Prevalence morbidity and mortality among heroin users and methadone patients
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**An Increase in Overdose Mortality During the First Two Weeks After Entering or Re-entering Methadone Treatment in Amsterdam**

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**Abstract**

**Aims:** It has been suggested that starting and temporarily discontinuing methadone treatment is related to an increased risk in overdose mortality. This study describes the incidence of overdose mortality in relation to time after (re)entering or leaving treatment.

**Design:** A dynamic cohort of 5200 Amsterdam methadone clients was observed during treatment and *a maximum of 1 year* after treatment.

**Findings:** Between 1986 and 1998, 29729 person-years *py* and 68 overdose deaths were recorded, leading to an overdose mortality rate of 2.3/1000 *py* *2.2 during and 2.4 after treatment*. A modest increase was observed during the first 2 weeks after (re)entering treatment; 6.0/1000 *py* *Rate Ratio: 2.9; 95% Confidence Interval: 1.4; 5.8.* Directly after leaving treatment no increase was observed.

**Conclusions:** Inhaling heroin, common among Amsterdam heroin users, is thought to account for low OD mortality rates both during and after treatment. Accumulation of methadone, inadequate assessment of tolerance of known clients re-entering treatment and concurrent periods of stress or extreme heroin use when entering treatment are mentioned as possible explanations of the increased risk within the first 2 weeks. An Australian study reported a much higher increase. The modest increase in Amsterdam is explained by low background risk of overdose mortality, low starting dosage and the low-threshold to treatment.
**Introduction**

Heroin users have a high risk of death, especially death due to overdose OD. It has been shown repeatedly that methadone treatment reduces the risk of a fatal heroin overdose.\(^1\)\(^2\)\(^3\)\(^4\) Daily methadone dosages enhance the opiate users’ tolerance to opiates and may decrease the amount of heroin used.

However, methadone may not only prevent overdose death but also be the cause of it.\(^5\) This can be accidental due to misjudgement of a client’s tolerance by the physician or misjudgement by the opiate user buying methadone at the black market or combining methadone with heroin. Methadone can also be used as a means to commit suicide. Two recent studies indicate that the number of deaths prevented exceeds the number of deaths caused by methadone treatment.\(^6\)\(^7\)

Daily regular methadone use is presumed to be safe. The risk of overdose may be expected to be higher during periods of transition, i.e. periods after (re)entering or discontinuation of methadone treatment. Some studies indicate increased overdose mortality during the first weeks of treatment.\(^8\)\(^9\) Until now, overdose mortality rates during these first weeks were calculated by only Caplehorn and Drummer. They observed an extremely high \(\text{OD-mortality rate, that was 97.8 fold higher than the rates observed during treatment and 6.5 fold higher compared to the after-treatment rate.}\)

In Amsterdam, different types of methadone treatment programmes are available.\(^10\) Annually, approximately 2200 opiate users with social, behavioural or psychiatric problems and low motivation to quit their habit of illicit drug use receive methadone in ‘low-threshold programmes’ at the Municipal Health Service MHS. In the near future, abstinence is not a realistic objective for these people and the reduction of harm caused by the continuous use of illicit opiates and other drugs is a major goal.\(^11\) In addition, approximately 1100 socially stabilised opiate users - those with stable housing, regular income, health insurance - receive methadone treatment from their general practitioner GP. They receive a methadone prescription once every week or once every fortnight. Furthermore, approximately 300 opiate users who are motivated to achieve abstinence of illicit drug use participate in methadone reduction programmes annually. The latter two programmes will be regarded as ‘high-threshold programmes’ in this study. Ideally, someone would enter and maintain in treatment until sustained abstinence of drugs is reached. In reality however, temporary withdrawal from treatment is common and people may have multiple experiences with entering and discontinuation of treatment. If the OD mortality rates show a high increase during these transition periods this would have a substantial effect on mortality among heroin users.
In order to prevent methadone prescription at multiple locations to the same person at the same time, every methadone prescription in Amsterdam is registered at the Central Methadone Register. This register has been used to construct a study population and describe the incidence of overdose mortality.

The aim of this study is 1. to quantify the possible differences in overdose mortality rates within different time-periods during or following discontinuation of methadone maintenance treatment and 2. to study the possible influence of patient characteristics and prior treatment experience.

Methods
Selection and description of the study population
The study population consists of methadone clients in methadone treatment in Amsterdam and former methadone clients who have left methadone treatment less than one year ago. The study-period ran from January 1, 1986 until December 31, 1998. In order to describe the time at risk after methadone treatment properly, only those drug users who were likely to stay in Amsterdam when they were not receiving treatment were selected. Foreign heroin users are more likely to reside in Amsterdam temporarily, and therefore, the population was restricted to methadone clients who had a known address in Amsterdam and were born in The Netherlands, Surinam, the Dutch Antilles, Turkey or Morocco - major ethnic minorities in the Netherlands. A total of 5200 methadone clients met all selection criteria.

Observation time
Observation time was defined as a period during methadone treatment or a period of maximal 1 year after methadone treatment. One year after discontinuation, individual observation time was censored. If a person re-entered treatment, observation time started again. In case of death, observation time was terminated at date of death. Not all 5200 methadone clients participated in the study at the same time; the average size of the population during the study-period was 2287.

The study population was a dynamic cohort. As all methadone prescriptions were registered at the CMR, the size of the treatment population and individual period of treatment participation could be measured precisely at any moment. Moreover, we were able to distinguish transition periods after (re)entering or discontinuation of treatment from other periods during or after treatment. The first 10 weeks after entering or leaving treatment were classified from 1 to 10. After more than ten weeks of observation time during or after treatment, person time was classified in one category. In case of interruption, counting started again with week 1.
Observation time was measured in weeks but commonly expressed in person years *py*. Fifty-two first weeks of methadone treatment - of multiple individuals - was equal to 1 *py* of *first week treatment experience*. Observation time after discontinuation of methadone treatment was calculated individually by the summation of all full calendar weeks - *Monday until Sunday* - in which no methadone prescription was registered. In total 41,448 first weeks of methadone treatment were observed. Only 2,148 - 5% - of these first weeks were absolute first weeks, 95% of the first week observation time was contributed by clients re-entering methadone treatment.

**Cases**

In Amsterdam, coroners of the MHS examine all deaths that are not natural or suspected to be not natural. Only in case of doubt as to whether death may be caused by a criminal offence, is autopsy and toxicological analysis performed. Based on the coroners' records, the overdose deaths are extracted annually. Overdose deaths are defined as acute deaths occurring after the use of illicit drugs - *heroin, cocaine, amphetamine, MDMA* - or methadone, caused presumably by these drugs. Although drugs are often combined with alcohol or benzodiazepines, overdose deaths that are due to alcohol and/or benzodiazepines only are not considered as overdose deaths. Information to determine whether an overdose death is accidental or intentional is often insufficient. Therefore, both accidental and intentional overdose deaths were considered as cases in this study.

**Date of death**

In this study date of death was of major importance. The official date of death however, was the date of the declaration of death by the coroner or physician. Date of death, as stated in the coroners' reports was assumed to be the 'real date of death'. Overdose fatalities occurring during treatment or within a period of 3 days after last methadone prescription were considered as cases during treatment. Casualties occurring within the period from the 4th until the 17th day after leaving methadone treatment were considered to be overdose deaths during the first 2 weeks after treatment.

**Analysis**

The high-risk period was determined by comparing all person time of the first, second third etc. week after starting and after leaving methadone treatment with the number of overdose deaths occurring in this first, second third etc. week. We determined whether there was a higher OD mortality rate after transition periods and, if so, how many weeks this elevation continued. Next, high risk periods were compared to low risk periods using a Poisson regression analysis.
Information available from the Central Methadone Register was used to distinguish other subgroups. Based on differences in gender, age, 10-years categories, country of birth, The Netherlands versus other countries, calendar year, three categories, former treatment modality, low-threshold treatment or high-threshold treatment, and period since first treatment, four categories, subgroups were distinguished. Multivariate Poisson-regression was used to describe differences between these subgroups in respect to overdose mortality and to control for potential confounding. Differences in overdose mortality rates were expressed as rate ratios. Multivariate analyses were performed using the Epidemiological Graphics, Estimation and Testing package EGRET."}

Results

Description of the study population

Table 1 describes the study population consisting of 5200 methadone clients. It shows that the majority was male, 77%, N = 4002, and born in The Netherlands, 69%, N = 3586. As the study period proceeds the same individual may appear in different categories of time dependent variables e.g., age, duration of treatment, treatment status and modality. Many clients, 71%, participated in the study when they were in their 30s; some of them also contributed person time to lower or higher age categories. In total 50% of the observation time belongs to the 30-39 years age category.

Furthermore, Table 1 shows that not all participants received methadone treatment during the study period. 96 percent did so. Four percent received only methadone in 1985, the year preceding the study period. Therefore, in 1986, they contributed observation time within the after treatment category only. Almost all subjects, 99%, contributed to the after treatment category indicating that temporary discontinuation of treatment is common. Most observation time was obtained during methadone treatment, 63%. During the study period, time in treatment increased and time after treatment decreased. Between 1986 and 1989, 57% of observation time was spent during treatment; between 1995 and 1998, this was 68%. Many subjects, 49%, experienced both periods of low-threshold and periods of high-threshold treatment. In total, 86% of the participants received low-threshold and 63% received high-threshold methadone treatment.

More than half, 59%, of the participants already received treatment before 1986; 41% received their first treatment during the study period. Gradually, fewer new clients applied for methadone treatment. In 1986, 247 new clients entered the study population, in 1998 only 71. The average age of the 2226 people entering the population for the first time during the study period was 30.4 years. The average age of the study-participants increased persistently from 30.2 years
Table 1 Description of the study population: individuals, person time, cases and percentage of time after treatment

<table>
<thead>
<tr>
<th>NS: non-significant</th>
<th>Individuals#</th>
<th>Person-years py</th>
<th>Fatal overdose</th>
<th>% py after treatment</th>
<th>OD-mortality rate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5200 100%</td>
<td>29729 100%</td>
<td>68 100%</td>
<td>37%</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4002 77%</td>
<td>22910 77%</td>
<td>61 90%</td>
<td>38%</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1198 23%</td>
<td>6819 23%</td>
<td>7 10%</td>
<td>35%</td>
<td>1.0 &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>3586 69%</td>
<td>20348 68%</td>
<td>61 90%</td>
<td>34%</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Other countries*</td>
<td>1614 31%</td>
<td>9382 32%</td>
<td>7 10%</td>
<td>42%</td>
<td>0.7 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Year of study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1986-1989</td>
<td>3660 70%</td>
<td>9382 32%</td>
<td>20 29%</td>
<td>44%</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>1990-1994</td>
<td>3702 71%</td>
<td>11502 39%</td>
<td>36 53%</td>
<td>35%</td>
<td>3.1 NS</td>
<td></td>
</tr>
<tr>
<td>1995-1998</td>
<td>3265 63%</td>
<td>8846 30%</td>
<td>12 18%</td>
<td>32%</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Time since first MMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year</td>
<td>2148 41%</td>
<td>1122 4%</td>
<td>7 10%</td>
<td>51%</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>1-6 years</td>
<td>4655 90%</td>
<td>9969 34%</td>
<td>24 35%</td>
<td>47%</td>
<td>2.4 &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>7-11 years</td>
<td>3222 62%</td>
<td>10709 36%</td>
<td>29 43%</td>
<td>34%</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>&gt; 11 years</td>
<td>2084 40%</td>
<td>7929 27%</td>
<td>8 12%</td>
<td>26%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 years</td>
<td>126 2%</td>
<td>138 0%</td>
<td>0 0%</td>
<td>57%</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>20-29 years</td>
<td>2532 49%</td>
<td>7284 25%</td>
<td>19 28%</td>
<td>47%</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>30-39 years</td>
<td>3671 71%</td>
<td>14742 50%</td>
<td>40 59%</td>
<td>36%</td>
<td>2.7 NS</td>
<td></td>
</tr>
<tr>
<td>40-49 years</td>
<td>1768 34%</td>
<td>6475 22%</td>
<td>8 12%</td>
<td>28%</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>50-59 years</td>
<td>323 6%</td>
<td>968 3%</td>
<td>1 1%</td>
<td>26%</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>33 1%</td>
<td>122 0%</td>
<td>0 0%</td>
<td>20%</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Treatment modality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-threshold MMT</td>
<td>3251 63%</td>
<td>12928 43%</td>
<td>2 32%</td>
<td>29%</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Low-threshold MMT</td>
<td>4464 86%</td>
<td>16801 57%</td>
<td>4 68%</td>
<td>43%</td>
<td>2.7 NS</td>
<td></td>
</tr>
<tr>
<td>During / after treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>4977 96%</td>
<td>18747 63%</td>
<td>42 62%</td>
<td>0%</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>After treatment</td>
<td>5127 99%</td>
<td>10983 37%</td>
<td>26 38%</td>
<td>100%</td>
<td>2.4 NS</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1 Description of the study population


Figure 1 shows the size of the study population during the total study period. On average 2287 clients were contributing observation time to the study. In 13 years this resulted in 29,729 person-years of observation time. At each moment in time, people were entering or leaving methadone treatment. On average 5.0% of the study population entered treatment one or two weeks previously and 4.5% left treatment 1 or 2 weeks previously. Most of the time -68% - was obtained more than 10 weeks after leaving or entering methadone treatment. From 1986 until 1989 64% of observation time was
Transition periods and overdose mortality

<table>
<thead>
<tr>
<th>Number of weeks</th>
<th>Person-years</th>
<th>Number of OD deaths</th>
<th>Incidence per 1000 py</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>x 10,000</td>
<td>x 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>During treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1 and 2</td>
<td>7.8</td>
<td>1.5</td>
<td>9</td>
<td>6.0</td>
<td>3.1 - 11.5</td>
</tr>
<tr>
<td>Weeks 3 - 10</td>
<td>18.9</td>
<td>3.6</td>
<td>4</td>
<td>1.1</td>
<td>0.4 - 2.9</td>
</tr>
<tr>
<td>&gt; week 10</td>
<td>70.7</td>
<td>13.6</td>
<td>29</td>
<td>2.1</td>
<td>1.4 - 3.1</td>
</tr>
<tr>
<td><strong>After treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks 1 and 2</td>
<td>6.9</td>
<td>1.3</td>
<td>2</td>
<td>1.5</td>
<td>0.4 - 6.0</td>
</tr>
<tr>
<td>Weeks 3 - 10</td>
<td>13.9</td>
<td>2.7</td>
<td>6</td>
<td>2.2</td>
<td>1.0 - 4.8</td>
</tr>
<tr>
<td>&gt; week 10</td>
<td>36.1</td>
<td>6.9</td>
<td>18</td>
<td>2.6</td>
<td>1.6 - 4.1</td>
</tr>
</tbody>
</table>

Table 2  Number of weeks, person-years and OD mortality rates at different time periods

obtained more than 10 weeks after entering or leaving treatment, during the years 1995 - 1998 this increased to 72%. Person time spent during transition periods decreased during the study-period.

Sixty-eight overdose casualties were observed. Relatively few overdose casualties were observed among females, ethnic minorities and high-threshold treatment participants. Moreover, the percentage of deaths during the last calendar period 1995 - 1998 -18% - is low compared to the person time that is collected during this period -30%. Ten percent died during the first year of treatment although this category comprised only 4% of the total person time.

**High-risk period**

Table 2 shows the number of overdose deaths and the number of weeks of observation time that were collected. During treatment 42 subjects experienced a fatal OD. Nine of them suffered a fatal OD during the first 2 weeks after (re)entering treatment, 4 people died during the 3rd until the 10th week and 29 overdose casualties died more than 10 weeks after entering methadone treatment. Overdose mortality rates were 6.0/1000 py, 1.1/1000 py and 2.1/1000 py respectively. The overdose mortality rate among those who have participated in treatment continuously for a period longer than 2 weeks was 1.9/1000 py.

Twenty-six people suffered a fatal overdose after treatment. Two of them died within the first 2 weeks after leaving methadone treatment. Between the 3rd and 10th weeks after leaving methadone treatment 6 people died and the remaining 18 died more than 10 weeks after leaving methadone treatment. Overdose mortality rates
Baseline: female, ethnic minority, year of first treatment, high-threshold treatment, not during the first 2 weeks after (re)entering treatment alpha= 7.96, Incidence: 0.3/1000 py (95%CI:0.1 - 1.3)

LRS: Likelihood Ratio Statistic;
Deviance on 9640 DF 440.9 LRS 7 DF 52.6 P < 0.001

<table>
<thead>
<tr>
<th>First 2 weeks after (re)entering treatment</th>
<th>LRS</th>
<th>DF</th>
<th>Beta</th>
<th>Rate ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.7</td>
<td>1</td>
<td>1.05</td>
<td>2.86</td>
<td>1.42 - 5.78</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Variables in the model:

| Born in the Netherlands | 17.3 | 1 | 1.62 | 5.03 | 2.3 - 11.1 | < 0.001 |
| Male                     | 12.2 | 1 | 1.19 | 3.28 | 1.5 - 7.2 | < 0.001 |
| 1 until 6 years since first treatment | -.85 | 0.43 | 0.18 - 1.0 | |
| 7 until 11 years since first treatment | -.66 | 0.52 | 0.23 - 1.2 | |
| > 11 years since first treatment | 11.9 | 3 | -1.57 | 0.21 | 0.08 - 0.6 | < 0.01 |
| Low-threshold modality    | 4.7  | 1 | 0.56 | 1.76 | 1.1 - 2.9 | < 0.05 |

| First 2 weeks after (re)entering treatment | 6.4  | 1 | 1.03 | 2.82 | 1.39 - 5.70 | < 0.01 |

Table 3  Poisson-regression model, increased risk during the first 2 weeks with and without adjustment for confounding

were 1.5/1000 py, 2.2/1000 py and 2.6/1000 py, respectively. In total, overdose mortality rates outside treatment were 2.4/1000 py.

The high-risk transitional period seems to be limited to the first 2 weeks after (re)entering methadone treatment. These first 2 weeks were the very first 2 weeks for only 1 out of 9 fatalities. The others (re)entering treatment, two after a period of only 1 full week of absence, 1 after a three weeks period of absence, 4 after a period between 10 weeks and 6 months, the longest period of absence was 1 year and 1 month.

Influence of potential confounders and effect modification

The rate ratio of the first 2 weeks of methadone treatment compared to other periods during the study period was 2.9 (95%CI: 1.4; 5.8). This rate ratio could be biased if a specific high-risk subgroup was over-represented in this two weeks period. Although possibilities to control for potential confounders were limited in this study, we could determine subgroups with a potentially increased risk. The results of the multivariate Poisson regression model conducted in order to adjust for potential confounding are shown in Table 3. Large rate ratios were observed when comparing males and females - adjusted rate ratio of 3.3, 95%CI:1.5 - 7.2- and Dutch and ethnic minorities - adjusted rate ratio of 5.0, 95% CI: 2.3; 11.1. Moreover, incidence rates were higher among clients of the
low-threshold treatment programmes - adjusted rate ratio: 1.8, 95%CI: 1.1 ; 2.9 -
Rates were highest during the first year of treatment. The adjusted rate among clients that were registered more than eleven years ago was 4.8 - 95%CI: 1.7 ; 12.5 - times lower. Comparing the crude and adjusted rate ratio, we may conclude that the potential confounders gender, ethnicity, time since first treatment and treatment modality could not explain the higher overdose mortality rate during the first 2 weeks after entering treatment.

Discussion

The general overdose mortality rate in the study population - 2.3/1000 py - was low compared to figures presented in other studies. This may be related to the characteristics of the drug scene in Amsterdam. The fact that the majority of opiate users in Amsterdam do not inject their heroin - 60% of the opiate users treated at the MHS in 1990 and 85% in 1999 - is of major importance. Although overdose fatalities are not restricted to injecting heroin users, intravenous use is a major risk factor. Among injecting opiate users in Amsterdam a higher overdose mortality rate - 6.3 per 1000 py - has been reported. Injecting is especially rare among the major ethnic minorities in Amsterdam, who usually smoke their heroin - chasing the dragon. The adjusted overdose mortality rate among them was 5.0 - 95% 2.3-11.1 - times lower than the rate among Dutch drug users. Furthermore, Amsterdam has an ageing and decreasing population of chronic heroin users. The incidence of heroin use has decreased since the 1980s. Consistent with findings of Warner-Smith et al. overdose mortality was not statistically significantly related with age. However, overdose mortality rates decreased with time since first treatment. This may be explained by a decreasing frequency of heroin use in methadone treatment or by self selection; those methadone clients who remain in treatment will differ from those who definitely leave treatment or die.

This paper quantifies the differences in overdose mortality rates within different time periods during or following discontinuation of methadone maintenance treatment. Conducting this study, three arbitrary decisions that may influence the results have been made and need some comments. 1. The individual observation time was censored after one year without any registered prescription of methadone in Amsterdam. Because of this, person time contribution by people who were no longer at risk - those who became abstinent and did not relapse and people who left Amsterdam - was limited. 2. Before 1989 methadone registration was limited to the last prescription of each week. Therefore, the first full calendar week - Monday-Sunday - without methadone treatment was considered as the first week after treatment. In case smaller time periods or a period of 7 days was chosen, more people should have left methadone treatment temporarily by
definition. 3. All overdose deaths that occur within three days after methadone treatment were counted as 'during treatment deaths'. First, it was presumed that the protective effect of an elevated tolerance towards opiates would last some days after treatment. Secondly, as mentioned above, the denominator within treatment was slightly overestimated. This overestimation could lead to an underestimation of the mortality rate during treatment if all deaths that did not occur on a treatment day would be classified as 'after treatment overdose deaths'. Thirdly, in case of misclassification of date of death, the wrong date was likely to be after the last treatment contact.

OD-mortality rates after treatment were not significantly higher than rates during treatment. In contrast to this, Langendam reported a significantly lower OD-mortality rates among injecting heroin users of Amsterdam during methadone treatment compared to rates outside treatment. The low risk of the non-injecting majority among Amsterdam opiate users could explain that the potential impact of methadone treatment among all heroin users - both injecting and non-injecting - would be limited. Furthermore, rates after treatment could have been influenced by periods of incarceration. An unknown part of the time after discontinuation of treatment was spent in prison. During their stay in prison heroin users would be at lower risk of overdose. In case a heroin user is detained outside Amsterdam and suffers a fatal overdose this may not be registered at the municipal health service in Amsterdam.

An important finding of this study was increased overdose mortality rates during the first two weeks after re-entering treatment; 6.0/1000 py compared to 1.9/1000 py during the succeeding weeks in treatment. After discontinuation of treatment the OD mortality rate was 2.4/1000 py. No significant increase was observed directly after discontinuation.

The rate ratio of the first two weeks of methadone treatment compared to other periods during the study period was 2.9 - 95%CI: 1.4; 5.8 -, a difference that could not be explained by differences in ethnicity, gender, period since registration, or treatment modality. The increased risk of OD death during the first 2 weeks is in line with other studies. However, the OD mortality rate during the first 2 weeks observed in Caplehorn & Drummer's study was more than a 10-fold higher; 70.4/1000 py. Apart from discussing the possible causes of the increase of OD mortality during the first 2 weeks after (re)entering methadone programmes, we will discuss the possible causes of the modest increase in the Amsterdam situation.

The period of increased risk during the first 2 weeks of methadone treatment may be due to methadone itself. Accumulation of methadone is likely to occur because of the long elimination half-life of methadone - mean 55 hours after a single dose and 22-25 hours
During chronic dosages, although during the study period, the methadone dosages prescribed at the municipal health service increased, new clients still started at a low dose. The average dosage for new clients during the first two weeks was 31 mg·SD:12· at 1986 and 34 mg·SD:17· at 1998. The average dosage prescribed to clients during the first 2 weeks after re-entering treatment increased from 35 mg·SD:16· at 1986 to 50 mg·SD:26· at 1998. Dosages during the remaining periods increased from 35mg·SD:15· to 61 mg·SD:25·.

Because tolerance to opiates may vary over time, proper assessment and review of tolerance prior to commencement of methadone treatment is important among both new clients demanding for treatment and known clients re-entering treatment, especially those re-entries returning to treatment after a period of incarceration. The period after release from prison has already been recognised as a high risk period. In case of drug users re-entering treatment immediately after imprisonment, part of the overdose cases occurring during the first 2 weeks after starting treatment might be attributed to the increased risk after imprisonment.

The period during which a drug user demands treatment may be a period of instability, stress and excessive drug use. Opiate users with help-seeking behaviour are more likely to make a suicide attempt. Therefore, accidental or intentional overdose fatalities may be more prevalent during these periods. In Amsterdam, the step to (re)enter treatment at one of the low-threshold methadone treatment programmes - or to demand for methadone treatment at one's own GP- may be lower and therefore opiate users entering treatment might be less desperate than in other countries.

It is tempting to calculate a proportion of overdose deaths that can be attributed to the increased risk of overdose mortality within the first 2 weeks of methadone treatment. It is true that, in case the observed surplus of overdose mortality during the first 2 weeks could be prevented, the number of overdose cases occurring during treatment would decrease with 15%. However, in order to attribute the surplus of OD deaths to methadone treatment, knowledge of a counterfactual reality is needed; what overdose mortality rate would have been observed among these clients in the period that they (re)entered treatment in case methadone treatment did not exist at all. Taking into account the special circumstances around the period of entering treatment, the number of prevented deaths could still exceed the number of OD deaths that can be attributed to treatment.

OD mortality rates were lower among females and participants of high-threshold methadone treatment. The decreased risk among female opiate users is also observed in other studies. Females seem to have more chance of surviving an overdose; the percentage of female overdose cases presented in a hospital between 1992 and 1996 was 27% which is thought to be more or less equal to the percentage of
female heroin users in Amsterdam · hospital-project, Municipal Health Service. Females may use drugs more often in company and therefore medical assistance can be alerted. The lower overdose mortality risk among married opiate users, reported by Davoli, could have a similar cause.14

The lower risk among drug users at high-threshold treatment, is due probably to the differentiated treatment system in Amsterdam. GPs provide methadone · tablets · to opiate users in weekly take-home prescriptions. This is unlikely to be a safer method than receiving methadone five times a week · liquid taken on the spot at working days and take-home tablets during the weekend · within the low-threshold programme. Similarly, abstinence-oriented treatment could lead to a higher risk for overdose mortality in case of relapse after losing tolerance to opiates.19 Within these high-threshold treatment populations we observe a lower overdose mortality rate. Most probably because GP prescription of methadone and abstinence oriented treatment is offered to specially indicated heroin users · i.e. considering abstinence oriented treatment; motivated to quit drug use and considering treatment from their general practitioner; social stability.

Conclusion
In general, overdose mortality rates are low both during and after methadone treatment, due presumably to the low prevalence of injecting heroin use. A modest increase in overdose mortality rates during the first two weeks after (re)entering treatment was observed. Accumulation of methadone during the first period, inadequate assessment of tolerance of known clients · e.g. after imprisonment · and a concurrent period of stress, instability and extreme drug use at the time of treatment demand are mentioned as possible explanations of the increased risk. An Australian study reported a much higher increase. The modest increase in Amsterdam is explained by a low background risk of overdose mortality, low starting dosage and low-threshold to treatment.
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4.2 Fatal Overdoses in Oslo, Copenhagen, Amsterdam and Frankfurt

Abstract
In the last decade Oslo has experienced a rising number of overdose deaths OD. In order to understand this problem, Oslo contacted three cities, Amsterdam, Copenhagen and Frankfurt, which are of similar size but have lower and decreasing/stable numbers of overdose deaths. Available information on overdose deaths, drug use and interventions was gathered and drug users, street level professionals, policy-makers and politicians were interviewed. The differences between OD mortality figures and particularly the high and rising number of OD fatalities in Oslo could be explained by differences in methods and definitions used to obtain figures, by the rising trends in heroin use, by a high prevalence of injecting use of mixtures of heroin and fluntrazepam, by a growing open drug scene and a limited availability of low threshold treatment. To reduce overdose mortality in the future, the reduction and dispersal of the open drug scene, accompanied by a large-scale implementation of professional low-threshold facilities is advised.

Introduction
Oslo - Norway - experienced a steep increase in overdose deaths during the nineties. In order to understand and deal with this problem, Rusmildeletaten in Oslo contacted three Northern European cities, Amsterdam - The Netherlands -, Copenhagen - Denmark -, and Frankfurt am Main - Germany -. These are similar in terms of size and economic level and have populations ranging from 500,000 to 725,000 - 1.0 million to 1.8 million including the surrounding districts - and all of them face a drug problem. The estimated numbers of opiate users are roughly similar, between 4000 and 6000. The numbers of fatal ODs vary widely, however. In 1999 the figures for Frankfurt - N = 26 - and Amsterdam - N = 28 - were relatively low, as against a high Oslo figure - N = 104 -, whereas moderate figures were observed in Copenhagen - N = 44 -. Also, in contrast to the increasing trend observed in Oslo, annual fatal ODs have decreased in Frankfurt and Amsterdam and remain stable in Copenhagen. This paper reports on a joint EU-supported project to analyse and evaluate the differences between the cities.
Figures for drug-related deaths are not directly comparable between the countries of the European Community, so the first question that needs to be asked is whether the variation in OD mortality figures between cities is due to different methods and definitions.

Not all drugs are equally dangerous. Heroin, which can cause fatal respiratory depression by influencing the respiratory centre of the brain, is considered to be the most important drug in relation to OD mortality. The next question, then, is whether differences in OD mortality trends are explained by variations in the heroin epidemics. Nor do all heroin users run the same risk: this varies, depending on the route of administration, and it is higher among injectors of heroin than among those who inhale their drugs. Concurrent use of heroin and barbiturates, benzodiazepines or alcohol increases the risk. Injection of benzodiazepines is especially related to higher risk. Higher rates of OD mortality are observed among homeless, HIV-infected and single heroin users. Use of heroin of an unexpectedly high purity is thought to be the cause of fatal ODs in individual cases, but at regional level analysis of the relation between the purity of street samples and the incidence of OD deaths gives mixed results. The nature of the drug scene - open, dispersed or hidden - might also be a factor, but scientific evidence for effects on overdose prevalence is largely non-existent here. Tolerance of an open drug scene is thought to be counterproductive, however: the high availability of drugs, attraction of new drug users, accumulation of health problems and loose social contacts lead to chaos and an increased risk of transmission of infectious diseases. All these factors relate to characteristics of the drug user culture and patterns of use, so it is important to evaluate whether differences are explained by variations in these areas.

Most overdoses do not lead to instantaneous death. If an ambulance is alarmed immediately, the victim's life usually can be saved. Fear of the police, however, can prevent drug users calling for help. Also, if drug users in public areas try to find hiding places to inject their drugs, safety from the police can become a danger in the event of an overdose. Safe injection rooms - or user rooms, or supervised injection facilities - permit an immediate response in the event of an overdose, thereby improving an individual's chance of avoiding overdose morbidity or mortality compared to overdoses occurring elsewhere. If drug-free treatment results in long-term abstinence it minimises the risk of an overdose. People who drop out and heroin users who relapse after completing their treatment are at higher risk, however. Similarly, in the case of prisoners who undergo detoxification during incarceration the period after release from prison is recognised to be a high-risk period. Methadone programmes have been shown to reduce OD mortality by reducing heroin use, maintaining high opioid tolerance and improving health through associated ser-
Methadone can also cause OD deaths, however. Higher rates of OD deaths are observed during the first two weeks of treatment. Co-prescription of heroin, in addition to methadone, is also thought to reduce OD mortality: the initial results of the Dutch heroin trial indicate an improvement in physical and mental health. These factors are directly related to the interventions chosen by the city authorities. The final question is whether the different overdose trends in the four cities are caused by different choices and drug policy options.

The project is designed to answer these questions is based on city reports and interviews with strategic informants in the cities, at both street level and the administrative and political levels. This paper focuses on the observed differences in the figures for, and trends in, OD mortality in the four cities. First we discuss whether the differences are real or due to different definitions and procedures. Having concluded that there are real differences, we discuss the possible explanations step by step: 1. differences in the onset and course of the heroin epidemics, 2. differences and changes in the characteristics of the drug-use culture, and 3. differences and changes in interventions and measures. Finally we make some recommendations on the choices that could be made, considering the situation in Oslo in particular.

Methods

The working group was set up in 1999 and consisted of a representative from each city plus a scientific consultant. The study was financed by the Municipality of Oslo and the European Union. The report has recently been published. The city representatives are from institutions with experience of drug research and policy at municipal level. Meetings of the working group were organised in all the participating cities and they visited the 'drug scenes'.

The two-year-project was divided in three parts. The first part involved describing the local situation: the characteristics of the city, drug use trends, drug treatment services and drug-related mortality. Mortality rates per 100,000 population were calculated, based on the number of residents among the OD deaths and the number of residents between 15 and 65 years of age. The material is organised in city reports describing both the present situation and the history behind it. The reports were used to analyse the findings and differences in a time sequence perspective. In order to have any effect on the overdose trend, changes in heroin use, drug user culture and measures taken by the cities have to precede observed variations in overdose mortality. Obviously, effects might be masked or exaggerated by concurrent other measures or influential factors. Also, it might be difficult to single out factors in drug policy or drug use patterns as they
often relate to, and are influenced by, one another. The time sequence analyses should be interpreted with due consideration to interactions and local variations.

The second and third parts of the project consisted of interviews. In each city, five heroin users and three street workers who deal with the OD problem professionally were interviewed using a semi-structured questionnaire. The selection of the respondents was based on diversity - e.g. drug users in- and outside treatment and a paramedic, police officer and social worker - and the ability to provide valuable information - experience of a non-fatal OD or involvement with fatal or non-fatal OD cases.

Based on the results of these interviews a second semi-structured questionnaire was developed to interview people who have an influence on municipal drug policy: representatives of the police and health care services, an administrator responsible for drug policy and two politicians from the municipal council. This questionnaire dealt with perceptions of the development of municipal drug policy and interventions to reduce overdose mortality. This information was used to read the findings and observations in the city reports in the light of opinions and experiences in the interviews. The final result was discussed in the research group to ensure comprehensive understanding of differences and similarities. Quotes from respondents are used to illustrate the results.

**Results**

**Scrutiny of the OD figures**

Before attempting to explain the differences in recorded OD mortality between the cities it is important to find out whether they are real or spurious. They could be caused by differences or changes in methodology and definitions. Fig. 1 shows the number of overdose deaths according to local registers in each city from the first known figures up to 1999. The differences and similarities in the methods and definitions are shown in Table 1. In Copenhagen and Oslo all cases suspected to be caused by an overdose are subjected to autopsy - toxicological analysis - after post mortem examination by the coroner. In contrast, in Amsterdam and Frankfurt an autopsy is only conducted if the coroner doubts whether death was the result of an overdose or a criminal offence.

In Amsterdam the figures are based on forensic coroners’ reports and collected by the Municipal Health Service. In the other cities deaths are recorded by the police. They are called ‘drug-related deaths’ rather than overdose deaths in Frankfurt and Oslo. Forensic medicine in Oslo, however, confirms that almost all deaths are overdose deaths. In all the cities suicide by intoxication with methadone or illicit drugs is considered as an overdose. OD deaths due to intesti-
Smuggling of cocaine have only been observed in Amsterdam - $N = 4$. The figures for Copenhagen - *Fig. 1* - are limited to officially registered residents of the city. In 1999 13 non-residents died from an overdose: including those deaths, 57 overdose deaths would have been reported. Non-residential OD deaths in the city accounted for a larger proportion of OD deaths in Oslo - 36% - and the majority of the cases in Amsterdam - 54%. In Frankfurt non-residents were included but could not be distinguished. None of the cities included overdoses in residents who died elsewhere. Table 2 shows the number of OD cases in 1999 and the rates per 100,000 residents in the 15-64 age group. Expressed in rates per 100,000 residents, the differences between the numbers of OD deaths in Copenhagen and Oslo are smaller than indicated in Figure 1.

The average age of the deceased was lowest in Frankfurt - 31 years, as against 34 in Amsterdam, 35 in Oslo and 37 in Copenhagen. In Amsterdam there was a big age difference between residential and non-residential OD deaths: the average was 28 and 41 respectively.
Derived from

<table>
<thead>
<tr>
<th>City</th>
<th>Derived from</th>
<th>Toxicology Conduct</th>
<th>Number may include other DRD*</th>
<th>Intentional OD included $\beta$</th>
<th>Non-residents included</th>
<th>Fatal OD of inhabitants occurring outside the city</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslo</td>
<td>forensics</td>
<td>Standard non-natural</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Copenhagen</td>
<td>forensics</td>
<td>Standard non-natural</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Frankfurt</td>
<td>forensics</td>
<td>Doubt OD/criminal offence</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>forensics</td>
<td>Doubt OD/criminal offence</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1 Definition, methods to derive the number of OD cases shown in Figure 1

Obviously, the official figures are not fully comparable and differences should be considered indicative rather than exact. The differences are large, however, and we can say that the number of OD fatalities in 1999 was relatively low in Amsterdam and Frankfurt, moderate in Copenhagen and relatively high in Oslo. As records of local OD mortality used methods and definitions that were constant over time, the trends should be uninfluenced by the differences. Oslo had a low, stable number of overdoses during the 1980s, with a steady increase after 1990 and a possible levelling-off in the last years recorded. OD mortality increased slowly in Amsterdam over the 1977-1984 period, since when it has decreased in the same gradual manner. In Frankfurt there was a relatively stable, moderately high figure from 1979 to 1985, followed by a sharp increase from 1985 and a dramatic decrease from 1992. OD fatalities in Copenhagen have remained relatively stable since recording started in 1982. Also, Copenhagen and Amsterdam never experienced peaks as high as those observed in Oslo and Frankfurt. During the project the perceptions of street professionals - ambulance personnel, police officers, social workers - confirmed that the trends were decreasing, increasing or stable as shown in Table 2.

Differences arising from the course of the heroin epidemics
One possible explanation for these differences is the timing of the heroin epidemics. Although heroin was first seen in all four cities during the seventies, the epidemics developed differently. Amsterdam
Cases limited to residents; this differentiation was impossible in Frankfurt, where all cases are considered to be residents.

<table>
<thead>
<tr>
<th>City</th>
<th>Registered OD cases 1999</th>
<th>Number of residential cases</th>
<th>Rates per 100 000 population 15-64 included</th>
<th>Trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslo</td>
<td>104</td>
<td>67</td>
<td>20.0</td>
<td>Increase since 1989, stabilising since 1996</td>
</tr>
<tr>
<td>Copenhagen</td>
<td>57</td>
<td>44</td>
<td>14.2</td>
<td>Stable since first figures in 1982</td>
</tr>
<tr>
<td>Frankfurt</td>
<td>26</td>
<td>&lt;26</td>
<td>&lt;5.9</td>
<td>Sharp increase 1985-1991, sharp decrease afterwards</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>28</td>
<td>13</td>
<td>2.5</td>
<td>Increase until 1984, slow decrease afterwards</td>
</tr>
</tbody>
</table>

Table 2: Present OD figures -1999-, rates per 100 000 population and agreed OD mortality situation as a basis for this study.

and Copenhagen experienced a major increase in the prevalence of heroin use during the mid-seventies and the first part of the eighties. In Frankfurt the number of heroin users strongly increased during the latter half of the 1980s and in Oslo during the 1990s. The overdose curves correlate with the presumed prevalence of heroin use. Copenhagen, however, never saw such a peaked curve as those found in the other cities. Also, the sharp increase and decrease seen in Frankfurt were unparalleled in the other cities. Therefore future trends in Oslo cannot be predicted on the basis of the material.

What we see is that the timing of a heroin epidemic is only one of several influential factors. One such factor is immigration of heroin users. An increasing number of non-residential -predominantly German- heroin users migrated to Amsterdam during the first half of the 1980s, after which the number gradually decreased. The peak of the Frankfurt curve is influenced by the immigration of heroin users from neighbouring cities. We are currently seeing an increasing number of non-residential heroin users in Oslo: the steep increase may be influenced by immigration. As Table 2 shows, however, even if OD cases are limited to residents, the prevalence in Oslo is still high.

A police officer in Oslo: 'Many people from other parts of the country came to town. It used to be just a summer phenomenon, but now it's all year round.'
Cultural explanations-characteristics of drugs, drug users and drug scene

To what extent could differences in OD mortality be caused by cultural factors, such as differences and changes in the kind of drugs being used, the route of administration, concurrent use of other drugs, the purity and price of drugs and the nature of the drug scene?

Shifting drug trends

Oslo experienced a shift from an amphetamine to a heroin-oriented drug scene in the years preceding the increase in overdoses, and this has obviously contributed to the increase in mortality. During the 1990s cocaine gradually became a more dominant drug in the heroin scenes in Frankfurt and Amsterdam, which might be influential in the decreasing trend in OD mortality in these cities. The youth culture, and associated drug use, has gradually changed in all four cities. Among the changes is an increase in the use of MDMA and cocaine-snorting: since the late 1980s in Amsterdam, Frankfurt and Copenhagen, where youngsters are reported to be avoiding heroin. In Oslo an increase in the use of MDMA, and to a lesser extent cocaine, is a phenomenon of the late nineties. Young people are also starting with heroin, however.

Route of administration

Differences in the route of administration no doubt explain part of the difference in OD mortality between Amsterdam and the other cities. In an Amsterdam sample of methadone clients 37% ever injected heroin and 13% did so last month. The main route of administration is inhal- ing-chasing the dragon- which is obviously less dangerous in terms of OD mortality -in the same sample 88% ever inhaled and 50% did so last month. The number of needles exchanged almost halved during the 1990s, which indicates a further decrease in injecting drug use and provides another explanation for the slow decrease in the numbers of OD deaths in Amsterdam. In the other three cities injecting remains the most common route of administration, though Copenhagen has experienced a gradual increase, to a level of 50% of users inhaling by 1999. In Oslo almost all use is through injection -95% in 1999.

Mixtures of drugs

The risk-enhancing effect of the concurrent use of heroin and benzodiazepines and/or alcohol is well acknowledged. Differences and trends in combining these substances are thought to be responsible for part of the differences and trends in OD mortality. Intravenous use of Rohypnol, flunitrazepam is often mentioned as a risk factor in Oslo. In the 1980s the use of Rohypnol*, was thought to be associated with increased OD mortality in Amsterdam.
Drug user in Oslo: "People can stand around down at 'Plata' and be almost fatally ill, but won't go home and shoot up before getting hold of some Rohypnol, because it doesn't work otherwise, they say."

Police officer in Amsterdam: "Nowadays drug users are more sensible...in the 1980s they used Rohypnol, combined with alcohol, under influence of these drugs people are still able to inject but unable to fix the right amount of heroin."

Purity and price of heroin
The purity of heroin HCL is lowest in Frankfurt - only 10%. In Amsterdam and Copenhagen 30%-pure heroin base is sold; in Copenhagen 70%-pure heroin HCL is also available. In Oslo the purity of heroin is 45%. Purity that is unexpectedly higher than the average is thought to be the most hazardous. Differences in purity between Germany and Amsterdam are perceived as one of the reasons for the higher vulnerability of German heroin users arriving in Amsterdam in the 1980s. As none of the cities except Oslo carry out regular measurements of purity the trends are unknown. In Oslo, however, the purity has remained roughly the same. The rising overdose number, therefore, does not relate to differences in purity.

The cost per gram is lowest in Frankfurt - € 25 - and Amsterdam - € 35 - , high in Oslo - € 75 - and again moderate in Copenhagen - € 100 - . In all probability cost is not directly related to the risk of overdose, but it may reflect the purity of the drugs and demand versus supply. Also, cost and purity might influence the route of administration. In Oslo a drug user argued that injecting is a more economic method. In Frankfurt - but also in Amsterdam - it was argued that the low purity of the drugs was a reason to inject. Prices seem to have dropped in all the cities, which rules out price as an explanation for differential trends.

Drug user in Amsterdam: "I bought it from a dealer. I know well who always tells me if the purity of the drugs he sells has changed. This time however, the dealer forgot..."

Nature of the drug scene
Drug users are visible in all four cities. At present the centres of Frankfurt, Copenhagen and Amsterdam have visible but dispersed drug scenes. Oslo has a growing drug scene concentrated in one area in the centre - 'Plata'. Until the mid-1990s the Oslo scene also was dispersed, and users were chased from place to place by the police. Frankfurt experienced a similar, growing, large open drug scene near
the centre - the Taunusanlage - in 1989-1991. The steep increase in overdose numbers seen in Frankfurt and Oslo coincides with the development of the open drug scenes. The Taunusanlage was closed down in 1992 by combined efforts on the part of the police, social services and health authorities, and this coincided with a sharp drop in overdoses.

**Differences in strategies and interventions**

To what extent can interventions and measures implemented to reduce OD mortality in the cities explain differences?

Emergency services, willingness to call for help

Specialist ambulance services - rapid response vehicles - are provided in Frankfurt and Copenhagen, whereas in Amsterdam and Oslo the normal ambulance services take care of ODs. In all the cities, however, drug users indicated that they did not always call for an ambulance. Either they did not always recognise the seriousness of the situation, or they were afraid that others would find out about their drug use. In none of the cities are the police supposed to take advantage of an overdose to arrest people. Anecdotal evidence, however, shows that this is not always the case.

Drug user in Amsterdam: 'I put him to bed and went to sleep as well. When I woke up he was lying in exactly the same position and I thought... this is bad news!'

Drug user in Copenhagen: 'The Police searched us and confiscated our money together with the drugs that we were carrying, and while this was going on my friend was lying there without anybody helping him.'

In all the cities administering Naloxone is a standard treatment for severe overdoses. Small or subcutaneous dose of Naloxone are recommended. Nevertheless, there are reports of people waking up in a disoriented state. As the half life of Naloxon is shorter than that of heroin and especially methadone, they are at risk of fresh overdoses.\[1][2][7]

Drug-free treatment, high-threshold methadone treatment

Abstinence-oriented treatment is available in all the cities. This kind of treatment is predominant in Oslo, which launched 'immediate measures' in 1992: drug users who indicated that they wanted treatment were admitted to treatment centres immediately. Oslo introduced high-threshold methadone treatment on a small scale - < 10% of users - in 1998. Participants are supposed to abstain from the use of illicit drugs.
Low-threshold methadone treatment

The rise in use and use-related problems was met with a change in emphasis, from abstinence-oriented treatment towards low-threshold maintenance, in all the cities except Oslo. Low-threshold means that these programmes are easily accessible, requirements vis-à-vis patients are limited to those needed to run the programme safely and there are no waiting lists. Large-scale, low-threshold methadone treatment is provided in Copenhagen since 1984 - Amsterdam since 1981 - and Frankfurt since 1992 - and about 40% - approx. 2000 - of opiate users are reached on a daily basis. In all the cities, including Oslo, more stable methadone patients can be treated by their general practitioners. In Amsterdam heroin is experimentally being co-prescribed as part of methadone treatment for a selected group of drug users who have replaced their heroin use with methadone alone. Heroin of known quality and purity is used under supervision, and concurrent medical facilities are available. In Frankfurt a heroin trial is currently in preparation.

Social worker in Frankfurt: 'people are more in contact through the methadone programme. this also leads to the fact that they do not run around the streets in a physically weak condition - something that would endanger them further'.

Incarceration

In the case of prisoners who undergo detoxification during incarceration the period after release from prison is recognised to be a high-risk period. This can be prevented by maintaining tolerance of opiates with methadone during imprisonment. Methadone is prescribed to incarcerated drug users in Amsterdam and Copenhagen - and since 1999 in Oslo - This treatment is not available for all addicted prisoners, however; it depends on the prison regime and whether a patient is already receiving methadone treatment.

Drug user in Amsterdam 'Especially if people are incarcerated for only a short time, they will be focused on drugs. After they are released they start using the amount they used to take.'

User rooms

Using drugs on the street, in a dark place, in a hurry etc. was mentioned as a risk factor by respondents in the street level interviews. User rooms where people can take their drugs undisturbed in a hygienic, well-lit environment may reduce the number of overdoses. Also, supervision and a quick response in the event of an overdose is thought to reduce the number of fatal overdoses. User rooms were introduced in Frankfurt in 1995 and more have been provided since
then. Amsterdam reintroduced its user rooms on a smaller scale in 1997, since when the number has gradually increased. No user rooms are available in the other cities, although Copenhagen recently decided to introduce one. Drug users in all four cities recommend the implementation of user rooms in order to reduce OD deaths.

Ambulance nurse in Frankfurt: 'A well-kept helping facility that is also checked regularly, where the staff are trained in respiratory first aid, have the right equipment, know how to use it and know how to call for help in case of emergency minimises the risk.'

Police measures
Like treatment measures, police measures differ from one city to another. In Amsterdam, Frankfurt and Copenhagen police prevent gatherings of drug users. The police are particularly active in Copenhagen - the 'fine bus'. In Amsterdam drug users can be expelled from the Red Light District and Central Station area for a limited period if they gather or take drugs in public. During the second half of the 1980s the growing open drug scene in Frankfurt - at the Taunusanlage - was tolerated by the Municipality in a period of 'hands-off' drug policy. In 1992 the open drug scene was closed down as a result of police action flanked by concurrent action on the part of the Municipality - agreements with nearby cities about 'their' drug users - and the health services - low-threshold methadone programmes. The Oslo situation parallels the situation in Frankfurt during the 1980s in letting an open scene develop. Although the police in Oslo are worried by the growing number of drug users at Plata, they think police action will only move the problem instead of solving it.

Police in Oslo: 'We have said that the police can of course help move the drug users away from Plata, but we have to really think about this. Where do we really want to have them? They will band together somewhere no matter what.'

Dangers from prescription drugs
To cut down on the prescription of certain benzodiazepines, especially Rohypnol®, and barbiturates in Amsterdam the MHS advised general practitioners to change their prescription patterns. According to the respondents in Oslo, however, the main supply of Rohypnol®, comes from illegal imports. Measures to change prescription practices would only limit the availability of this drug to a moderate degree.

Table 3 summarises the main differences between the four cities as regards the prevalence and incidence of heroin use, the nature of the heroin scene and the measures implemented.
How do these differences in the prevalence of heroin use, drug culture and measures by the authorities relate to overdose trends? The Frankfurt example is of particular interest: here we find a steep increase in overdoses until 1991, obviously associated with a steep increase in the prevalence of heroin use, the development of an open drug scene and the immigration of drug users from nearby cities to Frankfurt. The decrease that started in 1992 is thought to be related to concerted action on the part of the Municipality, police and health services leading to the closure of the open drug scene. The main elements were a substantial police campaign flanked by large-scale, low-threshold facilities -methadone treatment- and a policy to encourage the remigration of non-residential heroin users. User rooms were introduced three years after the peak and did not turn the tide. They are highly valued in the city, however, and may contribute to preventing overdoses in the present situation.

In Amsterdam large-scale methadone treatment was already in place in 1981, whereas the peak in overdose mortality occurred in 1984: this is thought to be associated with the immigration of heroin users to Amsterdam, especially from Germany. These 'drug tourists' were used to a low purity of heroin, had injecting as their main route of administration, were reluctant to call for help, and had limited access to methadone treatment. Consequently they were more vulnerable...
able to death from an OD. The subsequent gradual decrease in OD mortality is thought to be related mainly to the decreasing number of foreign heroin users and the concurrent decrease in injecting drug use. On top of this the efforts to cut down on the prescription of Rohypnol®, and barbiturates may have lowered OD mortality. The habit of inhaling heroin is thought to be a major factor related to low OD mortality among residents. User rooms and experimental co-prescription of heroin were introduced on a small scale after the observed decrease in OD mortality, in 1997 and 1998 respectively.

The prevalence of heroin use in Copenhagen has been more stable than in the other cities. The city has not experienced a period of increased immigration of heroin users nor the emergence of an open drug scene. Low-threshold methadone treatment has been available on a relatively large scale. Overdose mortality has to some extent been associated with intravenous misuse of crushed methadone tablets and shorter-acting opioids such as ketobemidon. The moderate but relatively stable level of overdoses is likely to reflect this situation.

The Oslo trend is characterised by strong investment in prevention and drug-free treatment during the seventies and eighties. This policy did not prevent substantial incidence of heroin use after 1990, similar to that experienced earlier by the other cities. Immigration of heroin users to Oslo is probably contributing to the increasing mortality. In comparison with the other cities Oslo has more cumulative risk factors. It has a predominantly injecting heroin culture with widespread intravenous use of benzodiazepines such as flunitrazepam -Rohypnol®- and high-level alcohol consumption. An open drug scene is growing, moreover. Needle exchange and crisis intervention teams have been introduced, but there is no large-scale, low-threshold methadone programme to step up contact with heroin users.

**Discussion**

This multi-city study has several limitations. The regional methods and definitions used to obtain OD mortality figures vary, information on the circumstances of death was limited and the comparative approach rests on several crude city characteristics. Also, the numbers of heroin users and prevalence of use were not estimated using the same methodology. The interpretation of the material depended on the research group's ability to disentangle complex phenomena.

Some of the findings seem to be robust, however. There are marked differences between the cities in the prevalence of overdoses, which can be explained partly but not entirely in terms of differences in heroin use. Copenhagen and Amsterdam had an early increase in prevalence but never experienced any dramatic increase in overdoses. The likely explanation is that both cities introduced high-availability, low-threshold methadone programmes at an early stage. In addition,
Amsterdam has had a drug user culture dominated by inhalant use. Copenhagen has never had any immigration of non-resident users.

Another finding is that both Frankfurt and Oslo experienced a period of stable low prevalence of overdoses combined with a restrictive drug policy and an abstinence-oriented treatment system. The policy did not, however, prevent increasing heroin use with a concomitant steep increase in overdoses, in Frankfurt from 1985 and in Oslo from 1990. The situation grew worse with the development of open drug scenes, along with despondency and confusion on the part of the responsible city authorities. After a period of increasing harm and nuisance Frankfurt developed a systematic response, with combined measures to close down the drug scenes, return non-residents and provide addicts with low-threshold methadone treatment and viable social alternatives. In Oslo the answer has been partly to step up the present policy and partly to develop low-threshold health programmes and high-threshold methadone programmes, both of insufficient capacity to reach the majority of addicts. The likely conclusion is that increasing heroin use within a repressive system creates a difficult situation, marked by stigmatisation and stressing of segregated, often self-destructive addicts. Any change of policy needs to be based on a combination of closing down the destructive drug scenes and integrating users in an alternative setting. The single measure characteristic of the three cities that have avoided or halted the increase in overdose numbers is low-threshold methadone treatment.

As indicated, the cities have introduced several other measures. The actual impact of methadone treatment, user rooms etc. cannot be quantified. Even if it could, the effects cannot be extrapolated from one city to another. Probably the effects are associated with the characteristics of the drug culture. Given the low OD mortality risk of Amsterdam heroin users the additional preventive effect of user rooms or methadone treatment is thought to be more limited than that of similar interventions in Frankfurt. The effectiveness of future initiatives to reduce overdose deaths should therefore be evaluated.

The choice of cities has undoubtedly influenced the recommendations in this study. Apart from Oslo, the drug policies of the selected cities have moved away from the traditional approach, aimed at preventing drug use and curing drug users. The results may have been different if cities with more restrictive policies had been included, such as Stockholm ·Sweden·, or cities of similar size in the United States. In many respects the analysis presented in this study, however, is in line with a recently published study on the response of Victoria ·Australia· to the rising number of OD deaths during the 1990s¹⁶, and parallels the Swiss experience.²²
As for Oslo, the study indicates that increased availability of methadone maintenance is a prerequisite in any change of policy. This, however, will not be sufficient without combined measures to close down the drug scenes and create viable alternatives, as is illustrated by the striking similarity between Oslo in the 1990s and Frankfurt in the 1980s. In both cities an open drug scene emerged, owing to an increasing prevalence of injecting heroin use and a hands-off municipal drug policy. We believe that reduction and dispersal of the open drug scene is of the utmost importance. Police intervention alone will probably not solve the problem, however. The Swiss experience shows that closure of the open drug scene should be accompanied by higher availability of low-threshold methadone treatment.

Police action is likely to be more effective and more acceptable to drug users if it is flanked by a variety of medical and social services. Ultimately the message is one of replacing segregation and stigmatisation with integration.

A restrictive policy is often thought to prevent an increase in drug use. It might therefore be feared that introducing harm reduction measures could lead to higher number of drug users. Our study does not support this notion. The level of heroin use seems to be the same at present in all four cities in spite of different policies. Intravenous drug use in Amsterdam decreased during the past decade and the same thing seems to be happening, to a lesser extent, in Copenhagen. Low-threshold methadone treatment reduces the amount of heroin taken. The Municipality of Oslo needs to find ways of discouraging immigration from other cities and encouraging immigrant heroin users to return home. Efforts should also be made to cut down on the prescription of Rohypnol and to replace this benzodiazepine with less harmful ones.

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REFERENCE RATES IN MORTALITY STUDIES AMONG OPIATE USERS

Abstract
Objective Background Mortality studies among drug users are generally single-group studies. Alongside the crude mortality rate the Standardised Mortality Ratio SMR is a widely used summary statistic. However, the SMR does not always improve the comparability of study populations with different age and sex distributions. SMRs are calculated relative to different reference rates - based on different regions and time periods - and age and sex-specific rate ratios - opiate users vis-à-vis the general population - are expected to be heterogeneous.

Design This study is based on the results of nine European cohort studies carried out by the European Monitoring Centre for Drugs and Drug Addiction EMCDDA. A Poisson regression model describes the association between age, gender and mortality rates among opiate users.

Results Mortality rate ratios - opiate users vis-à-vis the general population - are heterogeneous: lower in the older age categories and higher among males. Valid comparison of mortality among opiate users can not be obtained when the general population is used as a reference. Specific 'Opiate user reference rates' are presented.

Conclusions The reference rates provided in this study can be used to calculate comparable SMRs and improve the comparability of single-group mortality studies among opiate users.

Introduction
Mortality Rates MR among opiate users are consistently higher than the rates observed among the general population. Reported mortality rates among opiate users vary widely, from 9 per 1000 person-years py among non-injecting heroin users in Amsterdam to 72 per 1000 py among Swedish street addicts on a waiting list for methadone treatment in Stockholm. Most mortality cohort studies among opiate users are single-group studies. When analysing single groups the number of cases observed in the study group is compared with the number of cases expected to occur in the general population. To calculate the number of expected cases, rates for the reference population stratified by age and gender are multiplied by the amount of person time for similar strata in the study population. The ratio of observed to expected cases is called the Standardised Mortality Ratio.
The SMR adjusts for differences of age and gender distribution between the study population and the reference population. Results based on SMRs must be interpreted carefully, however, since they depend on a chosen reference population and have no absolute meaning. SMRs reported in studies with different age and sex distributions are only comparable when the reference population is similar and the stratum-specific rate ratios are homogenous.\textsuperscript{13}

A mortality rate of 27.4 per 1000 py was observed among intravenous drug users \textit{IVDU} in Oslo \textit{- Norway}, a figure 31 times higher than the rate expected in the general population.\textsuperscript{15} The rate is similar to that observed among substance abusers on welfare in New York City - 26.4 per 1000 py. The age-adjusted rate ratio of the study group to the New York population, however, was 5.2.\textsuperscript{16} Although it is tempting to compare these measures by using the ratio between the two SMRs, we cannot say that - adjusted for age and gender differences - the latter population had a six times higher risk. This problem is already recognised among studies of opiate users. Although the SMR of a Swedish cohort of opiate users established in 1981 - 1982 was significantly higher - 22.3 95% confidence interval 18.0, 26.0 - than that of a cohort established using similar methodology in 1971 - 1972 - 14.8 95%CI 10.4, 19.3 - , inter-cohort comparison using Cox regression did not show significant differences. Two explanations were given, the increased life expectancy of the Swedish population and the differences in age and sex distribution between the two cohorts.\textsuperscript{17,18} This example indicates the problem of different reference populations \textit{similar region but different time period} - and bias as a result of heterogeneity in stratum-specific rate ratios.

This heterogeneity has also been described in other studies of mortality among opiate users. Rate ratios generally decline with age and are higher among females than males.\textsuperscript{19,20,21} Joe \textit{- 1982} reported death rates of 9.5 per 1000 py among the under-21s and 28 per 1000 py among addicts in the over-30 age group, whereas the mortality rate in the general US population was fourteen times lower - 0.7 per 1000 py - in the youngest and three times lower - 6.3 per 1000 py - in the oldest age group.\textsuperscript{22} Similar excess mortality rates were observed among male and female heroin users in Rome - 9.1 and 8.5/1000 py respectively. The SMR was twice as low among males as among females, however, - 9.3 and 18.1 respectively.\textsuperscript{23} Similarly, Bschor \textit{- 1982} reported 12-fold higher mortality among male opiate users - crude rate: 17.2/1000 py - and 29-fold higher mortality among female opiate users - crude rate: 14.4/1000 py.\textsuperscript{24} Differences between male and female SMRs are related to the sex differential in mortality rates in the general population, which are higher among males. The extent to which male mortality exceeds female mortality, however, varies during lifespan, reaching its peak in early adulthood.\textsuperscript{25} The European Monitoring Centre for Drugs and Drug Addiction
EMCDDA set up working groups to provide empirical data and improve the comparability of data. One of these working groups studies mortality among known populations of opiate users. So far nine cohorts have been established in nine European countries, regions or cities: Amsterdam, Barcelona, Denmark, Dublin, Hamburg, Lisbon, Rome (Lazio region), Sweden and Vienna. Using the data from the EMCDDA cohorts, stratum-specific mortality rates can be calculated to serve as reference rates in other mortality studies and provide a comparable single outcome measure of mortality studies among opiate users.

**Methods**

*Study population*

Data from nine cohorts of opiate users collected by the EMCDDA Working Group were used for the analysis. All cohorts consisted of prevalent and incident treatment participants, who were followed up using similar methodologies. Table 1 shows the selected periods and amount of person time for each cohort. Most cohort studies were started and followed during the 1990s; the Vienna and Sweden cohorts included observation time from the late 1980s as well. The amount of person time ranged from 4164, observed in the Swedish cohort during 1987-1991, to 18963, observed in the Roman cohort observed during 1992-1996. Cohorts were followed up and vital status assigned using national or municipal registers. Age at entrance ranged from 15 to 49 years and was coded in six five-year categories. A more detailed description of the various cohorts and methodologies has been published elsewhere.

*Analysis*

The aim of the study was to describe the relation between mortality, opiate use, age and gender in order to provide reference rates. To limit the possible confounding effect of trends over calendar time a maximum of five years were described for each cohort. During follow-up the age of the population increases and trends in calendar time may interfere with the relation between mortality and age. During the five years individuals could contribute observation time to a maximum of two age categories. Observation time was censored at the date of death or, as the study is limited to opiate users in the 15-49 age range, at the date of the person's 50th birthday.

In order to examine whether the mortality rate ratio between cohort participants and the general population varies across age and gender categories, multivariate Poisson regression analysis was performed. Mortality rates for the general population were calculated using data on the total number of deaths and inhabitants stratified by age and sex in all countries of the European Union EU. Where possible
Table 1  Location, period and size of cohorts

<table>
<thead>
<tr>
<th>Country/City</th>
<th>Selected Period(s)</th>
<th>Person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vienna</td>
<td>1989-1993</td>
<td>9076</td>
</tr>
<tr>
<td>Dublin</td>
<td>1994-1997</td>
<td>10344</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>1994-1998</td>
<td>12063</td>
</tr>
<tr>
<td>Rome (Lazio)</td>
<td>1992-1996</td>
<td>18963</td>
</tr>
<tr>
<td>Lisbon</td>
<td>1992-1996</td>
<td>6935</td>
</tr>
<tr>
<td>Denmark</td>
<td>1996-1999</td>
<td>17245</td>
</tr>
<tr>
<td>Hamburg</td>
<td>1991-1995</td>
<td>7292</td>
</tr>
<tr>
<td>Sweden</td>
<td>1987-1991</td>
<td>4164</td>
</tr>
<tr>
<td>Barcelona</td>
<td>1992-1996</td>
<td>11578</td>
</tr>
<tr>
<td>All cohorts</td>
<td>1987-1999</td>
<td>97603</td>
</tr>
</tbody>
</table>

The national statistics for 1995 were used. The Poisson regression model can be described by the following equation:

\[
\ln MR = \alpha + \beta_1(\text{age}) + \beta_2(\text{sex}) + \beta_3(\text{age} \times \text{sex}) + \beta_4(\text{opiate users}) + \beta_5(\text{age} \times \text{opiate users}) + \beta_6(\text{sex} \times \text{opiate users}) + \beta_7(\text{cohorts})
\]

The logarithm of mortality incidence rate MR changes linearly with equal-increment increases in age \( \cdot \) categories coded 0 to 6: 15-19 to 45-49 years, sex \( \cdot \) categories 0,1: female, male \( \cdot \) and the exposure variable opiate users \( \cdot \) i.e. participation in one of the EMCDDA cohorts, categories 0,1: no, yes \( \cdot \) Differences between individual cohorts are also indicated \( \cdot \) categories 0-8, 0: Lisbon cohort. The age variable was used as both a continuous and a categorical variable: the continuous variable is shown. Other variables are categorical. The \( \alpha \) represents the logarithm of the estimated mortality rate of the subgroup with the lowest mortality rate, females in the general EU population in the youngest age category, 15-19 years. The \( \beta x \) represents the logarithm of the rate ratios. The product terms represent departure of the previously indicated multiplicative effects.

Based on the results of the Poisson regression analysis, estimated stratum-specific rates for opiate users, rate ratios and rate differences between opiate users and the general EU population are shown. Two types of SMR are also calculated, the first taking the EU population as a reference, the second using the expected rates among opiate users obtained from the Poisson regression analysis. The Poisson distribution is used as a probability model to calculate the 95% confidence intervals of the SMRs.
Table 2  Age and gender distribution of cohorts

<table>
<thead>
<tr>
<th>Country/City</th>
<th>Gender</th>
<th>Mean</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Union</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cohorts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vienna 1989-1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dublin 1994-1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amsterdam 1994-1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rome 1992-1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisbon 1992-1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark 1996-1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamburg 1991-1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden 1987-1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barcelona 1992-1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Description of the study population

Table 2 shows the age and gender distribution of the population aged 15 to 49 years, the combined cohorts of opiate users and the nine cohorts separately. Compared to the population, the youngest age category -15-19 years-, the oldest age category -40-49- and females were all underrepresented among opiate users. The cohorts of opiate users varied in terms of age and gender. The Amsterdam -1994-1998- and Danish -1996-1999- cohorts were the oldest, the Dublin -1994-1997-, Lisbon -1992-1996- and Vienna -1989-1993- cohorts were the youngest. On average 25% of person time was observed among women only 18% in the Lisbon and Rome cohorts, whereas women contributed 30% and 37% of the total person time in the Sweden and Vienna cohorts.

Table 3 shows the observed numbers of deaths and mortality incidence rates. The total observation time represents 97,603 py, the total number of deaths is 2230, leading to an average mortality rate of 23.4 per 1000 py. The highest mortality rates were observed in the Barcelona -62.1- and Sweden -34.1- cohorts. The lowest mortality rates were observed in the Vienna -9.1-, Dublin -10.9- and Amsterdam -14.2- cohorts.
Table 3  Observed deaths and incidence rates

<table>
<thead>
<tr>
<th>Country/City</th>
<th>PY</th>
<th>Deaths</th>
<th>IR per 1000</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vienna</td>
<td>9076</td>
<td>83</td>
<td>9.1</td>
<td>7.4; 11.3</td>
</tr>
<tr>
<td>Dublin</td>
<td>10 344</td>
<td>113</td>
<td>10.9</td>
<td>9.1; 13.1</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>12 063</td>
<td>171</td>
<td>14.2</td>
<td>12.2; 16.5</td>
</tr>
<tr>
<td>Rome (Lazio)</td>
<td>18 963</td>
<td>367</td>
<td>19.4</td>
<td>17.5; 21.4</td>
</tr>
<tr>
<td>Lisbon</td>
<td>6935</td>
<td>135</td>
<td>19.5</td>
<td>16.4; 23.0</td>
</tr>
<tr>
<td>Denmark</td>
<td>17 245</td>
<td>383</td>
<td>22.2</td>
<td>20.3; 24.8</td>
</tr>
<tr>
<td>Hamburg</td>
<td>7292</td>
<td>169</td>
<td>23.2</td>
<td>19.9; 26.9</td>
</tr>
<tr>
<td>Sweden</td>
<td>4164</td>
<td>142</td>
<td>34.1</td>
<td>29.4; 39.6</td>
</tr>
<tr>
<td>Barcelona</td>
<td>11 578</td>
<td>719</td>
<td>62.1</td>
<td>52.5; 73.5</td>
</tr>
<tr>
<td>All cohorts</td>
<td>97 603</td>
<td>2280</td>
<td>23.4</td>
<td>22.4; 24.3</td>
</tr>
</tbody>
</table>

Multivariate Poisson Regression Analysis

Table 4 and Fig. 1 show the results of the Poisson regression analyses. The baseline mortality rate is the estimated rate for females in the general population of the European Union in the 15-19 age range, who had the lowest mortality rate according to the estimates from the Poisson regression analysis, 0.22 per 1000 py. In comparison with the baseline category, the youngest male category in the European Union shows a mortality rate 3.05 times higher. Mortality rates increase with age, among females 1.44 times higher with each 5-year age category. The increase with age is less among males \( \cdot 1.44 \cdot 0.92 = 1.32 \cdot \) with each age category. Thus the male:female ratio decreases with increasing age categories and is 1.89 among the oldest age group \( \cdot 45-49 \text{ years} \cdot \).

As in the general population, the lowest mortality rates among opiate users were observed among the youngest category of females. Among the youngest category of opiate users, however, the male:female ratio is only half that observed in the general population \( \cdot \text{i.e.} \ 3.05 \cdot 0.50 = 1.53 \cdot \). Similarly, a lower increase in mortality rates with increasing age category was observed among opiate users compared to the general population \( \cdot \text{among males and females the rate ratios were 1.22 and 1.31 per age category respectively} \cdot \). Among the highest age category male and female rates are approximately equal.

Table 4 also shows the rate ratios for the various cohorts compared to the Lisbon cohort. In this analysis the Lisbon cohort was
In IR: natural logarithm of the Incidence Rate; alpha in Poisson regression model
In RR: natural logarithm of the Rate Ratio; beta in Poisson regression model
95% CI: 95% Confidence Interval

**Table 4** Results of Poisson Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>In IR</th>
<th>Rate Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females EU population 15-19 yrs</td>
<td>8.438</td>
<td>0.22 0.21-0.22</td>
</tr>
<tr>
<td>Age 5-year categories</td>
<td>0.364</td>
<td>1.44 1.43-1.45</td>
</tr>
<tr>
<td>Male</td>
<td>1.116</td>
<td>3.05 2.98-3.12</td>
</tr>
<tr>
<td>Male * Age</td>
<td>-0.080</td>
<td>0.92 0.92-0.93</td>
</tr>
<tr>
<td>Opiate users reference cohort</td>
<td>3.749</td>
<td>42.46 34.71-51.95</td>
</tr>
<tr>
<td>Opiate users * Age</td>
<td>-0.099</td>
<td>0.91 0.88-0.93</td>
</tr>
<tr>
<td>Opiate users * Male</td>
<td>-0.698</td>
<td>0.50 0.45-0.55</td>
</tr>
</tbody>
</table>

**Individual Cohorts** reference: Lisbon

<table>
<thead>
<tr>
<th></th>
<th>In IR</th>
<th>Rate Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vienna</td>
<td>-0.796</td>
<td>0.45 0.34-0.59</td>
</tr>
<tr>
<td>Dublin</td>
<td>-0.584</td>
<td>0.56 0.43-0.72</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>-0.718</td>
<td>0.49 0.39-0.62</td>
</tr>
<tr>
<td>Rome (Lazio)</td>
<td>-0.147</td>
<td>0.86 0.71-1.05</td>
</tr>
<tr>
<td>Lisbon</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Denmark</td>
<td>-0.181</td>
<td>0.83 0.68-1.02</td>
</tr>
<tr>
<td>Hamburg</td>
<td>0.066</td>
<td>1.07 0.85-1.34</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.382</td>
<td>1.47 1.16-1.86</td>
</tr>
<tr>
<td>Barcelona</td>
<td>1.034</td>
<td>2.81 2.34-3.39</td>
</tr>
</tbody>
</table>

Table 5 shows the estimated mortality rates among opiate users, rate ratios and rate differences compared to the EU population by age and sex. In terms of Greenland & Rothman 1998, the age and sex-specific mortality rates between opiate users and the general population show both rate-ratio heterogeneity and rate-difference hetero-
The highest rate ratios - 42.5 - were observed among the youngest females - age 15-19 years -. The lowest estimated rate ratio of opiate users to the EU population was 11.7; this was found among males in the oldest age category - 45-49 years -. In the EU population the mortality rate among 45-49 year old males was 3.6 per 1000 py - 16.5 times higher than among the youngest females -, whereas a rate of 42.3 per 1000 py was estimated among the oldest male opiate users - 4.6 times higher than among the youngest females -.

In contrast to rate ratios, rate differences increased with increasing age categories. Although the relative mortality hazard decreased, the absolute hazard increased. The lowest estimated rate difference was observed among the youngest female opiate users - 10.9 per 1000 py -.

The highest estimated rate difference was observed among the oldest female opiate users - 43.1 per 1000 py -.
Table 6 shows the observed mortality rates and expected rates based on stratum-specific reference rates for the European population and the reference rates shown in Table 5. It compares the SMRs of the individual cohorts based on the opiate users reference rates and the EU reference rates. The results of the opiate users are similar to the results of the Poisson regression analysis in table 3.

The expected rates based on this study are higher than those for the general population, as they reflect the average mortality rate observed among opiate users. The differences between the expected rates reflect the differences in age and sex distribution in these cohorts. The relative differences between the expected rates for populations with different age or sex distributions are smaller if reference rates for opiate users are used, with the result that the differences between the cohorts also appear to be smaller. The age and sex-adjusted mortality rates for the Danish cohort are 31% higher than for the Lisbon cohort if the EU population is taken as a reference, but only 20% if reference rates for all the cohorts are used. Similarly, the SMR for the Dublin cohort is 34% higher than those observed in Amsterdam if the EU rates are used as a reference, but only 14% higher if the cohort is used as a reference.
### Discussion

Our study confirms that mortality among opiate users is consistently higher than that expected in the general population and that mortality rates among opiate users vary widely. The variation observed between the cohorts reflects the differences reported in the literature. The study also describes the heterogeneity in the age and sex-specific rate ratios and rate differences between opiate users and the general population. The rate ratios between opiate users and the general population are lower among older and male opiate users. In contrast, the differences between the mortality rates of opiate users and the general population increase with age and are higher among males. Stratum-specific reference rates - Table 4 - are calculated based on the relation between sex, age and mortality rates among nine cohorts of drug users. These reference rates offer more realistic 'expected' values than those derived from the general population, and more homogeneous rate ratios across different strata, thus enabling more comparable, single-outcome parameters to be reported in single-group mortality studies of opiate users.

SMRs are widely used in occupational health studies. A common experience when studying cohorts of employed individuals is that the
risk of dying in the first few years after entering the cohort is less than in the general population - the healthy worker effect.\textsuperscript{118} e.g. an SMR of 0.63 was reported among Canadian air force pilots.\textsuperscript{119} Instead of the healthy worker effect 'the sick heroin user effect' may be applicable in these studies. Tobacco dependence, poverty and mental illness are associated with the start and/or continuation of heroin use and partly explain the higher mortality rates.\textsuperscript{119,121,122}

Participants in cohort studies of opiate users · including these nine cohorts · are generally not 'random samples' of opiate users but prevalent or incident treatment participants recruited from treatment centres or hospitals. They do not include anyone who manages to stop using opiates without professional help\textsuperscript{123} or, in the case of those who request treatment, the period from the start of heroin use to the request for treatment · median duration five years ·. The study population is thus generally limited to genuinely opiate-dependent persons. The admission criteria may also vary from one treatment centre to another, contributing to differences in mortality rates between cohorts. The high rates observed in the Swedish sample are no doubt due partly to the selection of the hospitalised · in-patient · population; these data are probably valid only for severely addicted persons.\textsuperscript{17}

A detailed explanation of the differences in regional mortality rates is beyond the scope of this study and will have to be the subject of a subsequent study. Some remarks can be made, however. The high rates observed in Barcelona are due to AIDS-related mortality from the HIV epidemic among drug users.\textsuperscript{124} In the study period AIDS and drug overdose were the leading causes of death among the general young adult population in this city.\textsuperscript{125} Most probably this is a temporal phenomenon, a substantial decrease was observed after 1996 · EMCDDA annual report ·. The low rates in the Amsterdam cohort are partly due to the fact that only a minority of these drug users inject: inhaling heroin heated on foil · chasing the dragon · is associated with lower risk.\textsuperscript{11}

Adjusted SMRs can be obtained from published studies if the numbers of person-years stratified by age and sex and the total numbers of deaths are given. The study by Eskild · 1993 · conducted among IVDU with known HIV status in Oslo would give an 'opiate user SMR' of 1.47 · 95\%CI: 1.19, 1.82 ·, similar to the SMR of the Swedish cohort presented in this study.\textsuperscript{15} Based on the data in Friedman's study\textsuperscript{4} · data limited to age 18-54, assuming similar gender distribution across age categories · an opiate user SMR of 1.03 · 95\%CI: 0.76, 1.42 · can be calculated. Although the mortality rates were approximately equal and the SMR in the Oslo study population was six times higher than that in the New York population, we may conclude that, adjusted for differences in age and sex distribution, the mortality rates among the Oslo opiate users are 1.43 times higher than those among substance abusers on welfare in New York City.
Limitations and remarks

The EMCDDA strives to improve the comparability of cohorts of opiate users using similar follow-up procedures and similar variables at intake. The cohorts described in this study are partly based on cohorts that have already been studied, Italy, Sweden, Austria, or cohorts constructed from available data, and the criteria were not always met completely. The study only used a limited quantity of data: age, sex, time of follow-up and date of death. Ideally national registers should be used to check vital status at follow-up. The Amsterdam and Dublin cohorts, however, used regional registers to update vital status, so the mortality rates for this cohorts may be underestimated. Within the limited follow-up period this is not expected to lead to a major bias, nor is it expected to influence age and sex differences as regards mortality.

The absolute incidence rate depends on the selected cohorts and the selected time period, but it can be regarded as an average mortality rate as reported in the literature. In this study four cohorts showed higher mortality rates and four lower.

The relation shown here between age, gender and mortality rates was an average observed among the nine cohorts. The largest cohorts, Rome, Barcelona, had more influence on the relations than the smaller samples, but these large cohorts did not show extremely low or high relations between mortality and age or sex. The Vienna cohort did show an extreme relation between mortality and age, the increase with age category was higher than that observed in the general population.

The bias caused by the heterogeneity in the age and sex-specific rate ratios is fairly small compared to the major differences in mortality rates between cohorts, so specific reference rates may seem to be of limited use. When more homogeneous populations, e.g. in a similar region at different time periods or with similar drug use characteristics, are compared, however, the differences may not be that great. In an ageing population of opiate users, for example, a constant SMR may mask a gradual increase in mortality over time. In this paper SMRs are calculated with similar reference rates. As the Oslo-New York example shows, the SMRs found in the literature are based on different reference rates and show much more variation.

Conclusion

The reference rates presented here can be used to enhance the international comparability of single-population mortality studies among opiate users and provide a starting point for explaining differences between cohorts. The relations shown between age and sex are considered reliable for opiate users observed in the 15-50 age range, and
the mortality rates are an approximate average of those observed in longitudinal studies of opiate users, thus providing a meaningful expected number of deaths in single-group mortality studies of opiate users.

We would like to encourage the use of an SMR with the presented rates among opiate users as a reference. Moreover, data of single group mortality studies should be presented in a stratified manner, i.e. numbers of deaths, person-years of observation time differentiated by age and sex. This would allow others to compare different studies with meta-analyses.

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