Increasing drug-related mortality rates over the last decade in Scotland are not just due to an ageing cohort: a retrospective longitudinal cohort study

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ABSTRACT

Background. In Europe, North America, and Australia, mortality due to drug-related (DR) causes among people who inject drugs (PWID) is a major issue. Our objective was to characterise temporal trends in DR mortality rates in a large cohort of PWID in Scotland over the past decade, all of whom had been diagnosed with hepatitis C virus (HCV) infection, and to investigate factors associated with DR mortality.

Methods. Retrospective longitudinal cohort study linking Scotland's national HCV Diagnosis Database and deaths registry. The study cohort consisted of all individuals with likely injection drug use-related route of HCV acquisition, who had been diagnosed with HCV between 1991 and 2018, and were alive and aged under 65 years on 1 January 2009. We used Lexis expansion to adjust for ageing cohort effects and calculated the mortality rate from an underlying/contributing DR cause over the period 2009–2018. We fitted Poisson regression models to estimate the temporal trend adjusting for attained age, sex, referral setting, region, and viraemic status at baseline.

Results. Among the study population (*n*=35,065; 236,914 person-years), a total of 1900 DR deaths occurred; the DR mortality rate increased from 5.6/1000 [101 deaths] in 2009 to 12.4/1000 [342] person-years in 2018. Increasing trends were observed for all age-groups except 55-64 years. The overall DR mortality rate was highest for referrals for HCV testing from prison (11.0/1000) and hospital settings (10.0/1000). Mortality increased with calendar time period, with significantly raised adjusted rate ratios (RRs) from 2015 (RR=1.40, 95% CI:1.16-1.69) to 2018 (RR=2.23, 95% CI:1.88-2.64), compared with 2011-2012, for older age (35-44: RR=1.37, 95% CI:1.20-1.56; 45-54: RR=1.32, CI:1.14-1.53) compared with <35 years, for persons diagnosed with HCV since 2009 (RR=1.34, 95% CI:1.21–1.49), and for prison and hospital referrals (RRs of 1.30, 1.37) compared with GP referrals.

Conclusion. Increasing DR mortality rates in Scotland over the past decade are not just due to an ageing cohort. Harm reduction services will likely need to expand and adapt to reverse the recent upward trends in DR mortality in PWID.

Keywords: Mortality; illicit drug use; Scotland; hepatitis C virus

INTRODUCTION

Of the four nations of the UK, Scotland had the highest population-level drug-related (DR) mortality rate in 2018 of 29.8 per 100,000 – about four times the drug poisoning mortality rate for England and Wales in 2018 (ONS, 2020) – which is potentially the highest DR mortality rate in the European Union (NRS, 2019), and one of the highest DR mortality rates worldwide (Degenhardt et al., 2011). Trends in annual deaths suggest that the situation has become markedly worse in the last few years. In Scotland the annual number of drug−related deaths doubled between 2008 and 2018 from 474 to 1187, with a 27% rise observed between 2017 and 2018 (NRS, 2019). Both the magnitude of, and the observed increasing trend in, DR mortality rates constitute a public health crisis for Scotland (Nicholls et al., 2019).

Between 2001 and 2011, decreased DR mortality rates have been reported for males aged 15–29 years; however, rates increased in the 30-44 year age-group (Brown et al., 2019) – this suggests that the raised DR rates in later years might simply reflect a cohort of drug users becoming older, with cumulative risk behaviours and/or worsening health with age leading to premature mortality (Pierce et al., 2015) – an 'ageing cohort effect'. However, other explanations are possible, such as evolving drug choices amongst current users over time (for instance, changing patterns of polydrug use, such as illicit benzodiazepines in combination with heroin, or an increase in injecting relative to other modes of administration, as seen for e.g., cocaine), austerity (which impacts on provision of addiction treatment), homelessness, and (less plausibly) a changing age distribution of new users. It is therefore of importance to distinguish an ageing cohort from other possible drivers of an increasing DR mortality trend (House of Commons, 2019).

The principal objective of our study was to investigate temporal trends in DR mortality rates among people who inject drugs (PWID) in Scotland over the past decade (2009-2018), and to quantify associations between DR mortality and factors such as age, sex, and region. We utilised the record linkage of data on individuals diagnosed with hepatitis C virus (HCV) – a condition predominantly affecting those who inject drugs in Scotland and associated with a two-fold increased DR mortality risk (Merrall et al., 2012) – to examine trends in DR mortality among PWID

diagnosed with this infection. Studying DR mortality among Scotland's HCV-diagnosed cohort has the advantage of providing a suitable denominator to permit age and time effects on mortality rates to be distinguished, and also helps understand and improve the initiatives of Scotland's HCV Action Plan to co-locate HCV testing and management with drug addiction services (Hutchinson et al., 2015).

METHODS

The study design was a retrospective longitudinal study of a large open cohort of PWID who have been diagnosed with HCV infection in Scotland, and whose details are maintained in the HCV Diagnosis Database (Shaw et al., 2003)..These data are routinely electronically linked to Scotland's national deaths registry, which facilitates analysis of mortality (whether associated to HCV infection or to other factors such as drug use).

Study cohort

Around 90% of HCV acquired in the UK is through injecting drug use (e.g., an estimated 83% of all HCV diagnosees 1991-2010: McDonald et al., 2014; estimated 88% of prevalent HCV patients in England in 2015: Harris et al., 2019). Our study population was defined to consist of all individuals who are likely to be PWID (excluding patients with confirmed other routes of HCV acquisition) who were diagnosed with HCV (i.e., tested HCV antibody-positive) in Scotland between 1991 and 2018 and were not known to have died before 1 January 2009 (Fig. 1). This definition of 'likely PWID' applies to 95.2% of the HCV diagnosis cohort alive on 1 January 2009. Of our study population, 48.9% had PWID risk and 51.1% unknown risk. The proportion of diagnoses in the HCV Diagnosis Database with unknown route of HCV acquisition has been previously demonstrated to be largely represented (approximately 72%, based on data up to 2010; it is likely even higher at present) by PWID (McDonald et al., 2014).

Definition of drug-related mortality using cause of death data

We defined DR deaths to comprise all deaths with an underlying and/or contributing cause in the following International Classification of Diseases, 10th Edition (ICD-10) categories: drug disorders

(ICD-10: F11-16,19), accidental poisoning (ICD-10: X40-44), intentional self-poisoning (ICD-10: X60-64), assault by drugs (ICD-10: X85), and poisoning, indeterminate intent (ICD-10: Y10-14). Underlying cause refers to the disease/injury or accident/act at the head of the chain of morbid events leading directly to death; contributing causes may have contributed to the death but are not considered part of the chain leading to death. Our definition uses the same ICD-10 code-set as the 'baseline' definition used by National Records of Scotland (NRS) (NRS, 2019); however, the NRS definition requires that a drug listed under the Misuse of Drugs Act (1971) was present in the body at time of death (except for deaths in the drug disorders category). Thus, our definition is less restrictive than the NRS definition of DR mortality.

Statistical analysis

Mortality rates from an underlying or contributing DR cause were calculated using standard person-time methods, over a 10-year analysis period (1 January 2009 through 31 December 2018). Persons with missing data on sex and/or date of birth (n=752) were excluded from analyses of mortality rates (Fig. 1). Censoring for outward migration was carried out on basis of information in Scotland's Community Health Index (CHI) database, linked to the HCV Diagnosis Database via the patients' CHI identifiers. An initial period of follow-up (*a priori* set at six months) was excluded to reduce the potential impact on mortality rates from HCV testing being carried out as a consequence of worsening health prior to death. Follow-up was administratively censored upon each person's 65th birthday, as the 65+ years age-group is less likely to comprise active PWID. Thus follow-up for each person started six months following their HCV diagnosis date and ended at the earliest of date of death (from any cause), migration, 65th birthday, or 31 December 2018. Follow-up time before 1 January 2009 was disregarded, as we analysed DR mortality in the period 2009-2018 only. We used graphical methods to explore mortality trends stratified according to referral setting (motivated by evidence for an increased risk after release from prison: Seaman et al., 1998; Bird & Hutchinson, 2003), period of HCV diagnosis (McLeod et al., 2014), and by region (Scottish Health Board).

We used Lexis expansion to divide follow-up by calendar year and attained age (age-bands: <35, 35-44, 45–54, 55-64 years), which still allowed us to test and adjust for potential ageing cohort effects. Lexis expansion is a method to 'slice up' follow-up time according to multiple time-changing variables, such as increasing calendar time and increasing age. For each slice, the number of events, person-time, and event rate can be calculated; for instance, for all persons who are aged 50-54 years in the year 2015. Poisson regression models were fitted to estimate the mortality trend over calendar time (fitted as a categorical variable with the following levels: 2009-10, 2011-2012, and then single years up to and including 2018), adjusting for attained age, sex, referral setting for HCV testing (categorised as: drug/counselling, GP, hospital, prison, and other; the latter category includes genitourinary medicine clinics, renal units, haemodialysis centres, etc), viraemic status (positive, negative; defined using quantitative RNA threshold of 12 IU/ml), PWID risk factor (reported or inferred), region (i.e., Scottish Health Board; categorised as Greater Glasgow & Clyde, Grampian, Lothian, Tayside, and other), and period of HCV diagnosis (<2009, 2009-2018). The last covariate was included because Scotland's HCV Action Plan Phase II (launched in May 2008) encouraged former PWID to be tested and led to increased diagnosis rates (McLeod et al., 2014).

As previous research observed strong effect modification by sex of the association between age and drug-related mortality (Bird et al., 2003; Pierce et al., 2015; White et al., 2015; Gao et al., 2016; Gao et al., 2020), we investigated a model variant specifying a sex x attained age-group interaction term. A linear time trend was also tested in place of the categorical variable for calendar time, with model fits compared using a likelihood ratio test. Missing data on HCV viraemia status and region were imputed using modern multiple imputation methods (White et al., 2011) and the R package *mice.* A complete case analysis was also conducted (further details in Supporting Information).

To address the issue of potential bias due to earlier diagnosed members of the study population having longer follow-up compared with those diagnosed more recently (i.e., possible attenuation of DR mortality rates among early diagnoses due to higher likelihood of ceasing drug use), in sensitivity analysis we censored follow-up for each cohort member to a fixed maximum (*a priori* set at three years) following HCV diagnosis. In a second sensitivity analysis, we restricted the cohort

to those who had reported a history of injecting, to reduce the heterogeneity in DR mortality risk from including an unknown number of never-injectors.

Overdose deaths analysis

Because the vast majority of DR deaths in Scotland fall into the category of accidental poisoning (overdose) (NRS, 2019), it was also of interest to characterise the distribution of specific combinations of substances detected in pathology in persons dying from drug overdose, and to investigate temporal trends in mortality from the most frequently occurring combinations. The methods and results for this analysis are reported in the Supporting Information.

RESULTS

Among the study population (*n*=35,065 alive at the start of the follow-up period), 68% were male, 36% were aged under 35 years at the beginning of follow-up, and 54% had been diagnosed with HCV before 2009 (Table 1). A total of 1,900 DR deaths occurred in 236,914 person-years of follow-up. The DR mortality rate increased from 5.6/1000 person-years in 2009, when 101 deaths occurred, to 12.4/1000 person-years in 2018, when 342 deaths occurred among the cohort. The rising temporal trend (Fig. 2) was independent of attained age (for males, for age-bands up to 45-54 years) and referral setting, although there was indication of a more marked increase among those diagnosed in prison and drug treatment settings (Fig. S1). The overall DR mortality rate was highest among persons referred for HCV testing from prison settings (11.0/1000 person-years); rates for referrals from hospital, drug/counselling services, GP, and other settings were 10.0/1000, 7.6/1000, 8.5/1000, and 2.1/1000, respectively).

There were no visibly differing trends in mortality rates between the three HCV diagnosis 'cohorts' (i.e., diagnosed in period: <2003 vs. 2003-2008 vs. 2009-2018) (Fig. S2). Similar rising trends were also apparent when stratifying by health board region (Fig. S3). Although distributions of some variables did differ between diagnosis period (Table 2), namely age-group at start of follow-up – as would be expected – and reported vs. inferred PWID risk, and the proportion referred for HCV testing from drug/counselling settings and the proportion RNA-positive increased over time, there

was no reason to suspect that the principal regression analysis results might be affected by these differences.

Poisson regression using Lexis expansion indicated that, adjusting for attained age and other confounders, the DR mortality rate increased over the analysis period, with adjusted rate ratio (RRs) for calendar time period varying between 1.03 and 2.23 (in comparison with the reference period 2011-2012), which increased monotonically over time (Table 1); RRs were significantly raised from 2015 with respect to the reference period. Higher mortality was associated with older age (35-44: RR=1.37, 95% CI: 1.20-1.56; 45-54: RR=1.32, 95% CI: 1.14-1.53), compared with the <35 years age-group, for referrals for HCV testing from prison and hospital settings (RRs of 1.30 and 1.37, respectively) compared with the GP setting, for persons diagnosed with HCV since 2009 (RR=1.34, 95% CI: 1.21-1.49), and for persons residing in Tayside (RR=1.18, 95% CI: 1.00-1.39), compared with Greater Glasgow & Clyde. Lower mortality rates were associated with age 55-64 years (RR=0.57, 95% CI: 0.44-0.74), for persons whose PWID risk was inferred (RR=0.56, 95% CI: 0.51-0.63) compared with reported, and with residing in Grampian (RR: 0.77, 95% CI: 0.65-0.91).

The likelihood ratio tests indicated that fitting an *attained age x sex* interaction term did not improve model fit (deviance of 5.3, $P>0.15$), across regression models fitted to each imputation set), and that compared with fitting a single coefficient for period (thus modelling calendar time as a linear effect), the categorical calendar period variable led to a significantly improved model fit (deviance of 32.0, $P<0.001$ across imputation sets).

The complete case Poisson regression analysis (n=31,073) indicated similar estimated RRs (see Supporting Information, Table S1) to those reported in Table 1 in the main analysis (n=35,065). The adjusted RRs for calendar time period increased from 1.02 in 2009-2010 to 2.30 in 2018 (compared with 2011-2012); the RRs for the periods 2015, 2016, 2017, and 2018 were statistically significant.

Sensitivity analyses

The first sensitivity analysis, in which follow-up time was censored at three years following HCV diagnosis, also indicated an increasing mortality rate trend and persistent effects of attained age (Fig. S4, Table S2), although statistical power was low due to a relatively small number of outcomes. In this analysis (which necessarily excluded all persons diagnosed with HCV before 2006) there were 337 DR deaths over 40,595 person-years of follow-up; adjusting for all covariates, the relative risk for DR mortality associated with calendar time period was significantly raised between 2016 and 2018 (with respect to 2011-2012), with RRs varying between 2.25 and 2.70 (Table S2). The second sensitivity analysis, restricting to the sub-cohort with reported injecting history, indicated a very similar trend in DR mortality risk with calendar year period as in the main analysis, but with slightly attenuated adjusted RRs (Table S2).

DISCUSSION

An increase in DR mortality rates as observed in a large cohort of HCV-diagnosed persons with reported or inferred injection drug use as route of HCV acquisition replicate increasing temporal trends in DR deaths at the population level in Scotland. Mortality rates in the HCV cohort increased with age (up to 45-54 years), but we also found significant increases of 43% to 125% from 2015 through 2018 (compared with the rate in 2011-2012), even after adjustment for attained age. This evidence contradicts the assumption that rising DR trends are a product of an ageing cohort effect (House of Commons, 2019). We also observed increased relative risks of DR mortality that were associated with younger middle-age (35–54 years), residing in Tayside, and prison and hospital referral settings for HCV testing (compared with GP referrals). The lack of a temporal trend and generally lower DR mortality rates for the 55-64 years attained age category may reflect that by this age, many PWID will have ceased injecting, or may reflect the impact of competing causes of death in this age-group (Gao et al., 2019).

Importantly, as with previous analyses of Scottish problem drug user cohorts (Merrall et al., 2012; 2013; White et al., 2015), our analysis of Scotland's HCV-diagnosed cohort allowed a denominator population to be defined when estimating DR mortality rates and inferring associations between these rates with calendar time, age, and other factors. DR deaths in this cohort between 2009 and

2018 represented 27.1% of the total (NRS-defined) drug-related deaths in the Scottish population in the same period, and represented 29.4% of Scotland's total overdose [ICD-10 X40-44] deaths between 2011 and 2018 (NRS, 2019), although as noted above our definition of DR death is less restrictive than the NRS definition, suggesting that our findings are conservative (however, 92% of the DR deaths we identified were also classified as such by NRS: F. Dixon, pers. comm.). Previous analyses of DR mortality lack such a denominator; the size of the drug-using population is challenging to determine, and consequently the entire population, or strata defined according to age- and/or deprivation within the national population serve as the denominator. The general population rate is informative with regard to across-time or between- country comparisons of the mortality burden attributable to drug use, but cannot elucidate whether a person who uses drugs in one place or time is more or less likely to suffer a drug-related death (Millar & McAuley, 2017). An age-period-cohort analysis of DR mortality among Scotland's males in 1979–2013 suggested an increasing trend in the 1990s that was attributable to the 1960–1980 birth cohorts, particularly for those living in the most deprived areas (Parkinson et al., 2018). Our study complements this work, by demonstrating that among an open cohort of current/former PWID, an increasing trend in DR mortality observed over the last decade (until 2018) appears to be independent of attained age, and thus an ageing cohort does not provide a sufficient explanation when DR deaths during 2015-2018 are taken into account.

Increasing DR mortality rates with age have been previously reported; analysis of a large cohort of opioid users in England (2005-2009) indicated the highest crude mortality rate due to DR poisoning for the attained age group 45-64 years, namely 4.5 per 1,000 person years (Pierce et al. (2015). In Scotland, an analysis conducted on a relatively young cohort of 69000 drug users attending drug treatment services over the period 1996/7 through 2005/6, Merrall et al. (2012) reported a raised risk (HR=1.22) for >34 years compared with ≤34 years. Among Scotland's methadone clients, a strong association between age 45+ years and methadone-specific death (HR=3.1; compared with attained age 25-34 years) has been reported for 2009-2015 (Gao et al., 2020).

Our finding of increased relative risks of DR mortality associated with prison and GP/hospital referral settings for HCV testing is consistent with previous work. The first two weeks after release from prison is a recognised high-risk period for death from a DR cause in Scotland and elsewhere (Seaman et al., 1998; Bird & Hutchinson, 2003; Merrall et al., 2010; Farrell & Marsden 2008), as is the first four weeks following hospital discharge (Merrall et al., 2013; White et al., 2015). Given the success of naloxone kit provision upon prison release for preventing opiate-related deaths (Bird & McAuley, 2019), similar provision of kits (and training in their use) at community HCV testing/treatment sites may have a positive effect on DR mortality in this population.

In our cohort, 43% of persons who died from overdose had three classes of drug detected simultaneously (opioids, benzodiazepines, psychotropic). Regression analysis conducted specifically for overdose deaths (Table S2) indicated a steeper rising trend over time (RRs of 1.61 to 3.91 for the years 2013 through 2017) compared with that observed in the main analysis. This relatively high proportion of polydrug detections among all overdose deaths is consistent with evidence from other countries showing association between polydrug use and DR mortality risk (Gjersing et al., 2013). An encouraging finding from this analysis was the decrease between 2011-2014 and 2015-2017 in the proportion of overdose deaths with alcohol detected, from 0.75 to 0.49, which suggests that advice regarding moderation of alcohol intake among HCV diagnosees may have been effective.

We acknowledge several limitations. First, there may be unmeasured confounding. For example, we did not account for socioeconomic inequalities – for instance using deprivation measures – as an explanatory or confounding factor. DR mortality rates are higher in Scotland's most deprived areas (Brown et al., 2019), and mortality rates increased in the most deprived quintile in 2012-2017 compared with the previous 6-year period (Fenton et al., 2019). In agreement, the study of McPhee et al. (2019) for the period 2008-2017 indicated a disproportionate number of DR deaths occurring in persons under 35 years, and in the most deprived (5%) areas. Second, due to the restricted number of outcomes available, we had limited power to test assumptions of a constant hazard of

mortality per attained age-category; some of the increased mortality hazard attributed to time could be due to ageing within an age-band.

Third, our cohort definition did not distinguish between past and current injecting drug use, and persons with unknown route of HCV acquisition were included, of which a proportion will not have PWID risk (though we estimate this to be at most 28%). The reduced relative risk (RR of 0.56) observed for PWID whose route for acquiring HCV infection was inferred suggests that reported PWID risk may indicate current or recent injecting at time of HCV diagnosis; our analysis might therefore underestimate the true DR mortality rate among PWID (although sensitivity analysis restricting to those with reported injecting drug use indicated only a slightly higher crude mortality rate; this was 9.5 compared with 8.5 per 1,000 persons years in the main analysis). Fourth, we lacked data that could help elucidate the causes of increasing DR mortality over our analysis period, such as potential changes in delivery of opiate addiction treatment, or polydrug use (though the distribution over broad categories of substances detected did not vary appreciably between 2011-2014 and 2015-2017). Finally, our cohort consists only of those PWID diagnosed with HCV; because HCV-infected PWID may have a higher DR mortality rate compared with HCV-uninfected PWID (Merrall et al., 2012), our findings should ideally be replicated in other cohorts.

PWID in Scotland have a high prevalence of chronic HCV infection, which was estimated at 32% based on a bio-behavioural survey conducted in 2017/2018 (Palmateer et al., 2020). To meet the WHO hepatitis elimination goals for 2030, scaling-up testing/diagnosis of HCV infection and broadening direct-acting antiviral treatment to PWID – already commenced in Scotland – are essential. Although such programmes are expected to avert severe liver sequelae and deaths in this population, mortality due to competing DR causes might increase. The current results suggest that because rising DR mortality rates – at least among PWID younger than 55 years – are already occurring in this population, healthcare and drug treatment services should work to prevent this trend from continuing. The shift in the provision of HCV treatment from specialist liver centres to the community offers an opportunity to address the DR mortality and blood-borne virus (BBV) syndemics simultaneously, potentially through initiatives such as the supply of naloxone at testing

appointments and/or injecting equipment transactions, and the joint management of opiate substitution therapy and BBV treatment.

In summary, this study of a large cohort of PWID who have been diagnosed with HCV suggests that rising DR mortality rates observed over the past decade among Scotland's population are not solely attributable to an ageing cohort effect. To reduce mortality risk in PWID from DR causes, HCV services will need to adapt to the complex needs of this subpopulation. Furthermore, strategies for the elimination of HCV should integrate with those addressing wider health harms for PWID.

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Table 1. Characteristics of study cohort (*n*=35,065), with total DR deaths and crude DR mortality rates (per 1,000 person-years), and rate ratios from both univariate and multivariable Poisson regression analysis (URR and RR, respectively) using multiple imputation.

	N (%)	*n*	P-years	Rate (95% CI)	URR (95% CI)	RR (95% CI)
Overall	35065	1900	236914	8.0 (7.7-8.4)	–	–
Calendar time period (time-dependent)						
2009-2010	–	207	37542	5.5 (4.8-6.3)	0.98 (0.81-1.19)	1.03 (0.85-1.24)
2011-2012	–	245	43393	5.7 (5.0-6.4)	Ref.	Ref.
2013	–	145	23559	6.2 (5.2-7.2)	1.06 (0.86-1.32)	1.08 (0.88-1.32)
2014	–	164	24795	6.6 (5.6-7.7)	1.19 (0.97-1.45)	1.16 (0.96-1.42)
2015	–	208	25928	8.0 (7.0-9.2)	1.43 (1.18-1.73)	1.40 (1.16-1.69)
2016	–	281	26792	10.5 (9.3-11.8)	1.88 (1.58-2.25)	1.85 (1.55-2.20)
2017	–	308	27372	11.3 (10.0-12.6)	2.07 (1.75-2.46)	2.02 (1.71-2.40)
2018	–	342	27531	12.4 (11.1-13.8)	2.25 (1.90-2.67)	2.23 (1.88-2.64)
Sex Male	23683 (68)	1308	159117	8.2 (7.8-8.7)	Ref.	Ref.
Female	11382 (32)	592	77797	7.6 (7.0-8.3)	0.95 (0.86-1.04)	0.95 (0.86-1.05)
Attained age* in years (time-dependent)						
<35	12498 (36)	307	48823	6.3 (5.6-7.0)	Ref.	Ref.
35-44	13657 (39)	884	95486	9.3 (8.7-9.9)	1.55 (1.36-1.77)	1.37 (1.20-1.56)
45-54	6851 (20)	630	69827	9.0 (8.3-9.8)	1.51 (1.31-1.74)	1.32 (1.14-1.53)
55-64	2059 (6)	79	22778	3.5 (2.8-4.3)	0.58 (0.45-0.75)	0.57 (0.44-0.74)
Period of HCV diagnosis						
<2009	18885 (54)	1178	162532	7.3 (6.8-7.7)	Ref.	Ref.
2009-2018	16180 (46)	722	74381	9.7 (9.0-10.4)	1.26 (1.15-1.39)	1.34 (1.21-1.49)
Referral setting for HCV testing						
Drug/counselling	4500 (13)	259	30519	8.5 (7.5-9.6)	1.17 (1.00-1.37)	0.92 (0.78-1.08)
Hospital	8951 (26)	577	57210	10.1 (9.3-10.9)	1.35 (1.18-1.53)	1.37 (1.21-1.56)
GP	8620 (24)	425	55887	7.6 (6.9-8.4)	Ref.	Ref.
Prison	2345 (7)	175	16060	10.9 (9.3-12.6)	1.49 (1.25-1.79)	1.30 (1.09-1.56)
Other	3531 (10)	53	25692	2.1 (1.5-2.7)	0.31 (0.23-0.42)	0.30 (0.23-0.40)
NK	7478 (21)	411	51545	8.0 (7.2-8.8)	1.06 (0.92-1.22)	1.11 (0.96-1.29)
HCV viraemia status						
RNA-positive	25341 (72)	1408	179886	8.2 (7.8-8.7)	Ref.	Ref.
RNA-negative	6368 (18)	382	44614	8.6 (7.7-9.5)	1.03 (0.92-1.15)	1.06 (0.94-1.19)
NK §	3356 (10)	110	21413	5.1 (4.2-6.2)	–	–
PWID risk Reported	17926 (51)	1351	143013	9.5 (9.0-10.0)	Ref.	Ref.
Inferred	17139 (49)	549	93900	5.9 (5.4-6.4)	0.62 (0.56-0.69)	0.56 (0.51-0.63)
Region (Health Board)						
Greater Glasgow & Clyde	12094 (34)	718	84479	8.5 (7.9-9.1)	Ref.	Ref.
Grampian	3794 (11)	171	27287	6.3 (5.4-7.3)	0.74 (0.62-0.87)	0.77 (0.65-0.91)

Lothian	4636	(13)	198	29382	6.7	(5.8-7.7)	0.79	(0.68-0.93)	0.89	(0.76-1.04)
Tayside	2918	(8)	188	18491	10.2	(8.8-11.7)	0.95	(0.85-1.06)	1.18	(1.00-1.39)
Other	11617	(33)	625	77274	8.1	(7.5-8.7)	1.20	(1.02-1.40)	0.97	(0.87-1.09)
NK §	6	(0)	0	1	0		–		–	

Note. NK = not known. P-years = person-years. 95% confidence intervals (CIs) for rates calculated using the Poisson method.

* *N* (%) refers to age category at the start of follow-up (the later of 1 January 2009 or 6 months after HCV diagnosis) and number of deaths (*n*) refers to attained age category.

† Not included in the Poisson regression analysis. § Category not used in the Poisson regression as missing values were imputed, using the R package *mice*.

Table 2. Comparison of main characteristics of study cohort according to period of HCV diagnosis.

	HCV Diag. <2003		HCV Diag. 2003-2008		HCV Diag. 2009-2018	
	N	(%)	N	(%)	N	(%)
Sex Male	7438	(68)	5390	(67)	10855	(67)
Female	3459	(32)	2598	(33)	5325	(33)
Age at start of follow-up (years)						
<35	2648	(24)	3575	(45)	6275	(39)
35-44	5198	(48)	2759	(35)	5700	(35)
45-54	2428	(22)	1259	(16)	3164	(20)
55-64	623	(6)	395	(5)	1041	(6)
Referral setting for HCV testing						
Drug/counselling	1044	(10)	840	(11)	2616	(16)
Hospital	3130	(29)	1955	(24)	3866	(24)
GP	2601	(24)	2129	(27)	3530	(22)
Prison	1017	(9)	346	(4)	982	(6)
Other	1560	(14)	631	(8)	1340	(8)
NK	1545	(14)	2087	(26)	3846	(24)
HCV viraemia status						
RNA-positive	7148	(66)	6341	(79)	11582	(73)
RNA-negative	1888	(17)	1502	(19)	2978	(18)
NK	1861	(17)	145	(2)	1350	(8)
PWID risk Reported	7807	(72)	5006	(63)	5113	(32)
Inferred	3090	(28)	2982	(37)	11067	(68)
Region (Health Board)						
Greater Glasgow & Clyde	4209	(39)	2718	(34)	5167	(32)
Grampian	1401	(13)	900	(11)	1493	(9)
Lothian	1427	(13)	1000	(13)	2209	(14)
Tayside	727	(7)	497	(6)	1674	(10)
Other	3133	(29)	2873	(36)	5611	(35)
NK	0	(0)	0	(0)	6	(0)

Note. NK = not known.

Fig. 1. Flowchart describing the study population size before and after application of various exclusion criteria.

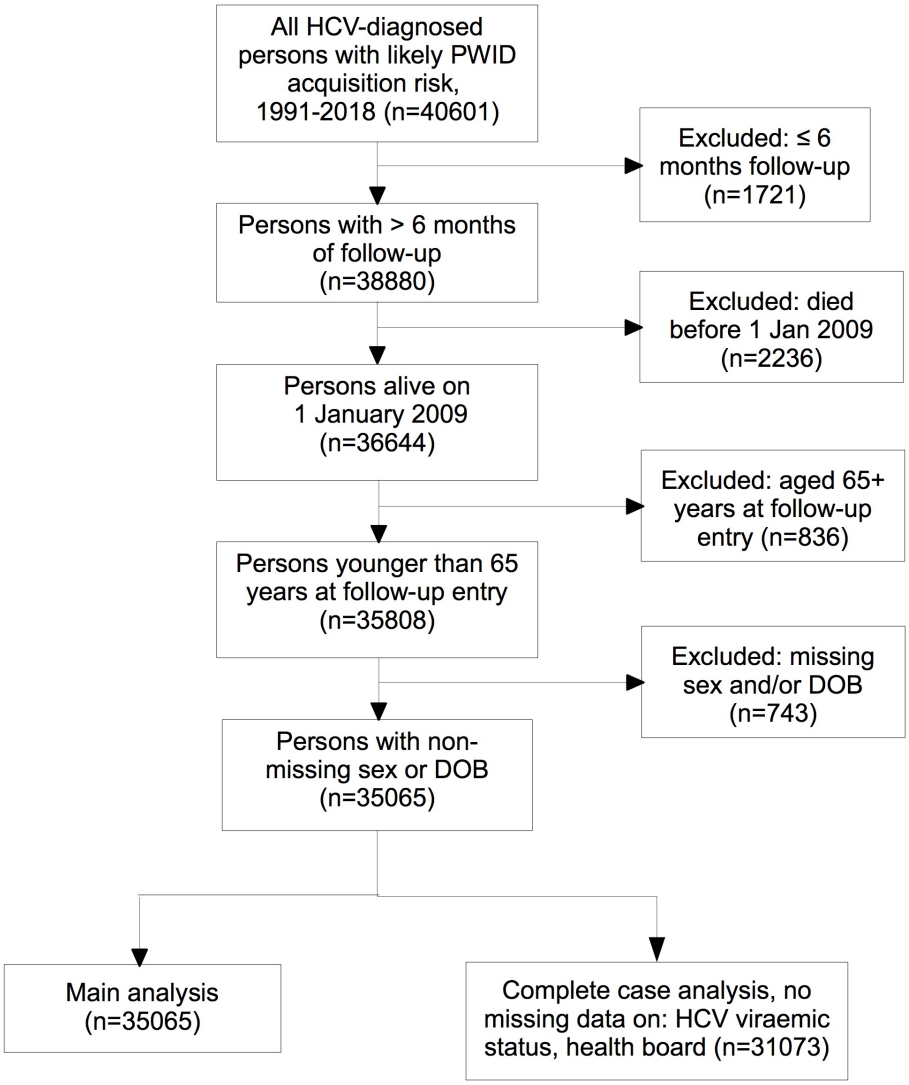

Fig. 2. Drug-related mortality rates among Scotland's HCV-diagnosed PWID over the period 2009-2018, age-aggregated and stratified by attained age-group (upper panel). DR mortality rates for males (lower left panel) and females (lower right panel) only. 95% confidence intervals omitted for clarity.