Prevalence morbidity and mortality among heroin users and methadone patients

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Abstract
The objective was to determine the tuberculosis incidence and related factors among drug users in 3 methadone maintenance programmes in Amsterdam to see whether the present screening procedures are adequate. The study population was selected from the Central Methadone Register CMR. Cases were identified during hospitalization and during routine screening of ambulatory methadone clients. The data were generated by drug and tuberculosis departments of the Amsterdam Municipal Health Service MHS. From 5044 clients, 43 new cases were identified. The incidence of tuberculosis was 386 per 100 000 person years $py$ and increased with age and period of registration with the CMR. After correction for age, sex and period of registration, the incidence among clients of the general practitioners GP was the lowest. The incidence rate among the general MHS clients is 9 times higher and in the MHS programme for prostitutes and illegal foreigners it is 27 times higher than in the GP population. The increased risk for drug users treated at the MHS indicates lifestyle as a risk factor; MHS clients are more involved in the drugs scene than GP clients. On the basis of this study, periodic screening limited to clients of the MHS would seem to be adequate for the present.

Introduction
The incidence of tuberculosis varies not only between countries but also within countries. On the whole, the incidence is low in Western countries, and high in many of the developing countries. However, this is not the case in all Third World countries. In Morocco the incidence is high: in 1990 there were 103 cases per 100 000 inhabitants, compared with Surinam with only 7.1 cases per 100 000 inhabitants during the same year.$^{10}$ In 1990 there were 9.2 tuberculosis cases in The
Netherlands and 10 cases in the USA, per 100,000 inhabitants. Until the end of the 1980s, the number of new cases in both countries declined steadily, after which the decline came to a standstill in The Netherlands and changed into an increase in the USA.

The observed decline in the USA was stronger among whites than among non-whites. The relative risk for non-white persons compared to white persons rose from 2.9 in 1953 to 5.3 in 1987. The incidence of tuberculosis among females is approximately half the incidence among males in both blacks and whites. In The Netherlands too, the incidence among individuals with Dutch ethnicity is still declining -5.4 per 100,000 in 1990-, whereas it is increasing slightly among foreign citizens. In 1990, the incidence among the non-Dutch part of the population was 87 per 100,000; this is almost 18 times the incidence among the Dutch.

An increase has been observed in subgroups of the Dutch as well. In Amsterdam, the incidence among Dutch males aged 25-49 years rose from 16 per 100,000 in 1984 to 35 per 100,000 in 1990. The increase in this group is at least partly attributable to the HIV epidemic. The elderly, prisoners, drug users, homeless and alcoholics are particularly susceptible to tuberculosis. The vulnerability lies either in a decline in physical condition causing tuberculosis reactivation, or in a lifestyle exposing them to new infection. Age, length of stay in shelters and intravenous drug use appear to be related to active tuberculosis among homeless people with physical ailments. In 1979, before the outbreak of the HIV epidemic, Reichman et al. stated that drug users were a new high-risk group for tuberculosis. That time the incidence in New York was 27 per 100,000 persons. In the municipal methadone maintenance programme, the incidence was almost 20-fold higher, namely 510 cases per 100,000 persons.

With the HIV epidemic among drug users, the probability of active tuberculosis increased as a result of an ineffective cellular immune system. Among HIV positive drug users with a positive tuberculin test, the incidence of active tuberculosis is 8% per year. The overall probability that a latent tuberculosis infection will express itself in the form of active tuberculosis in an immunocompetent person is approximately 10%. Moreover, the development of Multidrug-resistant tuberculosis MDR-TB within this high risk population gives reason for concern. Inadequate therapy in the sense of insufficient drugs, or too short therapy and lack of compliance of the patient is considered to be the cause of the MDR TB.

In Amsterdam, the total number of drug-addicts is estimated to be 7000. According to recent estimations this number should be 5000; see chapter 5 figure 2A. Approximately one third are from the Netherlands, 25% from 'ethnic groups' -born in Surinam, the Dutch Antilles, Turkey or Morocco- and 40% are from other foreign countries.
The majority of the 1700 ethnical drug users were born in Surinam. One third of the estimated 3000 foreign drug users has a residence permit and is permanent resident of Amsterdam. The majority of the foreign drug users has no residence permit, and most of them are temporarily residing in the city.

Amsterdam has an extensive network of low-threshold drug relief agencies. The MHS and 200 general practitioners are the main providers. Harm reduction is the main objective and methadone prescription is the core activity within these services. The services are limited to those citizens who are registered as citizens of Amsterdam. Basic medical care, for the destabilised, active drug users, is provided for by the MHS. Methadone prescription by the GPs is limited to the more stabilized drug users, with a diminishing addiction and a stable social life. Only within the programme of the MHS is screening for tuberculosis mandatory. Every year approximately 3500 people use these agencies.

The objective of this study is to determine the incidence of tuberculosis among drug users receiving methadone from the MHS and GPs in Amsterdam. Incidence rates in the period of 1989-1993 and differences in incidence rates between subgroups are presented. As an additional spin-off, the study tentatively answers the question whether the existing policy of methadone prescription to large numbers of stabilized drug-users by the GPs without mandatory periodical screening for tuberculosis is acceptable.

Methods

Study population

Information from the Central Methadone Registers CMR was used to define the study population. Since 1980, the CMR has registered all methadone prescriptions in Amsterdam. For each client, a number of individual details are collected: gender, date of birth, country of birth and methadone, e.g. dosage, date of first prescription and prescribing physician. Methadone is dispensed in various programmes in different locations: police stations, jails, therapeutic programmes by the Jellinek Centre, and in methadone maintenance programmes by the GPs and Municipal Health Service. Approximately 90% of the methadone is dispensed through the low-threshold programmes of the MHS and GPs.

Methadone can be supplied from different locations in the course of 1 year. The various locations are divided into 3 categories, each one excluding the other two. The first two are MHS locations: 1. the Prostitution and Foreigners Outpatient Clinic PFO for prostitutes and illegal foreigners and 2. the general outpatient clinics or methadone bus for the Dutch resident active drug users that are not eligible for the GP methadone programme. The third category is the...
GP-clients. The clients in the worst circumstances are in the PFO; in addition to their addiction they work as prostitutes and/or are illegal foreigners to whom medical care and methadone is only provided in cases of serious health problems. The out-patient clinics provide intensive medical and social care to clients with a problematic addiction history who are not able or motivated to detoxify. The methadone bus programmes provide methadone exclusively to clients who need less help in the medical and social area. General practitioners offer help to drug users who are more stabilized and to some extent integrated.

Clients receiving methadone maintenance treatment from GPs and MHS and who were living in Amsterdam, were selected. Drug users with an address outside Amsterdam and drug users being supplied with methadone less than 7 times in the year of observation were excluded from the study. Moreover, to prevent overestimation of the incidence, persons who turned to the Drug department for help because of tuberculosis were excluded from the study. These clients are defined as clients having tuberculosis diagnosed during the first month of the study. Finally those persons with a known history of tuberculosis having a relapse within the observation period were excluded.

Determination of the observation time
The study period runs from January 1989 through December 1992. The individual observation time is determined per calendar year. The start of the individual observation time is the first month of the year concerned in which methadone is supplied at least 7 times. The 31 December of the year concerned marks the end of the individual observation time. In the event of death, the date of death marks the end of the observation period and if tuberculosis is diagnosed in a person, the date of the diagnosis marks the end of the observation time.

If a client is provided with methadone at different locations in 1 calendar year, the total observation time of that year is attributed to the location at the top of the hierarchy, irrespective of the number of supplies in that location. The order of rank is, successively, PFO, general outpatient clinic or bus and GP. This hierarchic division takes into account the fact that the client populations have a decreasing degree of social and medical problems.

Case-finding
The information on tuberculosis cases comes from 3 sources. First, through the Hospital Project of the MHS, which counsels all drug-users hospitalized in Amsterdam. The second source of information is the 6 monthly tuberculosis screening by X-ray of all methadone clients of
the MHS at the tuberculosis department, a civil servant agency of the MHS. Thirdly, all cases of tuberculosis in Amsterdam are reported to the tuberculosis department, including drug users not known at the drug department. Cases of tuberculosis reported in a year during which a client was not in treatment are omitted from the study.

In the period 1989-1992 a total of 80 drug users were diagnosed as having tuberculosis in Amsterdam. Ten cases were diagnosed in 1989, 20 in 1990, 30 in 1991 and another 20 during 1992. In all cases tuberculosis was diagnosed through a microbiological specimen or a bacterial culture. Eventually, 43 cases were included in the study.

Eight patients had a relapse and were not included. Six of these cases obtained methadone at the MHS and 2 did not receive methadone during the study period. Of the 72 cases in which tuberculosis was diagnosed for the first time, 10 were not registered with the CMR, but were registered with the hospital project or tuberculosis department of the MHS. Three cases were registered but did not receive methadone in the whole of the study period. Nine cases did receive methadone during the study period but did not during the year tuberculosis was diagnosed and 1 case had been supplied with methadone during less than 7 days in the year concerned. These 10 cases all received methadone at the MHS, 4 of them at the PFO. In 6 cases, tuberculosis was diagnosed within 1 month after the first supply of methadone. Five of them were clients of the MHS and 1 of the GP.

**Analysis**

The trend in incidence was studied using a Poisson regression technique, in which the 4 annual cohorts are grouped into a single cohort.
**Table 2**  Distribution of person years *py* per subgroup and methadone programme

with different values on the dummy-variable `year`. To carry out a Poisson regression the condition `constant rate over time` has to be met.\(^\text{113}\) Analyses to distinguish sub groups were also carried out using Poisson regression. Subgroups are distinguished by age, sex, country of origin and time and location of methadone distribution.

**Results**

**Description of the study population**

The study population consisted of 5044 individuals studied for 1 or more years. Those who were observed for 1 year · 33% of all clients · contributed only 10% of the total observation time. Long-term methadone maintenance clients predominate in the study.

In Table 1, the socio-demographic profile of the study population during the study period is presented. For each year, approximately 71% of the study population are males. The mean age rises during the study period: in 1989 it was 32.8 years and in 1992 34.8 years. The mean length of registration with the CMR increases as well, from 5.2 years in 1989 to 6.9 years in 1992. This implies that the mean age of the clients entering the study population during the period of study is lower than that of those leaving the study population.

Every year, approximately 65% of the study population originates from Western countries including The Netherlands. The percentage of persons from Surinam or the Dutch Antilles fell from 19.6% in 1989 to 17.6% in 1992, whereas the contribution of persons from the Mediterranean rises from 7.1% to 9.3%. As a whole the population is dynamic, but quite stable in terms of sub-populations during the study-period.

Table 2 shows that the PFO differs from the 2 other categories by its relatively small contribution to the observation time of males, per-
Tuberculosis among opiate users

120 0 0
0 0 0
0
0
0

Figure 1 Annual incidence of tuberculosis of drug users in methadone maintenance programmes with 95% confidence intervals

sons older than 35 years and persons who have been registered with the CMR for five years or more. This was to be expected, considering the PFO's specific target groups. Most of the GP clients belong to the category older than 35 years and are registered over more than 5 years with the CMR.

Tuberculosis incidence in the total study period
Forty-three new cases of tuberculosis were diagnosed. The total observation time was 11,117 person years. The mean incidence of tuberculosis in the total study period 1989-1992 therefore amounted to 386 per 100,000 py · 95% C.I.: 287-522 per 100,000 py ·

Tuberculosis incidence patterns
The annual incidence of tuberculosis with 95% confidence intervals is shown in Figure 1. The annual incidence rates are based on 7, 10, 18 and 8 cases respectively. The figures do not show a statistically significant increase over the 4 years. The incidence is lowest in 1989;
**Table 3** The incidence of tuberculosis in subgroups - univariate.

213/100,000 py. In the following years it was higher. Only in 1991 does it deviate significantly with 670 per 100,000 py. This is seen as a temporary upswing of the high endemic incidence of tuberculosis among the study population.

**Tuberculosis incidence of different subgroups**
This is given in Table 3. The univariate analyses show that the incidence is significantly \( p < 0.05 \) higher among males, older clients \( > 35 \) years, and clients who have been known with the CMR for 5 years or more. Moreover, the incidence in clients originating from Surinam or the Dutch Antilles is higher than in Westerners. Incidence is highest
CMR: Central Methadone Register
PFO: Prostitutes and Foreigners Outpatient Clinic
CP: General Practitioner

Deviance 537.8; df = 12735
Likelihood Ratio Statistic: 43.9; df = 5 p < 0.001 alpha = 7.61 (SE = 0.67)

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<th>SE</th>
<th>P-value</th>
<th>RR</th>
<th>95% CI</th>
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<td>2.32</td>
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<td>0.73</td>
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<td>0.03-0.46</td>
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<td>PFO</td>
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<td>0.42</td>
<td>0.010</td>
<td>2.94</td>
<td>1.30-6.66</td>
</tr>
</tbody>
</table>

Table 4 The multivariate Poisson regression model for tuberculosis incidence among drug users in methadone maintenance programmes

The mean incidence of tuberculosis among the Amsterdam drug users in the study population is 386 per 100,000 py in the study period. This is 10 times as high as the incidence in the general population of this
Figure 2  The annual incidence of tuberculosis in The Netherlands, Amsterdam and drug users in methadone maintenance programmes 1989–1992

city. In Amsterdam the incidence is 4 times as high as in The Netherlands generally. In the period 1989-1992 a total of 904 cases of active tuberculosis was diagnosed in the city. Of these cases 80 were known drug users. This implies that drug users making up an estimated 1% of the Amsterdam’s population account for approximately 9% of tuberculosis-cases. In Figure 2 the incidence of tuberculosis in The Netherlands, Amsterdam and the study population is shown in a diagram. How the sudden increase in tuberculosis among drug users in 1991 should be interpreted is not clear.
Males · Rate Ratio RR = 4.7 compared to females · drug users older than 35 years · RR = 2.0 compared to those of 35 years or younger · and drug users registered with the CMR for 5 years or more · RR = 2.3 compared to those registered for less than 5 years · run a higher risk of tuberculosis. The reasons for the association between the incidence and the variables of age and period of methadone consumption are twofold. First, the chance of contact with mycobacterium tuberculosis increases with age and with the time spent within the group of drug users. Secondly, a longer addiction period and higher age reduce the physical condition, increasing the probability of disease. The difference between males and females is not easy to explain. However, it is a known fact that in the general Amsterdam population tuberculosis occurs more often in males than in females; only 30% of all tuberculosis patients in Amsterdam in 1990 are female.

The incidence of tuberculosis appears to be closely related to the programme in which methadone is supplied. Clients of the General Practitioners run a 9 times · 95%CI: 2.2-33 · lower risk of tuberculosis than those being provided for by the general out-patient clinic or the methadone bus. Despite the fact that the PFO treats more females, more drug users younger than 35 years and drug users registered with the CMR for less than 5 years, the risk of contracting tuberculosis is 3 times higher · 95%CI: 1.3-6.7 · for this group than for the clients of general out-patient clinics or the methadone bus. The close relation between incidence figures and methadone location suggests that the deviant lifestyle related to drug use could account for the increased incidence of tuberculosis among different drug users. This type of lifestyle is especially common amongst clients of the MHS. Clients of the MHS generally have more police contacts than clients of the GPs.117 The clients of the PFO are persons who, in addition to their drug addiction, are also characterized by working as a prostitute and/or being illegal foreigners. Their lifestyle is probably more hazardous than drug addiction alone. Among these illegal foreigners there will be a negative selection by health: on the one hand because of a higher reluctance of this group to obtain care with a government agency; on the other because the Amsterdam 'deterrent policy' for illegal foreigners increases this reluctance even more. Only in the case of serious health problems, often HIV-related, is a long term methadone programme offered.

One of the undesired effects with respect to tuberculosis, a communicable disease, is the daily contact between the clients in the methadone programmes of the MHS. General practitioners however, prescribe 'take home methadone' for a period of a few weeks at a time. Thus, the GP-clients rarely get into contact with one another. This provides another reason to be alert for tuberculosis in the MHS programmes.
Although HIV infection was not included as a variable in this study, this infection is an important risk factor for tuberculosis. In 23 of the 43 cases (53%) infection with HIV is known, whereas among drug users receiving methadone at the MHS an estimated 14% has been infected with HIV. In the study of Selwyn et al., among intravenous drug users, all tuberculosis cases were found to be HIV positive. The differences in incidence between the various methadone locations can probably also, at least partly, be traced back to differences in HIV prevalence. This, again, is connected with lifestyle.

Despite the fact that the tuberculosis incidence among foreigners is 18 times higher than among the native population, the country of origin does not appear to be a significant factor. This is due to the high tuberculosis incidence within the population studied. Consequently, mean age and period of registration with the CMR - i.e. period of involvement in the drug scene - are more important risk factors in this study.

Conclusion

In this study, the most important predictors for tuberculosis among drug users in Amsterdam were age, period of registration with the CMR and type of methadone programme - MHS versus GP. The factors age and period of registration are related to the period of drug use. The factor 'type of programme' can be interpreted as a lifestyle indicator: GP clients are less involved in the drugs scene than MHS clients, plus there is a probable impact of a difference in terms of HIV prevalence.

Preventive measures for tuberculosis through drug relief agencies are necessary. On the basis of this study, it seems sufficient to limit mandatory tuberculosis screening in Amsterdam to the clients of the MHS. However, the fact that at least 30% of the drug users being diagnosed as having tuberculosis for the first time were not in touch with any of the drug relief agencies at that time is a cause for concern. In order to prevent the dissemination of tuberculosis among drug users and the general public, the reach of the MHS methadone programmes should be improved.

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De HIV prevalentie onder druggebruikers die methoden verstrekt kregen bij de drugsafdeling van de GGZCO te Amsterdam.
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Abstract

Aim: To describe the pulmonary function and prevalence of dyspnoea among methadone patients and to study the relation with exposure to heroin by inhaling.

Study population: A sample of 100 patients from methadone maintenance treatment - 84% male, average age 42 years.

Measurements: Questionnaires were used to measure life-time exposure to heroin, cocaine, cannabis, tobacco, and symptoms of dyspnoea. Spirometry was performed and residual difference of measured FEV₁ - Forced Expiratory Volume in 1 second - from the age, sex, height and ethnicity predicted value ΔFEV₁ was used as a main outcome parameter.

Findings: The median ΔFEV₁ was -0.26 litres - interquartile range - 0.70; +0.12. Twenty per cent experienced dyspnoea while 'walking at a normal pace with someone of their own age'. History of cigarette smoking was reported by 98%; heroin smoking by 88%. Multiple linear regression analysis showed a statistically significant association between heroin-smoking and ΔFEV₁, logistic regression analysis showed an association between heroin-smoking and prevalence of dyspnoea.

Conclusions: Chronic heroin smoking seems to be related to an impaired lung function and higher prevalence of dyspnoea. However, part of the observed lung function impairment will be caused by tobacco smoking. Further research is needed to quantify the effect of heroin smoking and disentangle the effect of smoking heroin and tobacco.
Introduction

"Chasing the dragon" implies that heroin is heated on foil and heroin vapour is inhaled through a straw. To enhance evaporation, a mixture of base-heroin and caffeine is generally used. Since the start of the heroin epidemic in the early seventies in Amsterdam, chasing the dragon has become the dominant route of administration. Nowadays, 85% of the heroin users in Amsterdam smokes its heroin. Trends towards smoking heroin are observed in Spain, the UK and Ireland. Chasing the dragon is considered to be a safer mode of heroin use than injecting. Risks of fatal overdose, HIV, HBV and HCV infection are more prevalent among injectors. Chasing the dragon however, is not without risks. Overdose mortality may occur and in individual cases, lethal leukoencephalopathy has been reported.

It is known that heroin affects the pulmonary function. It affects the respiratory control centres which may lead to fatal pulmonary depression. Like other opiates, heroin is known to release histamine and case series of asthma triggered by inhalation of heroin have been reported. Injecting heroin may cause septic emboli originating from an infection at the injection site or tricuspid valve endocarditis or foreign body emboli originating from contaminants or fillers in the injectate. Furthermore, infectious diseases such as TB and pneumonia are more prevalent among heroin users, especially among HIV infected drug users. Lung-function studies among small samples of ex heroin injectors indicated a decrease of diffusing capacity rather than obstructive complications. Lung function studies among samples of heroin inhalers are not known.

At the Amsterdam methadone treatment centres there is an increasing concern about the pulmonary function due to chronic use of heroin by chasing the dragon. However, little is known about the effect of heroin smoking on pulmonary function. The Amsterdam population of heroin users may provide valuable information about the chronic effects of smoking heroin on pulmonary function. The aim of this study is to describe the lung function and complaints of dyspnoea among heroin addicts treated with methadone and to study the relation with the exposure to heroin by chasing the dragon, controlling for other causes of lung function impairment.

Methods

Study population and data collection

The study was conducted at a methadone maintenance outpatient clinic of the Municipal Health Service MHS of Amsterdam. Patients of this treatment centre are generally not able or willing to stop using illicit drugs. The major goal of methadone maintenance treatment is to reduce the harm that is caused by the use of these drugs.

Three times a year all patients of the methadone treatment are
subjects to a periodical medical check up. For the purpose of this study the lung function of the patients was measured during this check up. The protocol was approved by the medical ethical committee of the Municipal Health Service and the University of Amsterdam. A trained research assistant asked 123 patients to perform a spirometric test before filling out a questionnaire. In this way the answers of the questions could not influence the technician when spirometry was conducted. Three patients refused to co-operate. Twenty patients appeared to be unable to conduct the spirometric test according to criteria of quality and reproducibility of the American Thoracic Society but did fill out the questionnaire. In this article we focus on the 100 patients who performed a valid spirometric test.

**Measures outcome**

Two measures of outcome were used in this study: reported complaints of dyspnoea based on the Modified Medical Research Council questionnaire and the Forced Expiratory Volume in 1 second (FEV1). Six hierarchical questions - shown at Table 1 - considering shortness of breath were asked. Generally the two most severe categories of shortness of breath - *while walking at their own pace and at rest* - are considered as having dyspnoea. In order to prevent empty cells when conducting the logistic regression analysis, patients who answered 'Yes' to the question 'Are you suffering from shortness of breath when you walk at a normal pace with someone of your own age?' were considered to have complaints of dyspnoea too. The spirometer *Vitalograph 2170, Spirotrac IV* was used to measure the FEV1. Only one spirometer was used and all measures were performed by one technician. The residual difference of the measured FEV1 from the age, sex, height and ethnicity predicted value (ΔFEV1) was used as main outcome parameter. Moreover, the percentage of the client's predicted FEV1 value was calculated (%FEV1. Predicted values are based on the guidelines of the European Respiratory Society. A race-adjusted correction factor was applied to the data obtained in black participants by multiplying the predicted value of FEV1 by a factor 0.9 as recommended by the American Medical Association.

<table>
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<tr>
<td></td>
<td>Negroid:</td>
<td>FEV1 predicted = FEV1 predicted Caucasian · 0.9</td>
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**Exposure**

Heroin use by chasing the dragon is the exposure variable of interest in this study. The variable indicating the life time exposure to heroin
by chasing the dragon was constructed by multiplying the frequency of heroin use \( \text{number of days during the last thirty days of heroin use} \) and the total number of years that heroin was used. This variable ranged from null \( \text{never chasing the dragon} \) to a maximum value of \( 900 \text{ years and 30 days a month} \). As 12 percent had a zero exposure, an ordinal variable of 8 groups of approximately equal size were constructed. The value 0.0 was directed to the lowest exposure group \( \text{equivalent to zero exposure} \); the value 1.0 to the highest exposure group \( \text{equivalent to a duration of exposure of more than 20 years and daily use} \).

**Confounders**

The vast majority of patients uses other drugs than opiates that may have additional harmful effects. This may bias the observed relation between heroin and lung function. In this study exposure to heroin by smoking is the variable of interest and exposure to other drugs \( \text{smoking of cocaine, cannabis and cigarettes} \) are potential confounders. Similar to the exposure to heroin by chasing the dragon, the exposure to marihuana and cocaine by inhalation is constructed by multiplying the period of use \( \text{in years} \) with the frequency of use \( \text{last 30 days of use} \). Subsequently, based on the percentage of non-exposure \( \text{-21% among base-cocaine and 29% among marihuana} \) ordinal variables of 5 and 4 groups of approximately equal size were constructed \( \text{highest category was equivalent to a duration of more than 12.4 and 13.0 years and daily use of cocaine or marihuana respectively} \).

Exposure to tobacco was calculated by multiplying duration and frequency of use \( \text{mean daily number of cigarettes during the last 30 days} \) and expressed in pack-years. One pack-year is the equivalent to the exposure of one packet of cigarettes a day during one year. Tobacco exposure is expressed as a continuous variable in which one increment equals 10 pack-years of exposure. Among unexposed subjects the average \( \Delta FEV_1 \) is expected to be null in all age categories. However, among heroin addicts, tobacco smoking is common and the average \( \Delta FEV_1 \) is expected to show higher negative values with increasing age. In the analysis, age is a continuous variable in which the age of 20 is set to zero and one increment equals 10 years age difference.

In addition to exposure variables, other variables are related to the exposure to heroin by inhaling and/or pulmonary function. The variables that were evaluated are \( \text{body-mass index} \; \text{BMI: Weight (kg)/length(m)^2} \; \text{lower than 18} \); \( \text{a lifetime history of tuberculosis TB or pneumonia treated with antibiotics during the last two years} \) and \( \text{reported symptoms of bronchial allergic or non-specific hyper-responsiveness} \). These variables could be confounders but also intermediate steps between exposure and disease or even symptoms of
pulmonary impairment. Only in the first case statistical adjustment would be necessary. Therefore two analyses were conducted, one with additional adjustment for BMI, TB/pneumonia and bronchial hyperresponsiveness and one without this adjustment.119

Analyses
Multiple linear regression was applied to describe the relation between the exposure to heroin by smoking and ΔFEV₁, logistic regression was applied to describe the relation between the exposure to heroin by smoking and the occurrence of dyspnoea. The results of the linear regression and logistic regression analysis are presented in three steps. The first model shows univariate relations of exposure to smoking of heroin, cocaine, cannabis and cigarettes. Controlled for each other’s influence these relations are presented again in the second model. In the third model additional variables were added: Body Mass Index < 18, complaints of bronchial hypersensitivity, history of TB · life-time · or pneumonia · two years · Moreover, crude data are presented in scatter plots showing the ΔFEV₁ and prevalence of dyspnoea in each exposure category.

Next to the FEV₁ the FVC · Forced Vital Capacity: the total volume that can be expired after maximum inhalation · is measured. The FVC was 7.10 · sd: 0.98 · and the FVC % predicted was 100% · sd: 15.9 · The mean FEV₁/FVC ratio was 0.73 · sd: 0.6 · The maximum value of the FEV₁/FVC ratio was 0.93; indicating that the decreased FEV₁ was not the consequence of a decreased FVC.

Results
Description of the study population
Hundred patients successfully completed the questionnaire and spirometry. Their average age was 42.4 years · standard deviation sd: 6.7 · The youngest was 22, the oldest 57 years old. The majority was male · 84% · and white · 77% ·

Exposure
All patients reported that they had used heroin, 88% used heroin by chasing the dragon. Moreover, 79% reported they ever inhaled cocaine and 71% had a history of smoking cannabis. During the last 30 days, 52 patients inhaled heroin, 49 cannabis and 49 cocaine. Less than half · 41 · had ever injected their drugs. Only 13 out of 100 patients had recently injected heroin, 11 of them both heroin and cocaine.

All patients but 2 had ever smoked cigarettes. Only one of the ever smokers did not smoke during the month preceding the interview. Among cigarette smokers, the median age of starting cigarette use was 15 years. The average period of cigarette use was 26 years.
Bold: considered as complaints of dyspnoea in this study

Are the following remarks applicable to you?
I suffer from shortness of breath when

<table>
<thead>
<tr>
<th>Degree 0: 'No' to all following question</th>
<th>N</th>
<th>Median ΔFEV₁ liters</th>
<th>Median %FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree 1: I am in a hurry on flat ground</td>
<td>15</td>
<td>-0.26 -0.71; -0.03</td>
<td>93 78-99</td>
</tr>
<tr>
<td>Degree 2: I climb stairs or walk up a small hill at a normal pace</td>
<td>18</td>
<td>-0.36 -1.20; -0.07</td>
<td>89 68-98</td>
</tr>
<tr>
<td>Degree 3: I walk at a normal pace with someone of my own age</td>
<td>9</td>
<td>-1.02 -0.51; -0.21</td>
<td>85 69-93</td>
</tr>
<tr>
<td>Degree 4: I walk at my own pace on flat ground</td>
<td>6</td>
<td>-0.89 -2.14; -0.45</td>
<td>75 36-89</td>
</tr>
<tr>
<td>Degree 5: I am at rest</td>
<td>7</td>
<td>-0.75 -1.24; -0.26</td>
<td>76 67-93</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>-0.26 -0.70; 0.12</td>
<td>93 78-104</td>
</tr>
</tbody>
</table>

Table 1 Definitions of different categories of dyspnoea and ΔFEV₁, %FEV₁

Complaints of dyspnoea and ΔFEV₁
The outcome variables - complaints of dyspnoea, ΔFEV₁ and %FEV₁ - are shown in Table 1. Forty-five patients reported no complaints of dyspnoea. Twenty-two patients reported dyspnoea of the third degree or higher. The ΔFEV₁ ranged from -3.0 until +1.1 litre. The average value was -0.32 ±sd:7.7- and the median value was -0.26 litres, inter quartile range IQR: -0.70; +0.12. The %FEV₁ ranged from 19 until 129 with an average value of 91 ±sd:20.1- and a median of 93 ±IQR: 78-104. Table 1 shows a decreasing ΔFEV₁ and %FEV₁ with increasing degree of dyspnoea. Normal ΔFEV₁ and %FEV₁ values are observed among those without any complaints of dyspnoea. Spirometric results among methadone patients with dyspnoea to the third degree and higher - mean ΔFEV₁: -0.89 litre, %FEV₁: 74% - are lower than among patients with none or minor complaints - mean ΔFEV₁: -0.16 litre, %FEV₁: 96%, both t-tests p < 0.001.

FEV₁ and the use of drugs
Figure 1 shows the relation of exposure to smoking heroin, cocaine or cannabis and ΔFEV₁. ΔFEV₁ values vary widely among the high heroin exposure and low cocaine exposure categories. Two subjects with symptoms of dyspnoea and FEV₁ values that are more than 2.5 litres lower than expected, show extreme exposure values. They are included in the zero exposure group of cocaine and cannabis, and in the higher exposure groups of heroin.

Table 2 shows the results of the multivariate regression analysis. In Table 2A univariate relations are shown. Age was not significantly related to a decreased ΔFEV₁. Differences in exposure to cigarette
smoking did not show a significant relationship with the ΔFEV₁. The degree of heroin exposure by smoking was significantly related to a decreasing ΔFEV₁. The highest exposure category showed a FEV₁ value 0.57 litre lower than the none-exposure category. We did not observe any significant relation between exposure to cannabis or cocaine and ΔFEV₁.

Table 2B shows the results after controlling for age and influence of multiple drug use. Although exposure to base-cocaine is positively correlated with exposure to heroine by chasing the dragon $r^2 = 0.4 \; p < 0.001$, associations between cocaine, heroine and ΔFEV₁ appear to be stronger after adjustment. The FEV₁ values showed a decrease with increasing heroin inhaling exposure and an increase with increasing exposure to cocaine by inhaling. This effect is probably caused by patients with an extremely low ΔFEV₁ who belonged to the higher heroin inhaling exposure categories but never inhaled cocaine. Figure 1.

If the two most extreme values are omitted from the analysis, the ΔFEV₁ still shows a significant decrease with increasing exposure to heroin inhalation $\cdot p = 0.05$. The significant association with cocaine, however, disappears $\cdot p = 0.32$. Similarly, if the square %FEV₁ is used to limit the influence of the lower values, the multivariate analysis still shows a significant association $\cdot p = 0.03$ with heroin exposure and increase of square %FEV₁ with increasing cocaine inhalation disappears $\cdot p = 0.33$. 

Figure 1 Ordinal exposure to heroin
- inhaling, cocaine - inhaling and cannabis in relation to the ΔFEV₁ and dyspnoea.
A BMI lower than 18 was observed in 26% of the patients, whereas 49% reported complaints of bronchial hyper-responsiveness and 21% a history of TB. 7 patients lifetime, or Pneumonia - 17 patients during past two years. Table 2C shows the influence of these potential confounders on the relation between heroin and FEV1. In the univariate analysis the variables history of TB or pneumonia and complaints of bronchial hyper-responsiveness are significantly related to heroin exposure. $X^2$ linear by linear association: $p < 0.05, p < 0.01$. The variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 18</td>
<td>-0.33</td>
<td>-0.64 ; 0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>History TB / Pneumonia</td>
<td>-0.25</td>
<td>-0.61 ; 0.11</td>
<td>0.17</td>
</tr>
<tr>
<td>Bronchial Hyper-responsiveness</td>
<td>-0.49</td>
<td>-0.76 ; -0.21</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.13</td>
<td>-0.36 ; 0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>-0.05</td>
<td>-0.14 ; 0.04</td>
<td>0.49</td>
</tr>
<tr>
<td>Cannabis</td>
<td>0.05</td>
<td>-0.30 ; 0.40</td>
<td>0.88</td>
</tr>
<tr>
<td>Cocaine smoking</td>
<td>0.48</td>
<td>0.06 ; 0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>Heroin smoking</td>
<td>-0.61</td>
<td>-1.08 ; -0.15</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2  Linear regression analysis: exposure versus $\Delta$FEV1
Table 3 Logistic regression analysis: exposure versus dyspnoea

BMI<18 did not show a significant relation with the level of heroin exposure. In the univariate analysis all 3 variables showed a significant associated with ΔFEV1: data not shown. In the multivariate analysis only the variables complaints of bronchial hyper-responsiveness and BMI<18 were significantly related to the ΔFEV1. The higher prevalence of methadone patients with symptoms of bronchial hyper-responsiveness and exposure to heroin by inhaling partly explains the relation between heroin and ΔFEV1.
**Dyspnoea and exposure to drugs**

Table 3 presents the results of the logistic regression analysis of the relation between dyspnoea and the exposure to drugs. These results show large similarities with those of the linear regression analyses described above. Among the methadone patients, heroin exposure was associated with an increased prevalence of dyspnoea. Reported differences of exposure to cocaine, cannabis or cigarettes were not statistically significant related to the prevalence of dyspnoea. Dyspnoea was reported more frequently among patients with complaints of bronchial hyper-sensitivity. In contrast to results of the linear regression analysis, no significant association between dyspnoea and BMI is observed. The association between 'history of TB and/or pneumonia' and heroin exposure by 'chasing the dragon' partly explains the relation between heroin and prevalence of dyspnoea - data not shown. After additional adjustment the odds ratio of heroin exposure and dyspnoea is not significantly higher than one.

Analysis performed with a more narrow definition of dyspnoea -13% that reported to experience a short of breath while walking at their own pace or in rest- showed similar results. However, due to the low number of values per cell odds ratios and confidence intervals are inflated - data not shown.

**Discussion**

This study demonstrates that methadone patients show an impaired lung function both if we consider complaints of dyspnoea and \( \Delta \text{FEV}_1 \) and \( \% \text{FEV}_1 \). In a sample of the general population with a comparable age and gender distribution only 1% with serious complaints of dyspnoea - when walking at his own pace or at rest- would have been expected. In this study 13% of the patients reported such complaints of dyspnoea. The median \( \% \text{FEV}_1 \) was 93 - sd = 20. The average \%FEV\(_1\) observed at a population survey conducted within various regions of the Netherlands - N = 2588 - was 108 - sd = 17.  

Furthermore, data suggest a relation between heroin use by chasing the dragon and an impaired lung function. We were able to construct subgroups reflecting differences in life-time exposure to heroin by chasing the dragon by taking into account differences in routes of administration - injecting versus chasing the dragon -, differences in duration of inhaling heroin and frequency of inhaling heroin during the last month of use. \( \Delta \text{FEV}_1 \) values decreased and prevalence of dyspnoea increased with increasing heroin exposure. Bias towards zero is possible if heroin inhalers lowered their consumption due to an impaired lung function. Due to limitations of a transversal study and limited accuracy of life-time exposure to heroin quantification of the effect is not possible. The effect of patients who failed spirometric
test is expected to be limited. They were older - average 49 years - but exposure to heroin or cigarettes nor the severity of the reported symptoms of dyspnoea significantly differed from the others.

An impaired pulmonary function was not shown among all subjects of the highest category of exposure to heroin by inhaling. So probably, if inhaling of heroin is causally related to an impaired lung function, not all heroin users are equally vulnerable. In this respect a similarity with cigarette smokers may arise. Non-specific airway responsiveness is considered to predispose some cigarette smokers to develop Chronic Obstructive Pulmonary Disease. Only 15% of the cigarette smokers will eventually develop COPD. Among heroin inhalers there may be a susceptible subpopulation too. For example, it could be hypothesised that those who inhale heroin and also show a histamine release after exposure to opiates are specially vulnerable.

Bronchial hyper-responsiveness and history of TB/pneumonia seem to be partly responsible for the association between heroin and ΔFEV1 and dyspnoea respectively. It is not exactly clear whether these variables should be considered as confounders, intermediate factors, or symptoms of pulmonary impairment. If we consider these variables as intermediate factors or symptoms, additional adjustment would be incorrect. The variables could also be confounders. A history of TB and pneumonia for example, could be indicative for poor living conditions and therefore occur more prevalent among those with the highest exposure to heroin administered by inhaling. If this is the case, adjustment is justified. However, those who are not exposed to heroin by chasing the dragon, injected their heroin and their living conditions are not expected to be better.

Considering a causal mechanism it may be important to realise that the purity of heroin that is inhaled in Amsterdam is approximately 30%. Caffeine is the main adulterant. However, caffeine administered orally, is a bronchodilator and appears to improve lung function in people with asthma. All but two study participants smoked tobacco, the average exposure of cigarettes among the total group is estimated to be 20.2 packyears. Although the validity of a retrospectively calculated exposure variable is limited, we may assume that part - possibly most - of the pulmonary impairment in this population can be attributed to the smoking of cigarettes. Moderate to heavy cigarette smoking men have, on average, a 15 ml/year larger decline of FEV1 than non-smokers. Unfortunately, we cannot transpose these findings to this transversal study because people with a low %FEV1 are at higher risk for mortality. No statistical significant relation between exposure to tobacco and ΔFEV1 or dyspnoea was determined. This should be interpreted as the result of a lack of contrast among the methadone clients - almost everybody continuously smoked cigarettes - rather than a lack
of effect. Moreover, if heavy cigarette smokers lowered their consumption due to an impaired lung function, the reported contrast of tobacco exposure is likely to be lower than the real contrast again, bias towards zero. This could decrease the capability of the cigarette exposure variable to control for potential confounding. In this study, the relation between heroin smoking and \( \Delta \text{FEV}_1 \) or dyspnoea did not decrease after adding the number of pack years to the analyses. Moreover, the number of pack years of tobacco exposure as reported was not significantly related to the level of heroin exposure \( r^2 : 0.03; p = 0.78 \). This suggests that the real confounding bias will be limited.

Nevertheless, in order to improve the lung function, limitation of the exposure to cigarettes calls for special attention.\(^{127,128}\) Cannabis exposure was not significantly related to a decreased \( \Delta \text{FEV}_1 \) or increased prevalence of dyspnoea. Other studies concerning the effect of cannabis on pulmonary function offer conflicting results. Tashkin concluded that the \( \text{FEV}_1 \) did not decline due to cannabis smoking\(^{129}\) but Taylor observed altered spirometric results \( \text{FEV}/\text{FVC} \) among non-tobacco smoking cannabis dependent individuals at age 21 years.\(^{130}\) Moreover, it is suggested that airway inflammations are more prevalent among combined marijuana and tobacco smokers.\(^{131}\) The apparently positive effect of cocaine on \( \Delta \text{FEV}_1 \) is considered to be an artefact and caused by the effect of a few subjects with a severely impaired lung function who never smoked base-cocaine. Possibly they did not start using base-cocaine because of their impaired lung function. In Amsterdam, cocaine smoking started during the 1980s, and increased during the 1990s. Although a negative effect of base cocaine on \( \text{FEV}_1 \) has not been observed, other physical problems may hinder oxygen uptake. Inhaling base-cocaine is associated with pulmonary inflammation and infiltration on X-ray\(^{132}\) and may cause a decreased diffusion of oxygen from the lungs to the blood.\(^{133,134}\)

**Conclusion**

The results of this transversal study suggests that chronic heroin use by chasing the dragon is related to an impaired lung function and higher prevalence of dyspnoea. More research is needed to quantify the possible effect, to disentangle the effect of smoking heroin and tobacco and to identify whether and what kind of particularly vulnerable subpopulations exists.

**Acknowledgement**

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REFERENCES


22 Forensic laboratory of Amsterdam, 2000. personal communication.


