



EMCDDA PAPERS

Mortality among drug users in Europe: new and old challenges for public health

Contents: Introduction (p. 2) | Methods and data sources (p. 3) | Key findings from recent mortality cohorts in Europe (p. 6) | Public health perspectives and implications (p. 13) | Conclusion (p. 15) | Glossary (p. 17) | References (p. 18)

Abstract: More than 6 000 drug users die of overdose each year in the European Union, and most of these deaths occur among problem drug users and involve opioids. In addition, many deaths related indirectly to drug use occur each year. To gain a clearer picture of the overall number of lives lost due to drug use in Europe, this paper builds on the results of an earlier work that looked at all-cause mortality among problem drug users. By linking data on entrants to drug treatment programmes with information from death registries, mortality cohort studies can determine death rates from all causes within the study population. The study presents data from nine European countries, including seven not previously studied using EMCDDA methodology. Among over 31 000 participants (22 % female), covering 203 000 person-years of follow-up, 2 886 deaths were recorded, 18 % among females. Overall crude mortality rate per 1 000 person-years follow-up was 14.2, but varied

geographically from 3.5 to 22.7. Cause of death was reported in 71 % of all deaths, half of which was accounted for by external causes: overdose (35 %), suicide (5 %) and other external causes (10 %). Somatic causes accounted for about 45 % of the known-cause deaths: HIV/AIDS (14 %), circulatory diseases (9 %), respiratory diseases (5 %) and other somatic causes (16 %). Risk of death among problem drug users was typically 10 or more times that among their peers in the general population. The analysis shows that the deaths of problem drug users are overwhelmingly premature and preventable.

Keywords drug-related deaths
cohort study drug overdose
opioid use

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Introduction

The prevalence of illicit drug use in Europe and the number of deaths related to drug use remain high by historical standards. Illicit drug overdoses are responsible for a considerable share of premature and avoidable mortality among young adults, accounting for an estimated 4 % of all deaths among those aged 15–39 in Europe (EMCDDA, 2013d). In some countries, the proportion is much higher: 21 % in Estonia, 14 % in Norway, 12 % in Ireland, 11 % in Finland and 10 % in the United Kingdom. Many of these deaths are related to injecting drug use and, in most cases, involve a combination of substances (Best et al., 2000; EMCDDA, 2013c). From 1990 to 2012, between 6 100 and 8 500 overdose deaths were reported each year in Europe. Despite major increases in the provision of drug treatment in Europe, the overall number of reported overdose deaths increased between 2003 and 2008, although it has since fallen back to an estimated 6 100 overdose deaths per year in 2012.

Overdoses, however, represent only part of the mortality related to drug use. In Europe, overdoses were estimated to account for roughly one-third to half of deaths among problem drug users (EMCDDA, 2011). A substantial number of deaths among problem drug users are indirectly related to drug use. Among these are deaths due to HIV/AIDS acquired through injecting drug use, deaths due to other blood-borne infections, traffic accidents and other accidents, violence and suicides. Also contributing to some of the non-overdose deaths among drug users are the health and social problems associated with problem drug use, such as social exclusion, homelessness, chaotic lifestyles, concomitant mental health problems, or concomitant excessive use of alcohol or tobacco.

The high levels of mortality among drug users are a cause for concern both at the individual and the societal level. The number of problem opioid users (those injecting opioids or using the drug regularly or over a long time) in Europe is cautiously estimated at about 1.3 million (EMCDDA, 2014), and the greatest share of morbidity and mortality related to

illicit drug use is found among these opioid users, particularly those injecting.

Overall mortality among problem drug users is studied primarily by following cohorts of problem drug users over time. Cohort studies capture all deaths among the participants regardless of their supposed relation to drug use, of their cause, and of the practices of coding the cause of death in mortality registries. This approach identifies the whole spectrum and intensity of deaths, and can reveal the risks to life associated with long-term drug use.

Beyond overdoses, mortality related to drug use is a complex phenomenon, with a number of dimensions that require different data sources and methodology, such as cohort studies, to help explain them.

Objectives and content

The first aim of this paper is to present the most up-to-date picture given by cohort studies of the overall mortality among opioid drug users in Europe, and to ascertain and quantify the various causes. Secondly, the paper seeks to identify, where data are available, changes over time and differences between countries. The third aim of the paper is to identify areas where further data and research are necessary in order to inform policymaking and prevent these avoidable deaths.

The remainder of this publication consists of three sections. In the first of these sections, key findings from recent mortality studies in Europe are presented. The second section presents the result of a pooled study involving cohorts in nine European countries. The final section looks at the public health implications of the findings of cohort studies.

Information on risk and protective factors and on the options available for prevention and other interventions are not covered by this publication. Updated documents on prevention of overdose are referred to though and briefly discussed.

Methods and data sources

The data sources and methods used are presented in the sections below. Further information on cohort studies is given in text boxes.

Mortality cohort studies in Europe

The overview of mortality cohort studies among drug users in Europe is based on a 2011 EMCDDA Selected Issue. The main European mortality studies that were analysed for the Selected Issue were outlined in an appendix. The studies were selected primarily to cover as many countries as possible, and according to the size of the population followed up. Recent long-term follow-up studies conducted at national level and enrolling between 3 000 and 5 000 participants were available for Croatia, Germany, Latvia, Norway, Poland, Slovenia and Sweden. While many of these studies have been published, some countries provided cohort data that are as yet unpublished. The participants in the cohort studies analysed were predominantly problem drug users, most of whom were engaged in opioid substitution treatment or some other form of treatment for opioid dependence at the time of their enrolment. Studies conducted in other settings, such as juvenile correctional institutions, are available for some countries.

This publication supplements the Selected Issue with an updated review of the papers on mortality published in Europe since 2011, and by a review of recent national reports (2011 data, reported in 2012) to the EMCDDA. In 2012, seven national reports included information on cohort studies: Cyprus, the Czech Republic, Lithuania, Luxembourg, Norway, Slovenia and the United Kingdom, although not all of these provided results of recent studies.

Multisite pooled cohort study

Rationale and added value of pooling European studies

For the present paper, cohort studies carried out in nine European countries have been analysed together. The rationale for conducting a pooled analysis was to improve the statistical power of cohorts, which on their own are often limited to a few thousand participants enrolled. In particular,

the pooled study allows analysis of sub-groups like women or people who died from specific causes such as suicide or disease related to hepatitis C virus infection.

European multisite cohort studies

The present European multisite study was conducted in 2012–13 and covers nine countries. The latest multisite study is similar in approach to the COSMO study, the first European multisite study coordinated by the EMCDDA (Bargagli et al., 2006a; Bird, 2010). Some links and comparisons can be made between the two exercises.

The present study: recruitment settings and methods

The impetus for the present cohort study springs from the data collection for the 2011 Selected Issue, when a number of countries reported summaries of the findings of cohort studies (EMCDDA, 2011; Giraudon et al., 2012). The EMCDDA decided to conduct a pooled analysis of different national datasets in order to gain better insights into mortality among problem drug users. Key issues to be addressed included trends in mortality, comparison of mortality between countries and, in order to analyse cause-specific mortality, a gain in statistical power.

The study population was made up of cohorts of opioid users enrolled in treatment (mainly opioid substitution treatment), collated by the EMCDDA national experts on drug-related deaths. Datasets shared between experts and the EMCDDA were fully anonymised, and any information that would compromise the anonymity of the participants or breach the national regulations was deleted from the datasets before they were shared. The format of a minimum dataset had been recommended to all contributing experts, following the EMCDDA cohort protocol (see box on the EMCDDA cohort protocol). The core dataset included age, gender and primary drug, date and cause of death if the person had died, and the dates necessary to compute the length of time followed up (date of enrolment and end of follow-up, whether for end of study, loss to follow-up or death). Information on cause of death was available for all cohorts except for those from Amsterdam and Poland. The different data analyses were conducted with SPSS and Stata. Several data analysis workshops were conducted in the course of the study.

What are cohort studies and what do they tell us?

The information analysed in this paper is mainly derived from longitudinal follow-up studies of groups — ‘cohorts’ — of problem drug users, which systematically identify the causes of all deaths among the cohort. Cohort studies may be classified by whether they use an active or passive follow-up. Active follow-up studies (e.g. by periodical interviews) allow researchers to measure behaviour over time, for example the duration of treatment over the years, or whether the person has changed his or her primary drug. Passive follow-up methods link records between lists of drug users and mortality registries, but cannot collect information on the subsequent drug-use or drug-treatment history of the participant after enrolment in the study.

Mortality cohort studies among problem drug users can determine overall and cause-specific mortality rates and can estimate the excess mortality of drug users, compared with their peers in the general population. Cohort studies also detect changing patterns in the causes of death (Darke et al., 2007). Large-scale cohort studies can also help to determine the impact of interventions. For example, cohort studies provide insight into the trends of HIV/AIDS-related mortality among injecting drug users, which decreased dramatically after the introduction of effective HIV treatment.

Findings from cohort studies can be used to produce national estimates of deaths among all problem drug users. For that, mortality rates can be extrapolated from cohort studies to local or national estimates of the number of problem drug users (Cruts et al., 2008). Another approach that can be used to estimate the number of deaths due to drug use is to derive drug-attributable fractions from mortality cohort studies and apply these fractions to the causes of death that are most frequently related to drug use

(e.g. HIV/AIDS, accidents, suicide and poisonings) and which are recorded in the general population mortality registries. Findings from cohort studies can also contribute to the validation of data from other sources, for example, the number of drug-induced deaths reported in mortality registries.

Cohort studies have both strengths and limitations when used for the study of mortality among drug users. The capacity to provide information on mortality from all causes among drug users, beyond drug-induced deaths, is the main advantage of mortality cohort studies. Their main limitation is that they may underestimate the number of deaths when some subjects are lost to follow-up. In addition, the results may not be readily generalised to other populations of drug users.

Finally, comparability between studies can be compromised by differences in recruitment settings (e.g. treatment centres, outreach services, needle exchange services), populations of drug users enrolled (e.g. cocaine users, arrestees) and study design (e.g. enrolment of current drug users, retrospective studies of persons treated some years ago) (Degenhardt et al., 2011a).

In addition to mortality cohorts, other follow-up studies, with different primary objectives or recruitment criteria can also be used to monitor mortality. Examples include the VEdeTTE studies in Italy (Bargagli et al., 2006b; Vigna-Taglianti et al., 2007), the primary objective of which was to assess treatment outcome, studies among those arrested for drug law offences in France (Lopez et al., 2004), and studies of injectors with hepatitis in the Czech Republic (Lejckova and Mravcik, 2005, 2007).

EMCDDA cohort protocol

To assist European countries in carrying out useful and harmonised studies, the EMCDDA together with national experts produced a protocol on conducting and analysing mortality cohort studies (EMCDDA, 2012). The protocol recommends the use of treatment centres as the setting for recruitment of patients into cohort studies. Treatment centres are usually able to recruit a relatively representative sample of problem drug users in treatment, typically, opioid users. Treatment centres are also an appropriate setting for the collection of personal identifiers needed to trace the participants in mortality registries. There are, however, limitations associated with recruiting drug users in these settings, as the findings are not necessarily transposable to other drug users, particularly

those not in treatment. To facilitate comparison across studies, the EMCDDA also recommends the use of prospective studies that focus on current drug users: participants are enrolled on entry to drug treatment and the study looks at mortality over the following months or years. Some studies are retrospective, that is to say the individuals have been enrolled in the past, at the moment of intake to treatment. However, in these studies, there might be gaps, errors and non-standard data, which will be difficult or impossible to complete or correct. The EMCDDA stresses the necessity of confidentiality and protection of identifiable personal data. Ethical approval and participants' consent are needed, as is compliance with national regulations and laws.

Nine cohorts were included in the pooled analysis. These studies covered either national or city populations (Figure 1). All cohorts consisted of opioid users who entered treatment during the period 1995–2011. The data were linked to national registers of all deaths (or the municipal register in the case of Amsterdam). Crude mortality rates (CMRs) and standardised

mortality ratios (SMRs) were examined by country, age and sex. SMRs were calculated from the expected numbers of deaths in the European population (27 EU Member States) in 2006, using data extracted from Eurostat. These computations were done separately for the overall mortality and the cause-specific mortality.

The COSMO study and its successor

The COSMO study was the first European multisite cohort study to be coordinated by the EMCDDA. In common with the current pooled analysis, it required agreement on a common core dataset and involved a number of data analysis workshops. The study population was made up of cohorts of opioid users who entered treatment during the period 1990–99. Deaths among the subjects were traced back by linking the cohorts with national or municipal registers. Eight European sites were included in the COSMO Study: Spain (Barcelona), Portugal (Lisbon), Italy (Rome), Denmark, Ireland, United Kingdom (London), the Netherlands (Amsterdam) and Austria (Vienna). The sites were all in countries that joined the European Union before 2004.

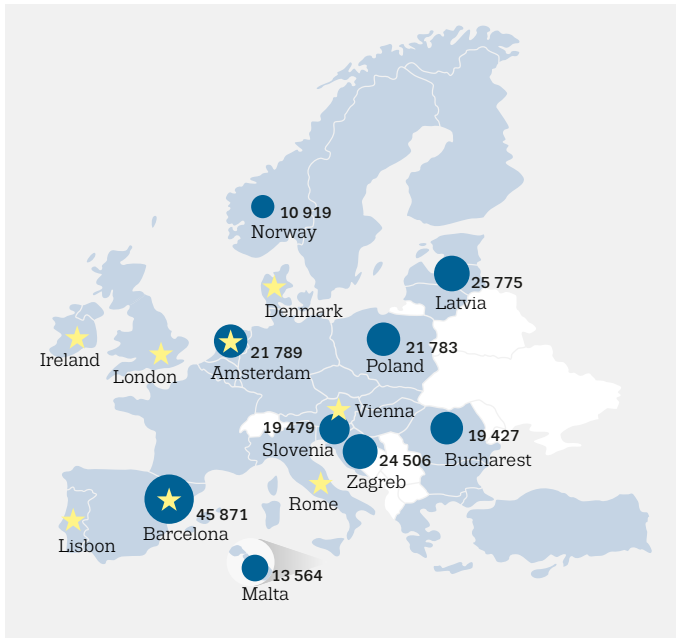
The pooled analysis includes cohorts from seven countries that were not involved in the COSMO study (Croatia, Latvia, Malta, Norway, Poland, Romania and Slovenia), and the majority of which are in the eastern half of the European

Union. The cohorts in the Netherlands (Amsterdam) and Spain (Barcelona) were involved in the COSMO study. The follow-up of the cohort in the Netherlands has been extended to 2009 for this analysis, which adds seven years of follow-up compared with COSMO. The cohort in Barcelona has also been updated (recruitment from 1997 to 2007 for this exercise, compared with 1999 to 2001 for the COSMO analysis).

The current exercise provides an insight into mortality among drug users in a time when effective HIV treatments were readily available to this group, which was not the case in the 1990s when the COSMO studies were carried out. The lack of effective HIV treatment in the 1990s was reflected in the many deaths among drug users accounted for by HIV/AIDS. This was particularly the case in Portugal, Italy and Spain, where the prevalence of HIV infection among drug users was high.

FIGURE 1

Countries and cities participating in the 2012–13 pooled analysis and the COSMO study, showing number of person-years for each pooled analysis site (circles) and location of COSMO sites (stars)



NB: 2012–13 pooled analysis sites: Amsterdam (Netherlands), Barcelona (Spain), Latvia, Malta, Norway, Poland, Romania (Bucharest), Slovenia, Zagreb (Croatia). COSMO sites: Amsterdam (Netherlands), Barcelona (Spain), Denmark, Ireland, Lisbon (Portugal), London (United Kingdom), Rome (Italy), Vienna (Austria).

Key findings from recent mortality cohorts in Europe

A review of cohort studies in Europe

This brief review of cohort studies in Europe comprises three parts. First, some of the key findings of the 2011 Selected Issue are presented. Of particular interest are the mortality rates and excess risk of mortality among participants in cohort studies compared with the general population, and the most common causes of death. Secondly, an update is presented, based on the data reported in the 2012 Reitox national reports (2011 data). Finally, the findings of a selection of published papers on cohort studies among drug users are presented. The papers cited include large international reviews and national studies carried out in European countries.

Mortality rates and excess mortality in cohorts of problem drug users

Cohort studies point to an excess risk of mortality for problem drug users compared with their peers of the same age and gender in the general population. Overall, the mortality for drug

users is roughly 10 to 20 times that of the general population of the same age and gender (EMCDDA, 2011). Excess mortality risk is usually higher in females than in males, largely due to lower mortality rates among women in the general population. In addition, excess mortality risk is usually higher in younger drug users than in older ones, again largely due to lower mortality rates among their peers in the general population.

For problem drug users, the excess risk of death from certain causes is particularly high; chief among these are overdose, suicide, end-stage liver disease due to hepatitis C virus infection and heavy alcohol use, and violence. Again, mortality rates due to these causes are usually much lower in the general population.

Most common causes of death among problem drug users

Four broad categories of causes of death among problem drug users have been identified in the literature, namely overdose, disease, suicide and trauma (Darke et al., 2007). Among diseases, conditions related to blood-borne viruses (HIV, hepatitis B and hepatitis C viruses), neoplasms, other liver diseases, and diseases of the respiratory and circulatory systems can be associated with drug use. Trauma refers to serious or critical wounds or bodily injuries such as from accidents (traffic accidents, falls, drowning) and violence, and also includes assault and homicide.

Among problem drug users, in particular, cause of death may not be clear-cut. Those with severe drug problems, especially opioid users, comprise a very vulnerable population. Often, they have additional problems such as psychiatric co-morbidity, social exclusion, difficulties in accessing services, alcohol use and dependence, all of which can cause considerable harm in their own right.

Results from the studies presented in the Selected Issue, which are also supported by results from other reports, show that while there can be great variation between studies, a rough generalisation can be made that between one-third and half of deaths among problem drug users are due to overdose, and between one-fifth and two-fifths are due to suicide and trauma (Best et al., 2000; Darke et al., 2007; Degenhardt et al., 2011a; EMCDDA, 2011; Giraudon et al., 2012). Less than one-tenth of the deaths recorded in recent cohort studies are attributed to HIV/AIDS. A substantial proportion of drug users die from 'other causes', which appears mainly to include somatic and chronic conditions such as liver diseases, cardio-vascular and pulmonary conditions, cancer and infections other than HIV. In the studies cited in the Selected Issue, 'other causes' typically accounted for about one-quarter of all deaths, although this category can represent up to half of the recorded deaths in some cohorts.

Mortality cohort studies reported in the 2012 Reitox national reports

Five of the 30 national focal points reporting to the EMCDDA presented new developments or data from cohort studies in their 2012 national reports.

For the Czech Republic, results of a number of studies were presented in the Selected Issue (EMCDDA, 2011; Lejckova and Mravcik, 2005, 2007; Záborský et al., 2011). Mortality rates for patients in substitution treatment were relatively low, ranging from 3.5 to 7.2 deaths per 1 000 person-years, similar to the mortality rates estimated in other countries in central or eastern Europe (see below). The mortality rate among clients enrolled in the substitution treatment register was estimated at 1.7 per 1 000 (Reitox National Report, 2012); this, however, is an underestimate, as deaths are recorded as a reason for terminating treatment, rather than traced through systematic linkage with the mortality register. Some deaths are probably not reported to the study by physicians and are therefore not counted.

A recent study among a cohort of very young injectors, whose principal drug was methamphetamine or heroin, found that mortality was high in males (4.8 deaths per 1 000 person-years overall), in particular in the first three years after enrolment and due to external causes exclusively (overdose and accidents) (Záborský et al., 2011).

In Lithuania, data from the State Mental Health Centre suggested a mortality rate of 8.4 deaths per 1 000 patients dependent on drugs and psychotropic substances registered in 2011 (42 out of 5 935 drug users). As there was no systematic linkage of the treatment register with the general mortality register, the mortality rate may be an underestimate. Three-quarters of the reported deaths were among opioid users (33/42). The proportion of patients who were opioid users or users of other drugs is not reported. The mean age of death has increased over the years and reached 42.5 years in 2011. The cause of death was known for only half of the cases. Of those, about half died of external causes and the remainder died of somatic causes.

In Slovakia, a retrospective cohort study among drug treatment clients in Bratislava found the highest mortality rates among those dependent on sedatives (25 deaths per 1 000 person-years), followed by those dependent on opioids (7.3 deaths per 1 000 person-years).

In Norway, 54 deaths from various causes were reported during 2011 among clients registered in the opioid substitution programme. There were 6 640 clients enrolled in the programme at the end of 2011, indicating a total mortality rate of about 8 per 1 000 person-years among those in substitution treatment. The majority of deaths among those in

substitution treatment were due to somatic causes and injuries. It is generally accepted that the annual mortality rate among untreated injecting heroin users in Norway is in the range of 2–4 %.

In a study of Norwegian substitution treatment clients for the period 1997–2003, an annual mortality rate of 2.4 % was found prior to treatment and 3.5 % post-treatment among those who terminated substitution treatment. In the same study, the annual mortality rate was 1.4 % for those receiving substitution treatment, among whom the main causes of death were somatic causes (55 %), overdose (27 %) and trauma (18 %). However, for the observed times prior to and after substitution treatment, overdoses dominated as the main cause of death (Clausen et al., 2008, 2009). The annual mortality rate for substitution treatment clients has gradually decreased in Norway since 2002, from an estimated 15 per 1 000 to a current rate of 8 per 1 000 ⁽¹⁾.

Other recently published cohort studies

To supplement the short review of the 2012 national reports, some recently published papers of interest are mentioned below. This selection of reviews and original papers on European cohorts is not intended as a comprehensive literature review. Some recent findings published on deaths related to stimulants are also presented (see boxes on mortality among cocaine users and among amphetamines users).

A Scottish study on premature mortality among injecting drug users used a 'life-course data' approach to collect retrospective data on family life, employment and health. It found that early life adversity was apparent for many cases, with a steady progression into early criminal behaviour and drug misuse. It suggested that more qualitative studies are needed to highlight areas which might require early intervention (Copeland et al., 2012).

Also in Scotland, a large linkage study was conducted on patients in contact with drug treatment services between 1996 and 2006. The overall SMR fell over time from 6.4 (95 % CI, confidence interval, 6.0–6.9) in 1996–2001 to 4.8 (95 % CI 4.6–5.0) in 2001–06. More than half of the deaths were due to overdose. Alcohol misuse increased the risk of overdose, suicide and deaths from digestive system diseases. The authors concluded that individuals diagnosed with hepatitis C virus infection are particularly vulnerable and may need additional support (Merrall et al., 2012).

In Norway, a linkage study with a 33-year follow-up period was conducted among anti-HCV-positive injecting drug users

⁽¹⁾ The data included in the multisite pooled study are from 1997 to 2003 only.

admitted to residential drug treatment in 1970–84. The study found that, among this group of drug users, who had been exposed to the virus at some point in their lives, the all-cause mortality rate was 18 per 1 000 person-years. The main cause of death was overdose (45 %), followed by suicide (9 %) and accidents (8 %). Among those testing positive for HCV RNA, which is taken to indicate an active infection, liver disease was the cause in 7.5 % of deaths. The authors concluded that overall mortality is high among the study group and that, in the first three decades after HCV

infection, mortality rates among HCV RNA-positive individuals were not different to those among HCV RNA-negative individuals. However, among injecting drug users with chronic HCV infection who have survived until 50 years of age, HCV infection emerges as the main cause of death (Kielland et al., 2013a).

Most published papers on mortality among drug users focus on opioid users but there is a growing literature on mortality and morbidity related to cocaine use (see box).

Mortality among cocaine users

In recent years, cocaine has been detected in an increasing number of drug-induced deaths and drug-related emergencies reported in European countries (Corkery, 2012; EMCDDA, 2013c). The available data do not permit a clear picture of trends in cocaine-related deaths in Europe as a whole. For Spain and the United Kingdom, the countries with the highest rates of cocaine use in the general population, an increase was observed before 2008, but the most recent data suggest the numbers have since decreased. The same trend was observed for emergencies related to acute cocaine intoxications (EMCDDA, 2013b; Mena et al., 2013).

Cocaine is very rarely identified as the only substance contributing to a drug-induced death (Corkery, 2012), and long-term use causes complex and interlinked harms (Dinis-Oliveira et al., 2012).

A recent review on mortality among cocaine users (Degenhardt et al., 2011b) included nine studies in Brazil, Canada, the United States and three European countries (France, Italy, Netherlands). Crude mortality rates ranged from 0.54 to 4.6 per 100 person-years. The main causes of mortality, where known (Brazil, Canada, Italy, United States), included fatal gunshots (Brazil), overdose, HIV/AIDS, trauma and infections related to injecting, vascular diseases and suicide. The authors concluded that there are limited data

available on the extent of elevated mortality among problematic or dependent cocaine users, and that it is unclear how generalisable the results may be to other populations.

A recent Danish cohort study, among individuals in treatment for cocaine use, showed an excess mortality risk of 6.4 compared with peers of the same age and sex in the general population (Arendt et al., 2010). Dependent cocaine users show high rates of attempted suicide. Suicide attempts among cocaine users are not restricted to those who inject the drug: a study in Australia showed that 10 % of cocaine users who had never injected a drug also had this history (Darke and Kaye, 2004). More recently, in Spain, a cohort study found that short-term mortality in a sample of young Spanish primary cocaine users was five times (4.7; 95 % CI 2.4–9.0) that of their peers in the general population. The authors hypothesised that the excess mortality may largely be explained by a history of opioid use or the risk of starting such use. Although differences between subgroups did not reach statistical significance, mortality appeared to be lower among those who had never used opioids compared with those who had used opioids at some time in their life. Similarly, mortality appeared to be lower among those who at baseline neither used opioids, nor injected nor smoked cocaine compared with those reporting any of these risk behaviours at baseline (Barrio et al., 2013).

There are growing concerns in Europe about the prevalence of use and harms related to amphetamines, including methamphetamine, at least in some countries (see box).

Mortality among amphetamine and methamphetamine users

A review of the literature on mortality cohort studies among problem amphetamines users found that crude mortality rates ranged from 0 in Australia to 2.95 per 100 person-years in Thailand (Singleton et al., 2009). Studies carried out in Europe found mortality rates ranging from 0.49 in Czech Republic to 2.89 per 100 person-years in the Netherlands, with studies also reported in Sweden and Finland. The Czech cohort study included in this review reported an excess mortality risk of 6.2 in comparison with non-using peers. Only three of the identified studies reported on causes of death (102 cases in total), and the majority were due to violence, injuries, accidents, and overdoses. There was suggestive evidence that injection of amphetamines was associated with higher mortality than other primary routes of administration. The authors of the review concluded that given the widespread use of problem amphetamines use, the known non-fatal adverse effects of use and the mortality rates reported, cohort studies investigating the morbidity and mortality associated with such drug use should be a research priority.

A recent large study was conducted among persons hospitalised in California for methamphetamine, alcohol, opioid, cannabis or cocaine-related disorders (Callaghan et al., 2012). The study found that the methamphetamine cohort had a higher excess mortality risk (4.7 compared with the general population), than did users of cocaine, alcohol or cannabis, but lower than that of opioid users (5.7). It stressed the relative lack of long-term cohort studies of mortality risk among individuals with methamphetamine-related disorders compared with users of other substances. The authors list methamphetamine along with cannabis and cocaine as drugs lacking long-term mortality cohort studies.

Results of the multisite pooled study

Patients enrolled

A total of 31 218 people were enrolled in the pooled cohort, with follow-up amounting to 202 947 person-years. Females made up 22 % of the subjects and accounted for 21 % of the person-years followed up. The mean age at enrolment was 28.6 years (28.7 for males and 28.2 for females), but this varied across countries. For both genders, the age-band 25–29 accounted for the largest number of person-years followed up (Figure 2).

The gender distribution varied across countries from 68 % males in Norway to 84 % in Slovenia, but in most of the countries around 80 % of the participants were males (Table 1).

The age distribution also varied across the different study sites, with Amsterdam, Norway and Barcelona having the oldest participants at the time of enrolment, whereas in Bucharest and Malta, more than two-thirds of the participants were younger than 25 at the time of enrolment (Table 1; Figure 3).

FIGURE 2
Distribution of person-years followed up in the nine sites, by age-band and gender

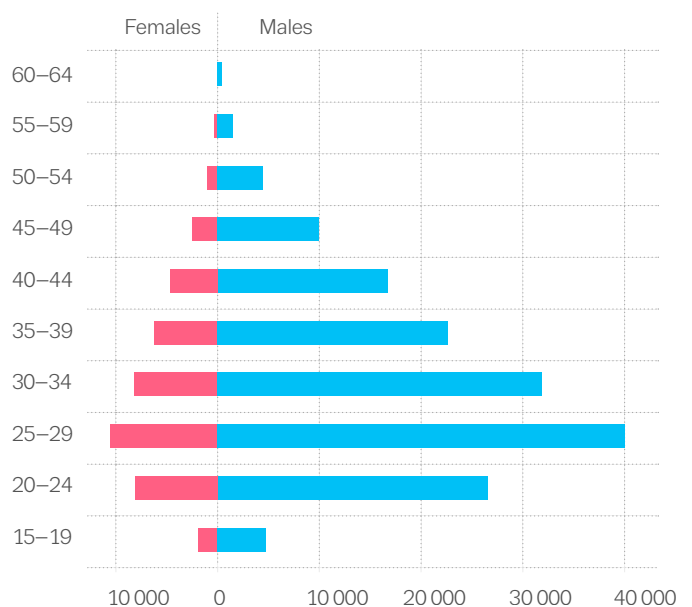
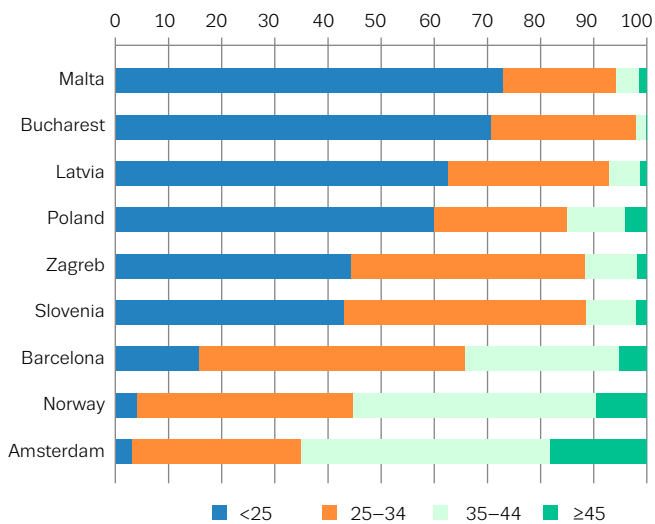


TABLE 1
Cohorts of regular or dependent opioid users, aged 15 to 64 years old, in the nine European sites contributing to the pooled analysis

Country (city for sub-national samples)	Enrolment period	End of follow-up	Mean age at enrolment (years)	% of males	Inclusion criteria and setting	Person-years followed up (number of participants)	Mean observation time in years	% of the participants in the pooled dataset	Number of deaths	All-cause mortality rates/1 000 person-years (95 % CI)*	Standardised mortality ratio (95 % CI)
Croatia (Zagreb)	Jan. 2000 to Dec. 2006	Dec. 2010	27.04	77.9	Injectors Treatment	24 508 (3 056)	8.0	9.8	230	9.4 (8.3–10.7)	8.5 (7.4–9.6)
Latvia	Jan. 2000 to Dec. 2011	Dec. 2011	24.36	79.6	Opioid users	25 774 (3 599)	7.2	11.5	417	16.2 (14.7–17.8)	18.0 (16.4–19.8)
Malta	Jan. 1994 to Jun. 2008	Dec. 2008	23.35	83.7	Opioid users	13 548 (1 659)	8.2	5.3	47	3.5 (2.6–4.6)	3.5 (2.6–4.6)
Netherlands (Amsterdam)	Jan. 1996 to Dec. 2002	Mar. 2009	38.14	79.1	Opioid users	21 694 (2 566)	8.4	8.2	348	16.0 (14.4–17.8)	5.1 (4.6–5.7)
Norway	Jan. 1997 to Dec. 2003	Dec. 2003	36.11	68.1	Opioid users Opioid maintenance treatment	10 922 (3 787)	2.9	12.1	210	19.2 (16.8–22.0)	10.8 (9.4–12.4)
Romania (Bucharest)	Jan. 2001 to Nov. 2008	Sep. 2010	23.34	82.5	Opioid users	19 428 (2 584)	7.5	8.3	110	5.7 (4.7–6.8)	6.9 (5.7–8.3)
Slovenia	Jan. 2004 to Jul. 2007	Dec. 2010	27.13	76.4	Opioid users	19 476 (3 189)	6.1	10.2	132	6.8 (5.7–8.0)	6.5 (5.5–7.7)
Poland	Jan. 2000 to Dec. 2004	Dec. 2006	26.01	80.4	Opioid users Inpatient treatment mainly	21 782 (4 728)	4.6	15.1	495	22.7 (20.8–24.8)	21.5 (19.7–23.5)
Spain (Barcelona)	Jan. 1997 to Dec. 2007	Dec. 2008	32.43	77.4	Opioid users	45 814 (6 050)	7.6	19.4	897	19.6 (18.3–20.9)	11.6 (10.9–12.4)

* CI, confidence interval.

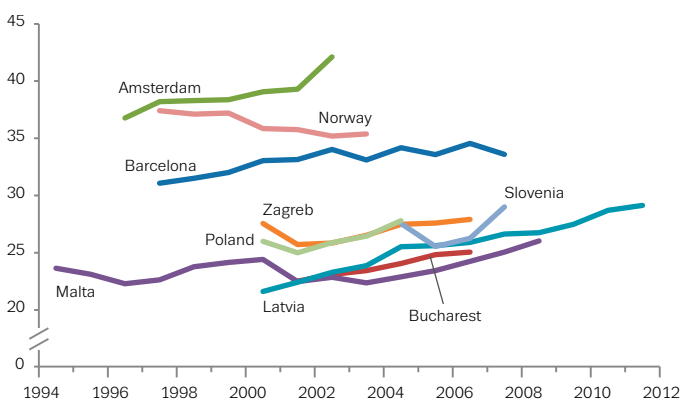
FIGURE 3
Distribution (%) of the participants by age-band at the time of enrolment



An ageing trend was observed among participants, with age at enrolment increasing over time in most cohorts. Norway did not follow this pattern and showed a downward trend in age at time of enrolment (Figure 4).

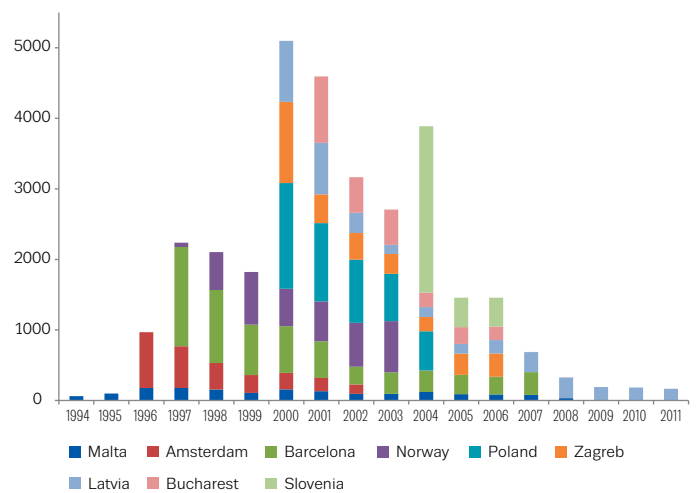
The largest contributors to the total number of persons enrolled were the cohorts from Barcelona (19%), Poland (15%) and Latvia (11%). These cohorts accounted respectively for 23%, 11% and 13% of the number of person-years followed up. Participants were enrolled and followed up from 1994 to 2011, but those who entered at the beginning of the last decade make up the bulk of the cohort (Figure 5).

FIGURE 4
Mean age (years) of participants at time of enrolment



NB: For Bucharest, 2007 and 2008 data (two new patients only) are not represented in the figure.

FIGURE 5
Numbers of persons enrolling annually in the nine sites of the pooled study



Mortality rates and excess risk

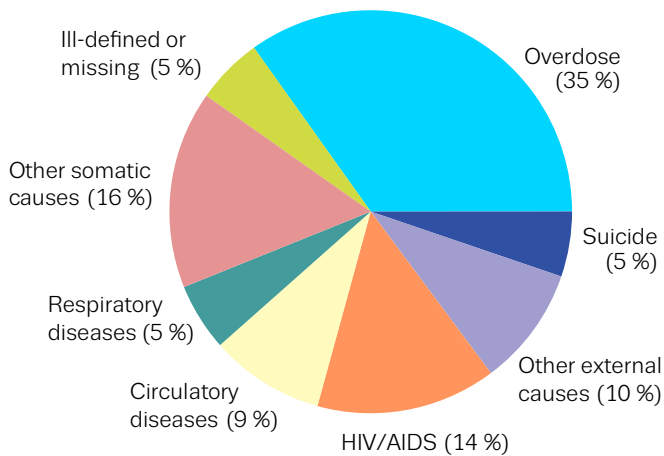
Across the nine studies, 2 886 deaths were recorded, 512 (18%) of which were of females. The overall crude mortality rate for the pooled cohort, computed with the total number of deaths over the 202 947 person-years followed up, was 14.2 (95% CI 13.7–14.7) per 1 000 person-years followed up. The mortality rates varied from 3.5 per 1 000 person-years in Malta to 22.7 per 1 000 person-years in Poland (Table 1).

Caution must be exercised when making comparisons between the different studies, as there are differences in the time of enrolment, in the coverage (either national or limited to a large city), settings, age distribution and characteristics of the cohorts. The pooled mortality rate must also be cautiously interpreted, bearing in mind the different sizes of the cohorts and the variability of their respective mortality estimates. For these reasons, some previously published multisite studies did not present any pooled results and reported only the country estimates (e.g. Bargagli et al., 2006a). A pooled CMR is presented here to place the findings in the perspective of other pooled results published in the recent literature; it should be noted, however, that different methods were used in these studies. Mathers et al. (2013) reported a pooled CMR of 23.5 deaths per 1 000 person-years (95% CI 21.8–25.8), with mortality rates varying across different settings. Degenhardt et al. (2011a) reported a pooled all-cause CMR of 21.0 per 1 000 person-years (95% CI 19.3–22.6).

The overall standard mortality ratio (SMR) for the pooled cohort was 10.0 (95% CI 9.7–10.4), ranging from 3.5 Malta to 21.5 Poland (Table 1).

FIGURE 6

Main causes of death among the pooled cohort, where the cause of death is reported



NB: Data for seven of the nine sites, covering 2 043 deaths.

Causes of death

The cause of death was reported for 2 043 (71 %) of all deaths. This information was not accessible for the cohorts in the Netherlands and Poland, where national regulations on data protection do not permit the linkage of the study data with the mortality register that is necessary to ascertain the cause of death.

Half of the deaths for which the cause was known were due to external causes (50 %), mainly overdose, though also including suicide, traffic accidents, other accidents and homicides (Figure 6). The most frequently reported somatic causes of death were HIV/AIDS and diseases of the circulatory and respiratory systems.

Deaths from unknown or ill-defined causes are relatively rare in the present pooled study (overall 5 %), compared with some cohorts reported in the literature (Degenhardt et al., 2011a; EMCDDA, 2011; Ferri et al., 2007; Hickman et al., 2003). In two of these studies, however, (Bucharest, 6 %, and Zagreb, 11 %) the proportion of ill-defined causes is higher, approaching the proportion found in earlier studies, for example in Italy (11 %) (Ferri et al., 2007) and in England (12 %) (Schifano et al., 2005).

Previous studies have found that the death of an opioid user is commonly attributed to several underlying causes. This finding points to the ill-health associated with long-term drug use and the difficult living conditions experienced by many problem opioid users. In particular, multiple causes were

more likely to be reported for somatic deaths (Clausen et al., 2009). This raises another caveat, as each death is classified by only one cause. This approach may fail to account for the complexity of the interlinked causes and determinants of deaths.

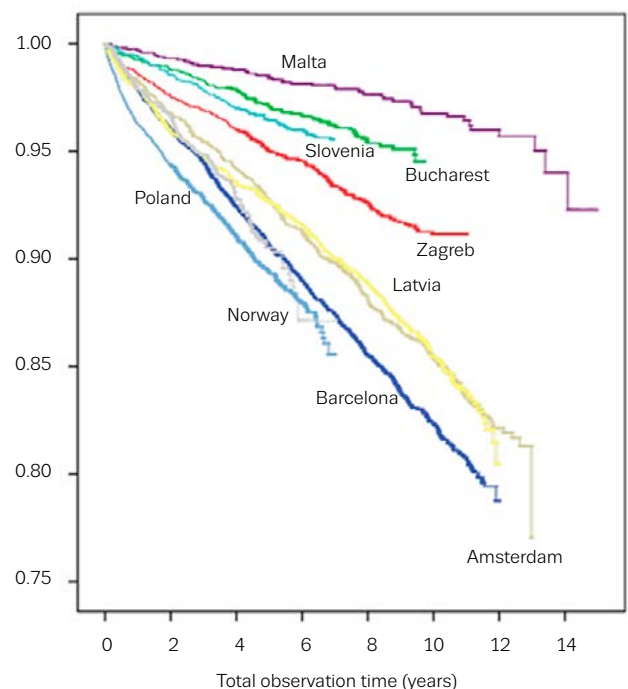
Survival

Survival analysis provides an insight into how the risk of death accumulates over time (Figure 7). The cohorts in Amsterdam, Barcelona, Latvia, Norway and Poland show the lowest survival rates, with up to one-tenth of the participants dying within the first 5 to 8 years of follow-up, and one-fifth within 12 to 13 years of follow-up. In contrast, the cohorts in Bucharest, Malta, Slovenia and Zagreb showed higher survival rates.

In these studies, the mortality risk was quite constant over time, within locations, following the enrolment of participants in a study. This is in part explained by a sustained level of risk, and by the ageing cohort, over the years. With regard to the effect of a cohort growing older on the risk of mortality among the participants, an initial analysis indicates that the risk associated with external causes remains at similar levels for the different age bands, but mortality due to somatic causes increases with age.

FIGURE 7

Cumulative survival curves in cohorts of regular or dependent opioid users, aged 15 to 64 years old in nine European sites



Public health perspectives and implications

Many studies conducted in Europe but gaps remain

Most European countries have now produced some evidence from cohort studies on mortality among drug users. The present pooled cohort study analysis includes some of the most recent data, with some participants followed up to the end of 2011. It also provides new insights into drug-related mortality in seven countries, mainly located in the eastern half of the European Union, that had not participated in COSMO.

Gaps, however, continue to exist in the information available. For some countries, the available data are old, with no recent record linkage with mortality registries (e.g. 2003 for Norway and 2008 for Barcelona). Some other countries, where national figures of drug-induced mortality are high, increasing, or both, lack on-going mortality studies (EMCDDA, 2013a; EMCDDA, 2013c; Giraudon et al., 2012). That is the case in Austria, Finland, Ireland and Sweden, for example. Finally, some countries that participated in COSMO (Denmark, Italy, Ireland, Portugal) are missing from the present pooled studies.

Main findings of the pooled analysis

The pooled analysis is the only European coordinated study on mortality among cohorts of problem drug users to be carried out in recent years. Mortality rates among drug users participating in the study were found to be high, with an overall rate of 14 deaths per 1 000 person-years followed up. In terms of excess mortality risk, problem drug users were typically 10 or more times more likely to die compared with their peers in the general population. Mortality rates and excess mortality differed widely between countries.

Pooling data from the different studies enabled a better insight into the causes of death, especially from causes that are not frequent enough to be discussed in smaller cohorts. Overall, half of the deaths for which information was available were attributed to external causes, primarily overdose, but also including suicide, accidents and violence. The remaining deaths were attributed to somatic causes, and related to infections (HIV and viral hepatitis), as well as other liver diseases and problems of the circulatory and respiratory systems. A small proportion of the deaths, 1 in 20, was coded with unspecific or ill-defined codes, but this varies between countries.

Comparison with the COSMO multisite study

These findings can be compared, to a certain extent, with those of the EMCDDA-coordinated multisite COSMO study

(Bargagli et al., 2006a), which was conducted among participants enrolled in eight countries during the 1990s. In common with the COSMO study, the present exercise found that overall mortality rates and excess risk are high, that males and older drug users have higher mortality rates compared with female and younger drug users, and that overdose remains the most common known cause of death among opioid users.

Only the cohort studies carried out in Amsterdam and Barcelona provided data for both the COSMO study and the present study. The present study found that the overall mortality rate of the Barcelona cohort (CMR 19.6 per 1 000 person-years in the period 1997–2007) has halved compared with the exceptionally high value found in the COSMO study (CMR 37.6 per 1 000 person-years in the period 1992–2001).

HIV accounted for a large part of overall mortality in the COSMO cohorts. During the 1990s, in Spain and in other COSMO cohorts in the south-west of Europe, HIV-related mortality was high, due to the epidemic of HIV infection among injecting drug users. At that time, HIV/AIDS was the cause of around one-third or more of deaths among opioid users: 38 % in Barcelona, 41 % in Lisbon and 32 % in Rome.

The decrease in overall mortality observed in the Barcelona cohort can be accounted for partly by the decrease in HIV-related mortality, which fell from 14 deaths per 1 000 person-years in the COSMO study to 4.45 deaths per 1 000 person-years in the present study. Also contributing to the decline in overall mortality was the decrease in overdose mortality — from 13 to 4.9 deaths per 1 000 person-years.

In the Amsterdam cohort, the overall mortality rate reported in the present study is unchanged from that found in COSMO (CMR 16.4 deaths per 1 000 person-years in 1996–2002; 16.0 deaths per 1 000 person-years in 1996–2009). This may be explained by the smaller impact of antiretroviral treatment, as levels of HIV-infection were low in Amsterdam compared with Barcelona, and by the lower mortality rate in Amsterdam during the first period. With its older age profile, the Amsterdam cohort may be expected to witness an increase in somatic deaths, related to the long-term consequences of previous or current drug use. However, this cannot be verified, as information on cause of death is not available for this study.

Apart from Barcelona and Amsterdam, COSMO and the present study are based on different sites, which limits comparability. If a simple typology can be suggested though, some northern European countries of the present analysis (Latvia, Norway and Poland) might be grouped. The crude mortality rates per 1 000 person-years found in these northern cohorts (Latvia, 16.2; Norway, 19.2; Poland, 22) were high, and quite similar to the mortality rates found in some of the COSMO studies recruited 10 years earlier (Lisbon, 15.4; Denmark, 17.4; Rome, 20). It can

be noted that the relatively high overall mortality rates found among drug users in some cohorts in the north of Europe mirrors to some extent the European geography of reported overdose deaths. In 2012, the eight highest national mortality rates from drug overdose in Europe were reported by countries located in the north — in descending order of mortality rate: Estonia, Norway, Ireland, Sweden, Finland, Denmark, the United Kingdom and Lithuania (EMCDDA, 2014).

However, the remaining, 'eastern countries' of the current analysis (Croatia, Malta, Romania and Slovenia) reported mortality rates below 10 per 1 000 person-years.

Any attempt to put these findings into perspective must be considered with caution, due to differences in recruitment settings, time of enrolment and age distribution in particular. Nevertheless, the results point to some improvements. One example is the reduction in HIV-related mortality observed in Barcelona that followed the introduction of antiretroviral treatment. The lower mortality rates observed in some of the countries in the eastern half of the European Union may reflect the later spread and different impact of the heroin 'epidemic' in those countries. In particular, HIV prevalence among drug users in these eastern EU Member States is much lower than it was in Italy, Portugal and Spain in the 1990s. Despite a number of the cohorts reporting relatively low mortality rates, in half of the countries represented in the study, deaths among drug users are at high levels.

Overdose deaths remain at historically high levels in some of the cohorts in the present study. The overdose mortality rate in Norway (11.8 deaths per 1 000 person-years) is comparable to or higher than the overdose mortality rates in some COSMO studies in the 1990s, with death rates per 1 000 person-years of 13.0 recorded in Barcelona, followed by London (7.4), Denmark (7.1), Rome and Vienna (both 6.6).

In comparison with results collated in a recent systematic review and meta-analysis, the mortality rates and excess risk found in the nine European cohorts of the current study are within the range reported from cohorts in North America, central Europe and Australasia, and lower than cohorts in Asia or some western European studies published in the 1990s or the beginning of the 2000s. The review authors noted the very high heterogeneity across studies, and suggested that study characteristics predict mortality levels and should be taken into account in future studies (Degenhardt et al., 2011a).

Mortality studies: revealing the harms related to drugs

Mortality data from cohort studies can be used to describe the trends in overall levels and causes of death among drug

users. Data from this source can also provide a complementary indicator to assess the burden of mortality related to drugs in the European population. In particular, the mortality rate related to overdoses observed in the cohorts should be consistent with the number of overdoses reported in the country's mortality registries, and with the estimated number of problem drug-users. Any inconsistency can point to an underestimation by the municipal or national statistics of the real number of fatal overdoses occurring and should be taken as a signal for the country to audit its recording of overdose deaths. This was illustrated by a cohort study conducted in Sweden, which estimated that the Swedish national causes of death register underestimated drug-related deaths by 37 % (Nyhlen et al., 2011).

Limitations

Comparisons of mortality rates and excess risk are valid only if all deaths in a cohort are identified and mortality is not underestimated — which may occur, for example, if the data linkage misses some deaths. When comparing cause-specific mortality rates across countries, it is important to take differences in coding of the cause of death into account. In addition, the cause of death is not always clearly identified — and this varies between countries with the result that large 'unknown' or unspecific categories are evident in some studies. Furthermore, for data protection reasons, some countries impose limitations on access to data on cause of death (e.g. the Netherlands and Poland).

Most cohort studies focus on treatment populations, and it is difficult to transfer their results to other more hard-to-reach populations of drug users (those not in contact with drug treatment). Hard-to-reach drug users should be a priority for new studies, as they are likely to be more disadvantaged, at higher risk of dying and to warrant priority interventions. Information is also lacking about mortality of problem or intensive users of drugs other than opioids.

As cohort studies usually consider samples of those in treatment, and as treatment, in particular continuous and good quality opioid substitution treatment, reduces mortality risk (Cornish et al., 2010; Hickman et al., 2011; Kimber et al., 2010), the risk observed in these studies may represent a minimum estimate of mortality risk for opioid users not in treatment.

Finally, limited work has been carried out in Europe on the aetiological fractions of deaths caused by illicit drug use (e.g. the proportion of all deaths due to suicide in the population that can be attributed to problem drug use). One cause of death for which the illicit-drug attributable fraction has been estimated for European countries is HIV/AIDS mortality, but other causes need to be included, and cohort studies can play an important part in this work.

Prevention, treatment and responses: several priorities

Mortality risk among drug users is heavily influenced by the drugs used and how they are consumed, with heroin being the drug most strongly associated with elevated mortality risk, and injecting the most risky form of administration. Risk of death is increased by older age, long-term use of drugs (in particular heroin), polydrug use, somatic and psychiatric co-morbidity, and not being enrolled in drug treatment (Bargagli et al., 2007; Clausen et al., 2008; Cornish et al., 2010; Degenhardt et al., 2009).

Overdoses continue to account for a high share of deaths among opioid users, and this can be addressed, as there is evidence of good practices to reduce the number of overdoses. This was detailed in the Selected Issue (EMCDDA, 2011), and is not covered in this report. More evidence has been collated recently to support prevention, and can be briefly referred to though (EMCDDA, 2013e; Frisher et al., 2012). Frisher et al. report that there are many reasons for fatal overdoses and no single measure is likely to have a significant impact by itself. Rather, there is evidence that many interventions may reduce overdose, particularly in settings where the drug user is in contact with treatment or emergency services. However, it is important to bear in mind the distinction between overdose prevention at the clinical and at the population level. At the clinical level, specific interventions are available and have been shown to be effective (e.g. pharmacological treatment). At the population level, where many drug users are not in contact with services, overdose reduction depends on behavioural change by drug users themselves (e.g. avoiding co-use of opioids and other depressant drugs). Overdose prevention is a multifaceted problem. Purely technological interventions were thought likely to have a relatively limited impact. Rather, overdose involves personal and societal issues; only when these are addressed is the level of fatal overdose in Europe likely to decrease.

Bearing this in mind, particular attention might be given to increasing the availability of take-home naloxone (EMCDDA, 2013c), and to some sub-groups of users who have particularly high all-cause and overdose-related mortality risk (Hedrich et al., 2012; Lyons et al., 2010; Merrall et al., 2010; Zlodre and Fazel, 2012). Deaths due to suicide and trauma should be considered as preventable, although these causes have received less research attention than overdoses (EMCDDA, 2011).

Finally, somatic causes may represent an increasing share in the mortality of older and former opioid users (Beynon et al., 2010; Stenbacka et al., 2010). In some countries, this is related to cohorts of drug users becoming older, and, to some extent, the success of well-conducted opioid

substitution treatment, which prevents fatal overdose. In this context, morbidity and deaths related to hepatitis, and liver disease in general, among older opioid users will become an increasing concern. Twenty or more years after becoming infected with the hepatitis C virus, these current and former drug users face cirrhosis and end-stage liver disease, which in some cases is complicated by heavy alcohol use. It is likely that the window of follow-up in most cohort studies is not long enough to capture the full burden of morbidity and death caused by liver diseases (Merrall et al., 2012; Kielland et al., 2013a, 2013b).

Improving cohort studies and their usefulness for policymaking

Increased coordination and comparability between the many cohort studies that are underway in European countries could deliver deeper insights and be of considerable value, both at national and European level. Improved cooperation and collaboration between treatment services and researchers conducting mortality studies may lead to a better understanding of the phenomenon.

Gaining a better understanding of drug-related mortality in Europe will also require the implementation of cohort studies in those Member States that have not yet done so. The insights such studies offer into mortality among problem drug users and into the effectiveness of interventions require relatively little investment. There is no need to set up expensive multisite prospective studies, with extensive questionnaires and follow-up interviews. At the simplest level, all that is required is linkage of data between treatment centres and mortality registries, which can be achieved by cooperation between the institutions responsible of the respective databases — within the scope allowed by national regulations on personal data protection. The EMCDDA helps in this task by promoting standard methodology (EMCDDA, 2012), offering technical assistance and by disseminating the findings of studies.

Conclusion

This exercise provides an updated picture of the 'old problems' such as HIV-related mortality among problem drug users and an insight into new studies. It points to continuing problems such as overdose and suicide, and problems that are growing in scale as opioid users get older, and as the effects of chronic HCV infection in particular and long-term ill-health in general are increasingly reflected in mortality statistics. The deaths among problem drug users are overwhelmingly premature and preventable, especially so for those due to overdose, suicide and trauma.

Use of opioids, in particular heroin, continues to account for the majority of deaths related to illicit drug use in Europe. Mortality cohort studies conducted in many European countries provide valuable insights into the harms related to opioids and, in particular, heroin. But as patterns of drug use continue to change, new studies are needed to monitor the effects and impact of these changes on public health. Less evidence is available from cohort studies on users of stimulants such as cocaine, amphetamine and methamphetamine. Cardiotoxicity

of cocaine and, to a lesser extent, amphetamine and methamphetamine warrants attention, as the numbers using these illicit stimulants are an order of magnitude greater than the number of opioid users, and some countries report increasing levels of use of some of these drugs. Similarly, synthetic opioids such as fentanyl have caused 'outbreaks' of overdoses in recent years (Mounteney et al., 2012), and there is increasing concern about deaths related to misuse of medicines in some European countries (Giraudon et al., 2013).

Glossary

- | **Cohort study:** a type of longitudinal study that follows a group of people (cohort) over time, with the purpose of analysing risk factors and identifying events that occur to these people (e.g. illness, death). Cohort members may be tracked by re-contacting them or by record linkage, which involves checking their status in other databases (e.g. mortality registry).
- | **Crude mortality rate:** a measure of the number of deaths (in general or due to a specific cause) in a population, scaled to the size of that population, per unit time. It is typically expressed as either deaths per 100 or 1 000 individuals per year.
- | **Drug attributable fraction:** the fraction of deaths (overall or due to specific causes) in a population to which drug use is the main or a contributing cause (e.g. the proportion of HIV/AIDS deaths that is attributable to injecting drug use).
- | **Drug-induced deaths:** defined by the EMCDDA as those of 'people who die directly due to use of illegal substances, although these often occur in combination with other substances such as alcohol or psychoactive medicines. These deaths generally occur shortly after the consumption of the substance.' These deaths are also known as overdoses or poisonings.
- | **Problem drug use:** the EMCDDA operationally defines problem drug use as 'injecting drug use or long-duration/regular use of opioids, cocaine and/or amphetamines'. Most cohort studies on drug users are conducted among problem drug users, and in particular among problem opioid users. The problem drug use EMCDDA key indicator was recently revised, and now focuses on a slightly broader concept, high-risk drug use.
- | **Standardised mortality rate:** a crude mortality rate that has been adjusted for differences in age composition between the study population (here, drug users) and a standard population. The EMCDDA recommends using the European standard population to facilitate comparisons across studies.
- | **Standardised mortality ratio (SMR):** a measure of the 'excess risk of mortality' of a specific group (in this report, drug users), compared with their peers of same age and gender in the general population. It is calculated as the observed number of deaths in the study, divided by the number of deaths that would be expected, based on the age and sex-specific mortality rates in the general population (e.g. an SMR of 15 means that the drug users in the study have a 15 times higher mortality than their peers of the same age and gender in the general population). The EMCDDA recommends using the European standard population as a reference to facilitate comparisons.
- | **Survival analysis:** a form of time-to-event analysis in which the event considered is the death of participants in the study, and time is measured from the participants' enrolment in the study (e.g. 90 % survival after five years).

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