis B (469 [38%] of 1233), and external causes for hepatitis C (1108 [28%] of 4008) and hepatitis B and hepatitis C co-infection (50 [27%] of 186).

A fifth to a quarter of deaths took place within 6 months of diagnosis of hepatitis (hepatitis B 27%, hepatitis C 17%, hepatitis B and C 19%). After exclusion of these cases, the hepatitis B, hepatitis C, and co-infected groups

	Description	Sex	Viral hepatitis notification											
			Hepatitis B				Hepatitis C				Hepatitis B and C co-infection			
			Observed deaths	Rate	SMR	95% CI	Observed deaths	Rate	SMR	95%CI	Observed deaths	Rate	SMR	95% CI
	All liver related		227	11·7	12·2	10·7–13·9	503	13·9	16·8	15·4–18·3	31	29·3	32·9	23·1–46·7
		Men	192	18·5	13·0	11·3–14·9	363	16·2	15·1	13·6–16·7	25	31·4	29·4	19·9–43·5
		Women	35	3·9	9·3	6·6–12·9	140	10·2	23·9	20·3–28·2	6	22·9	64·2	28·8–143
B15–B19†	Viral hepatitis		34	1·8	37·6	26·8–52·6	90	2·5	50·5	41·1–62·1	6	5·7	107·8	48·4–240
		Men	27	2·6	36·4	24·9–53·0	61	2·7	40·2	31·3–51·6	6	7·5	115·5	51·9–257
		Women	7	0·8	43·0	20·5–90·2	29	2·1	110·1	76·5–159	0			
B942†	Sequelae of viral hepatitis		31	1·6	34·2	24·0–48·6	110	3·0	57·3	47·5–69·1	8	7·6	118·6	59·3–237
		Men	26	2·5	35·0	23·9–51·5	78	3·5	47·5	38·1–59·4	6	7·5	96·7	43·4–215
		Women	5	0·6	30·2	12·6–72·6	32	2·3	114·8	81·2–162	2	7·6	370·4	92·6–1481
C22†	Liver cancer		131	6·7	27·8	23·4–33·0	117	3·2	16·7	14·0–20·1	8	7·6	39·7	19·9–79·5
		Men	110	10·6	29·6	24·6–35·7	83	3·7	15·4	12·4–19·1	7	8·8	39·2	18·7–82·2
		Women	21	2·3	21·0	13·7–32·3	34	2·5	21·2	15·1–29·6	1	3·8	43·9	6·2–312
K70†	Alcoholic liver disease		16	0·8	2·1	1·3–3·4	96	2·7	7·9	6·5–9·6	4	3·8	9·8	3·7–26·1
		Men	16	1·5	2·6	1·6–4·2	73	3·3	7·2	5·8–9·1	2	2·5	5·4	1·4–21·6
		Women	0				23	1·7	11·0	7·3–16·6	2	7·6	52·3	13·1–209
K71–K77†	Non-alcoholic liver disease		15	0·8	3·4	2·0–5·6	90	2·5	12·7	10·4–15·6	5	4·7	23·7	9·9–56·9
		Men	13	1·3	3·8	2·2–6·6	68	3·0	12·5	9·8–15·8	4	5·0	21·3	8·0–56·8
		Women	2	0·2	1·9	0·5–7·7	22	1·6	13·6	9·0–20·7	1	3·8	42·8	6·0–304
B20–B24	HIV		35	1·8	9·2	6·6–12·9	49	1·4	5·2	4·0–6·9	6	5·7	18·3	8·2–40·8
		Men	33	3·2	9·1	6·5–12·8	46	2·0	5·1	3·8–6·8	6	7·5	18·6	8·4–41·5
		Women	2	0·2	12·9	3·2–51·6	3	0·2	11·8	3·8–36·6	0			
C81–C96	Lymphoid		35	1·8	1·7	1·2–2·4	62	1·7	1·9	1·5–2·5	2	1·9	2·4	0·6–9·6
		Men	22	2·1	1·6	1·0–2·4	40	1·8	1·9	1·4–2·5	2	2·5	2·9	0·7–11·6
		Women	13	1·4	2·0	1·2–3·5	22	1·6	2·1	1·4–3·2	0			
ABS	Drug related		31	1·6	1·4	1·0–2·0	989	27·4	19·3	18·1–20·5	41	38·7	24·7	18·2–33·5
		Men	26	2·5	1·6	1·1–2·3	759	33·8	17·7	16·5–19·0	37	46·4	24·6	17·8–34·0
		Women	5	0·6	0·9	0·4–2·2	230	16·8	27·6	24·2–31·4	4	15·3	25·3	9·5–67·4

Total=all linked deaths. Rate reported per 10 000 person years. SMR=standardised mortality ratio, adjusted for age, sex, and calendar year. Deaths, rate, and SMR calculated only including hepatitis cases where death occurred at least 6 months after hepatitis diagnosis and information about age at diagnosis and sex were available. ABS=Australian Bureau of Statistics definition of drug related deaths, includes ICD 10 codes of: F11-F16, F19, F55, X40–X44, X60–X64,X85, Y10–Y14 and corresponding ICD9 codes. *For deaths before 1997, corresponding ICD9 codes were used. †Consist of "All liver related".

Table 3: **Causes of death related to viral hepatitis in NSW 1990–2002 by ICD-10 code**

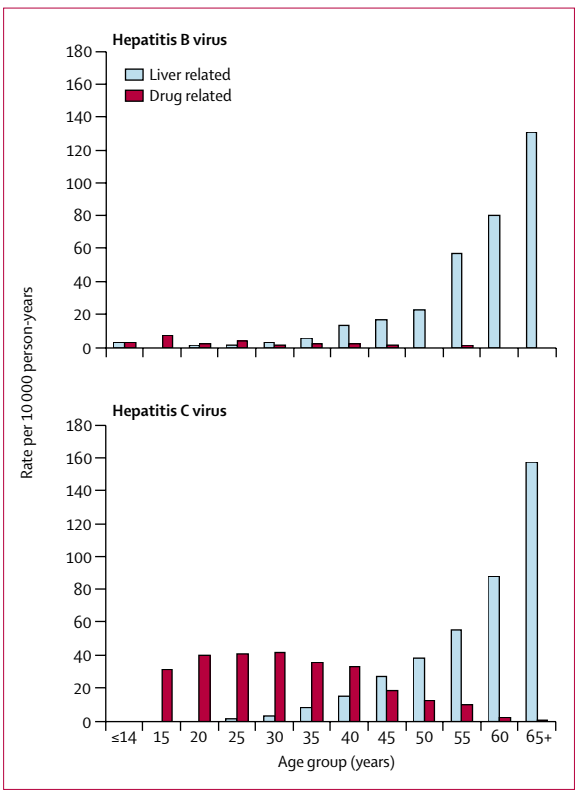

Figure 1: **Incidence of liver related and drug related deaths by age group and type of viral hepatitis**

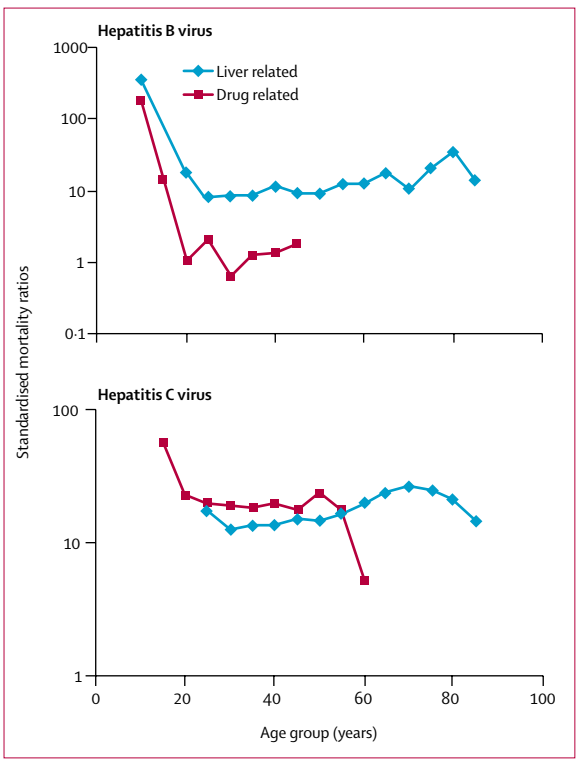

Figure 2: **Standardised mortality ratios for liver-related and drug-related deaths by age group and type of viral hepatitis**

contributed a median of 5·3, 4·6, and 3·5 years of follow-up per person, respectively.

The incidence of death and standardised mortality ratios comparing mortality in the hepatitis-diagnosed population with the general population of NSW, for all causes of death, are shown in table 2. The overall incidence of death was greatest for people with hepatitis B and C co-infection, followed by hepatitis C, and hepatitis B (141·7, 92·5, and 46·1 deaths per 10 000 person-years, respectively). Standardised mortality ratios for all cause mortality were significantly raised in all three groups and showed the same relation as incidence with type of hepatitis (standardised mortality ratios 5·6, 3·1, and 1·4, respectively).

Liver related mortality in all three hepatitis groups was 12 to 33 times greater than in the NSW population (table 3). The comparative risk was greatest for people with co-infection (standardised mortality ratios 32·9, 95% CI 23·1–46·7) followed by those with hepatitis C (16·8, 15·4–18·3) and hepatitis B (12·2, 10·7–13·9) mono-infections. Although the incidence of liver-related death was higher for men than women with hepatitis C (16·2 *vs* 10·2 deaths per 10 000 person-years), women had a higher standardised mortality ratio than men (23·9, 20·3–28·2 *vs* 15·1, 13·6–16·7). The relation between age and liver-related death was similar across hepatitis groups with low mortality rates below the age of 30–40 years, followed by an exponential rise in mortality rate with increasing age at risk (figure 1). Standardised mortality ratios for hepatitis B and hepatitis C liver-related mortality increased over the 50–70-year age-groups (figure 2).

Hepatocellular carcinoma accounted for more liver related deaths than any other liver-related diagnostic code in the hepatitis B group (131 [58%] of 227). The risk of death from hepatocellular carcinoma in all hepatitis groups was significantly raised, but was significantly lower in the hepatitis C infected group (standardised mortality ratios 16·7, 95% CI 14·0–20·1) than either the hepatitis B (standardised mortality ratios 27·8, p<0·0001) or hepatitis B and C co-infected groups (39·7, p=0·017; table 3). Death coded as viral hepatitis and sequelae accounted for the greatest excess mortality in all hepatitis infection groups with standardised mortality ratios of around 36, 48, and 113 in the hepatitis B, hepatitis C and hepatitis B and C co-infected groups, respectively (table 3).

Excess risk of death from alcohol-related liver disease in those with hepatitis C and those with hepatitis B and C co-infection was three to four times greater than for the hepatitis B infection group (table 3). The association between sex and alcohol-related liver disease differed across the three infection groups: women were at greater excess risk in the hepatitis B and C co-infected group (p=0·026); at increased excess risk, though not significantly, in the hepatitis C group (p=0·079); and in

the hepatitis B group all deaths from alcohol-related liver disease were in men.

The risk of drug-related death was marginally raised in people with hepatitis B infection (standardised mortality ratio 1·4, 95% CI 1·0–2·0) but markedly raised in people with hepatitis C (19·3, 18·1–20·5) and with hepatitis B and C co-infection (24·7, 18·2–33·5) compared with the NSW population. The excess in hepatitis C drug-related deaths was significantly greater than for liver-related deaths (p=0·012), as was the absolute rate for drug-related deaths (27 per 10 000 person-years, 95% CI 26–29) compared with liver-related death (14 per 10 000 person-years, 13–15).

The age distribution of drug-related deaths was similar between the hepatitis C and the co-infected groups and markedly different from the distribution of liver-related deaths (figure 1, co-infection data not shown). In these two infection groups, drug-related deaths were predominant in age groups between 15 and 40 years. Women were at greater risk of excess drug-related death than men only in the hepatitis C group (table 3). Standardised mortality ratios for women were consistently greater than for men 15–44 years of age (figure 3). The greatest difference between sexes was at younger ages, and was statistically different for people between 15 and 24 years of age (men 17·1, 21·4–23·0; women 56·9, 39·2–79·9; p<0·0001).

Over time, in those with hepatitis C infection, the rate of drug-related death was constant at 35–43 deaths per 10 000 person-years between 1995 and 1999, and dropped significantly to 27 per 10 000 person-years in 2000–02 (p<0·0001). Liver and non-liver non-drug-related death rates remained constant between 1995 and 2001, and fell slightly in 2002 (figure 4). Standardised mortality ratios for liver and drug related deaths declined slightly from 1995 to 2002 (figure 5). The number of liver-related deaths linked to hepatitis C rose from ten in 1993 to 81 in 2001.

Standardised mortality ratios for deaths that were not drug related or liver related were marginally though significantly raised for hepatitis B (1·1, 1·0–1·2), and significantly raised for the hepatitis C (1·9, 1·8–2·0) and the co-infected groups (3·2, 2·6–4·0). Standardised mortality ratios for deaths other than HIV (1·4, 1·3–1·5), alcohol-related liver disease (2·2, 2·1–2·3), and drug-related death (4·1, 3·3–4·9) also remained significantly raised.

Raised standardised mortality ratios for infection-related mortality (table 2) could be attributed mainly to viral hepatitis and also to HIV-related death (table 3). Excess HIV mortality was significantly greater in the hepatitis B and co-infected groups (p=0·01) than in the hepatitis C mono-infected group (p=0·004). Excess mortality from neoplasms (table 2) could mainly be accounted for by hepatocellular carcinoma in the hepatitis B infection group (standardised mortality ratio neoplasms excluding hepatocellular carcinoma were 1·0, 95% CI 0·9–1·2), but was also contributed to by lymphoid malignancies in all hepatitis groups (table 3), partly attributed by malignancies of uncertain origin in the hepatitis C and co-infected groups (3·6, 2·4–5·4 and 7·4, 1·0–52·5), and attributed by lung cancer in the hepatitis C infected group (1·5, 1·2–1·9). Excess mortality from blood and immune disorders was evident for the hepatitis B and hepatitis C groups (9·3, 4·2–20·6 and 15·1, 9·4–24·2); all causes of death were for chronic conditions that could have required transfusion of blood products, apart from 2 of 17 within the hepatitis C group. Excess mortality for mental and behavioural reasons was evident in the hepatitis C and co-infected groups (15·0, 13·9–16·3 and 23·6 16·1–34·7), and 488 (93%) of 590 and 23 (88%) of 26 of these deaths, respectively, were coded as resulting from drug dependence.

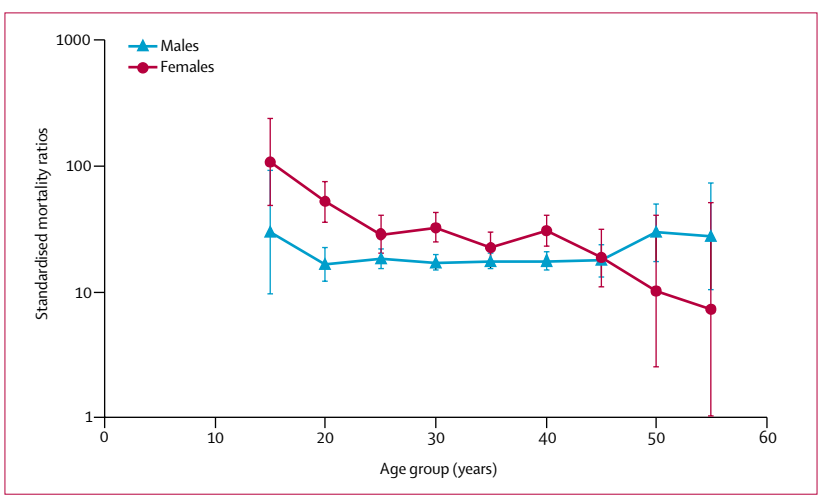

Figure 3: **Standardised mortality ratios for drug-related death by age group and sex in people diagnosed with hepatitis C infection**
Bars=95% CI.

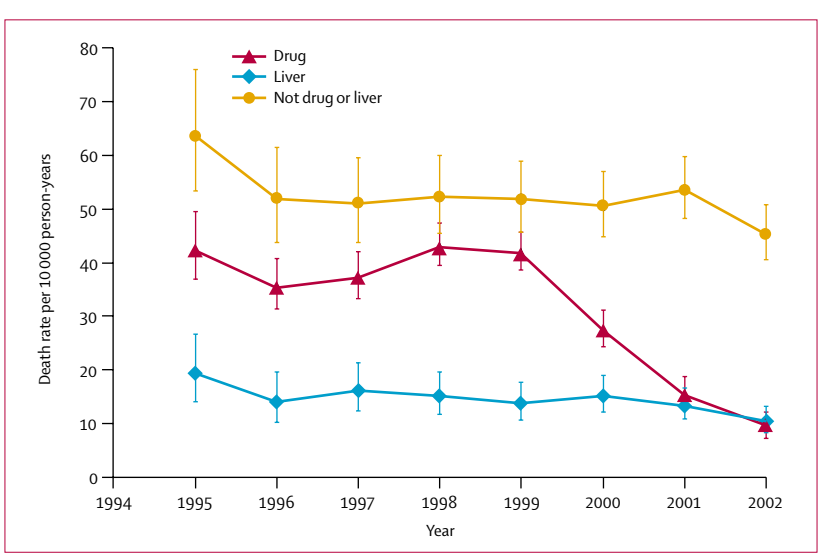

Figure 4: **Death rate by cause and year in people diagnosed with hepatitis C infection**
Bars=95% CI.

Discussion

In this large-scale study of liver disease-related mortality and all cause mortality in people diagnosed with community acquired hepatitis B and hepatitis C infection, the overall mortality rate was around one and a half to five times greater than the standard population, with the greatest excess in people diagnosed with hepatitis B and C co-infection. The main cause of hepatitis B deaths was liver related, particularly hepatocellular carcinoma, whereas in the hepatitis C and the co-infection groups drug-related deaths were most frequent. The excess risk of drug related death in people with hepatitis C was significantly greater for women than men, particularly in younger age groups.

Divergent results have been reported in other cohort studies regarding the relation between all cause mortality and hepatitis B and hepatitis C infection. Hepatitis B studies from China report a three times greater risk of death,[10,21] and a hospital based Italian study reports a five fold increased risk.[9] Studies of community acquired hepatitis C infection in random or population based samples have shown significantly increased risks of death of a similar magnitude to the three times increased risk detected in our study.[22,23] However, other hepatitis B and hepatitis C studies, done in selected populations such as transfusion recipients, hospital based cohorts, and military recruits, have reported no significantly increased risk of all cause mortality.[8,11–15]

The associations between hepatitis B, hepatitis C, and co-infection, liver related mortality, particularly hepatocellular carcinoma, have been frequently reported in previous studies and are consistent with the findings in our study.[8,21–26] The age distribution of liver-related deaths was similar across the three infection groups in our study and indicates the generally slow rate of progression from infection to severe liver disease for both hepatitis B and hepatitis C infection. The rate of liver-related death from diagnosis in the mono-infected groups is also indicative of a slow progression and low individual risk of liver disease for those with community acquired infection. However, relative mortality rates were higher in those 50 to 70 years of age, which suggested faster disease progression in older infected people. The standardised mortality ratio for hepatocellular carcinoma was noticeably higher in women than men for hepatitis C, but not hepatitis B. Being of southeast Asian background is a common risk factor for hepatitis B acquisition in Australia,[27] and is thought to be associated with low alcohol use. Conversely, hepatitis C infection in Australia is largely through intravenous drug use, which is also associated with high alcohol use, as illustrated by the higher standardised mortality ratios for deaths from alcohol-related liver disease in the hepatitis C groups.[28,29] Therefore, the higher standardised mortality ratios for hepatocellular carcinoma in women than men with hepatitis C, but not hepatitis B, might be related to differing alcohol use in these populations.

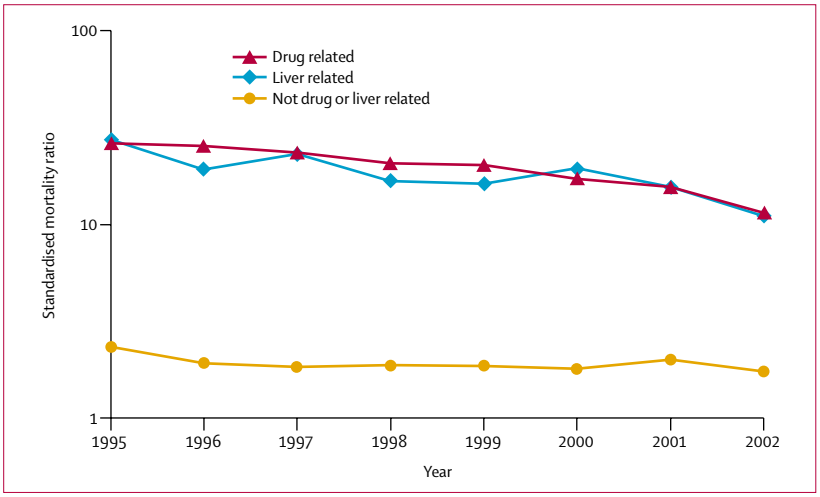

Figure 5: **Standardised mortality ratios by cause and year in people diagnosed with hepatitis C infection**

The drug-related mortality in people with hepatitis B and hepatitis C in our study is consistent with the known epidemiology of these two blood-borne viruses in Australia. The estimated proportion of infection acquired by intravenous drug use in Australia is 5% for hepatitis B and 80% for hepatitis C, respectively.[27,28,30] The relation between suicide, accidental or drug related deaths, and hepatitis C has been previously noted, but raised risks of between 5 and 10 in other studies[12,23] are significantly lower than our study. Factors such as age, hepatitis C risk group distribution, and the study setting are likely to influence these mortality risks. A hospital-based setting that included older individuals with later stages of liver disease is unlikely to include many people still at risk of drug-related death. Similarly, populations where intravenous drug use is not the main risk factor for transmission, such as in transfusion-acquired populations, are unlikely to find associations with drug related deaths. Further, causes of death in this study have been categorised to specifically capture drug-related death.

The relation between hepatitis C infection and drug-related mortality by age and sex are similar to those of a cohort study in Scotland on intravenous drug use that detected the highest excess risk of mortality in young female drug users.[31] The higher standardised mortality ratios for young women than for men in our study could be explained by the rarity of drug-related death in young women without hepatitis C infection. The relation between hepatitis C, intravenous drug use and drug-related death in NSW is also manifest in reduction in drug-related death in our study from 2000 onwards. This trend probably mirrors the dramatic reduction in the availability of heroin and substantial reduction in the number of heroin overdoses during this time in NSW.[32,33] The only marginal reduction in drug-related standardised mortality ratios over time is likely to indicate coinciding reduction in the background rate of drug-related death. Future mortality trends, including distribution of deaths

and causes of death, will depend on rates of intravenous drug use in people with hepatitis C, liver disease stage distribution, and the potential effect of treatment in the hepatitis C population. The rapid escalation of the hepatitis C epidemic in Australia during the 1990s means that a large proportion of the hepatitis C population have early liver disease.

The study population was derived from the state notifications database and is largely representative of the infected populations (especially for hepatitis C infections) in Australia. An estimated 70–80% of hepatitis C and 60% of hepatitis B prevalent chronic infections have been diagnosed and reported to notification systems in Australia.[27,28,34,35] The high proportion of diagnosed cases relates to high rates of hepatitis B and hepatitis C screening in at-risk populations in Australia. For example, surveys of intravenous drug users attending needle and syringe programs indicate that 60–70% have been tested for hepatitis C in the previous 12 months.[32] The undiagnosed population is probably at lower risk of drug-related or liver-related death, and only a true population-based random sample study could accurately estimate risk for all exposed people.

There is a large burden of hepatitis B and hepatitis C in developing countries, especially in parts of Asia and Africa.[36,37] Generalisation of our study findings to these countries is problematic because of the differences in the underlying cause of infection, particularly the association between intravenous drug use and hepatitis C in our study. Further, in developing countries competing mortality risks might differ considerably. Therefore, there is a need for similar community-based studies in developing countries.

Our study has several limitations. The study population included cases of notified acute hepatitis B infection and acute hepatitis C infection, although these cases represented less than 2% of total notifications. Additionally, notification of hepatitis C is based on anti-hepatitis C antibody rather than hepatitis C RNA detection. According to a review of hepatitis C clearance studies, an estimated 25% of notifications would represent people who have spontaneously cleared infection.[38] Thus, standardised mortality ratios for causes of death directly related to hepatitis C infection could be underestimated by as much as 25%. The number of cases of hepatitis C treatment related clearance would be small, since fewer than 1000 people per year were treated in NSW during the study, and treatment response rates have only improved in recent years.[30] The number of people with chronic hepatitis B who receive antiviral therapy has also been low in Australia. Because date of infection was unknown, risk in this study pertains to risk from date of diagnosis and is likely to overestimate risk of death from time of infection. Median age at time of hepatitis C infection is estimated to be 20–25 years, whereas the median age at notification in the study population was 34 years.[28] Time from hepatitis C infection to cirrhosis is protracted, often more than 30 years with more severe liver-related outcomes taking even longer to become evident.[14,39] Further, the results of this study describe outcomes soon, within 10 to 12 years, after diagnosis of infection. Standardised mortality ratios might also have been slightly underestimated because of people migrating and dying overseas.

Information about source of infection and country of birth were not available from the notification data. This omission is of particular concern with regard to hepatitis B associated mortality because of the estimated high proportion of non-Australian born cases.[27] Further we did not have information about hepatitis delta virus co-infection, which increases the risk of hepatocellular carcinoma, in people with hepatitis B infection. The higher mortality ratios related to HIV in the hepatitis B than the hepatitis C group is likely to result from a higher prevalence of HIV co-infection in people with hepatitis B. The prevalence of HIV in people with hepatitis C is low because of limited HIV transmission through intravenous drug use in Australia.[28] These issues highlight the limitation of identifying deaths through the death registry without access to hospital records and information about underlying conditions and risk factors. Further the sensitivity and specificity of data linkage in this study is unknown and likely to be less than 100%.

We show a high excess mortality risk associated with hepatitis B and hepatitis C infection and liver disease, particularly hepatocellular carcinoma. The effects of hepatitis B and hepatitis C treatment on infection-related mortality are yet to be seen. Mortality risk associated with drug use in people with hepatitis C was high, especially for young people. Our data highlight the need for dual strategies for reduction of morbidity and mortality related to hepatitis C: a focus on reduction of drug-related harm for young groups and on reduction of liver disease progression in older groups.

Contributors

J Amin contributed to the study design, the acquisition, analysis, and interpretation of data, and drafting the article. M Law and G Dore contributed to the study conception, design, and the interpretation of data; M Bartlett contributed to the acquisition of data; J Kaldor contributed to study conception and design. All authors revised and approved the final version for publication.

Conflict of interest statement

We declare that we have no conflict of interest.

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