FINAL REPORT

Implementation, follow-up and analysis of cohort studies on mortality among drug users in European Union member States

EMCDDA project CT.97.EP.03

Department of Epidemiology

Lazio Region Health Authority: **Carlo A Perucci**

Marina Davoli

Anna Maria Bargagli

EMCDDA: **Julian Vicente**

Richard Hartnoll

Key participants: **Daniele Risser (Austria)**

Lene Haastrup (Denmark)

Erkki Vuori (Finland)

Axel Heinemann (Germany)

George Kanatas (Greece)

Marcel Buster (The Netherlands)

Joseph Barry (Ireland)

Filipa Ferraz de Oliveira (Portugal)

Teresa Brugal (Spain)

Daniel Svensson (Sweden)

Matthew Hickman (United Kingdom)

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Contact details

Department of Epidemiology
Lazio Region Health Authority
Via S. Costanza, 53
00198 Rome
Italy
Phone: + 39 6 51686493
Fax: + 39 6 51686463
E mail: toss.oer@sirio.regione.lazio.it

European Monitoring Centre for Drugs and Drug Addiction
Ruaz Cruz Santa Apolonia 23/25
1149-045 Lisboa
Portugal
Phone: + 351 1 811 3023
Fax: + 351 1 813 7943
http://www.emcdda.org

Further copies can be obtained from the EMCDDA at the above address.

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Executive summary

Drug abuse is known to have serious health consequences. The health effects of drug abuse could be measured in terms of occurrence of diseases or disabilities, either as incidence or prevalence. For the purposes of comparison between countries and over time, studies on incidence and prevalence of diseases among drug users are difficult to conduct due to the low reliability of morbidity measures. Overall and cause-specific mortality can be considered an indicator of health effects of drug abuse. Data on drug related deaths are often used to measure mortality among drug users. These data, on top of problems in comparability across countries, represent only part of the mortality attributable to drug addiction. Longitudinal studies of drug users can be used to measure overall and cause-specific mortality. In order to develop an ongoing monitoring system of mortality of drug addicts across Europe, the EMCDDA commissioned two projects in 1997 and 1998, co-ordinated by the Department of Epidemiology of Lazio Region Health Authority.

All Member States of the European Union were informed, through the National Focal Points, about the aim and the methodological aspects of the project. Most of countries expressed strong interest and identified experts and research groups to be involved in the project.

During the earlier phase of the project a stable work group including experts from each participating country and the EMCDDA was established for collaborating in the development and implementation of the standardised methodology (see Annex 1 for participating countries and study sites).

Moreover, the EMCDDA also contacted experts from Central and Eastern European countries involved in the Phare project on Drug Information System, to investigate the availability of data required to carry out a cohort mortality study on drug users. Most of the Central and Eastern European countries provided the information required to check the feasibility for carrying out a cohort study and some of them declared their interest in future involvement.

Experts from Bulgaria and Romania were attending a meeting organised in the framework of the EMCDDA project in 1998 and expressed their strong interest in taking part to further stages.

The project has been developed according to the following phases.

A. identification of partners among Member States of the European Union who were conducting or had advanced plan to carry out a cohort study on mortality of drug users:
- Austria
- Denmark
- Finland
- Germany

- Greece
- Ireland
- Italy
- The Netherlands
- Portugal
- Spain
- Sweden
- United Kingdom

B. Identification in each country of research groups with experience in planning and conducting cohort studies.
C. Collection and revision of published studies on mortality of drug users that have been undertaken in Europe but also in other countries and critical revision of methods used and results obtained from the selected studies.
D. Draft of a standardised protocol to assess overall and cause specific mortality rates among drug users.
E. Evaluation of the feasibility of implementing the standardised methodology in different European countries in terms of:
  - accessibility to health records of drug users
  - availability of the sources for ascertaining vital status and causes of death;
F. Draft of the final version of the standardised protocol;
G. Identification in each participating country of:
  - study site
  - study population
  - treatment centres involved in the cohort enrolment;
H. Pooled comparative analysis of available retrospective cohorts.

State of the art of the project

All European countries participating to the project are ready to enrol and follow-up prospectively a cohort of drug users recruited in treatment centres according to the standardised protocol developed during the project.

The following study sites have access to a retrospective cohort or already started the enrolment of the cohort:
- Rome
- Barcelona
- Lisbon
- Greece

- Hamburg
- Denmark
- Amsterdam
- Sweden
- England
- Dublin

The pooled comparative analysis was possible only for Rome, Barcelona, Sweden and Amsterdam. Comparability of results was hampered by the heterogeneity of periods of enrolment and follow-up, setting and study population and classification of causes of death. The necessary information on severity of drug use and socio-demographic characteristics were available only for Rome and Barcelona. A Poisson regression analysis of determinants of overall mortality was carried out for the two latter cohorts.

Conclusions

The feasibility study has shown that:

➢ Retrospective analysis of mortality data is worthwhile in those countries where mortality rates have never been estimated, but only when access to the necessary information is easily available. The results of the pooled comparative analysis were useful to define the criteria needed for comparability of data.

➢ Prospective mortality cohort studies are both necessary and possible in all countries participating to the study. Agreement has been reached regarding the standardised protocol: enrolment and follow-up procedures, methods and dataset structure

1. Preface

The overall objective of the project is to promote and co-ordinate the setting up of cohorts of drug users recruited through treatment centres, in order to monitor the mortality risk of problematic drug users in Europe, taking into account the different pattern of drug use.

This report presents the results of two projects commissioned in 1997 and 1998 by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and carried out by the Department of Epidemiology of Lazio Region Health Authority, in co-operation with a team of key experts from European Union member States.

2. Background and rationale

Drug abuse is now globally widespread, a serious public health problem in Western Europe and an increasing phenomenon in Eastern Europe as well. It is widely recognised that there are considerable methodological difficulties in assessing the extent and consequences of drug abuse; nevertheless, it is generally accepted that the abuse of drugs can have serious implications for individual and public health. Drug abuse appears to be responsible of physical and psychological disorders causing disability and of a high proportion of deaths in particular in the young population (1-6).

Mortality can be considered an indicator of health effects of different exposures, given its high level of reliability and validity. This is particularly true for overall mortality, while, when cause-specific mortality is considered, temporal and geographical heterogeneity in methods used to classify causes of death must be taken into account.

In most European countries data on drug-related deaths (acute or drug induced) are commonly used for describing mortality of drug addicts, but many methodological problems impair the use of this indicator. Different sources of data on drug-related deaths are actually available across and within countries, such as public health authorities, the police or judiciary authorities. The main limitation of this indicator is the lack of both consensus regarding the definition of "drug related death" and the method of classification. Although most European countries have national and/or regional mortality registers where deaths are coded on the basis of the International Classification of Diseases (ICD), there is a wide heterogeneity of "cause" of death definition and, consequently, of the codes applied. There is no code of the International Classification of Diseases specific for "drug use"; therefore drug related deaths can be classified among mental disorders (subheading: substance dependence) or among injury and poisoning. Therefore, the figures on the extent and pattern of drug-related deaths across and within countries are difficult to be compared.

Despite these considerations, estimates of mortality rates among drug users are produced as the number of drug-related deaths over the general population or the "observed" population of drug addicts.

This kind of indicator might be heavily biased, both in geographical and temporal comparisons, by different factors other than the heterogeneity and/or validity of drug-related death definition, such as:

- heterogeneity of occurrence of drug use;
- heterogeneity of determinants of health of drug addicts;
- heterogeneity of effectiveness and/or availability of health services.

Moreover, another limitation of using drug-related deaths to approximate mortality of drug addicts, arises from the evidence that drug users do actually die also from other causes.

The most valid study design to measure the actual mortality rate among drug addicts is a longitudinal cohort study of drug users followed-up over time.

A narrative literature review of published studies on mortality among drug addicts was carried out in the framework of the EMCDDA cohort mortality project promoted in 1997.

Longitudinal studies have been carried out in some European countries, all of them showing high mortality rates among drug addicts. Comparability of these studies only on the basis of published data is difficult, because the information necessary to identify the characteristics of the cohort enrolled in each study is often lacking. For those studies with this information available, a wide heterogeneity of the enrolment criteria of drug users in the studies (type of drug used, severity of use, **….**), of the follow-up procedures (vital status and cause of death ascertaiment and coding) and of the methods of data-analysis is observed, hampering geographical and temporal comparisons.

A standardised instrument for monitoring overall and cause-specific mortality among drug addicts could ensure comparability of results across and within countries. Reliable estimates of mortality rates among drug addicts in different countries and time periods might help to understand the possible role of the social context and of different intervention policies.

3. Objectives

The overall objective of the project is to implement a standardised methodology for measuring and comparing overall and cause-specific mortality rates among drug users in member States of European Union.

The specific objectives are:

- to identify in each participating country:
  - the study site
  - treatment centres involved in the cohort enrolment
  - the study population
- to carry out a retrospective mortality study in EU member States where cohorts of drug users have been already enrolled and followed-up in order to analyse:
  - temporal trend of mortality rates among drug users recruited at treatment centres
  - possible determinants of mortality risk

4. Overall Output of the Project

4.1 Literature review

Published studies on mortality among drug users were identified through computerised searches (MEDALARS databases) from January 1980 till December 1996, using the subject headings of: *narcotic dependence or substance abuse/mortality or overdose/mortality; epidemiology.*

Moreover, a handsearch of the studies published before 1980 has been conducted following the references in the papers selected through the computerised searches. The latter method have not yield an exhaustive list of papers on mortality of drug users but allowed for tracing the most quoted and significant papers published between 1965 and 1979. Searches were limited to English language publications.

Out of 340 papers that were identified, 66 have been selected to be reviewed because of their relevance for the project (see Annex 2).

The results of the searches are summarised in the following table:

Number of papers collected		
	European countries	**Other countries**
Longitudinal studies	24	9
Cross-sectional studies	14	6
Case-control studies	1	1
Letters, editorials and reports	7	4

A total of 20 papers dealing with studies carried out in countries outside Europe have been included because of their particular significance. Letters, editorials and reports have been also included because of their contribute in clarifying some important issues related to drug users mortality. The results of the literature review (critical revision of each paper selected and for longitudinal studies a

more detailed description of methods used to ascertain vital status and causes of death) are described in the final report prepared in 1997 the Department Epidemiology of the Lazio Regional Health Authority and delivered to the EMCDDA.

4.2   Feasibility study

Objectives

I.   To define the type of drug addict to be enrolled in the prospective cohort and the overall expected characteristics of the study population;

II.   to define the recruitment site/s and the possibility of access to health records of drug users;

III. to investigate the availability of birth and death registers, or alternative ways of ascertaining vital status of residents and their reliability and accessibility;

IV. to develop a standard basic data record structure to be produced by each centre.

Results and comments

The preliminary phase of the feasibility study mainly dealt with the definition of the study population and assessment of enrolment procedures. In particular the possibility of including both drug addicts in treatment and also outside treatment was considered. In all countries the most feasible option was to enrol drug addicts entering treatment facilities, because of identifiers of each individual enrolled are necessary to assess vital status and ascertain cause of death. Moreover, drug addicts seeking treatment, even though not representative of the overall population of drug addicts, represent the most problematic part of this population where most of serious health effects actually develop.

The feasibility study showed that in most countries the available study population will be mainly constituted by addicts entering treatment centres even though with some differences regarding both type of substance abused and treatments undertaken (for details see Local Reports). In Sweden, the proportion of drug addicts attending Outpatient Public Treatment Centres using opiates as main drug is about 20% while 25% are amphetamines injectors. Moreover, in Finland opiates users generally do not undertaken methadone treatment while in The Netherlands (Amsterdam), Ireland (Dublin) and Germany (Hamburg) the study population will include only opiates addicts entering methadone programmes.

It was established to enrol all drug addicts entering treatment services specifying the main substance of dependence, defined as "primary drug". Moreover, only residents will be recruited because of in some countries there are problems in tracing migrants.

It was considered that at present most drug addicts entering treatment in European countries are opiates users. Non opiates users (cocaine, amphetamines, cannabis etc.) entering treatment constitute a very selected group, and mortality figures derived from this sub-population may be highly biased and non representative of the source population. Moreover, because of the problem of

statistical power in analysing mortality rates of small population must be taken into account, it was suggest to carry out local analysis as well as a comparative analysis for both opiates and non-opiates users where they do not represent a selected groups.

Concerning the definition of study population, it was also established to recruit both subjects already in treatment at the moment of the beginning of the prospective study (prevalent cases) and new entrants (incident cases). These two groups will be considered separately in the final comparative analysis.

Data availability and follow-up procedures

The availability and accessibility to information on drug addicts and sources of data for ascertaining vital status and causes of death were checked in the early phase of the project through a specific questionnaire and discussed with the experts from participating countries.

Table 1 (see Annex 3) describes the availability of the sources of data to ascertain vital status (on national and local level) and their accessibility.

4.3 Standardised protocol

This protocol was developed taking into account the results of the feasibility study and according to the suggestions derived from the discussion with experts from each country on the following issues:

1. Definition of the study population
2. Data collection
3. Follow-up procedures
4. Cause of death determination and coding
5. Data analysis

A. Objectives

a. To estimate overall and cause-specific mortality among drug addicts recruited in treatment centres
b. To analyse temporal trends in overall and cause specific mortality
c. To compare mortality among drug addicts with mortality of the general population
c. To compare mortality of drug addicts across countries

B. Definition of cohort

Both retrospective (where available) and prospective cohort studies will be carried out.

The study population will include "incident" and "prevalent" individuals with respect to treatment, enrolled and followed up at variable points in time (*dynamic cohort*). Incident subjects are those starting treatment for the first time or starting a new treatment; prevalent individuals are those already in treatment at the moment of enrolment.

C. Study population

The study population will consist of a cohort of drug addicts (by injection or other routes of administration) entering a treatment centre at least once during the study period. This definition of "case" is according to the EMCDDA-Pompidou Group draft protocol that will be implemented in all EU countries. This protocol is compatible with the widely used "Drug treatment reporting systems and the first treatment demand indicator" of the Pompidou Group.

D. Inclusion criteria for the enrolment

Inclusion criteria to enrol subjects into the cohort are the following:

a) entering treatment centre during the defined recruitment period

b) availability of data for ascertaining vital status

- name and surname (or other identifiers such as social security number)
- date and place of birth

c) availability of information on

- place of residence
- date of entry into treatment centres.

For each individual the date on which observation begins will correspond to the date of entry treatment centre: if a subject applies to different centres or refers to a centre more than once during the recruitment period, the date of entry into the study will correspond to the less recent one (when he/she refers to the treatment centre for the first time during the study period).

The date of entry treatment centres will have also to be obtained to distinguish "incident" and "prevalent" cases at the beginning of the study (at the moment of enrolment).

All centres will provide data describing characteristics of the original study population together with the reasons for exclusion.

E. Confidentiality

The study does not involve data collection from drug addicts themselves. Only information already available on clinical records will be used. Identifiers are only necessary at local level to ascertain vital status. The protocol will be cleared by the appropriate institutional ethical committee of the study site involved.

Each centre will have to adopt specific and effective procedures to ensure the absolute confidentiality of the information gathered. The data on drug users enrolled will have to be managed by a limited number of people, all of whom will be bound by official secrecy. All data analysis and reporting will be done without identification of any individual's name and drug use status.

F. Data collection

A standardised data form will be developed for gathering information from patient records available at the participating treatment centres in order to produce a standard data record structure.

The following information will be gathered at the moment of entry into the cohort for each drug addict:

- data necessary to assess vital status:
    - name and surname or other identifiers such as social security number
    - date and place of birth
- place of residence
- gender
- legal nationality
- date of entry into treatment centre
- type of drug used (the one that currently predominantly maintains the addiction)
- route of administration of primary drug
- frequency of use of primary drug
- other drugs used
- marital status
- educational level
- employment status
- major occupation
- age at first injection (specify: ever/currently)
- first treatment ever (yes/no)
- type of initial treatment assigned
- data on specific laboratory test (HIV, HBSAg, HCV) performed.
- date of last contact with treatment centre
- vital status
- date of death
- cause of death

G. Follow-up

Each centre will be responsible of ascertaining vital status and cause of death.

Follow-up will start for each drug addict enrolled from the time of entry into the cohort (the date of entry into treatment centre) to the end of the study period or to the date of death. There are different options to treat losses to follow-up in the analysis. The more conservative approach consisting of assuming losses to follow-up alive at the end of the study period will be adopted.

The vital status will be ascertained through the population registers of the last municipality of residence at the end of the follow up; if population registers will not be available, different sources of vital status data will be used i.e. national, regional and local mortality registers (in this latter case all

subjects not found are supposed to be alive). However, for each country the characteristics of the source and the extent of accuracy of vital status data will have to be described.

The validity of a cohort study depends on complete ascertaiment of the events of interest and correct computation of the population at risk. Major accuracy should be put in tracing subjects especially as regards migrant drug users and in limiting the proportion of losses to follow up to a maximum of 5% of the subjects enrolled.

Cause of death will be ascertained through record linkage with general population mortality files, if available, or through death certificate revision. A 90%-95% cause of death determination rate in the study population is a desiderable target.

To compare cause specific mortality among drug users in different countries, coding of the cause of death should be made according to the last revision of the International Classification of Diseases (ICD). Causes of death will be classified by a nosologist trained in the rules specified by the ICD volumes. Taking into account that some countries are changing from ICD IX to ICD X, conversion tables will be developed to avoid heterogeneity in coding causes of death across countries.

H. Data Analysis

The quality and completeness of each form will have to be checked before the data are entered in a database (the standard structure of the database will be agreed taking into account the essential data to be collected in each centre) for the purpose of correcting errors where possible and of verifying any data not supplied.

Data analysis will include a number of analytic strategies. One aspect of analysis will involve calculation of person-years at risk of dying; each subject will be considered from the date of first enrolment through the end of the study period, or to the date of death or loss to follow up.

- Local analysis

    Direct standardised rates will be calculated for each cohort using as a standard the local population truncated at 15-59 years.

    Standardised Mortality Ratios (SMRs) and their 95% confidence intervals will be used to compare the mortality experience of drug users with that of the national population for the same age, sex and period. The expected numbers of deaths will be calculated using sex and age specific local mortality rates.

- Pooled analysis

    Direct standardised rates will be calculated for each cohort using as a standard the European population truncated at 15-59 years (or the person-years at risk of the pooled cohort) for making temporal and geographical comparisons.

    The analysis of the heterogeneity of mortality could be conducted by using Poisson Regression and including as covariates both individual data and geographical indicators.

5. Local Reports

5.1 England

In England the National Treatment Outcome Research Study (NTORS) cohort is eligible for inclusion in the retrospective and prospective phase of the project.

The NTORS is a longitudinal study run by the National Addiction Centre involving 1075 patients, 90% are opiates users, recruited on entry into four treatment modalities: inpatient Drug Dependency Units (DDU), Residential Rehabilitation Units, Specialist Drug Agencies practising methadone maintenance and reduction treatments. The follow up period begun in 1995. This cohort was enrolled for evaluating treatments considering different outcomes for which an active follow up is necessary but mortality is also included.

NTORS has flagged the enrolled subjects with the Office of National Statistics and therefore will receive notices of death and of causes mentioned on the death certificates.

Characteristics of the study population:

1075 patients entered into four treatment modalities from February to July 1995

122 from 8 inpatient DDUs

286 from 15 residential rehabilitation units

458 from 16 specialist agencies practising methadone maintenance treatment

209 from 15 specialist agencies practising methadone reduction

90% heroin users

74% males

mean age 29.3 (SD= 6.7)

mean duration of heroin use 9.0 years

80% with at least one previous treatment contact.

After 1 year 16 deaths (1.5%) identified.

After 3 year 36 deaths identified.

Missing information with regard to the standardised protocol

- Educational status
- Results of HBV, HBC, HIV tests

They are exploring the feasibility of setting up another retrospective mortality cohort of heroin users under 27 years of age in treatment in 1996.

5.2 The Netherlands (Amsterdam)

One possible source of information to select the study population is the Central Methadone Register (CMR). CMR registers all clients of methadone programmes (mainly methadone maintenance programs) in Amsterdam, data are gathered from:

- Municipal Health Service (MHS)
- GPs (only a few information available)
- Consultation Office for Alcohol and Drugs (CAD) in Amsterdam
- methadone administration at police stations.

CMR data are useful for both retrospective and prospective mortality studies. For historical cohort studies however only basic information concerning the characteristics of the study population is available. Only for subjects entering Municipal Health Service more detailed information are available then only subjects entering MHS could be included in the prospective cohort. It is possible to access the Mortality Registry and it maybe possible to access the Population Registry.

Amsterdam has begun in 1985 enrolment of a cohort of opiates users entering methadone programmes, with annual follow-up. By 1996 the cohort had approx. 5,000 subjects.

The study population is limited to opiates users who are born in the Netherlands, Morocco, Turkey, Surinam or Dutch Antilles (the major ethnic minorities) who have an address in Amsterdam. Opiates users born in other countries and drug users living in other Dutch towns are excluded.

The Amsterdam methadone programmes are differentiated. Opiate users who want to reduce or stop their illicit drugs use are treated with methadone at the Jellinek. Here, often short-term methadone treatment with reductions schedules is offered. Opiate users who are socially stabilised; stable housing, regular income and health insurance are treated at their General Practitioner. Here, they get methadone prescriptions every one or two weeks. Opiate users who can not control their drug (and methadone) use or clients with behavioural problems are treated at the Municipal Health Service (MHS). In general MHS clients are not willing or able to stop their drug use completely and harm reduction is a major goal.

Besides heroin, cocaine is a widely used drug among clients in methadone treatment. The majority of the opiate users (60% of the MHS clients at 1991) does not inject their drugs. Among Surinam opiate users (largest ethnic minority) injecting drug use is rare. During the study-period the population of opiate users in methadone treatment is getting. The average age at 1992 was 29 years and 36 at 1996. Time since first treatment is increasing rapidly as well.

Table 1: Description of the study population

Year of study	Proportion ethnic minority	Proportion Female	Mean Age	Proportion At GP	Proportion at Jellinek	Proportion at MHS	Mean # years since first contact	# of opiate users (study-population)
1985	0.33	0.25	29.4	0.37	0.01	0.77	2.7	2360
1986	0.33	0.24	30.3	0.42	0.00	0.73	3.4	2335
1987	0.32	0.24	31.1	0.44	0.00	0.74	4.1	2326
1988	0.32	0.23	31.8	0.40	0.00	0.73	4.9	2327
1989	0.32	0.23	32.6	0.37	0.05	0.72	5.5	2323
1990	0.31	0.23	33.4	0.40	0.05	0.69	6.2	2268
1991	0.31	0.22	34.1	0.36	0.11	0.68	6.8	2335
1992	0.31	0.22	34.7	0.33	0.13	0.68	7.4	2317
1993	0.30	0.22	35.7	0.31	0.12	0.68	8.0	2266
1994	0.31	0.22	36.4	0.31	0.11	0.69	8.6	2225
1995	0.31	0.22	37.3	0.33	0.11	0.68	9.2	2218
1996	0.31	0.23	38.1	0.37	0.13	0.65	9.8	2191
Total	0.31	0.23	33.7	0.37	0.07	0.70	6.3	27491

Observation time

Annually, observation time is defined as the period from the first methadone prescription of that particular year until the end of the calendar-year. In case of death, observation-time was censored at the date of death. During the 12 years period 4906 individual opiate users collected 23,557 person-years of observation.

Data source

The data of the study population are extracted from the Central Methadone Register (CMR). This register is constructed to avoid prescription of methadone at multiple locations to the same person during the same period. All clients who are registered at the Central Methadone Register have a unique identification number and all their methadone prescriptions are registered centrally. This way it is easy to determine whether clients are in treatment or not. However, because this register is developed to prevent double counting, only information of the methadone prescriptions and information to identify the client has been included. Additional information about the clients can not be given yet.

Cases

Information of deaths is extracted from the population register of Amsterdam, the hospital project of the municipal health service and coroners. The hospital project co-ordinates hospital admissions of opiate users in Amsterdam, the coroners inspect all deaths due to a overdose of drugs. 304 Opiate users died during observation-time, 60 of them died due to an overdose.

Mortality rates

Table 2 shows the observation time, number of deaths and mortality rates per year. Mortality rates vary form 6.8 (1986) to 19.5 (1994) and are increasing over time. Of the total mortality 20% is due to a drug overdose.

Table 2: Description of mortality and observation-time during the study period

Year of study	Person-years observation time	# death during observation-time	# Overdose deaths	Mortality rate / 1,000 py
1985	1942.54	15	8	7.7
1986	1921.13	13	4	6.8
1987	1952.94	19	7	9.7
1988	1965	26	7	13.2
1989	1992.67	12	4	6.0
1990	1963.62	24	6	12.2
1991	1988.23	34	8	17.1
1992	2028.32	29	5	14.3
1993	1993.06	33	2	16.6
1994	1932.23	37	5	19.1
1995	1965.63	28	1	14.2
1996	1912.55	34	3	17.8
Total	23557.93	304	60	12.9

Mortality rates over time and adjustment for age

Figure 1 shows the relative risks over time compared to the incidence rate of 1985. An increasing mortality rate can be observed. However, adjustment for age is necessary. Crude relative risks and age adjusted relative risks are shown. When the year of study is entered into the model as a continuous variable the Poisson-regression analysis shows an average annual increase of mortality-rate of 8.3%. The age adjusted annual increase is 5.6% (rate ratio: 1.056; 95% CI 1.019-1.095).

Figure 1: The increase of the mortality rate, crude and adjusted for age
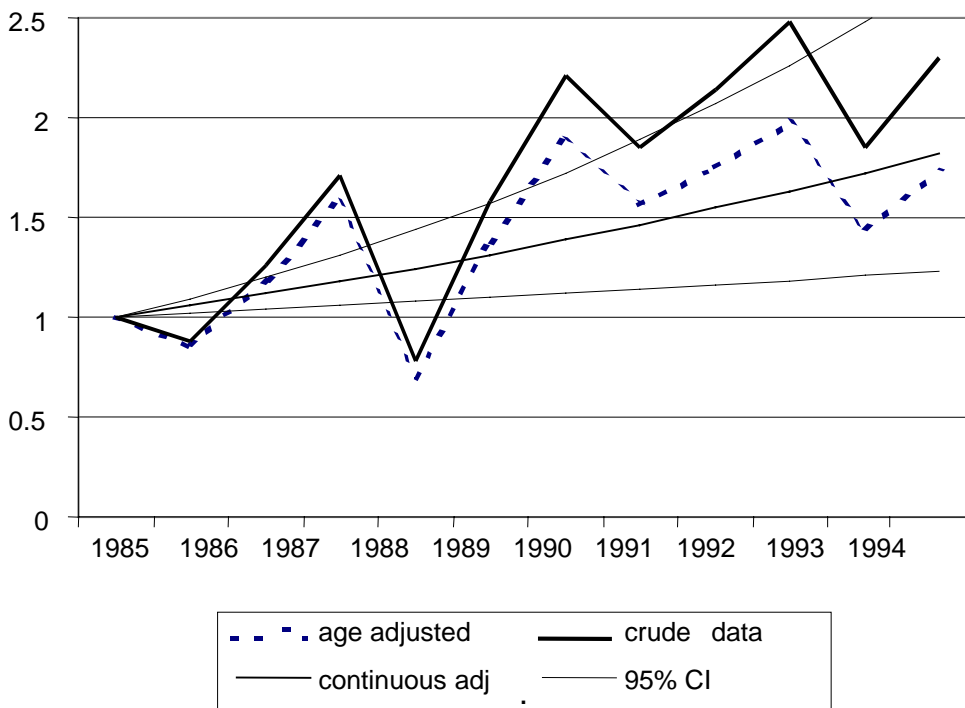
Comments

The Central Methadone Register is developed to prevent double prescriptions of methadone and not to perform mortality studies. Within the register all methadone prescriptions and all people in treatment (receiving methadone) are known exactly. Individuals can be followed during treatment. During treatment, every client belongs to the study population of opiate users in Amsterdam by definition; all of them are in Amsterdam and all of them are using opiates (at least methadone). After treatment however, the risk of misclassification is larger, opiate users can migrate from Amsterdam or stop using drugs.

To reduce the misclassification bias only a selection of the study population is studied. Foreign opiate users and opiate users not officially living in Amsterdam are presumed to be more likely to migrate and are excluded from the study. Furthermore, the possible bias is reduced by a limitation of the period of follow up after treatment. Annually a new cohort is constructed. When an individual is incorrectly classified as an opiate user in Amsterdam, only a short period of time would be incorrectly counted as observation time. Ideally the population would be linked with the register of population of Amsterdam. This may be realised in the future. However, this design assures that all members of the study population are Amsterdam opiate users during the year of study. A dynamic cohort with an approximately constant size but changing individuals is created. This dynamic cohort can be analysed with the Poisson Regression.

Classical cohort studies are describing selected groups of individuals who are defined as opiate users at the start of the study period. Information about the mortality risks and survival probabilities of the

cohort can be calculated. Questions about the proportion that dies and the proportion that reaches stable abstinence after a certain time-period can be answered. However, it does not answer questions about mortality-rates among the actual (dynamic) population of opiate users.

This design shows the mortality rate within a defined population of opiate users. The results show the mortality rates of the dynamic population of opiate users who participate or recently participated in methadone programmes. However, questions about the proportion of individuals dying or reaching stable abstinence after a certain time-period can not be answered. A monitoring study and a classical cohort study give answer to different questions.

This design is more flexible than a classically designed cohort study. Annually, the study can be extended by adding more (independent) variables or treatment centres. Parallel studies of opiate users of other countries or people using other kinds of drugs can be performed and compared.

Within classical cohort design, individuals who participated in treatment once will stay a member of the cohort. To produce mortality figures annually, data of every participant should be checked every year. They will be labelled as opiate users, even if they have left treatment for years. Ethically, a design in which treatment participants are followed during treatment and a short period after treatment is preferable. Censoring observation time after the last contact with the treatment centre could lead to an underestimation of the mortality rate. For example, when an opiate user is admitted at a hospital with a terminal disease.

This study is performed within the available ongoing registration of the methadone programmes. These data can be generated annually and in the near future it will be possible to add more variables to the majority of the treatment participants. The national mortality register can provide (aggregated) data about the causes of mortality. A national register of drug users (not only opiate users) participating in treatment (LADIS) contains more background information of the individuals. This register however, is anonymous, and (at the moment) mortality data can not be linked to it.

5.3 Spain (Barcelona)

In Barcelona about 1,800 subjects start treatment yearly. Methadone maintenance, treatment with other agonists and drug-free programmes are mainly offered. Treatment centres collect data according to the Pompidou protocol.

The cohort enrolled from 1992 includes all patients residing and censured in the city of Barcelona, who begin treatment for addiction of illegal drugs (heroin, cocaine, ecstasy ..) in specialised outpatients centres in Barcelona. In 1997 the study population was composed of 3,500 subjects from treatment centres and 700 from prisons. Of this population, 80% were opiate users, 50% injectors, 25% HIV positive, 25% alcohol consumers.

All variables mentioned in the standard protocol are available except for marital status and employment. It is possible to access to Population and Mortality Registries.

5.4 Italy (Rome)

A retrospective cohort was enrolled between 1980 and 1991, including drug users attending two public treatment centres (PTCs) in Rome (n= 4,660, 95% heroin users), and followed-up until the end of 1992. This cohort was expanded using survivors as of 1992 as well as all subjects attending all treatment centres in the Lazio Region between 1992 and 1995 (n= 16,200). Follow up was continued until May 1997.

A preliminary analysis has been carried out of data from the cohort including all drug addicts entering treatment between 1980 and 1995 in Rome and followed-up through May 1997 (N=11,450). A total of 1,734 (15%) deaths were observed during the study period. Overall mortality constantly increased between 1980 and 1993 from 7.6/1000 to 29.4/1000, then levelled off (Figure 2). The major cause of death was overdose up to 1988-1989 and AIDS thereafter. AIDS mortality rates increased up to 1992-1993 (14.2/1000) remaining steady in the following years.

Figure 2 - Mortality among drug users in Rome, 1980-97
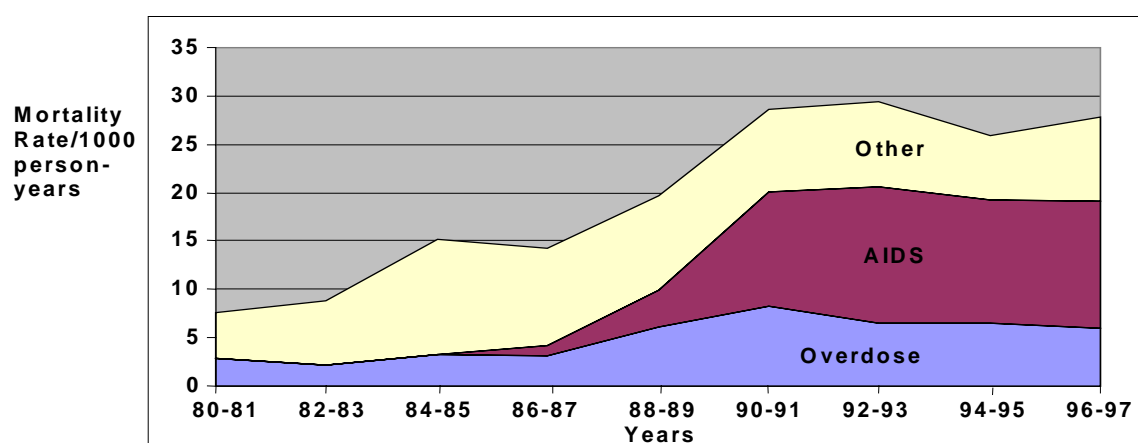
Women showed higher mortality rates from AIDS than men with the strongest difference in the more recent years. Overdose mortality rates were slightly higher among men, with no significant time changes.

In the framework of a national study (VEdeTTE) aimed to evaluate the effectiveness of treatments for heroin dependence offered in PTCs, a prospective cohort is being enrolled as from October 1998 including subjects attending 21 local PTCs. Enrolment will be continued for 18 months while follow up will be completed in two years. The expected dimension of the cohort is of 5,000 subjects. Detailed information will be gathered on entry about socio-demographic characteristics, pattern of use, health status, and during the study period about treatments received. All variables required by the standardised protocol are available, and access to Population and to Mortality Registries is possible.

5.5 Sweden

The source of information to select the study population is the Hospital Discharge Register (HDR).

All inpatients undergoing public treatment have their diagnosis entered in a database. This is also the case with treatment at "narcotic clinics", sorting under the psychiatric domain of the hospital treatment system.

Only a part of all drug-related treatments are done within the public hospital. The bulk of such treatment is done at private or public institution (Therapeutic Communities) from which there are a little data available. However, in a number a cases, the treatment at TCs does require a detoxification at a hospital. This refers to the absolute majority of the more severe cases, involving IVDUs and /or opiates.

A major problem is that only a few variables are registered in HDR and no data are available on drug use severity (such as route and frequency of administration of primary drug, other drugs used, age at first use, etc.): more detailed information would be available from Therapeutic Community but the involvement in the prospective phase of this kind of centres has still to be checked. Both Population and Mortality Registries are accessible.

5.6 Finland

On the basis of mortality data, 4,000-8,000 drug misusers have been estimated (misuse is defined as: intoxicating or recreational use of mind-altering drugs, forbidden by international conventions on narcotic and psychoactive drugs). The estimated number of people having ever misused drugs intravenously is 2,000-10,000, on the basis of the number of hepatitis C-infected persons.

Comprehensive post-mortem investigation system is available. Data are available on the number of all deaths with toxicological evidence of drug misuse among forensically examined cases of sudden, unexpected deaths.

A retrospective cohort of 8,000 alcohol and drug (cannabinoids, amphetamines, cocaine, opiates) misusers entering treatment in 1 clinic in Helsinki (Kettutie clinic) has been enrolled between 1990 and 1995, and followed-up. As of 31 May 1997, 299 deaths have been registered (3.7%). Kettutie clinic does not apply methadone treatment. The number of patients having methadone treatment is less than 50 in the whole Finland. It is not possible to distinguish the substance of abuse.

Within the framework of the planned central system for monitoring of drug abuse treatments, it will be possible to recruit a prospective cohort but only overall mortality can be analysed.

The main problem in Finland is the linkage of different sources of information: a permission must be obtained for linking different registers, moreover which pieces of information are being used have to be specified.

It is not possible to ascertain vital status of each subject but an agreement with the National Health Institute has been negotiated for obtaining a larger permission.

5.7 Germany (Hamburg)

In Germany 100,000-150,000 opiates users have been estimated, of which 25,000-30,000 in methadone programmes. In Hamburg 10,000-15,000 opiates users have been estimated. Access to data on outpatients on methadone treatment is possible through Municipal Health Services.

A retrospective cohort of 2,885 opiates users on methadone treatment has been enrolled between 1990 and 1996 in Hamburg at all local treatment institutions (mainly specialised outpatient departments; other institutions are: hospitals, GPs offering methadone). 142 deaths were registered at Forensic Institute until the end of 1996.

Using of Mortality Registry for ascertaining vital status (for the EMCDDA project) would be desirable for defining the number of non-registered cases in forensic statistics.

On September 1998 the Data Protection Agency in Hamburg gave the permission for using data about the enrolled cohort for the mortality project.

Enrolment of a prospective cohort of outpatients on methadone maintenance is already possible (about 400 subjects per year), while subjects on methadone detoxification treatment can be enrolled starting in a few months time (200 subjects per year).

All variables of the standardised protocol are available, except for place of birth, place of residence, major occupation and first treatment ever. Access is possible to both Population and Mortality registries.

5.8 Ireland (Dublin)

In Dublin 10,000-12,000 drug abusers have been estimated through capture-recapture method, using methadone list, police's register and general hospitals' data.

A retrospective cohort of 6,000 subjects, entrants on the methadone treatment from 1994 to the end of 1997, has been enrolled. For about 2/3 (4,000 people) receiving methadone in clinics fairly complete data on socio-demographic and drug use characteristics are available; less extensive information are available for subjects treated exclusively by GPs (data can be obtained for people who have died through a questionnaire). Health care centres involved in the enrolment:

1. Addiction centres: specialised centres where methadone is prescribed and dispensed
2. Satellite Clinics: sub-specialist centres where methadone is prescribed only
3. General Practice: setting where the health care treatment takes place within primary care physicians office

A prospective cohort of all methadone treatment subjects is also possible.

All required variable are available from clinical records.

Vital status can be ascertained only through the Mortality registry. Population registry is not accessible.

5.9 Denmark

The source of information to select the study population will be the National Statistics of drug abusers undergoing treatment, (IUS). During the last few years there have been great changes in the treatment available to drug abusers. The treatment sector has been allocated considerably more resources and new legislation on this area has clearly placed the responsibility for all types of treatment of drug abusers with the counties. The county drug-abuse treatment centres - and, in some areas, municipal centres - now send clients to out-patient treatment, in-patient treatment, methadone-supported treatment and drug-free treatment, usually at both private and public institutions.

In addition, new in-service training opportunities and increased support for research have supported the development of treatment. As of 1 January 1996, a new national register of drug abusers in treatment was established by the National Board of Health in co-operation with the Department of Psychiatric Demography at the Psychiatric Hospital in Aarhus, the Association of County Councils in Denmark, the Ministry of Health and the treatment centres. In the first phase it will be possible to see the numbers of persons undergoing treatment for drug abuse with a description of their situation and characteristics when they enter treatment. In a later phase it is intended that the register should be collated with other information, gradually providing more in-depth knowledge of the scope and development of the problems.

The register includes all persons that the county/municipal centres have sent for treatment for drug abuse irrespective of whether the typology of treatment is out-patient, day or residential in-patient, methadone-supported or drug-free.

This first report from the new register contains a description of the drug abusers admitted for treatment during the whole 1996 (N°=3,438). This is a minimum figure as drug abusers who enter treatment before 1 January 1996 are not included irrespective of whether they continued in treatment in 1996. Thus the statistics do not cover all drug abusers in treatment - as yet 30% of those admitted in 1996 had not previously undergone treatment for drug abuse.

Heroin, cannabis, methadone and benzodiazepines were the most frequently used substances immediately before admittance to treatment. For 4/5 of the clients, the main substance (the preferred one) is an opiate (i.e., heroin, methadone, morphine and the like), and most clients use the substance every day. The number of clients with opiate as the main drug are 2,230 in the 1996 population. The number of clients who have been using opiates in the last month before they were admitted for treatment is 2,608.

Clients admitted to treatment for drug abuse in Denmark in 1996

Number receiving treatment(%)	3.438
Not previously treated (%	30
Men/women (%)	73/27
Average age men/women (%)	32/32
Main substances: opiates(%)	81
Injection by previously treated heroin abusers(%)	67
Injection by heroin abusers not previously treated (%)	43
Earned income (%)	7
Benefits (%)	10
Cash benefit(%)	53
Early retirement pension (%)	23
Other income (%)	7
Number with own home (%)	56
Single men/women (%)	79/69
Children under 18 at home	524
Children in care under 18	461
Foreign nationality (%)	5,2
Of these: 1st generation immigrants (%)	3,9
Of these: 2nd generation immigrants (%)	1,2

Source: National Board of Health Register of drug abusers admitted to treatment in 1996

Information collected on clients admitted to and discharged from treatment for drug abuse:

1. County
2. Municipality which pays for treatment
3. Unique Civil registration number: day/month/year
4. Hospitalising institution: County/Municipality/Institution
5. Date of admission: day/month/year
6. Date of discharge: day/month/year
7. Previously treated: Yes/No/Unspecified
8. Present family situation: Single/Living with other people/Unspecified
9. Number of children under 18 living at home
10. Number of children under 18 of whom the client has parental custody
11. Number of children under 18 of whom the client has parental custody and who have been placed outside the home

12. Most recent place of residence at time of admission to treatment (own residence, rented room, family/friends, at an institution, support residence/communal residence, family care, shelter/boarding house, prison, on the street/no place of residence)

13. Nationality/citizenship (Danish, other country)

14. Immigrant/refugee (yes, no, unspecified)

15. 1st or 2nd generation immigrant

16. Highest completed course of education

17. Most important source of income

18. The client's abuse situation (methadone prescribed, methadone illegal, heroin, morphine/ketogan, temgesic, benzodiapins, amphetamine, cocaine, ecstasy, LSD, cannabis, solvents, other, alcohol).

Substances used <u>last month</u>

19. State primary substance

20. Age of debut

21. Frequency of administration (last month)

22. Usual route of administration

23. Client substance free during last month(yes/no)

24. Not possible to state primary substance (Yes/no)

25. Client does not provide reliable information about abuse (Yes/no)

26. Recent risk behaviour

27. Risk behaviour ever

Missing information compared to the standardised protocol

a) Scenario of treatment or type of treatment centre
    It is not possible to know which kind of treatment centre the client is admitted to. The treatment could be out-patient, day or residential in-patient, methadone-supported or drug-free. It is not possible to know the percentage using those treatment centres.

b) Age at first injection

c) Data on specific laboratory test (HIV, HBSAg, HCV) performed.

Sources of vital status and cause of death

The drug abusers have a unique civil registration number. The Danish Mortality Register is based on the same civil registration number. The civil registration numbers will be compared in the registers.

5.10 Portugal (Lisbon)

A cohort has been enrolled from 1 public treatment centre in Lisbon from 1992. In 1997 the study population was of 5,000 subjects, of which 98% are opiates users.

Data retrieval and linkage of data is complex but possible, although with a percentage of missing data. No information is available on type of treatment.

Assessment of vital status and cause of death can be obtained from Population Registry.

5.11 Austria (Vienna)

Vienna is still unsure if able to participate to the prospective phase, due to difficulties in data retrieval (legal problems in getting information).

A group of 2,000 opiate users has been enrolled between 1987 and 1998; data on subjects enrolled are being processed. Moreover, for the retrospective cohort only information on gender, date of birth and death and date of entry into treatment is available.

It is possible to access the Mortality Registry.

5.12 Greece

A retrospective study can be performed on a cohort of more than 1,000 subjects from two drug-free centres.

A prospective cohort is being enrolled from four substitution treatment centres since January 1996. At present the cohort has 1,300 subjects, plus 4,000 on the TCs waiting list.

A number of other institutions, drug-free Therapeutic Communities and drug-free outpatient clinics, were informed about the aim of the project and methodology used for assessing mortality rates but their involvement into the study have still to be defined.

All variables required are available. Cause of death is obtainable from death certificates, but not expressed in ICD codes. The National Mortality Registry has data in aggregated and anonymous form, and vital status is therefore not retrievable. Local Population Registries are accessible to obtain such information.

6. Comparative analysis of mortality among drug users in Barcelona, Sweden, Amsterdam and Rome

A pooled analysis of data from those cohorts with a dataset available, was carried out: mortality rates have been estimated for the cohorts enrolled in Barcelona, Sweden, Amsterdam, and Rome.

6.1 Descriptive analysis

Methods

- ***Description of cohorts (tables 3, 4, 5)***

The Swedish cohort was enrolled between 1987 and 1996 and followed-up through 1996. The cohort consisted of 14,112 (68% males) drug users recruited at inpatient Public Treatment Centres. DUs enrolled were mainly amphetamines (24%), morphine (21%) and cannabis (14%) users, in some cases subjects were either polydrugs users or with non specified main drug of abuse.

In the Amsterdam cohort 4,906 opiates users (77% males) entering outpatient methadone programs were enrolled and followed-up from 1985 to 1996.

The Barcelona cohort was enrolled between 1992 and 1993. This cohort includes 2,237 opiate users (76% males) entering outpatient treatment centres: 99% of them are heroin users. The follow-up period is from 1992 to the end of May 1998.

In Rome all drug users entering public treatment centres and non-governmental organisations were enrolled from 1980 to the end of 1995 and followed-up through May 1997: the total number of drug users enrolled was 11,270 (82% males), 90% of whom were heroin users and among those 70% were injectors.

Table 3. Description of the analysed cohorts

Place	Period of enrolment	Study population	Follow-up period
Barcelona	1992-93	DUs at outpatient centers: 98% heroin users	1992-98
Rome	1980-95	DUs at PTCs: 95% heroin users	1980-95
Sweden	1987-96	INPATIENT DUs at PTCs: mainly amphetamine, morphine, cannabis	1987-96
Amsterdam	1985-96	Opiates users in methadone programs	1985-96

Table 4. Description of analysed cohorts

Study site	# Subjects enrolled	% Male	Mean age at enrolment	# Deaths	(%)	Mean age at death
Barcelona	2237	76	28.2	560	(25.0)	31.7
Rome	11270	82	26.9	1590	(14.1)	33.0
Sweden	14112	68	32.6	1383	(9.8)	39.8
Amsterdam	4906	77	29.3	470	(9.6)	35.8

Table 5. Description of analysed cohorts

Age at enrolment	Barcelona		Rome		Sweden		Amsterdam	
	N	%	N	%	N	%	N	%
≤ 19	105	(4.7)	872	(7.7)	1146	(8.1)	224	(4.6)
20-24	517	(23.1)	3712	(32.9)	2189	(15.5)	1103	(22.5)
25-29	767	(34.3)	3471	(30.8)	2998	(21.2)	1458	(29.7)
30-34	580	(25.9)	1936	(17.2)	2728	(19.3)	1110	(22.6)
35-39	186	(8.3)	890	(7.9)	2001	(14.2)	615	(12.5)
40-44	54	(2.4)	277	(2.5)	1286	(9.1)	261	(5.3)
45-49	17	(0.8)	80	(0.7)	696	(4.9)	82	(1.7)
50+	11	(0.5)	35	(0.3)	1068	(7.6)	53	(1.1)
Total	2237		11273		14112		4906	
Mean (SD)	28.2	(6.2)	26.8	(6.1)	32.6	(11.2)	29.3	(6.9)

▪ *Analysis*

Age-standardised mortality rates were computed to analyse temporal trend; the direct method and the total population of Sweden, Amsterdam, Rome and Barcelona (15-49 years) as standard were used.

Results *(tables 6, 7; figure 3)*

During the study periods in the cohorts enrolled in Sweden, Amsterdam, Barcelona and Rome total number of deaths were respectively: 1385 (mean age at death: 39.8), 470 (mean age at death: 35.8), 560 (mean age at death: 31.7) and 1590 (mean age at death: 33.0).

Figure 3 shows the overall mortality trend of each cohort. The highest mortality rate was observed in Barcelona (82.4/1000 person-years) in 1994 and the lowest in Amsterdam where mortality rates ranging from 4,8/1000 person-years in 1989 to 12.2/1000 person-years in 1993. In the Roman cohort mortality rates was increasing from 1986 (7.8/1000 person-years) to 1991 (38/1000 person-years) and

decreasing afterwards until 1995. In the Swedish cohort overall mortality rates were constantly decreasing from 1987 (40.6/1000 person-years) until 1991 (15.9/1000 person-years) showing a slight increase afterwards (19.4/1000 person-years in 1994).

Table 7 shows the proportional cause specific mortality. Data were available for all cohorts except Amsterdam where only overdose was classified according to ICD codes. The main cause of death was AIDS for both Barcelona and Rome cohorts (respectively 43.6% and 31.8%). About 23% of deaths in the Roman and Swedish cohorts was attributable to overdose (ICD code: 304). A large proportion of deaths from injuries and poisoning (ICD code: 800-999) was registered both in the Swedish and Barcelona cohorts (40.6% and 38% respectively).

Table 6. Description of analysed cohorts

Age at death	Barcelona		Rome		Sweden		Amsterdam	
	N	(%)	N	(%)	N	(%)	N	(%)
≤ 19	8	(1.4)	14	(0.9)	7	(0.5)	0	
20-24	55	(9.8)	141	(8.9)	80	(5.8)	23	(4.9)
25-29	143	(25.5)	326	(20.5)	210	(15.2)	70	(14.9)
30-34	200	(35.7)	497	(31.3)	278	(20.1)	130	(27.7)
35-39	105	(18.8)	381	(24.0)	262	(18.9)	109	(23.2)
40-44	31	(5.5)	164	(10.3)	183	(13.2)	82	(17.4)
45-49	14	(2.5)	43	(2.7)	112	(8.1)	32	(6.8)
50+	4	(0.7)	24	(1.5)	253	(18.3)	24	(5.1)
Total	560		1590		1385		470	
Mean (SD)	31.7 (6.7)		33.0 (6.7)		39.8 (13.6)		35.8 (7.5)	

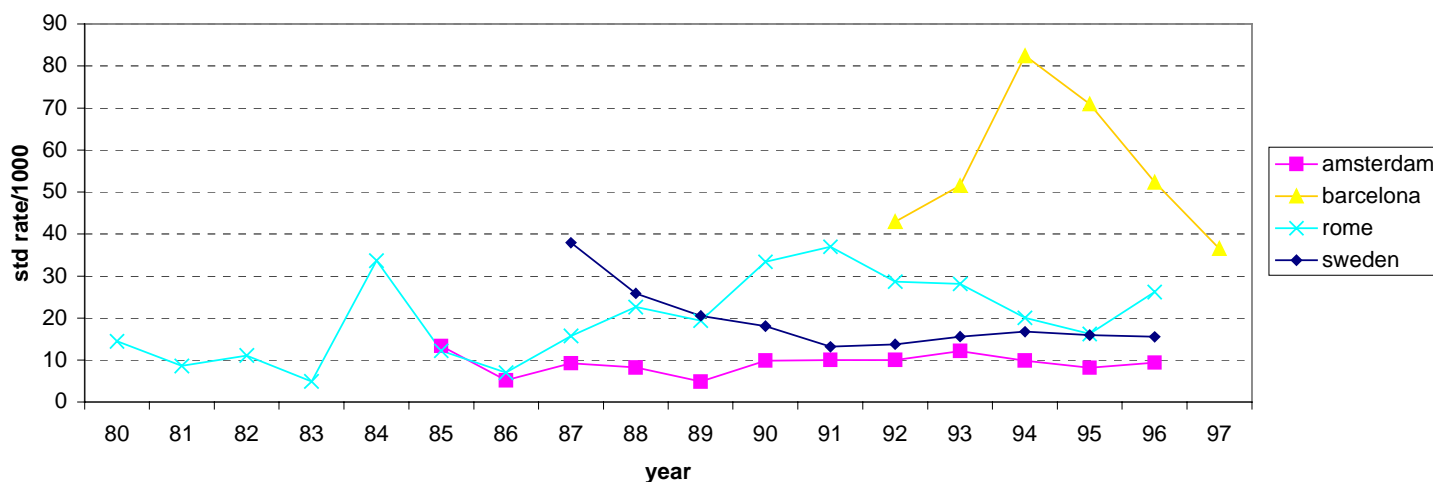*Fig. 3 Mortality from all causes: standardized mortality rates (males and females)*

Table 7. Proportional cause-specific mortality

Cause of death (ICD-IX code)	Barcelona		Rome		Sweden		Amsterdam	
	N	(%)	N	(%)	N	(%)	N	(%)
AIDS (279)	244	(43.6)	505	(31.8)	65	(4.7)		
Drug dependence (304)	1	(0.2)	365	(23.0)	328	(23.8)	90	(19.1)
All malignant neoplasms (140-239)	7	(1.2)	43	(2.7)	67	(4.8)		
Alcohol dependence syndrome (303)					35	(2.6)		
Diseases of nervous system (320-389)	1	(0.2)	10	(0.6)	20	(1.4)		
Diseases of circulatory system (390-459)	2	(0.4)	85	(5.3)	137	(9.9)		
Diseases of respiratory system (460-519)	16	(2.9)	20	(1.2)	42	(3.0)		
Diseases of digestive system (520-579)	30	(5.4)	111	(7.0)	57	(4.1)		
Ill-defined conditions (780-799)	7	(1.2)	64	(4.0)	24	(1.7)		
Injuries and poisoning (800-999)	213	(38.0)	205	(12.9)	563	(40.6)		
Other causes	19	(3.3)	30	(1.9)	47	(3.4)		
Unknown causes	20	(3.6)	152	(9.6)			380	(80.9)
All causes (000-999)	**560**		**1590**		**1385**		**470**	

Comments

Retrospective analysis revealed heterogeneity across cohorts making cross country comparisons difficult. Period of enrolment and follow-up, setting and size of the study populations are very different. Moreover, heterogeneity across sites exists with regard to age at enrolment and to sex ratio: the Swedish cohort is older and includes a larger proportion of females while an opposite pattern is observed in the Roman cohort. In Amsterdam, Barcelona and Rome, the cohorts mainly include opiate users in methadone treatment while in the Swedish cohort morphine users are only a minimum part of the total study population. Extensive information (on severity of drug use, HIV infection, some socio-demographic characteristics) were only available for the Barcelona and Rome cohorts allowing for further analysis (Poisson regression) to check determinants of mortality. The high mortality in Barcelona could be explained by the high prevalence of HIV infection in the cohort.

The analysis of cause specific mortality is difficult because of marked differences in coding causes of death in different countries. Mortality from overdose could be underestimated in the Barcelona and Swedish cohorts due to some possible misclassification as injury and poisoning.

6.2 Poisson Regression Analysis

Out of the four retrospective cohorts (Rome, Barcelona, Amsterdam and Sweden), only the cohorts enrolled in Rome and Barcelona did have some information on socio-demographic characteristics and pattern of drug use, collected at time of enrolment. The aim of the following analysis was to investigate the role of these variables as possible determinants of mortality among opiates addicts enrolled in treatment centres.

Poisson Regression is one of the possible statistical methods used to investigate the joint effect of several risk factors, adjusting for each other. This technique provides the natural multivariate generalisation of the standardised mortality rate method. For this purpose, the total person-time of follow-up is grouped into K categories on the basis of time and covariates, and the number of events N_k and person-time T_k in each category is recorded, together with the corresponding values of person-time-weighted averages of age t_k and covariates z_k.

Covariates considered as possible mortality determinants included in the analysis were: sex, age, educational level, employment status, route of administration, frequency of use and calendar period.

Age has been classified into the following categories: 15-19, 20-24, 25-29, 30-35 and 35 or more; educational level has been grouped into low (primary school or none), intermediate (junior secondary school) and high (secondary or university) for the Italian cohort, while it was divided into low (primary level of education) vs high (secondary level of education) for the cohort enrolled in Barcelona; occupation was grouped in stable, occasional or none; frequency of use was divided into three classes: less then once a week, once a week, and once a day or more; the variable "drug injected" (yes or not) was also included in the analysis.

Calendar year was divided into 5 years groups, (1980-84, 1985-89, 1990-94, 1995-97 for the last period) for the Italian cohort, and (1992-96, 1997-98) for the Spanish one.

Age and calendar year were included in the analysis as time dependent variables.

Results *(table 8)*

The Roman cohort was followed-up for a total of 62,769 person years at risk and 1,594 deaths were observed. The Spanish cohort involved 10,384 person years at risk and 552 deaths.

Rome

No significant difference was found in the mortality rates between males and females, while there was an increasing trend in the mortality rates by age, ranging from 13.6/1000 person-years for the age group 15-19 to 32.1/1000 person-years for the age group 35 or more, although the difference between RRs was not statistically significant. Educational level was found to be inversely related with mortality rates; compared with to the low educational level, Relative Risks for intermediate and high were, respectively, 0.68 and 0.59. On the other side occupational status was found to be positively associated with mortality: compared with stable workers, occasional workers were found to have

higher risk of mortality (RR=1.28) and unemployed the highest risk (RR=1.89). Slight and not significant decrease in the risks were found for more frequent use of drug and for non injectors. A strong increase of mortality risk was found in recent years, with RR of 5.5 and 13, respectively, in the latter two periods, 1990-94 and 1995-97 as compared to 1980-84.

Barcelona

The Poisson Regression analysis of the cohort enrolled in Barcelona revealed lower mortality rates and a statistically significant RR equal to 0.74 for females; moreover, an increasing trend in the mortality rates by age has been observed ranging from 37.8 for the age group 20-24, to 65.0 for 35 yrs or more). No significant RR has been found for educational level, while occasional workers or unemployed were found to have higher risk of mortality (RR=1.76) then stable workers. The higher risk of mortality (RR=2.79) has been observed for a frequency of use equal to once a week or more, while RR in more frequent of use of drug was not significant. Injecting use was found to have twice the risk of other routes of administration. Mortality rates were found to be lower in recent years, showing RR of 0.44 in the latter period (1997-98).

Table 8. Estimated Relative Risk of Rome cohort (1980-mid's1997) and Barcelona cohort (1992-mid's1998) calculated by the Poisson Regression

		Rome			
		Observed	Rate	RR	95%CI
Sex	Males	1300	20.7	1.00	
	Females	294	20.9	1.04	0.82 - 1.31
Age	15-19	15	13.6	1.00	
	20-24	144	12.2	1.08	0.26 - 4.51
	25-29	237	14.4	1.18	0.29 - 4.82
	30-34	495	22.3	1.56	0.38 - 6.37
	35+	613	32.1	2.67	0.66 - 10.89
Educational level	Low	414	29.3	1.00	
	Medium	277	18.7	0.68	0.56 - 0.84
	High	618	16.6	0.59	0.46 - 0.76
Occupation	Employed	411	18.5	1.00	
	Occasionally employed	778	21.1	1.28	1.04 - 1.58
	Unemployed	126	23.0	1.89	1.4 - 2.56
Frequency of use	less than once a week	18	19.1	1.00	
	once a week or more	20	14.7	0.70	0.30 - 1.61
	once a day or more	804	14.0	0.69	0.36 - 1.34
Route	Injected	790	12.6	1.00	
	Other	93	15.8	0.83	0.62 - 1.11
Calendar year	1980-1984	96	10.1	1.00	
	1985-1989	229	14.1	0.88	0.30 - 2.59
	1990-1994	725	25.7	5.57	2.25 - 13.79
	1995-1997	544	23.1	12.97	5.26 - 32.00

		Barcelona			
		Observed	Rate	RR	95%CI
Sex	Males	437	56.2	1.00	
	Females	115	44.1	0.74	0.55 - 0.99
Age	20-24	55	37.8	1.00	
	25-29	143	43.6	1.32	0.9 - 1.94
	30-34	200	61.0	1.75	1.2 - 2.55
	35+	154	65.0	2.30	1.56 - 3.41
Educational level	Low	402	53.8	1.00	
	High	111	43.2	0.85	0.65 - 1.11
Occupation	Employed	111	35.5	1.00	
	Occasionally employed	330	56.5	1.76	1.35 - 2.29
Frequency of use	Less than once a week	19	38.1	1.00	
	Once a week or more	30	73.1	2.79	1.19 - 6.52
	Once a day or more	329	48.7	1.71	0.81 - 3.63
Route	Injected	383	59.6	1.00	
	Other	58	26.7	0.43	0.31 - 0.60
Calendar year	1992-1996	480	60.2	1.00	
	1997-1998	72	29.9	0.44	0.32 - 0.61

7. Conclusions

The feasibility study has shown that:

- Retrospective analysis of mortality data is worthwhile in those countries where mortality rates have never been estimated, but only when access to the necessary information is easily available. The results of the pooled comparative analysis were useful to define the criteria needed for comparability of data.
- Information on variables associated to the mortality risk and describing the selection criteria of the study population enrolled in the study is essential to understand possible geographical and temporal differences in mortality of drug users.
- Prospective mortality cohort studies are both necessary and possible in all countries participating to the study. Agreement has been reached regarding the standardised protocol: enrolment and follow-up procedures, methods and dataset structure.
- During the next phase these tools will be used for cohort development, data collection and follow-up.

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Annex 1

Key participants and study sites

Spain   (*Barcelona*)

Teresa Brugal
Institut Municipal de la Salut, Barcelona City Health Department - PI Lesseps, 1, 08023 Barcelona
Phone + 34 93 4150066   Fax phone + 34 93 217 31 97
E-mail: tbrugal@imsb.bcn.es

Greece

George Kanatas
Okana Greek Organization for Combatting Drugs 19 Aristotelous Str Athens GR-104 33
Phone (00301) 8253756-59   Fax phone (00301) 8253760

Portugal   (*Lisbon*)

Filipa Ferraz de Oliveira
Dept of Public Health Faculty of Med Sciences Campo de Santana, 130 1198 Lisbon
Phone + 351 1 8803058   Fax phone + 351 1 8851920
E-mail: filipafo@mail.telepac.pt

Germany   (*Hamburg*)

Axel Heinemann
Institute fur Rechtsmedizin   Butenfeld 34 D-22529 Hamburg
Phone+ 49 40 47 17 31 30   Fax phone + 49 40 47 17 39 34

Finland

Erkki Vuori
Department of Forensic Medicine P.O.Box 40 (Kjtosuontie 11) FIN-00014
University of Helsinki
Phone + 358 9 19127482   Fax phone + 358-9-19127518
E-mail: erkki.o.vuori@helsinki.ti

The Netherlands   (*Amsterdam*)

Maria Prins   Marcel Buster
Municipal Health Service Amsterdam - Department of Epidemiology, Documentation and Health Promotion
Nieuwe Achtergracht 100
1018 WT Amsterdam
Phone + 31 20 555 5749   Fax phone + 31 20 555 5160
E-mail: mprins@gggd.amsterdam.nl
E-mail: mbuster@gggd.amsterdam.nl

Erik Van Ameijden
Trimbos Institute
E-mail: eameijden@trimbos.nl

Austria   (*Vienna*)

Daniele Risser
Institute of Forensic Medicine University of Vienna Sensegassez A-1090
Phone + 43 1 42 7765732   Fax phone + 43 1 42 779657
E-mail: daniele.risser@univie.ac.ab

Denmark

Lene Haastrup
National Board of Health Amaliegade 13   1012
1012 Copenhagen
Phone + 45 33 91 16 01   Fax phone + 45 33 93 16 36
E-mail: LNH@SST.DK

United Kingdom

Mattew Hickman – John Marsden
Centre for Research on Drugs & Health Behaviour – Dept of Social Science and Medicine
200, Seagrave Road SW6 IRQ London
Phone (44) 181 846 6565   Fax phone (44) 181 846 6555
E-mail: m.hickman@ic.ac.uk
E-mail: j.marsden@iop.bpmf.ac.uk

Ireland   (*Dublin*)

Joseph Barry
Eastern Health Board Baggot Street Clinic 19 Haddington Road
Dublin
Phone + 353 1 6600521   Fax phone + 353 1 6606352
E-mail: joebarry@tcd.ie

Sweden

Daniel Svensson
Folkhalsoinstitutet
103 52 Stockolm
Besoksadress: Olof Palmes Gata 17
Phone + 46 8 56613500   Fax phone + 46 8 56613505
E-mail: daniel.svensson@fhinst.se

EMCDDA

Julian Vicente
EMCDDA Rua Cruz de S Apolonia 23-25
1100 Lisbon
Phone + 351 1 811 30 23   Fax phone + 351 1 813 79 43
julian.vicente@emcdda.org

Italy   (*Rome*)

Carlo A Perucci   Anna Maria Bargagli   Marina Davoli
Osservatorio Epidemiologico Regione Lazio
Via S Costanza 53 00198 Roma
Phone + (39) 6 - 51686493   Fax phone + (39) 6 - 51686463 / 83
E-mail: toss_oer@sirio.regione.lazio.it

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TABLE A (1) : SOURCES TO ASCERTAIN VITAL STATUS AND CAUSE OF DEATH (AVALAIBILITY AND ACCE

Country *Study site*	National / local birth registers	National / local death registers	Accessibility to national / local registers	Code of cause of death
Austria *Vienna*	yes / yes	yes / yes	yes	ICD IX
Denmark	yes /	yes /	yes	1969 -1993: ICD VIII 1994 --->: ICD X
Finland	yes /	yes /	yes	up to 1995: ICD IX from 1996: ICD X
Germany *Hamburg*	/ yes	/ yes	yes	ICD X since 1998
Greece	yes / yes	yes/yes; the National Death Register is kept in aggregate and anonymous form	yes	ICD IX
Italy *Rome*	yes / yes	yes / yes; data on cause of death are available at the National Institute of Statistics with a delay of 2 years; a local (Lazio Region) Register of Causes of Death is available	yes	ICD IX

TABLE A (2): SOURCES TO ASCERTAIN VITAL STATUS AND CAUSE OF DEATH (AVALAIBILITY AND ACCESSIBILITY)

Country *Study site*	National / local birth registers	National / local death registers	Accessibility to national / local registers	Code of cause of death	Other sources of vital status/cause death
Portugal *Lisbon*	yes /	yes /	yes	ICD IX	Deaths from overdos the Forensic Departm
Spain *Barcelona*	yes / yes	yes / yes	yes	ICD IX	Coroner's registers (a violent deaths)
The Netherlands *Amsterdam*	yes/yes; only for DUs legally living in Amsterdam/the Netherlands	yes/yes; Central Bureau of Statistics (CBS), for Dus legally living in Amsterdam/the Netherlands	yes, but data should be analysed at CBS (CBS do not issue data of individuals)	ICD IX until 1995; ICD X since 1996	Drug Department of t Municipal Health Ser local organization for foreign DUs; hospital records, discharge le coroners' report; information from GPs
England	yes /	yes / yes	yes		
Ireland	*Dublin*	yes / yes	Population Register is not accessible	ICD IX ICD X: to be introduced in 1998	Coroners' ; police da

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| **Sweden** | yes / yes | yes / yes | yes; to link data from death and population registers an approval of ethical commission has to be obtained | ICD IX; from 1997 ICD X | no |

TABLE (B1): INFORMATION ON AVAILABILITY OF DATA ON DRUG USERS

Country	Accessibility to health record of drug users	Only in methadone treatment	Source for drug users enrolment
Austria (Vienna)	yes	yes	Centres for methadone maintenance programs
Denmark	no direct*		Private and public institutions (outpatient; inpatient; metha... supported and drug-free)
Finland	yes; from 1987 the Personal Data File Act limits linkage among different registers		1 clinic in Helsinky (Kettutie clinic). Metahdone treatment is delivered
Germany (Hamburg)	yes	yes	Outpatients Department for drug abuse; Psychiatric Depar... (hospital); Psychoterapeutic Department for drug abuse
Greece	yes		Substitution treatment centres
Italy (Rome)	yes; data can be retrived from the local Surveillance System database		Public Treatment Centres and Non Governmental Organiz...

* Source of information: National Statistics of Drug Abusers
undergoing treatment

TABLE B (2): INFORMATION ON AVAILABILITY OF DATA ON DRUG USERS

Country *Study site*	Accessibility to health record of drug users	Only in methadone treatment	Source for drug users enrolment
Portugal	yes		Treatment centres for addiction
Spain *Barcelona*	yes		Public non-residential treatment centre
The Netherlands *Amsterdam*	not direct**	yes	Central Methadone Register (CMR). CMR gathers from: Municipal Health Service (MSH)°°; GPs; Consultant Office for Alcohol and Drugs; methadon administration at Police Station
United Kingdom *England*	yes		The National Treatment Outcome Research Study (NTORS). The NTORS includes subjects recruited entry into four treatment modalities: inpatient units, residential programmes, outpatient methadone maintenance programmes, outpatient/community-b methadone reduction programmes
Ireland	yes	yes	Addiction Centre (where methadone is prescribed and dispensed); Satellite Clinics (where methadone is prescr only); GPs (less extensive information available)

Sweden	no direct°		Inpatient treatment at general and psychiatric hosp

** Source of data: Central Methdone Register (CMR)

° Source of data: Hospital Discharge Register

°° Only for subjects treated to Municipal Health Services detailed
informatiion are available