

# Ageing opioid users' increased risk of methadone-specific death in the UK: irrespective of gender

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## Abstract

*Aims:* For England, to examine whether illicit opioid users' risk of methadone-specific death increases with age; and to pool age-related hazard ratios (HR) for methadone-specific deaths with those for Scotland's methadone-prescription clients.

*Design:* National data-linkage cohort, linking the English National Drug Treatment Monitoring System and mortality database.

*Setting:* All services in England that provide publicly-funded, structured treatment for illicit opioid users.

*Participants:* Adults receiving prescribing treatment modalities for opioid dependence during April 2005 to March 2009: 129,979 clients followed-up for 378,009 person-years (pys).

*Measurements:* Fatal Drug Related Poisonings (DRPs), methadone-specific DRPs, or heroin-specific DRPs, by age-group and gender, with proportional hazards adjustment for substances used, injecting status and periods in/out of treatment.

*Findings:* There were 1,266 DRPs, of which 271 were methadone-specific (7 per 10,000 pys: irrespective of gender) and 473 were heroin-specific (15 per 10,000 pys for males, 7 for females). Per

10,000 pys, the methadone-specific death-rate was 3.5 (95% CI: 2.7-4.4) at 18-34 years, 8.9 (CI: 7.3-10.5) at 35-44 years and 18 (CI: 13.8-21.2) at 45+ years; but heroin-specific DRP-rate was unchanged with age.

Relative to 25-34 years, pooled HRs for UK clients' methadone-specific deaths were: 0.87 at < 25 years (95% CI: 0.56 to 1.35); 2.14 at 35-44 years (95% CI: 1.76 to 2.60); 3.75 at 45+ years (95% CI: 2.99 to 4.70).

*Conclusions:* International testing, and explanation, are needed of UK's sharp age-related increase in the risk of methadone-specific death. Clients should be alerted that their risk of methadone-specific death increases as they age. [248 words]

**Keywords:** drug-related deaths; methadone-specific deaths; age-relatedness; gender; risk behaviours; pooling; age-related hazard ratios.

## **BOX**

### **What is already known**

In the past decade, record-linkage studies internationally have shown the value of opioid substitution therapy as a treatment which halves clients' risk of drugs-related death (DRD); that DRD-rates are lower for female than for male opioid users; increase with age beyond 35 years; and that the female advantage reduces for older clients.

In the UK, despite harm reduction measures such as methadone substitution therapy, DRDs have increased age-relatedly in the past decade.

One powerful record-linkage study, for Scotland's methadone-prescription clients in 2009-2013, has shown that the hazard of methadone-specific DRD increases sharply by age-group: irrespective of gender.

### **What this study adds**

By analysing the opioid-specificity of deaths for England's National Drug Treatment Monitoring System (NDTMS) cohort of nearly 130,000 opioid users who had started a prescribing treatment modality, most methadone, during 1 April 2005 to 31 March 2009, we confirm significantly age-related increased hazard for methadone-specific death.

Nearly half of the cohort's person-years were aged 35+ years; and age-effects persist after adjustment for risk-behaviours.

By pooling the two major UK studies, we show that opioid-dependent clients' risk of methadone-specific death nearly doubled at 35-44 years; and quadrupled at 45+ years.

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## Introduction

In the past decade, record-linkage studies in the UK and internationally have not only shown the value of opioid substitution therapy as a treatment which halves clients' risk of drugs-related death (DRD); but also that DRD-rates are lower for female than for male opioid users; increase with age beyond 35 years; and that the female advantage reduces for older clients [1-11].

To assess the role (if any) of prescribed methadone in explaining the above phenomena, Gao et al. [12] considered the two demographic risk-factors (age-group, gender) in addition to prescription source (general practitioner, other-source) and quintile for the quantity of prescribed methadone as being potentially informative about the 361 methadone-specific deaths experienced by 33,000 methadone-prescription clients in Scotland during 121,000 person-years of follow-up in 2009 to 2013. Their analysis revealed a steeply increased hazard by age-group, irrespective of gender (which was not prognostic) and that the top quintile for the baseline quantity of prescribed methadone conferred additional hazard.

Relative to 25-34 year olds in the Scottish methadone-prescription cohort, the adjusted hazard ratio (HR) for methadone-specific deaths was 0.5 (95%CI: 0.3-1.0) for those aged under 25 years, 1.9 (95% CI: 1.5-2.4) at 35-44 years and 2.9 (95% CI: 2.2 to 3.9) at 45+ years of age. Eleven percent of Scotland's methadone-prescription clients were aged 45+ years.

Scotland's substantial methadone-prescription cohort, the first to have demonstrated how steeply the risk of methadone-specific death increases with client-age, had the advantage of a national protocol in Scotland for toxicology at forensic autopsy. However, substantial numbers of Scotland's nearly 2 million methadone prescriptions issued over four years lacked a Community-Health Index (CHI)-number, meaning that they were not readily linkable to individual clients. For that reason, Gao et al. [12] could not analyse Scottish clients' periods on/off prescribed methadone.

We tested the Scottish results by re-analysing England's large National Drug Treatment Monitoring System (NDTMS) cohort of nearly 130,000 opioid users who had started a prescribing treatment modality during 1 April 2005 to 31 March 2009, 47% of whose person-years were aged 35+ years, similar to 48% at baseline for Scotland's methadone-prescription cohort. Besides adjusting for age-group and gender, information on NDTMS clients' periods in/out of treatment, declared injecting and misuse of alcohol, benzodiazepines and other drugs could be taken into account [1].

In this paper, for NDTMS opioid-user clients who received at least one day of opioid agonist prescribing (OAP), we aimed to:

- i) document the influence of demographic risk factors (age-group; gender) on clients' HR for DRP, methadone-specific DRP, heroin-specific DRP, having adjusted also for clients' declared injecting (ever) and misuse of alcohol, benzodiazepines, and other drugs;
- ii) repeat the above analysis with adjustment also for periods in/out of treatment;
- iii) pool age-related HRs for methadone-specific deaths from the Scotland's methadone-prescription cohort and England's OAP cohort.

## **Methods**

### Data

The cohort for this national record linkage study was identified from records in the National Drug Treatment Monitoring System (NDTMS) collected over the study period 1<sup>st</sup> April 2005 to 31<sup>st</sup> March 2009. NDTMS provides details on all structured treatment for substance misuse provided in England. Records are created for each treatment modality received by a given patient. Treatment modalities were categorised, as in Pierce et al. [1] into: opioid agonist prescribing (OAP), primarily methadone; psychosocial treatment; and residential

treatment. A treatment episode is defined as an unbroken series of treatment modalities. Data were supplied at the episode-level on: self-reported illicit drug injecting status (past month); and an optional self-report of up to three additional problematic psychoactive substances. In NDTMS, prescribing treatment was not differentiated as to methadone or buprenorphine because the vast majority was methadone [3].

Patients were included in the study cohort if they received at least one day of prescribing treatment over the study period and were aged 18 to 64 at their inclusion-date. The cohort analysed here is a sub-cohort of that described by Pierce et al. [1].

The cohort was linked to mortality records from the Office for National Statistics (ONS). For each death record, the underlying cause of death is coded according to the ICD-10 framework. A DRP was defined using ICD-10 codes using ONS's definition [13]. Additionally, for each death, the ONS created flags to indicate whether 'methadone' and/or 'heroin' and/or 'buprenorphine' were mentioned on the death certificate.

In England, the opioid-specificity of drug-related poisonings (DRPs) is determined by the drugs which are mentioned on the death-certificate. Analogous to Gao et al. [12], we define methadone-specific DRPs as those in which methadone was mentioned but neither heroin nor buprenorphine; and heroin-specific DRPs as those in which heroin was mentioned but neither methadone nor buprenorphine.

Treatment and mortality data were linked using a minimal identifier in each database (initials, date of birth, gender) and government region of usual residence. Prior analysis [1] indicated that 22% of minimal identifiers in the treatment population were shared by one or more individuals. These were removed from the analysis cohort. This resulting cohort comprised 129,979 individuals, see **Figure 1**.

### Statistical analysis

Survival analysis was undertaken for the outcomes: any DRP death; a DRP death that mentioned methadone on the death certificate but neither heroin nor buprenorphine (methadone-specific DRP); and a DRP death that mentioned heroin on the death certificate but neither methadone nor buprenorphine (heroin-specific DRP). Subjects entered the risk-set at their earliest OAP-treatment date during the period 1<sup>st</sup> April 2005 to 31<sup>st</sup> March 2009. They left the risk set at the earlier of their date of death, 65<sup>th</sup> birthday, or the end of data collection (31<sup>st</sup> March 2009).

From NDTMS, the demographic variables used for analysis were gender and time-updated age (categorised as 18-24; 25-34, 35-44, 45-64 years). In addition, the following patient-reported behavioural covariates, collected at the beginning of each treatment episode, were included as time-dependent covariates, defined from the date of first report: injecting status; problematic use of alcohol, benzodiazepines, crack cocaine, cocaine powder and amphetamines (the latter two substances combined due to a low level of reporting). A time-

dependent covariate for being in/out of treatment was also created to indicate whether the patient was enrolled in any structured treatment (prescribing or otherwise) using the treatment modality start and end dates.

For each outcome, Cox proportional hazard models were fitted to the data, using covariate as above. Interaction between age and gender was anticipated for DRPs [6, 14].

Per age-group (relative to 25-34 year olds), information about  $\ln$  HR is defined, in statistical terms, by the reciprocal of the variance of the cohort's estimated  $\ln$  HR for that age-group. When pooling the age-related HRs for methadone-specific deaths from the Scottish and English cohorts, we used age-group specific weights derived from the information contributed per age-group by each cohort; alternatively, a compromise common weighting was derived from the total information across all three age-groups (< 25 years; 35-44 years; 45+ years). Please see **Supplementary Information** for details on both calculations.

## Results

England's OAP cohort of 129,979 prescribing modality clients, followed-up for 378,009 person-years (pys), experienced 1,266 DRPs, an overall rate of 33 DRPs per 10,000 pys (95% CI: 31.6-35.3), of which 271 were methadone-specific DRPs and 473 were heroin-specific.

Overall, the OAP cohort's methadone-specific DRP-rate was 7 per 10,000 pys, irrespective of gender. By age-group, however, the methadone-specific DRP-rate was 3.5 (95% CI: 2.7-4.4) at 18-34 years, 8.9 (CI: 7.3-10.5) at 35-44 years and 18 (CI: 13.8-21.2) at 45+ years; whereas the heroin-specific DRP-rate of 12.5 per 10,000 pys was unchanged by age but much higher for males than females, see **Table 1**.

None of the behavioural risk-factors in **Table 1** had a materially different influence on heroin-specific versus methadone-specific DRPs, apart from having ever injected (a more accentuated HR for heroin-specific deaths). **Table 2** shows that the doubling of DRP-risk when out-of-treatment partitions as a nearly quadrupled risk of heroin-specific DRP but modest 20% out-of-treatment reduction in methadone-specific DRP risk ( $p \sim 0.12$ ). Other covariate influences are unchanged from **Table 1**.

The weights used for the Scottish methadone-prescription cohort in pooling age-group specific HRs (see **Introduction** for the Scottish results to be pooled) were 43% for under 25 years of age, 63% for 35-44 year olds, and 55% at 45+ years; alternatively, a common weighting of 58% may be preferred which is based on the sum of information across age-groups. The alternatives agree inferentially, see **Supplementary Information**. Relative to clients aged 25-34 years, the pooled HRs for methadone-specific deaths across Scotland's methadone-prescription client cohort and the English prescribing cohort (**Table 1**) were:

under 25 years of age, 0.87 (95% CI: 0.56 to 1.35); at 35-44 years, 2.14 (95% CI: 1.76 to 2.60); and at 45+ years, 3.75 (95% CI: 2.99 to 4.70).

## Discussion

The NDTMS prescribing cohort allowed us to validate, for England, the novel record-linkage findings from Scotland that opioid using clients' hazard of methadone-specific death rises steeply with age and is independent of gender. In addition, we have shown that these demographic influences hold up when adjustment is made for a triad of declared behavioural characteristics (injecting, misuse of alcohol and misuse of benzodiazepines) and for periods in/out of opioid substitution therapy, factors not addressed in the Scotland's methadone-prescription cohort.

Scotland's methadone-prescription cohort had an overall DRP rate of 63 per 10,000 pys compared with the OAP cohort's much lower rate of 33 DRPs per 10,000 pys. This major difference is partly accounted for because under half of the English clients had a history of injecting (declared or undeclared), a behavioural covariate which, as **Table 1** shows, doubles clients' hazard for DRP. Period effects cannot be ruled out between 2005-09 and 2009-13, the second of which coincides with re-focusing of the UK's drug policy away from harm reduction towards accelerated recovery.

Not only do we use the OAP cohort for validation, but we also pool age-related HRs from the two national cohorts for added precision. On the basis of UK's pooled HRs for methadone-specific deaths of 2.1 at 35-44 years and 3.7 at 45+ years, we recommend that a representative sample of 35+ year old methadone clients be offered electrocardiograms to establish what proportion of them (1%, 5% or 10%) has prolongation of the QTc segment (by 60 milliseconds or to above 500 milliseconds). Gao et al. [12] made this recommendation for clients aged 45+ years but we suggest that surveillance be extended to 35-44 year olds.

The availability of a large cohort with well over 100 methadone-specific DRPs is a considerable strength of England's validation study. England's OAP cohort of nearly 130,000 clients (1 April 2005 to 31 March 2009) and Scotland's methadone-prescription cohort of 33,000 clients (1 July 2009 to 30 June 2013; follow-up to 31 December 2013) were broadly similar in terms of age-distribution, number of methadone-specific deaths (271; 361) and average follow-up time. The Scottish clients' age-distribution was documented at baseline only [12], whereas the English cohort's was time-updated; and pys (378,000 versus 121,000) are consistent when allowance is made for the Scottish cohort's additional six months of follow-up in the second half of 2013.

There are some limitations. England does not have a national protocol for toxicology at forensic autopsy. Thus, England's classification of methadone-specific deaths is on a less firm basis than Scotland's. Details of prescribing were absent for the English cohort.



However, as the analysis by Gao et al [12] had emphasised that the age-related HRs increased just as steeply whether prescribed quantity was, or was not, fitted, the absence of quintile for prescribed methadone does not undermine our validation. Moreover, the English cohort's additional adjustment for behavioural covariates and for periods in/out of treatment did not mitigate the steep age-relatedness in HRs for methadone-specific deaths.

We can only speculate on the underlying cause for this steep age-gradient for methadone-specific DRP: QTc prolongation, renal or liver impairment or some other ill-understood aspect of the pharmacology of methadone in ageing clients. See Gao et al. [12] for detailed discussion. In brief, if methadone clients have renal or liver impairment, which increases as they age, they may experience, in effect, a longer than usual methadone half-life, increased permeability of the blood brain barrier by methadone and increased sensitivity to its central nervous system side-effects (including drowsiness). Indeed, some of JRR's methadone patients have expressed to him the opinion that, as they age, they don't seem to need as high a methadone dose.

More generally, too little is known about the gender-specific pharmacology of methadone in ageing opioid-dependent clients. Besides ECG monitoring [12], we suggest the need for a well-designed study which simultaneously assesses older methadone clients' estimated glomerular filtration rate (GFR: 60-89 mL/min/1.73 m<sup>2</sup> being mild renal impairment; 15-29 mL/min/1.73 m<sup>2</sup> marking severe impairment); liver function including progression to cirrhosis; and the half-life for methadone.

Similarly large national cohort studies of OAP clients, investigating how age-group and gender influence the opioid-specificity of client-deaths, are needed for generalizability outside of the UK.

## **Conclusion**

Only formal studies, not speculation, will resolve what can and should be done to moderate OAP clients' increased risk of methadone-specific death as they age. Consistent findings in two major UK cohorts represent sufficient grounds for methadone prescribers, at least in the UK, to bring to the attention of their clients that their risk of methadone-specific death increases as they age – for reasons that we do not yet fully understand. Clients can help to safeguard themselves by carrying a naloxone-kit [15, 16] and ensuring that their family and friends know how to intervene in the event of methadone overdose. [2,226 words]

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**Contributions:** SMB proposed the validation study for England to MP & TM who are its guarantors; TM holds privacy access permission for linkage of National Drug Data Warehouse (2005-2009) to Office for National Statistics mortality records, which was conducted in autumn 2011 to allow 2.5 years for the delayed registration of drugs-related deaths. SMB & JRR had instigated inquiries into Scotland's methadone prescribing and a possible link to Scotland's increased number of methadone-specific deaths and been co-authors of the initial study which demonstrated increased hazard for older clients; MP re-programmed previous analyses of the English cohort to focus on methadone-specific deaths; all authors contributed to the writing, referencing and review of the manuscript.

**Conflicts of Interest:** SMB served on Scotland's National Naloxone Advisory Group and was one of three co-principal investigators for the MRC-funded N-ALIVE pilot Trial of naloxone-on-release. SMB holds GSK shares. JRR chaired Scotland's National Forum on Drugs-related Deaths and serves on the committee which is updating UK's opioid prescribing recommendation. SMB and JRR were co-authors of the Scottish study for which this study provides validation.

**Data sharing statement:** The authors are bound by the conditions imposed on their access to the Drugs Data Warehouse but can assist others in how to achieve similar access.

**Transparency:** The lead author (as the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Ethics/privacy access approval:** Data were extracted from the Drug Data Warehouse for a cohort of opioid users, aged 18 to 64 years, actively using or being treated for opioid use, in England over the period 1st April 2005 to 31st March 2009. Deaths occurring in the cohort were established by case linkage to national mortality records. Data were rendered anonymous to the research team, via irreversible encryption of identifying information, prior to their release by source organisations.

Use of mortality records was approved by the Office for National Statistics Microdata Release Panel. Use of data from the Drug Data Warehouse was authorised by those organisations providing data. The NHS Central Office for Research Ethics Committees and The University of Manchester Research Ethics Committee advised that further approval was not required for a study of this type.

## Supplementary Information on weights used for pooling the logarithm of hazard ratios (ln HRs) for methadone-specific deaths across Scotland's methadone-prescription client cohort and England's OAP cohort.

### Under 25s

*Scottish cohort HR: 0.53 (95% CI: 0.27 – 1.04).*

Standard error for ln HR is  $[\ln 1.04 - \ln 0.27]/3.92$ , or 0.344. Information on ln HR from the Scottish cohort is the reciprocal of its standard error \* standard error, or 8.4496.

*English cohort HR: 1.26 (95% CI: 0.70 – 2.27).*

Standard error for ln HR is  $[\ln 2.27 - \ln 0.70]/3.92$ , or 0.300. Information on ln HR from the English cohort is the reciprocal of its standard error \* standard error, or 11.1025.

Information sum is 8.4496 + 11.1025, or 19.5521. **Relative weight of information in the Scottish cohort is 8.4496/19.5521, or 43%.**

### 35-44 year olds

*Scottish cohort HR: 1.91 (95% CI: 1.50 – 2.44).*

Standard error for ln HR is  $[\ln 2.44 - \ln 1.50]/3.92$ , or 0.1241. Information on ln HR is the reciprocal of its standard error \* standard error, or 64.9154.

*English cohort HR: 2.60 (95% CI: 1.89 – 3.57).*

Standard error for ln HR is  $[\ln 3.57 - \ln 1.89]/3.92$ , or 0.1622. Information on ln HR is the reciprocal of its standard error \* standard error, or 37.9903.

Information sum is 64.9154 + 37.9903, or 102.9057. **Relative weight of information in the Scottish cohort is 64.9154/102.9057, or 63%.**

### 45+ year olds

*Scottish cohort: 2.90 (95% CI: 2.14 – 3.93).*

Standard error on the ln scale is  $[\ln 3.93 - \ln 2.14]/3.92$ , or 0.1551. Information is the reciprocal of standard error \* standard error, or 41.5913.

*English cohort: 5.14 (95% CI: 3.66 – 7.21).*

Standard error on the ln scale is  $[\ln 7.21 - \ln 3.66]/3.92$ , or 0.1730. Information is the reciprocal of standard error \* standard error, or 33.4276.

Information sum is  $41.5913 + 33.4276$ , or  $75.0189$ . **Relative weight of information in the Scottish cohort is  $41.5913/75.0189$ , or 55%.**

Applying the above derived weights, the pooled ln HRs per age-group and their associated standard errors are:

**< 25 years:** pooled ln HR is  $0.43 * -0.635 + 0.57 * 0.231$ , or  $-0.141$ ; standard error for pooled ln HR is  $\sqrt{\text{reciprocal of information sum, } 1/19.5521}$  or  $0.226$ . Hence, 95% CI for pooled ln HR is  $-0.584$  to  $0.302$ . **Finally, HR is 0.87 (95% CI: 0.56 – 1.35).**

**35-44 years:** pooled ln HR is  $0.63 * 0.647 + 0.37 * 0.956$ , or  $0.761$ ; standard error for pooled ln HR is  $\sqrt{\text{reciprocal of information sum, } 1/102.9057}$  or  $0.098$ . Hence, 95% CI for pooled ln HR is  $0.568$  to  $0.954$ . **Finally, HR is 2.14 (95% CI: 1.76 – 2.60).**

**45+ years:** pooled ln HR is  $0.55 * 1.0647 + 0.45 * 1.6371$ , or  $1.322$ ; standard error for pooled ln HR is  $\sqrt{\text{reciprocal of information sum, } 1/75.0189}$  or  $0.115$ . Hence, 95% CI for pooled ln HR is  $1.096$  to  $1.548$ . **Finally, HR is 3.75 (95% CI: 2.99 – 4.70).**

### Alternatively

If a common weighting scheme across age-groups is preferred, then the **running common weight for the Scottish cohort** should be:

**[8.4496 + 64.9154 + 41.5913]** or **114.9563** divided by the sum of information across age-groups

**[19.5521 + 102.9057 + 75.0189]**, which is **197.4767** and so the common weighting across age-groups for the Scottish cohort would be **114.9563/197.4767** or **58%**.

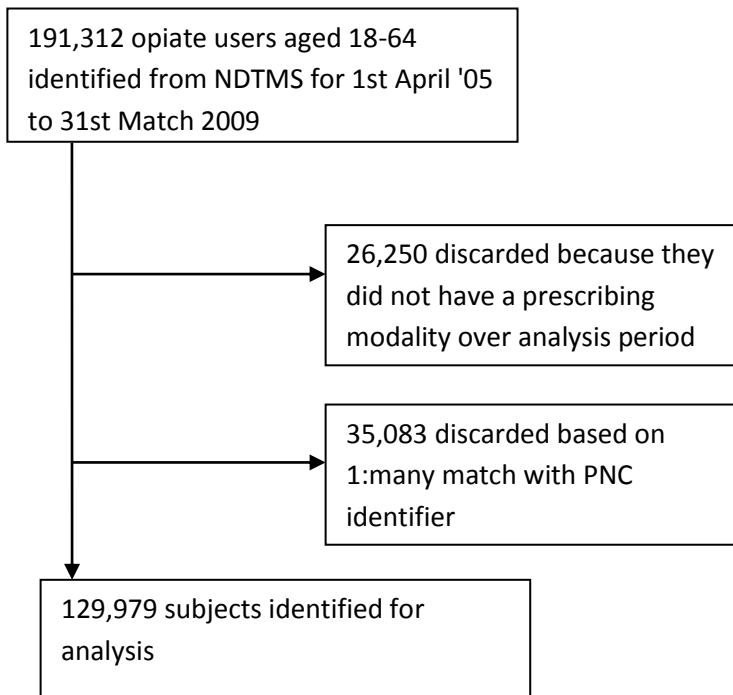
Applying the common weight of 58% across age-groups, the pooled ln HRs per age-group and their associated standard errors are:

**< 25 years:** pooled ln HR is  $0.58 * -0.635 + 0.42 * 0.231$ , or  $-0.271$ ; standard error for pooled ln HR is  $\sqrt{0.58 * 0.58 * 0.344 * 0.344 + 0.42 * 0.42 * 0.300 * 0.300}$  or  $0.236$ . Hence, the 95% CI for pooled ln HR is  $-0.733$  to  $0.1915$ . **Finally, HR is 0.76 (95% CI: 0.48 – 1.21).**

**35-44 years:** pooled ln HR is  $0.58 * 0.647 + 0.42 * 0.956$ , or  $0.777$ ; standard error for pooled ln HR is  $\sqrt{0.58 * 0.58 * 0.1242 * 0.1241 + 0.42 * 0.42 * 0.1622 * 0.1622}$  or  $0.099$ . Hence, 95% CI for pooled ln HR is  $0.583$  to  $0.971$ . **Finally, HR is 2.17 (95% CI: 1.79 – 2.64).**

**45+ years:** pooled ln HR is  $0.58 * 1.065 + 0.42 * 1.637$ , or  $1.305$ ; standard error for pooled ln HR is  $\sqrt{0.58 * 0.58 * 0.1551 * 0.1551 + 0.42 * 0.42 * 0.1730 * 0.1730}$  or  $0.1156$ . Hence, 95% CI for pooled ln HR is  $1.078$  to  $1.532$ . **Finally, HR is 3.69 (95% CI: 2.94 – 4.63).**

**Figure 1: Flow diagram of case-selection for the analysis cohort**



**Table 1** Proportional hazard analysis: DRP, methadone only and heroin only mortality associated with covariates, for opioid users who had a prescribing treatment modality over the period 1st April 2005 to 31st March 2009. (N=129,979; person-years (pys) = 378,009)

	Pys (k)	DRP				Methadone only				Heroin only			
		Deaths	CMR per 10k pys	Adjusted Hazard Ratio [95% CI]*	P value	Deaths	CMR per 10k pys	Adjusted Hazard Ratio [95% CI]*	P value	Deaths	CMR per 10k pys	Adjusted Hazard Ratio [95% CI]*	P value
Age													
18-24	33,588	74	22.0	0.92 [0.72, 1.18]	<0.001	14	4.2	1.26 [0.70, 2.27]	<0.001	36	10.7	0.99 [0.69, 1.41]	0.796
25-34	167,045	429	25.7	REF		57	3.4	REF		202	12.1	REF	
35-44	128,936	514	39.9	1.54 [1.35, 1.75]		115	8.9	2.60 [1.89, 3.57]		172	13.3	1.09 [0.89, 1.33]	
45+	48,530	249	51.3	2.08 [1.78, 2.44]		85	17.5	5.14 [3.66, 7.21]		63	13.0	1.11 [0.84, 1.48]	
Gender													
Male	257,948	971	37.6	REF	<0.001	188	7.3	REF	0.500	390	15.1	REF	<0.001
Female	120,151	295	24.6	0.73 [0.64, 0.83]		83	6.9	1.09 [0.84, 1.42]		83	6.9	0.49 [0.38, 0.62]	
Injecting, ever declared													
Yes	147,341	704	47.8	2.12 [1.88, 2.40]	<0.001	130	8.8	1.64 [1.27, 2.13]	0.001	277	18.8	2.47 [2.00, 3.04]	<0.001
No	194,901	418	21.5	REF		111	5.7	REF		135	6.9	REF	
Undeclared	35,857	144	40.2	1.95 [1.61, 2.36]		30	8.4	1.47 [0.98, 2.21]		61	17.0	2.51 [1.85, 3.40]	
Declared alcohol misuse													
Yes	45,557	258	56.6	1.68 [1.46, 1.93]	<0.001	48	10.5	1.44 [1.05, 1.98]	0.024	92	20.1	1.63 [1.29, 2.05]	<0.001
No	332,542	1008	30.3	REF		223	6.7	REF		381	11.5	REF	
Declared benzodiazepine misuse													
Yes	54,051	258	47.7	1.39 [1.21, 1.60]	<0.001	54	10.0	1.44 [1.07, 1.95]	0.017	95	17.6	1.34 [1.07, 1.69]	0.011
No	324,049	1008	31.1	REF		217	6.7	REF		378	11.7	REF	
Declared crack cocaine misuse													
Yes	136,746	469	34.3	0.97 [0.87, 1.10]	0.671	76	5.6	0.69 [0.52, 0.90]	0.006	170	12.4	0.91 [0.75, 1.10]	0.334
No	241,353	797	33.0	REF		195	8.1	REF		303	12.5	REF	
Declared cocaine/ amphetamine misuse													
Yes	49,451	188	38.0	1.04 [0.89, 1.22]	0.582	41	8.3	1.15 [0.82, 1.61]	0.420	84	17.0	1.29 [1.01, 1.64]	0.038
No	328,649	1078	32.8	REF		230	7.0	REF		389	11.8	REF	

\* Evidence for gender and age interaction - DRP model: p = 0.013; methadone only model: p = 0.350; heroin only model: p = 0.062.



**Table 2** Proportional hazard analysis: DRP, methadone only and heroin only mortality associated with treatment and covariates, for opioid users who had a prescribing treatment modality over the period 1st April 2005 to 31st March 2009. (N=129,979; person-years (pys) = 378,009)

	Pys (k)	DRP				Methadone only				Heroin only			
		Deaths	CMR per 10k pys	Adjusted Hazard Ratio [95% CI]*	P value	Deaths	CMR per 10k pys	Adjusted Hazard Ratio [95% CI]*	P value	Deaths	CMR per 10k pys	Adjusted Hazard Ratio [95% CI]*	P value
Treat													
In	283,801	790	27.8	REF	<0.001	217	7.6	REF	0.122	226	8.0	REF	<0.001
Out	94,298	476	50.5	1.98 [1.76, 2.23]		54	5.7	0.79 [0.58, 1.07]		247	26.2	3.72 [3.09, 4.49]	
Age													
18-24	33,588	74	22.0	0.90 [0.70, 1.15]	<0.001	14	4.2	1.27 [0.71, 2.28]	<0.001	36	10.7	0.93 [0.65, 1.33]	0.379
25-34	167,045	429	25.7	REF		57	3.4	REF		202	12.1	REF	
35-44	128,936	514	39.9	1.57 [1.38, 1.78]		115	8.9	2.59 [1.88, 3.56]		172	13.3	1.13 [0.92, 1.39]	
45+	48,530	249	51.3	2.18 [1.86, 2.55]		85	17.5	5.08 [3.62, 7.13]		63	13.0	1.22 [0.92, 1.62]	
Gender													
Male	257,948	971	37.6	REF	<0.001	188	7.3	REF	0.531	390	15.1	REF	<0.001
Female	120,151	295	24.6	0.74 [0.65, 0.85]		83	6.9	1.09 [0.84, 1.41]		83	6.9	0.52 [0.41, 0.65]	
Injecting, ever declared													
Yes	147,341	704	47.8	2.17 [1.91, 2.45]	<0.001	130	8.8	1.63 [1.26, 2.12]	0.001	277	18.8	2.58 [2.09, 3.18]	<0.001
No	194,901	418	21.5	REF		111	5.7	REF		135	6.9	REF	
Undeclared	35,857	144	40.2	1.77 [1.46, 2.15]		30	8.4	1.51 [1.01, 2.28]		61	17.0	2.08 [1.54, 2.83]	
Declared alcohol misuse													
Yes	45,557	258	56.6	1.73 [1.51, 1.99]	<0.001	48	10.5	1.43 [1.04, 1.96]	0.026	92	20.1	1.75 [1.39, 2.21]	<0.001
No	332,542	1008	30.3	REF		223	6.7	REF		381	11.5	REF	
Declared benzodiazepine misuse													
Yes	54,051	258	47.7	1.43 [1.25, 1.65]	<0.001	54	10.0	1.43 [1.06, 1.94]	0.020	95	17.6	1.45 [1.15, 1.82]	0.002
No	324,049	1008	31.1	REF		217	6.7	REF		378	11.7	REF	
Declared crack cocaine misuse													
Yes	136,746	469	34.3	0.97 [0.86, 1.09]	0.631	76	5.6	0.69 [0.52, 0.90]	0.007	170	12.4	0.91 [0.75, 1.11]	0.345
No	241,353	797	33.0	REF		195	8.1	REF		303	12.5	REF	
Declared cocaine/ amphetamine misuse													
Yes	49,451	188	38.0	1.06 [0.91, 1.24]	0.454	41	8.3	1.15 [0.82, 1.60]	0.429	84	17.0	1.33 [1.05, 1.69]	0.018
No	328,649	1078	32.8	REF		230	7.0	REF		389	11.8	REF	