Drug use, mortality and outcomes among drug users in the general population and in methadone maintenance treatment

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DRUG USE, MORTALITY AND OUTCOMES AMONG DRUG USERS IN THE GENERAL POPULATION AND IN METHADONE MAINTENANCE TREATMENT

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“The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.”

The second principle of the Constitution of the World Health Organization conforms to the Charter of the United Nations (WHO)
ABSTRACT

The two general aims of this thesis were to longitudinally analyse the association between drug use experience among young men and mortality and socio-economic situation up to late middle age and secondly the impact of methadone maintenance treatment on opiate dependents’ life course. Study I and II were based on a cohort of 48,024 of 50,465 men, born in 1949-51 and compulsory conscripted in 1969/70. Information about use of illicit drugs and not prescribed medical drugs classified as narcotics, alcohol, smoking, family, behavioural and social factors and assessed levels of intellectual ability and emotional control were extracted from the conscription survey. The conscription data were linked to the cause of death, conviction, inpatient care and LISA registers.

Study I analysed the association between main drug use at conscription and mortality. Study II analysed the probability among conscripts alive December 31, 2006 with various main drug use and risk and protective factors for favourable socio-economic outcome in education (≥ 12 years), work (be at work) and income (> median) in 1990 and 2006. Study III and IV were based on two cohorts of opiate dependent subjects admitted to Stockholm methadone maintenance treatment (MMT). Study I found that a significantly increased hazard ratio for mortality among stimulant, cannabis and unspecified drug users after adjusting for risk factors only remained for stimulant use (HR 1.82, 95% CI 1.002-3.31) after including drug injecting and hospitalizations with drug diagnosis and convictions during follow-up. HR to die was 4.19 (95% CI 3.35-5.24) among those drug users who were hospitalized with drug diagnosis, while other drug users had no increased HR compared to non drug users. Several factors were independently associated with mortality. Study II showed that the cannabis and hallucinogen groups had significantly higher OR to have an education twelve years or more but not a higher OR to be at work or to have an income over the median in 1990 and 2006 after adjustment for other factors. Drug users hospitalised with drug diagnosis had less probability for a favourable socio-economic outcome in 2006 than in 1990. Some (protective) factors, e.g. high intellectual ability, good contact with parents and having a father from social class I increased the probability for a favourable socio-economic situation, not least among those with few risk factors. In study III illicit drug use during MMT was analysed among 204 subjects first time admitted 1995-June 2000 in relation to retention, kind of psychosocial intervention, methadone dose and sex and up to December 31, 2000 using urine analyses data and medical records. Almost all patients relapsed to illicit drug use once. Those who were discharged had more relapse periods, more side misuse and lower methadone dose. A structured psychosocial intervention was associated with fewer relapse periods.

In study IV, the role of MMT for mortality, criminality, social assistance, inpatient care, coercive treatment was analysed among 157 subjects admitted 1989-91 and followed for 18-years. Data was linked between seven registers and medical journals. Criminality, inpatient care, coercive treatment, convictions and prison sentences were lower during MMT although it differed between those who remained in first MMT, was in the second MMT, discharged from first MMT or from second MMT.

The results showed that it is important to adapt protective interventions and treatment to the heterogeneity of young drug users and to opiate dependent users.
List of Publications

The present thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


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AIDS  Acquired immune deficiency syndrome
APA  American Psychiatric Association
CI  Confidence interval
CNS  Central nervous System
DALY  Disability-adjusted life year
DSM  Diagnostic and Statistical Manual of Mental Disorders
DSM-IV  Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DUG  Drug use group
EU  European Union
GABA  Gamma-aminobutyric acid
GC-MS  Gas chromatography-mass spectrometry
HAART  Highly active anti-retroviral treatment
HIV  Human immunodeficiency virus
HR  Hazard ratio
ICD  International Classification of Diseases
ICD-8  International Classification of Diseases, 8th revision
ICD-10  International Classification of Diseases, 10th revision
LISA  Integrated database for labour market research
LVM  The care of alcoholics, drug abusers and abusers of volatile solvents act
LSD  Lysergic acid diethylamide
MMT  Methadone maintenance treatment
MMTP  Methadone maintenance treatment programme
SiS  Statens institutionsstyrelse (The National Board of Institutional Care)
NAcc  Nucleus accumbens
NDUG  Non-drug use group
OR  Odds ratio
PH  Proportional hazard
RCT  Randomised controlled trial
SMR  Standard mortality ratio
SNBHW  Swedish National Board of Health and Welfare
THC  Delta-9-tetrahydrocannabinol
UNODC  United Nations Office on Drugs and Crime
VTA  Ventral tegmental area
WHO  World Health Organization
1 BACKGROUND

1.1 INTRODUCTION

Illicit drug use has since the 19th century been a major global problem, and a regional and national problem in Sweden. Knowledge about the prevalence of illicit drug use has increased, although sometimes the estimates are based on far from robust data (UNODC, 2009). The global annual prevalence of illicit drug use is estimated to be 172–250 million in 4,343 million of the world’s population aged between 15 and 64 years, of whom about 18–38 million were problematic drug users and about 11–21 million injected drugs in 2007 (idem). Longitudinal studies of principally clinical or criminal justice cohorts have shown that severe drug use is associated with important individual and societal problems, e.g. premature death (Tunving 1988; Hser et al. 2001) severe health (Hser et al. 2001), social and financial problems (Hser et al. 2001; SOU Missbruksutredningen 2010). General population studies have shown that the majority of adolescents who have used drugs do not progress to severe drug use (Kandel and Logan 1984). Several familial, behavioural, environmental and psychological factors are associated with initiating, and progressing to, severe drug use and negative life outcomes (Bry, McKeon, Pandina 1982; Stenbacka, Allebeck, Romelsjö 1992; Stenbacka 2003). There exist also factors which decrease or buffer these risks (Brook and Brook 1990; Hawkins, Catalano, Miller 1992; Stattin, Romelsjö, Stenbacka 1997; Jessor, Turbin, Costa 1998). Research on risk and protective factors has contributed to increased knowledge for prevention interventions. However, there is still a lack of knowledge about the association between drug use in adolescence and mortality, and about whether some factors from childhood and adolescence are associated with a favourable socio-economic situation among those who have used drugs. As opiate dependence is considered a chronic disease (McLellan et al. 2000) it is important to provide treatment adapted to patients’ needs over longer time periods. Methadone maintenance treatment (MMT) is an evidence-based treatment for opiate-dependent drug users. As for other chronic diseases, non-compliance with treatment is an important problem, with negative consequences after drop-out or discharge from treatment. Increased knowledge about the life course among methadone maintenance patients during a longer follow-up is needed to adapt treatment to patients’ needs. This thesis is consequently based on longitudinal studies of different populations and subgroups of drug users to analyse predictors and events for different outcomes during the life span.

1.2 DEFINITIONS

In this thesis, we have mainly used the terms “drug use” and illicit drug use and “drug users” for intake and users of illicit drugs, but in a few instances other expressions such as “drug abuse” and “drug abusers” have been used for the same phenomena. Since the beginning of the 20th century, the word “abuse” has been used to designate individuals who use illicit or non-medically prescribed psychoactive drugs. The term “drug abuse” was questioned in 1973 by the American National Commission on Marijuana and Drug Abuse, as it implied non-acceptable drug use without any further information. The term has a negative connotation, which motivates the coining of new terminology. The term “drug abuse” may as well not have been used at all in this thesis but there is some influence from Swedish drug vocabulary, which uses the term missbruk (The current governmental investigation into treatment for people with alcohol/or drug dependence/abuse is called “Missbruksutredningen”).
"Drugs" in this thesis are narcotics included in the UN international drug control conventions and/or included on the Swedish National Narcotics Drug list.

1.3 ILICIT DRUG USE IN THE WORLD

For thousands of years, human beings have been using natural plants containing psychoactive substances which have been considered to remedy diseases, relieve distress (e.g. pain, starvation, fatigue) or reinforce positive rewards such as emotional wellbeing and, e.g., euphoria at cultural celebrations and religious rites, though type of plant and occasion of use may have differed between geographical regions, cultures and time periods. The addictive properties of substances such as opium were observed early on. The trade of opium from British India to China in the 19th century provoked the two opium wars and contributed to millions of Chinese becoming opium users and dependent subjects (UNODC). In 1880, about 14% of the state income in British India came from this trade. The non-regulated trade of opium and new, synthesized drugs, e.g. cocaine, heroine and amphetamine, contributed to an increase in the drug use problem in several countries including the United Kingdom, the United States and Asian countries, at the same time bringing important economic profit to traders. Due to international protest against and criticism of the non-regulated trade and increased drug problems, an international conference for regulation of opium was held in Shanghai, China, in 1909. In 1912, the Hague Opium Convention was signed by eleven countries and was adopted by five countries in 1915. The convention declared the danger of using these drugs for health and regulated the licit trade of opium, morphine, heroin and cocaine. The convention document influenced also the creation of the Harrison Act in 1913 in the United States (idem).

After World War I, several conventions relating to drugs were signed by an increased number of countries. One of the current drug control conventions is the Single Convention on Narcotic Drugs of 1961. It includes opium, heroin, cocaine and cannabis, resolutions about treatment for drug addicts, illicit trafficking, and international control; membership of the Commission on Narcotic Drugs, which is the United Nations (UN) coordinator and policymaker for the United Nations Office on Drugs and Crime (UNODC) and regulations concerning illicit drugs (in the amendments from 1972). Another important convention is the Convention on Psychotropic Substances (1971), which includes amphetamines and other drugs. Of equal importance is the Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances from 1988 (UNODC, Treaties). The 20th century saw several drug epidemics: during World War I, after World War II and again during the 1960s (UNODC).

In 2007, cannabis was the most frequently used drug worldwide, with a global annual prevalence of about 143–190 million users (UNODC 2009). In the European Union (EU) there are about 22.5 million (7% of the total population) cannabis users aged 15–64 years (EMCDDA 2009). Amphetamine is the second most frequently used drug globally, with an annual prevalence of 16–51 million, followed by cocaine (16–21 million), opiates (15–21 million) and ecstasy (12–24 million) (UNODC 2009). In the EU in 2007, the annual prevalence of cocaine use was 4 million, compared with ecstasy (2.5 million) and amphetamines (about 2 million). Also in 2007 in the EU, about 1.4 million (1.2–1.5 million) of 3.4–4.1 million opiate users were injecting drug users or had long-term or regular opioid use. Opiates were present in about 75% of all deaths caused by narcotics (EMCDDA 2009). In 2004, it was estimated that drug-related disorders caused about 0.4% of the mortality in the world and contributed to about 0.9
1.4 ILLEGAL DRUG USE IN SWEDEN

In Sweden, medical and non-medical use of amphetamines as amphetamine (e.g. Benzedrin) and metamphetamines (e.g. pervitin) increased rapidly after their introduction into the country in the late 1930s (Goldberg 1968). In 1939 it became mandatory with medical prescription for amphetamines (idem). In 1942–1943 it was estimated that about 3% (200,000) of the adult Swedish population had used amphetamines, of whom (about 200) were severe drug users (idem). Physicians were alert to the risks of amphetamine use by the National Medical Board in April 1943, which contributed to a 40–60% decrease in prescriptions and sales. Amphetamines were classified as narcotics on the National Narcotics Drug List in 1944 (idem). In the 1950s, illicit use of amphetamine and opium derivatives among artists reached young delinquent groups. In 1959, phenmetrazine (Preludin) and methylphenidate (mainly Ritalina) were included as narcotic drugs under the National Narcotics Drug Act and became available only on prescription (idem). Since then, new drugs have been classified as narcotics and added to the list.

As the drug problem increased, a group of experts were nominated in 1965 to review the narcotics problem. In 1966 this group was reorganized into the Narcotics Drug Committee (Goldberg 1968). Several surveys among different subpopulations were performed during the late 1960s. Lifetime prevalence of drug use was about 5% among Swedish pupils from grade 9 to the final year of senior high school, and about 9% among pupils in grade 9 in Stockholm (April 1967) with cannabis being the dominant drug used by 75–80% (idem). In national surveys among pupils in grade 9 the experience of illicit drug use had decreased from 15% in 1971 to 3–4% during the late 1980s, but had again increased to 8% by 2009 (Hvitfeldt and Gripe 2009). In 1968, about 18% of Swedish conscripts had experience of illicit drug use; this figure had decreased to 6% by 1992 but again rose to 13% in 2006, of whom about 0.2% reported having used opiates during their lifetime (CAN 2009). In 2008, data from a national public health survey (FHI, 2009) showed that the lifetime prevalence of cannabis among 16–84-year-old subjects was 11% and about 150,000 subjects (2%) had used cannabis during the previous 12 months. The lifetime prevalence was highest among the younger subjects (20% among 16–29-year-olds).

In 1967, about 2,500 subjects were reported by different administrations, schools, hospitals, and associations who participated in a case-finding survey on frequent or injecting drug use in the Stockholm area (CAN 1998). In 1979, a national case-finding study identified about 10,000–14,000 severe illicit drug users countrywide. Of these, the majority was drug injectors and about 1,500–2,000 were daily or almost daily drug injectors. Stimulants were the dominating drug; about 30% of the injecting drug users had used heroin and poly-drug use was frequent (CAN 1998). In a national case-finding study performed in 1998, the number of heavy drug users (“injected drugs over the last 12 months or used illicit drugs daily or almost daily in the last 4 weeks”) was estimated to be 26,000. About 90% had injected drugs during the previous 12 months. Heroin use during the last 12 months had risen to 47% among severe drug users and as dominating drug had increased from 15% in 1979 to 28% in 1998. Stimulants had decreased from 77% in 1979 to 73% in 1998 and as dominating drug from 48% in 1979 to 32% in 1998 (CAN 2001). In 2004 it was estimated that about 7,000–8,000 heavy drug users were opiate-dependent, using mainly heroin (CAN 2009). In 2010, about 29,
500 subjects in Sweden were estimated to have harmful drug use or be drug-dependent (SOU Missbruksutredningen, 2010).

Current data show that the proportion of individuals <30 years of age and hospitalized for the first time in in-patient care with a drug diagnosis has increased since the 1990s (CAN 2009). Drug-related mortality in Sweden increased after heroin was introduced in the 1970s, from <45 deaths per year before 1977 to 403 in 2001 (idem). Deaths decreased to 310 in 2006 but again increased to 395 in 2007 (idem). The decrease was mainly among those aged 30–39 years and concerned opiate-related deaths (-50 %) (CAN 2009).

1.5 PSYCHOACTIVE SUBSTANCES AND METHADONE MAINTENANCE TREATMENT

Addiction is a complicated biopsychosocial process including neurobiological, learning and memory processes. In the neurobiological process, “the central dopamine neurotransmitter serves a variety of functions. These include the fine-tuning of motor control and cognitive function; modulating the salience of events and attention, learning and memory; bonding and attachment in relationships; and the planning and motivation of behaviour. Nearly all drugs of addiction act by increasing the release of dopamine in the nucleus accumbens (NAcc). This increase may be direct, as is the case with stimulants, which increase the release of dopamine by neurons of the ventral segmental area (VTA). Other drugs of addiction (e.g. alcohol, cannabis and nicotine) indirectly increase dopamine activity by influencing neurons which then change the amount of dopamine released into the NAcc. This may be the result of an inhibition of a disinhibiting response, such as occurs with opiates, as well as an excitatory response as with, e.g., nicotine (Hyman et al., 2006). Research is beginning to show that addiction also involves changes within a number of neurochemicals and neurotransmitter systems such as the endogenous opioids, glutamate, and gamma-aminobutyric acid (GABA)” (EMCDDA).

Barbiturates are central nervous depressants. Their effect ranges from mild sedation to anaesthesia. They act by increasing the action of GABA, and development of tolerance and dependence to barbiturates is possible (EMCDDA).

Benzodiazepines likewise are central nervous depressants. Their effect is to make the user feel calm and, depending on dosage, sleep. They act by facilitating the binding of the inhibitory neurotransmitter GABA at various GABA receptors throughout the central nervous system (CNS). As with barbiturates, development of tolerance and dependence is possible (EMCDDA).

Cannabis (and marijuana and hashish) from the hemp plant *Cannabis sativa* is the most frequently used illicit drug. It is usually smoked and passes from the lungs via the blood stream to the brain. The main component, delta-9-tetrahydrocannabinol (THC), was extracted from the cannabis plant for the first time in 1964 (NIDA). It increases the dopamine level in the brain’s reward centre and can distort important survival and hedonic functions such as thinking, memory, pleasure and time perception. A high density of cannabis receptors is present in the limbic system. Frequent cannabis use can lead to dependence. Cannabis increases the heart rate and has an effect on the lungs. Chronic marijuana use is associated with various mental problems. (NIDA)
There are different central stimulants, including amphetamine, Preludin, Ritalin, fenedrin. Amphetamine was synthesized from ephedrine during the 1900s. Short-term administration produces, among other sensations, euphoria, feelings of wellbeing, and increased concentration as the levels of dopamine, noradrenaline and serotonin increase. This increases also the blood pressure and pulse rate and induces release of the corticotropin factor, corticotrophin and cortisol. Repeated use can cause dependence and can lead to irritability, stereotypical behaviour and paranoid psychosis (NIDA).

The hallucinogen lysergic acid diethylamide (LSD) was synthesized in 1938. The drug produces hallucinations, changing sensations and feelings, and disrupts the interaction of nerve cells and serotonin. The serotonin system is involved in the control of behavioural, perceptual and regulatory systems. Lysergic acid diethylamide is not considered an addictive drug as it does not produce compulsive behaviour; however, it can create tolerance. Most users decrease or stop use over time (NIDA).

Opium (*Papaver somniferum*) has been used medically for thousands of years. It is the dried unripened seed pod of the opium poppy and is typically smoked, but can also be eaten. (NIDA)

Heroin was synthesized from morphine during the 19th century and is a depressant. It is transformed to morphine in the brain and acts primarily on the endogenous opioid system and also on the dopaminergic system. Opiate receptors (μ, δ, κ) are located in several areas of the brain and the brain stem, which are important for automatic life processes, e.g. breathing (heroin overdoses frequently involve suppression of respiration). Opiate receptors are also located in other areas of the body and are especially involved in pain and reward. Intravenous injection of heroin gives a feeling of euphoria, warm flushing of the skin, heaviness of the extremities and clouded mental functioning and is followed by a wakeful and drowsy state. Regular heroin use leads to tolerance in which users’ physiological and psychological response to the drug decreases and the dose has to be increased to achieve the same effect. Chronic use of heroin leads to physical dependence, which means that the body is adapted to the drug and withdrawal occurs if the drug is not taken or the quantity is reduced. During withdrawal, craving can occur which can precipitate continued use/relapse. Craving can persist years after heroin cessation. (NIDA)

**Methadone maintenance treatment (MMT)**

Methadone (methadone hydrochloride) is a synthetic opioid analgesic discovered in Germany in 1937, which was used as a painkiller during World War II when there was a shortage of morphine. Like heroin and morphine, methadone is an agonist on the μ-opioid receptors, and when it occupies the opiate receptors in dependent opiate users, it prevents withdrawal from heroin (morphine). When heroin is taken, methadone blocks the effect of heroin. Methadone is used for analgesia and for detoxification or maintenance in opioid addiction. The advantage of methadone compared to heroin for dependent subjects with high doses is that it is administered orally instead of being injected intravenously, it has 24-36 hours of duration of action compared to 3-6 hours for heroin, it does not give a sensation of euphoria, it takes 30 minutes for onset of duration while it is immediate for heroin and withdrawal symptoms occur after 24 hours compared to 3-4 hours for heroin (Kreek 2000).

In the mid-1960s, Dole and Nyswander introduced MMT for heroin addicts (Dole and Nyswander 1965). It consisted of a daily methadone dose of 80–120 mg for most of the heroin-addicted patients to create cross-tolerance to heroin and absence of abstinence.
and craving from heroin. The medical treatment in combination with psychosocial interventions contributed to less drug use, criminality, and injection-related death and enabled rehabilitation and integration in society. The first Swedish MMT programme (MMTP) was started by professor Gunne in 1967 at Ulleråker hospital in Uppsala. The positive effects of MMT were confirmed in randomised controlled trials (RCTs) in different countries (Gunne and Grönbladh 1981; Newman and Whitehill 1979; Vanichseni, et al. 1991). The Swedish RCT study was performed during the years 1977–1979 at Ulleråker’s MMTP (Gunne and Grönbladh 1981). The inclusion criteria to the MMTP were based on Dole and Nyswander’s initial criteria. Thirty-four opiate-dependent subjects, 20–24 years old, were randomized to MMT (17) or to no MMT (17) with the possibility to ask for drug-free treatment. The follow-up of the control group was done by personal contact, records and contact with administrations. After 2–7 years (median 4.1, for the experimental group v. 4.7, years for the controls), 13 (77%) of the methadone patients were at work and drug-free and two of these had left MMT. None in the control group had entered drug-free treatment, eight had begun MMT and six of these were drug-free, one was drug-free, four had died and the others were in institutions, prison or using drugs.

Research has confirmed that MMT contributes to lower criminality (Ball and Ross 1991; Marsch 1998; Stenbacka, Leifman, Romelsjö 2003; Teesson et al. 2007), less drug use (Marsch 1998; Teesson et al. 2007; Ball and Ross 1991) less injection use and transmission of infections (Marsch 1998; Teesson et al. 2007) better quality of life (Teesson et al. 2007; Ball and Ross 1991; Stenbacka, Leifman, Romelsjö 1998) and reduced mortality, (Clausen, Anchersen, Waal 2008; Gibson et al. 2008; Fugelstad et al. 2007; Caplehorn et al. 1996) also among patients with prior coercive drug-free treatment (Fugelstad, Ågren, Romelsjö 1998).

After a review of earlier RCTs, the Swedish Council on Technology Assessment in Health Care ((SBU 2001) stated in 2001 that maintenance treatment with methadone and buprenorphine is evidence-based treatment for heroin dependence. Johansson, Berglund, Lindgren (2007) performed a meta-analytical study of eight RCTs which confirmed previous results of the positive impact of methadone treatment on retention (six RCTs), opiate use (seven RCTs) and criminality (five RCTs). In Mattick et al.’s review (Mattick et al. 2009) of MMT versus no MMT, eleven RCTs were included. The results confirmed earlier reviews that MMT was associated with higher retention (seven RCTs) and less heroin use (six RCTs) but non-significantly lower levels of criminality (three RCTs) and mortality (four RCTs).

A methadone dose of 60–100 mg, with individual adjustments, is recommended for attaining positive treatment results (Faggiano et al. 2008). For some patients, a methadone dose of ≥100 mg is necessary to produce sufficient cross-tolerance to heroin (Donny et al. 2005; Fareed et al. 2009). Methadone maintenance treatment is regulated in national guidelines and legislations. The Swedish regulations followed Dole and Nyswander’s original model and demanded obligatory cooperation with the welfare services until January 2005 (SOSFS 1990:16(M)). The inclusion criteria were that only opiate users with at least 4 years of documented compulsive intravenous opiate use, at least 20 years of age, and previous attempts at drug-free treatments, as well as absence of advanced poly-drug use, were eligible for methadone treatment. Furthermore, the users had to apply for treatment of their own free will. The Swedish MMT policy includes fairly high methadone doses (e.g. at the Stockholm Dependence Centre in 2008, the mean dose was 90 mg) and frequent urine testing. At the national level, the number of patients in MMT at the same time was limited until the year 2005,
although the number did increase from 150 in 1983 (Socialstyrelsen) to 1,200 in January 2004 (SOSFS 2004:1(M)).

The discharge rules differed somewhat between the MMTPs. In the Stockholm MMTP, which started in 1985, discharge reasons were threat of violence, criminal acts leading to a prison sentence, dealing drugs, providing or smuggling narcotic substances and/or methadone, tampering with a urine specimen, and, from 1997, not using a dose of methadone according to prescription. Other reasons for involuntary discharge were (usually repeated) illicit drug use, non-compliance with treatment rules, the patient’s own decision, or appraisal by the MMTP that treatment was not contributing to the patient’s rehabilitation. Often, several factors had to be considered before a decision was made, as some positive developments in some domains could coincide with indications for discharge in other areas. Except for severely ill subjects, the discharged patients (including those who left treatment by their own decision) could not apply for readmission until 1 year after discharge.

In January 2005, new inclusion criteria with no upper limit to the number of patients were introduced (SOSFS 2004:8(M)) which included both methadone and buprenorphine maintenance treatments. The number of treatments in Sweden increased tenfold within a few years. In the new inclusion criteria, the number of years with documented opiate dependence was reduced to 2 years, the lower age limit remained 20 years and the patient had to have capacity to consent to the treatment plan. Rules for discharge were regulated and the time limit for readmission to MMT was reduced to 6 months. New inclusion criteria were introduced in March 2010 (SOSFS 2010:27 (M), which reduced the 2-year limit to 1 year of opiate dependence, possibility to enter before age 20 if other treatment attempts had been unsuccessful, and no obligatory cooperation with the welfare services. Under the new criteria, after discharge from MMT, a patient cannot be readmitted before a period of 3 months except for special medical reasons. Further, MMT cannot be prescribed to those with severe poly-drug use or during coercive treatment.

The new guidelines indicate that the Swedish policy of methadone and buprenorphine treatment today approaches the policy for maintenance treatments in other countries, with easy access to maintenance treatment. However, it is difficult to compare results from different countries and methadone programmes as there may be large differences in treatment policies, as well as cultural differences.

1.6 USE OF ILLICIT DRUGS, AND MORTALITY

The association between use of illicit drugs and mortality has been the subject of a large number of studies, principally based on follow-ups of different clinical or justice populations. These have shown that, overall, drug users have a markedly increased mortality compared with the general population. (Darke, Degenhardt, Mattick 2007). The mortality rate differs between users of different main drugs, but also between different time periods and places (idem). Opiate users have a higher standard mortality ratio (SMR) than stimulant users (Fugelstad et al 1997; Bartu et al.2004; Darke, Degenhardt, Mattick 2007), but few studies have included users of other main drugs or poly-drug use. These are mainly Swedish follow-up studies of treatment samples. In a 6–14-year follow-up (Tunving 1988) of 524 Swedish drug users hospitalized with an International Classification of Diseases, 8th revision (ICD-8), diagnosis of drug addiction (“dependence”) during the period 1970–1978 in Lund, Sweden, 62 subjects died, with an SMR of 3.5 (compared with the Swedish population). Male opiate users
had an SMR of 5.4 and female users of 8.0; male amphetamine users had an SMR of 2.5, male poly-drug users had an SMR of 3 and female poly-drug users an SMR of 2. In a study of mortality among 1,630 drug users in Stockholm County (Engström et al. 1991), who were hospitalized during 1971–1972 and followed until 1984, a total of 446 died. Of these, opiate users had an SMR of 18.3 (compared with the general population in Stockholm County), users of stimulants/cocaine had an SMR of 9.0, while users of sedative/hypnotics had one of 3.9, and mixed drug users had an SMR of 3.3. In an 11-year follow-up of 852 of these drug users, opiate users had an SMR of 19.4, central stimulants users of 9.4, cannabis users of 6.8 and users of mixed drugs, of 4.1 (Adamsson-Wahren, Brandt, Allebeck. 1997).

The causes of death among users of illicit drugs are frequently drug-related, e.g. overdose of intoxication, or other unnatural causes including injuries, accidents, infections such as human immunodeficiency virus (HIV) and hepatitis C, and homicide and suicide (Darke, Degenhardt, Mattick 2007; Eksborg and Rajs 2008). Multiple drugs and alcohol are frequently found in the body among dead drug users. The number of drugs/alcohol used previously has been found to be linearly associated with risk of unnatural death (Bråvik et al. 2009).

Some of the risk factors associated with premature death among drug users in clinical samples are gender (males have higher risk), older age, years of drug use, drug injection, type of drug, unstable social situation, HIV infection, other comorbidity and overall poor social functioning (Darke, Degenhardt, Mattick 2007).

The association between drug use among youth in the general population and mortality has rarely been analysed. Results from clinical studies are not necessarily valid in unselected samples of drug users in the general population, and it is possible that the mortality risk is lower than in clinical samples. In a 15-year follow-up of about 50,000 male conscripts aged 18–20 (Andréasson and Allebeck 1990), the relationship between use of cannabis >50 times, use of other illicit drugs, and drug injection and mortality disappeared after adjusting for social, familial and behavioural factors in multivariate analyses. Further research with a longer follow-up may contribute to knowledge about the possible association between various illicit drug use in late adolescence and mortality.

1.7 THE RELATION BETWEEN ILLICIT DRUG USE AND SOCIO-ECONOMIC SITUATION

Longitudinal epidemiological studies have shown that more advanced drug use during adolescence is associated with lower educational level, academic failure and lower income (Newcomb and Bentler 1986; Lynskey and Hall, 2000; Schuster et al. 2001; Merline et al. 2004; Fergusson and Boden 2008). Risk factors for initiation of and progression to severe illicit drug use have been identified in various domains, e.g. younger age at drug use debut, familial situation (e.g. heredity, parents’ substance use, low socio-economic status, low parental attachment), and environmental (urban area, drug availability), social (peers with substance use and/or criminality), behavioural (e.g. truancy, low school results, running away from home, criminality) and psychological conditions (anxiety and depressive disorders, impulsivity, sensation seeking, stress, and low self-confidence (Brook and Brook 1990; Hawkins, Catalano, Miller 1992; Stattin, Romelsjö, Stenbacka 1997; Hser, Longshore, Anglin 2007). Research has shown that an accumulation of risk factors is associated with an additional increase in risk (Bry, McKeon, Pandina 1982; Newcomb, Maddahian, Bentler 1986; Stenbacka, Allebeck, 8
Protective factors which decrease or buffer the risks for drug use have been identified in the same domains (Bry, McKeon, Pandina 1982; Hawkins, Catalano, Miller 1992; Newcomb and Felix-Ortiz 1992; Jessor et al. 1995; Jessor, Turbin, Costa 1998; Griffin et al. 2001; Fergusson, Boden, Horwood 2008). Some of these are competence factors such as decision-making, self-control and self-regulation skills (Griffin et al. 2001), emotional control, social competence intellectual ability (Stenbacka and Leifman 2001), familial factors, e.g. early parental attachment (Brook and Brook 1990; Hawkins, Catalano, Miller 1992) and absence of behavioural problems, good adaptation at school, and conventionality (Newcomb and Felix-Ortiz 1992; Jessor et al. 1995, Jessor, Turbin, Costa 1998). No studies have been found which has analysed risk and protective factors early in life which predict a favourable socio-economic outcome in middle age among those who used illicit drugs in late adolescence. More knowledge may be valuable for improving the theoretical and empirical basis for a supportive environment during upbringing, at schools and for prevention strategies among those who use different kinds of drugs. Favourable socio-economic outcome may be defined as favourable socio-economic situations within education, occupational class and income, as research has shown a low to moderate correlation between these outcomes, and as they are partly associated with different causal mechanisms (Geyer et al. 2006).

1.8 DRUG USE IN METHADONE MAINTENANCE TREATMENT, AND RETENTION

Research from Sweden and other countries (Stenbacka and Romelsjö 1997; Morral, Belding, Iguchi 1999) has shown that illicit drug use during MMT is an important reason for discharge from or dropping out of MMT. Knowledge about frequency and use of different illicit drugs during MMT and in relation to different psychosocial treatment approaches is limited and usually based on self-reports. Information about illicit drug use, which we can obtain through urine analyses, is rare because in many programmes, urine samples are taken markedly less frequently than in Sweden. Moreover, self-reported information can be biased by recall difficulties, social desirability and awareness of possible negative treatment consequences. Magura and Lipton (1988) have concluded that urine analysis is the most objective information about drug use. Methadone maintenance treatment with complementary psychosocial services, compared with MMT without such services, has been shown to be associated with higher retention in MMT (McLellan et al. 1993). Whether the impact of a structured psychosocial programme such as Moolchan and Hoffman’s four-phased model (Moolchan and Hoffman 1994), with daily group activities during the initial treatment period and a decrease in interventions as the performance increases, differs from that of individual counselling warrants study. Analyses of patterns and frequency of illicit drug use among MMT patients, their relation to gender and methadone dose, and analyses of whether the patterns of drug use differ between discharged and not discharged patients and whether type of psychosocial treatment is related to illicit drug use, methadone dose and retention, will be performed to gain increased knowledge for the adaptation of treatment interventions to patients’ needs.

1.9 METHADONE MAINTENANCE TREATMENT AND CHANGES IN THE LIFE SITUATION

Some researchers have proposed that multiple MMT experiences contribute to successive positive changes in different life areas (Anglin, Hser, Grella 1997). Repeated treatment experience is, on the other hand, more frequent among those with more severe drug and drug-related problems (idem). Dennis et al (2005) propose that multiple treatment experience should be seen as a sign of the chronicity of the drug
dependence. Longer follow-up studies of methadone patients show that few patients remain in treatment and several treatment periods are frequent (Dole and Joseph 1978; Maddux and Desmond 1992; Goldstein and Herrera 1995; SNBHW 2001; Bell et al. 2006) often due to relapses after discharge from MMTP. One Swedish national longitudinal follow-up study (Stenbacka and Romelsjö 1997) of all MMTPs included 205 patients who were interviewed (135 were randomly selected from Stockholm MMT, 26 patients from Uppsala MMT, all 24 MMT patients in Malmö and 20 patients in Lund). Data from records and registers were collected for 655 patients (465 men and 190 women). A control group was created, including 1,171 men and 312 women who were registered as drug injectors in the injection register in Stockholm and who fulfilled the criteria for methadone but had never entered MMT. The results showed that MMT contributed to decreased criminality, in-patient care and mortality during MMT.

Twenty per cent of the 257 discharged patients were discharged during the first 6 months while 48% were discharged within 2 years. The 1-year retention was 87% and the 2-year retention rate was 80%. The most frequent cause for discharge was illicit drug use. The results showed that being HIV-positive, having ten or more convictions before MMT, being male, being younger than 30, and a low methadone dose predicted discharge. After discharge from MMT, criminality increased but remained lower than before MMT, while in-patient care increased markedly.

Another Swedish study (Stenbacka, Leifman, Romelsjö 2003) showed that the incidence of convictions decreased during MMT, both for patients who remained in MMT and for those with several treatment periods. After discharge from MMT the incidence remained lower than before the first treatment period. Subjects who had two or more MMT periods had had higher incidence of convictions and arrests before the first MMT than those who remained in treatment.

In a Swedish national 9-year follow-up of 261 subjects (43 % HIV-seropositive) admitted for the first time to MMT in 1989–1991 (SNBHW 2004), a positive impact on in-patient care, criminality, social assistance, disability pension and death was confirmed during the follow-up period. By the end of the observation period 33% had died. Fifty-five per cent (n=48) of these had died after discharge from MMT, usually from poly-drug use. Of all patients, 26% (n=69) remained in their first MMT period. These results show that MMT patients had important health intervention and support needs also during MMT. Of all 261 patients, 157 were in Stockholm MMT and are subjects of an 18-year follow-up in this thesis work, of the impact of MMT on several important life areas.

1.10 THEORETICAL FRAMEWORK

Several theoretical models attempt to explain the processes of initiation of illicit drug use and dependence during the life span. Some models have used a career perspective with different phases including a parallel increase in involvement in a drug-related life style, development of dependence and later possible termination of the drug use career (see, e.g., Nordiska Rådet 1978). Winick (1962) proposes a “life-cycle” model which includes the conclusion that a majority of drug users “mature out” from drug use. Kandel et al. (1992) have proposed a gateway model with sequential different stages in which the use of licit drugs precedes marijuana, which precedes other illicit drugs. The life course perspective is integrated in the prevention research about substance use (Hawkins, Catalano, Arthur 2002). In drug use research the life course is studied by analysing transitions in drug use trajectories as a life event that can be a turning point and change the trajectory (Hser, Longshore, Anglin 2007). To perform life course
analyses, trajectory and path analyses are frequently used to study the association between early risk and protective factors and mediating variables with outcomes at several measurement points, e.g., cessation, relapse, etc (Hser et al. 2007). In this thesis, outcomes among groups of drug users’ different points in the life span will be analysed, which is especially possible in studies III and IV, with more measurement points. In life course research it is important to identify sensitive periods (Ben-Sclomo and Kuh 2002). Drug use is most frequently initiated before the twenties (Kandel and Logan 1984), which corresponds to an age when the brain is not yet fully developed. Results from earlier longitudinal studies of youths in late adolescence indicate that severe drug use in late adolescence may be associated with severe health problems (Stenbacka, Allebeck, Romelsjö 1992). However, much less is known about the course of drug use in the general population, including experimental drug users who have used drugs once or a few times. The life course theory can be seen as a general, useful theory for studies of drug-related consequences and factors influencing the probability of drug use, and is useful in providing data for continued use. The first two papers in this thesis work analyse the use of illicit drugs among men in late adolescence in the general population, and its association with mortality (Study I) and favourable socio-economic outcomes (Study II). The third (III) and fourth (IV) papers are follow-up studies of opiate-dependent subjects who have entered MMT. Opiate dependence is considered a chronic disease, in which events can provoke turning points, as with other chronic diseases. For opiate-dependent subjects, MMT can be a turning point and contribute to change in the life course.

An outline of the main points of the papers is given below.

**Study I**

- a) An association between various drug experiences at adolescence and mortality is influenced by factors early in life.
- b) This association varies depending on main drug use in late adolescence, and frequency and mode of use.
- c) Continued use, leading to drug-related hospitalization and criminality, is related to a very high mortality risk.

**Study II**

Association between use of different dominant drugs and the probability to attain a favourable socio-economic status.

- a) The study investigates the association between use of different dominant drugs and the probability to attain a favourable socio-economic status.
b) This probability is influenced by presumed negative factors (risk factors) and positive factors (protective factors).

c) Hospitalization with a drug diagnosis during follow-up reduces the probability of enjoying a favourable socio-economic status.

Study II.

Study III
The study investigates the incidence of relapse periods of illicit drug use per person and year at different time periods of MMT among those who remained in treatment and those who were discharged. It further studies the incidence of relapse periods per person and year by type of drug during MMT.

Study IV
a) In study IV, the subjects’ life course is analysed by investigating different factors related to drug use 4 years prior to MMT among subgroups with different experience of number of MMTs during the 14 years after admission to first MMT.
b) The incidence of in-patient care, and of in-patient care with opiate diagnosis, with other drug diagnosis, convictions and prison sentences is outlined for different groups.
c) The rate of different events during the 4 years before MMT and during each year thereafter is examined, for patients during MMT and after MMT.
d) The different groups are: patients who remain in treatment; patients who are discharged from MMT and not readmitted; patients who are in their second MMT at the end of the follow-up; and patients who have been discharged from their second MMT.
2 AIMS

The two general aims of this thesis work were (1) to longitudinally analyse the association between drug experience among young men and outcomes up to late middle age; and (2) to investigate the impact of MMT on opiate dependents’ life course.

Furthermore, the aim was to –
 analyse, among young men in the general population, the associations between use of different drugs and mortality up to late middle age (Study I);
 analyse the probability of and predictors for a positive socio-economic situation in middle age among young men in the general population with different drug experience (Study II);
 analyse illicit drug use and retention among opiate-dependent subjects in MMT (Study III); and
 analyse different life domains during the life course among opiate-dependent subjects after admission to MMT (Study IV).
3 MATERIALS AND METHODS

3.1 STUDY POPULATION
3.1.1 The conscription cohort

3.1.1.1 Study I
The two general population studies were based on 50,465 Swedish men who were compulsorily conscripted during the conscription year 1 July 1969 to 30 June 1970. All 49,411 conscripts born in 1949–1951 were included in study I and II. After exclusion of 1,374 subjects with no information about drug use and 13 with an erroneous death date, the cohort comprised 48,024 subjects. The aim of study I was to analyse the association between drug experience at conscription and mortality until late middle age. Of the 48,024 subjects, those with any self-reported use of illicit or non-medically prescribed drugs were included in a drug use group (DUG, n=8,767) and those with no reported drug use were placed in a non-drug use group (NDUG, n=39,257). Based on the question about the most frequently used drug, the DUG was divided into subgroups of main drug or no reported main drug: a stimulant group (n=221), an opioid (n=137), a cannabis (n=4,330), hallucinogen and other (n=293), sedative/hypnotic (n=472) and an unspecified drug group (n=3,314). The cohort was followed in three registers from conscription until 31 December 2004.

3.1.1.2 Study II
In study II, the aim was to analyse probability of and factors associated with a favourable socio-economic situation (having a job, having attained education of 12 years or more, and having an income above the median) among subjects alive in middle age with either stimulants, opioids, cannabis or hallucinogen and others as main drug at conscription. The final cohort included 35,825 living subjects (stimulants n=127, opioids n=78, cannabis n=3,160, hallucinogens n=215, no drug use n=32,245) after exclusion of conscripts deceased before 31 December 2006 and subjects with missing data on any variable included in the study. The cohort was followed until 31 December 2006.

3.1.2 Methadone maintenance treatment cohorts
3.1.2.1 Study III
The aim of study III was to analyse illicit drug use and retention in MMT among heroin-dependent subjects who were admitted to MMT for the first time. Of all 225 subjects who were admitted for the first time to the Stockholm MMTP between 1 January 1995 and 30 June 2000, 204 subjects (147 men, 57 women) were included in the study, after exclusion of four subjects who lacked results from urine analyses, eleven who did not participate in the treatment mode “The Old Team”, and 21 subjects who were transferred to another MMTP. The subjects were followed until discharge or until 31 December 2000. The patients were divided into two sub groups, “The Old Team” (n=131, 93 men, 38 women, admitted until June 11, 1998) with individual counseling and “The New Team” (n= 73, 54 men, 19 women) with psychosocial intervention following the Moolchan and Hoffmann’s model (those admitted June 12,1998 to June 30, 2000).
3.1.2.2 Study IV

The aim of study IV was to analyse mortality, criminality, social assistance, in-patient care, coercive treatment, and out-patient care in relation to MMT during an 18-year follow-up among 157 heroin-dependent subjects (115 men, 42 women) admitted for the first time to MMT in Stockholm between 1 January 1989 and 31 December 1991. The cohort were followed from 1 January 1985 (4 years before MMT) until 31 December 2003. The incidence of different outcomes was calculated among four subgroups (subjects who died during MMT were excluded), subjects who remained in the first MMT (n=25), subjects who had been discharged from first MMT and had not been readmitted (n=38), subjects in their second MMT (n=24), and subjects who had been discharged from their second MMT (n=45).

3.2 DATA COLLECTION

3.2.1 The Swedish conscript survey

Studies I and II include 49,411 out of 50,465 Swedish men born in 1949–1951, who were compulsorily conscripted during the conscription year 1 July 1969 to 30 June 1971. At conscription the conscripts were asked to answer two non-anonymous questionnaires. The first included questions about home and school backgrounds, and behavioural and psychological conditions, while the second included mainly questions about substance use, licit, illicit and non-medically prescribed use of drugs. Psychologists assessed emotional control on 5-point standardized Stanin scales. When needed, subjects were referred to a psychiatrist who, considering utility in the military services, diagnosed them according to the ICD-8. Overall intellectual ability was measured by transforming results from four tests measuring logic, verbal, inductive and technical abilities on 9-point Stanin scales into one value on the 9-point Stanin scale. The choice of risk factors was based on results from earlier research and included the following variables: father’s social group (social group I: proprietors, private entrepreneurs and high salaries in private and public sectors and social group 2: other salaries and small entrepreneurs versus social group 3: blue-collar workers), parents’ marital status (divorced v. not divorced), father’s alcohol consumption (occasionally/never v. sometimes/often), contact with the police/juvenile authorities (0 times v. ≥ once), smoking (0, 1–10, >10 cigarettes), alcohol consumption (calculated on answers to questions about quantity and frequency of beer, wine and spirit consumption, 0 g/wk v. 0.01–168 g/wk (not a risk factor), 168–280 g/wk, >280 g/wk), emotional control (very high–average v. low–very low), intellectual ability (high 789 v. average 654, low 321) and psychiatric diagnosis at conscription (no v. yes, alcohol and drug diagnoses excluded).

In study II, some variables were included as presumed predictors for a favourable socio-economic outcome. These were father’s social group (social group 2 and social group 3 versus social group I), and answers to the questions, Did you speak with your parents about your activities during leisure time? (never/seldom/sometimes v. often), How did you get on with your teachers in school? (poorly/not so well/rather well v. very well), How many friends do you have? (>5 v. ≤ 5), emotional control (very low/average v. high/very high) and general intellectual ability (1–6 v. 7–9/(app. > 110 IQ). Risk factors were partly the same as in study I, viz. father’s drinking habits, parents’ marital status, contact with the police or juvenile authorities, a psychiatric diagnosis, smoking and alcohol consumption (0=reference group 0–168 g of alcohol/week, 1=≥168 g/week).
3.2.2 The register of methadone maintenance treatment

Some patient information from the methadone maintenance treatment programmes treatment was registered by SNBHW for the time period 1989-2004 (SNBHW 2006). It includes all subjects in Sweden who applied to or were in MMT at any moment during that period. All MMTPs reported to the SNBHW the date for admission or rejection, data about the admission criteria, date of assessed dependence on opiate use, previous coercive and drug free treatment, other drug use, previous MMTPs, date of first methadone dose and dosage, information about discharge transfer to another MMTP and death. Information about date of first and last day of MMT, age, sex, first date of documented continued opiate use, drug-free treatments and discharge reasons was used in study IV.

3.2.3 The cause of death register

The cause of death register, administered by the SNBHW, includes all deaths among subjects registered as living in Sweden when death occurred, irrespectively of whether death occurred in Sweden or abroad. Missing data about cause of death are estimated to concern about 0.5% of all deaths until 1997, where after the coverage of deaths is regarded as total. The cause of death is diagnosed according to the ICD, which is periodically reviewed. The 8th revision of the ICD covers the period 1969–1986, while the ICD-9 was used for the years 1987–1996, and the ICD-10 has been used since 1997. Information about date of death (studies I, II and IV), underlying cause of death (studies I and IV), sex (study IV) and multiple causes of death (study I) was used.

3.2.4 The Swedish hospital discharge register

The register, administered by the SNBHW, was started in 1964 and has been covering all public in-patient care in Stockholm and Uppsala counties since 1972. Since 1983 it has a record of about 85% and since 1987 of about 98–99% of all hospitalizations in Sweden. Information about date for admission and discharge to in-patient care (studies I, II and IV) and ICD drug and psychiatric diagnoses (ICD-8, ICD-9 and ICD-10 used for study I) was used. In studies I and II, drug-related hospitalisation during follow-up was used as indicator for severe drug use during follow-up. In study I, ≥ one hospitalization with an opiate diagnosis, ≥ one hospitalization with a stimulant diagnosis (no opiate diagnosis), ≥ one hospitalisation with an “other drug” diagnosis and ≥ one hospitalisation with only cannabis diagnosis during follow-up was included as a risk factor for mortality.

In study IV, the number of subjects having an admission to in-patient care with a psychiatric diagnosis (yes/no), with an alcohol diagnosis (yes/no), or a number of admissions with an opiate diagnosis or other drug diagnoses (main or secondary) during the 4 years before MMT were extracted from the register. Number of admissions with other drug diagnoses and with psychiatric diagnoses during the 4 years before MMT were included in the multivariate analysis. The incidence of in-patient admissions, with opiate and other drug diagnoses during the 4 years before admission to MMT and each following year, was calculated for the different subgroups.

3.2.5 The integrated database for labour market research

In study II, the outcome variables education, work and income were extracted from the “Integrated database for labour market research” (LISA) register which is administered by Statistics Sweden (Statistics Sweden 2008). This database was started in 1990 and includes all subjects who are 16 years or older in Sweden on 31 December each year.
Annual data about e.g. education, income and employment as well as social assurance data are transmitted by the respective administration. The variables used in the study were: the highest level of education attained in 1990 and 2006 from the register of education at Statistics Sweden (≥ 12 years) being at work in 1990 and 2006 defined as having an income from work during at least one hour during the week of investigation in November or being on sickness benefit, parents' allowance or collecting occupational injury benefits. The information is based on information about income, pension and other statement delivered to the Swedish Tax Agency from employer (Kontrolluppgift (KU)-registret) and the register-based statistics about labour market (Registerbaserade arbetsmarknadsstatistikten (RAMS)) which includes employers and employees who have worked at least one hour each week during the month of November. Subjects working without being declared and those who live in Sweden but are working abroad are not in the KU-register and subjects with low appearance in the labour force have the highest risk to be misclassified. The annual disposable income over the median of the cohort was based on the variable “Disponibel inkomstindividens delkomponent av hushållets/familjens disponibla inkomst”, the individual part of the households/family disposable income including all income exempted and not exempted from taxation after deduction of taxes and other negative transfers (also e.g. social assistance) and is based on the income and fortune statistics.

3.2.6 The register of criminal convictions
This register includes dates for conviction, crime and sentence, type of crime and sentence. It has a total coverage of all convicted subjects in Sweden and is administered by Statistics Sweden. Information about number of convictions (studies I, IV) date of conviction (studies I and IV), prison sentences (study IV) and age at first conviction (study IV) was used. In study I the number of convictions during the follow-up period was included. In study IV, age at first conviction, number of convictions and prison sentences (yes/no) during the four years before MMT were included as risk factors for mortality and criminality during MMT and as predictors for being in MMT. The incidence of convictions and prison sentence was calculated for subgroups using information about date when the main crime was committed and date for prison sentence.

3.2.7 The out-patient register for Stockholm County
This register was started in 1995 and is run by Stockholm County and has reliable information about visits to out-patient care. Information about outpatient visits was used (study IV). As reporting of visits was linked to reimbursement for the clinics, there is probably very little attrition in these data.

3.2.8 The national register of social assistance
This register was started in 1985 and includes subjects who received economic assistance from the local welfare service. It is run by SNBHW. Statistics Sweden collects the information, which is reported yearly. The reliability of the information is considered as good as information reported from the municipalities is verified by Statistics Sweden and corrected when needed by the municipalities. Almost all municipalities had reported data each year. Some factors which may contribute to errors are information about moving and changes in the household. In study IV, information of received social assistance each year and information about mean number of months during which patients received social assistance (0-6, 6-12 months) during
the four years before MMT was used. Having received social assistance was included as a risk factor for mortality.

3.2.9 The register of coercive care of users

The register was started in 1982 and was first run by Statistics Sweden but has since 1994 been administered by the SNBHW. Substance users who refuse to enter voluntary treatment and are considered as being in danger of injuring themselves, ruining their lives or dangerous for the close family can be coerced into treatment. The actualisation of a possible LVM can be made by a close person, by the authorities who are in contact with drug users and are bound to make a demand to the social services and doctors in health care if they consider that they can not give essential care. The social services can decide about immediate coercive care or after the obligatory investigation including medical advice whether they should apply for coercive care at the Administrative Court (Förvaltningsrätten) which state in accordance to the Care of Alcoholics, Drug Abusers and Abusers of Volatile Solvents Act (Lag (1988:870 om vård av missbrukare i vissa fall)). The National Board of Institutional Care (Statens institutionssstyrelse (SiS)) has the authority for the LVM-homes, which provide care for the subjects. The decisions from the Courts are reported to SNBHW, and information about subjects in LVM-homes is reported to SNBHW from SiS. It may be some missing data in the reports from the courts and some data may be missing from the LVM-home. Variables used in study IV were dates for admission to LVM and discharge.

3.2.10 The urine analyses database

In study III, information about illicit drug use during MMT was obtained from the database at the Clinical Pharmacological Laboratory at Karolinska Hospital. This laboratory worked in close cooperation with the Stockholm MMTP and performed all urine analyses by routine immunochemical screening methods for methadone, opiates, benzodiazepines, amphetamines, cocaine, cannabis, barbiturates, LSD and propoxiphen. The specificity was estimated to be about 95% for cannabis and cocaine and 80% for other drugs. The analytical cut-off values were 300 ng/ml for morphine alkaloids, 20 ng/ml for cannabis, 50 ng/ml for cocaine, 300 ng/ml for stimulants and 100 ng/ml for benzodiazepines. This permitted a detection period after intake of about a half week. Confirmation analyses by gas chromatography-mass spectrometry (GC-MS) were undertaken if a positive screening result was denied by the patient, and were also performed randomly in about 10% of all positive cases. The patients’ identification codes registered in the data base were verified with the MMTPs records. The positive urine analyses were distributed by relapse periods, defined as one or several subsequent positive urine analyses and ending with the first negative result.

3.2.11 Medical records from Stockholm methadone programme

In study III, dates for admission to and discharge from Stockholm MMT, age, sex, reasons for discharge, treatment team, date of first methadone dose and dose adjustments, in-patient care, work status, drug-free treatments, education, and number of years of intravenous opiate use and other illicit drug use were abstracted from the medical records.

In study IV, data about HIV status, marital status, living conditions before admission to first MMT and methadone dose during first MMT for all 157 subjects were extracted from already collected data from patient records which had been part of an earlier

### 3.3 STATISTICAL ANALYSES

#### 3.3.1 The conscription cohort

**3.3.1.1 Study I**

The incidence of deaths per 1,000 person-years was calculated for drug groups and the NDUG. Cox proportional hazard (PH) regression analysis permits consideration of variation in follow-up time until death or censoring. The hazard ratio (HR) to die was calculated for the whole follow-up period and for each 10-year age interval by bivariate Cox PH regression with a 95% confidence interval (95% CI) for DUGs compared with NDUGs, as was the relationship between drug groups, each risk factor (see 3.2.1) and death for all individuals (n=48,024). The significant variables were included in multivariate analyses (n=40,970). The HR of dying, for the DUGs compared with the NDUG, was analysed in four models. Model 1 was adjusted for risk factors measured at conscription; model 2 = model 1 + adjustment for in-patient care with a drug diagnosis and convictions during the follow-up; model 3 = model 1 and drug injection 1 or ≥ 2 times; and model 4 = model 2 + drug injection as in model 3. The HR to die, for conscripts who reported drug use at conscription and were hospitalized with a drug diagnosis during follow-up and for those with no such hospitalization (see Appendix for diagnoses), was compared with the HR for NDUGs. Chi-squared tests were performed to analyse whether causes of death among drug groups differed significantly from the NDUG. The underlying causes of death (ICD diagnoses from the ICD-8–10) were divided into neoplasms, injuries and intoxication, suicide, undetermined suicide, circulatory diseases, alcohol (deaths with the word “alcohol” contained in the diagnosis), narcotics (codes 304, F11,12,14–16,18,19, O35.5, P04.4, 965, 968.5, 969.6, 969.7, T40.0–T40.3, T40.5–T40.9, T43.6, Z71.5, X42), and other causes, with a separate category for liver cirrhosis (codes 571.00–01, 571.0–571.3, K70), opiate diagnoses (codes 304.0, 965.0, F11, T40.0–3) and stimulant diagnoses (codes 304.4, 969.7, F15, T43.6). Separate analyses were performed for deaths with alcohol or narcotic diagnosis as an underlying or contributing cause of death. The computer program SAS (SAS Institute, Chicago, IL, USA), version 9.1, was used for the analysis.

**3.3.1.2 Study II**

Chi-squared tests were performed to analyse whether the drug groups differed from the NDUG with regard to background variables. Bi- and multivariate logistic regression analyses with a 95% CI were performed to calculate the association between the different drug groups and favourable socio-economic outcomes after adjustment for risk and protective factors. This was also done within the NDUG and within the DUG. Logistic multivariate regression was used to analyse the probability of favourable socio-economic outcomes among drug users with a hospitalization with a drug diagnosis during follow-up (see Appendix for diagnoses), drug users without such hospitalization and the NDUG. Within the drug group the probability for favourable socio-economic outcomes was calculated for different numbers of risks and protective factors and also for a subgroup of heavy drug users including subjects with ≥50 times drug use or drug injection (n=622). Interaction was calculated by introducing the interaction term risk factors x protective factors.
3.3.2 Methadone maintenance treatment cohorts

3.3.2.1 Study III

Chi-square tests with a significance level of \( p < 0.05 \) were performed to analyse illicit drug use during different time periods in the MMTP for all positive urine samples combined, and separately for opiates, amphetamines, benzodiazepines and cannabis. Poisson regression was used when calculating the number of relapse periods in relation to time at risk during treatment (time with drug use excluded) to adjust for differences in follow-up time. The number of relapse periods per person and year (incidence rate) was calculated as the total number of relapses divided by the total time in treatment for all persons during different time periods. Differences in illicit drug use and methadone dose, gender, age, initial psychosocial treatment and last adjusted methadone dose before 3 months, 6 months, 1 year, at 435 days (which represents the median time in treatment for the 84 subjects who were discharged) and each following year were analysed for subjects who remained in treatment on 31 December 2000, and discharged subjects. The incidence of relapse periods for each group served to calculate the relative risk for relapse to drug use for the discharged patients in comparison to those in treatment. The SAS software packet (SAS Institute, Chicago, IL, USA), version 9, was used for data analysis.

3.3.2.2 Study IV

The percentage of subjects alive on 1 January and entered at some point in each year during the period 1985–2003 in either the methadone maintenance register, the Swedish Hospital Discharge Register (also HIV-seropositive), the Register of Criminal Convictions (convictions, prison sentences), the Out-patient Register, or the Register of Coercive Care of Users was calculated. Cox PH bi- and multivariate regression analyses were used to analyse the association between risk factors and mortality and criminality during MMT. Only presumptive risk factors which fulfilled the PH assumption were included in the analyses (while coercive treatment, hospitalization with an alcohol diagnosis, number of in-patient admissions, opiate diagnosis and time in MMT were excluded). Logistic bivariate and multivariate regression analyses were performed to analyse the relationship between presumptive predictors and retention in MMT. Incidence rates of different outcomes were calculated as number of cases (e.g. admissions with drug diagnoses) divided by total person-time for the 4-year period before first MMT and for each following year for the different subgroups.
4 ETHICAL CONSIDERATIONS

All studies have been approved by ethical committees.

Research involving humans can violate the individual’s personal integrity and must be balanced against the benefits to be derived from the planned studies. In the four studies, individual data from register and patient records were linked via the national identification number, which then was replaced by a code only known to the responsible authority. The data were kept secure. No data were published that could be linked to individual subjects. Several applications for scientific studies using the conscript data have been approved by ethical committees. It has been deemed unnecessary to try to contact the subjects for improved consent. Such efforts would have been time-consuming, with difficulties to reach subjects, and probably selected participation due to deaths and poor health and various social problems, and would have invalidated the quality of the research. In some cases the ethics committee demanded that the public should be informed about the research, which has been done through the media. Longitudinal research with longer follow-up periods permits analysis of predictors for long-term outcomes. The possibility to use personal follow-ups in this type of study is limited as this would be associated with high financial costs and difficulties to track individuals and would be dependent on research groups. The conscription cohort, including more than 50,000 individuals for whom non-anonymous data have been collected once, is sufficiently large to perform longitudinal studies on drug users in the general population. The link between data from different registers has contributed to increased knowledge in several domains, which is of general interest for prevention and drug treatment. In studies III and IV, the subjects had been admitted to MMT before the debut of the studies, which made it difficult to contact each subject to ask for consent as mobility and mortality are high among heroin-dependent subjects.

ETHICAL APPROVAL
Studies I and II
The studies were approved by the Regional Ethical Vetting Board at the Karolinska Institute in Stockholm, on 28 February 2007 (Dnr 2007/174-31) and 29 October 2008 (Dnr 2008/1086-31/5).

Study III
The study was approved by the Research Ethical Committee at Karolinska Institute on 5 November 2001 (Dnr 01-310).

Study IV
The study was approved by the Research Ethical Committee at Karolinska Institute on 3 September 2001 (Dnr 01/288), 16 May 2005 and 19 December 2005.
5 RESULTS

5.1 THE CONSCRIPTION COHORT

5.1.1 Study I

The incidence of mortality per 1,000 person-years was lowest, 1.4/1,000 person-years, among the NDUG and the sedative/hypnotic group, while it was 2.2 among all the DUGs together and highest among the stimulant and opioid groups (5.9 and 3.7, respectively). During each 10-year interval the DUG and the cannabis group had a stable HR to die, of 1.46–1.90, compared with the NDUG. The stimulant group had the highest HR during each 10-year interval (range 2.8–5.3) with the exception of the age interval 31–40 years when the opioid group had an HR of 7.29. The DUGs, with the exception of the sedative/hypnotic group, had significantly more deaths with a narcotic diagnosis compared with the NDUG. The cannabis and stimulant groups had significantly more deaths by alcohol and narcotics. Of all drug users, 18% of the deceased had an alcohol and 8% a narcotic diagnosis as underlying or contributing cause of death, compared with 13% and 2% of the deceased in the NDUG and 14.5% (n=17) and 5% (n=6), respectively, of the 117 deaths in the excluded group (n=1,374). A higher frequency of drug use and one intake of either stimulants or an opioid or hallucinogen were associated with mortality.

The increased HR to die among different drug groups remained statistically significant for stimulants, cannabis and the unspecified drug group after adjusting for early risk factors (model 1), but for stimulants only after adjusting for drug-related hospitalizations and convictions during the follow-up period (model 2).

After inclusion of the variable drug injection (model 3, not shown in the Table), the HR for two or more drug injections was 2.57 (95% CI 1.92–3.44) while for the stimulant group, it was 1.95 (95% CI 1.08–3.55). After adjusting for in-patient care with drug diagnosis and convictions during follow-up (model 4, not shown in the Table), only the stimulant group (HR 1.82, 95% CI 1.002–3.31) had an increased hazard ratio.

Table 1. Cox proportional hazard (PH) regression analysis. The Table shows hazard ratios (HRs) to die among users of various main drugs (DUGs) in late adolescence, compared with non-drug users, before and after adjustment for early risk factors and events (drug-related hospitalizations, and convictions) during follow-up.

<table>
<thead>
<tr>
<th>Drug groups</th>
<th>Bivariate analysis (n=40,970) HR 95% CI</th>
<th>Multivariate analysis (n=40,970) HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>HR</td>
</tr>
<tr>
<td>Stimulants</td>
<td>158</td>
<td>4.53</td>
</tr>
<tr>
<td>Cannabis</td>
<td>3,473</td>
<td>1.70</td>
</tr>
<tr>
<td>Opioids</td>
<td>61</td>
<td>2.19</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>113</td>
<td>2.36</td>
</tr>
<tr>
<td>Sed/Hyp</td>
<td>169</td>
<td>1.61</td>
</tr>
<tr>
<td>Drug use not specified</td>
<td>1654</td>
<td>1.52</td>
</tr>
<tr>
<td>No drug use group (ref)</td>
<td>35,342</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Model 1: adjusted for father’s lower social group, divorced parents, father’s alcohol consumption, psychiatric diagnosis at conscription (drug and alcohol diagnoses excluded), contact with the police/juvenile authorities, smoking, alcohol consumption, emotional control, intellectual ability; model 2: model 1 + number of convictions and in-patient care with drug diagnoses during follow-up. 95% CI = 95% confidence interval; Sed/Hyp = sedative/hypnotics.

The variables father’s lower social group, father’s alcohol consumption (sometimes/often), contact with juvenile authorities and/or the police, smoking, low emotional control, low or average intellectual capacity, and psychiatric diagnosis remained independently associated with mortality. In the Cox PH multivariate regression analysis including the same risk factors and events during follow-up as in
the previous analyses (model 2, drug groups excluded), drug users with a drug-related hospitalization during follow-up had an HR of 4.19 (95% CI 3.35–5.24) to die, while drug users with no such hospitalization had no increased HR (1.08, 95% CI 0.96–1.22).

5.1.2 Study II

A higher proportion of subjects in the various DUGs compared with the NDUG had had contact with the police or juvenile authorities, had a psychiatric diagnosis at conscription, were smokers and/or had alcohol consumption ≥168 g/wk (p<0.05). The cannabis group had a higher proportion of subjects from social group I and higher intellectual ability compared with the NDUG (p≤0.001) and both the cannabis and the stimulant groups had a lower proportion of subjects with good or very good emotional control (p≤0.001). A majority in each drug group reported that they had used drugs ten times or less during their lifetime.

In a logistic multivariate regression analysis adjusting for risk and protective factors, the cannabis (odds ratio, OR, 1.60), opioid (1.71) and hallucinogen (1.76) groups had a higher OR to have an education ≥12 years compared with the NDUG in 1990, which result persisted for the cannabis and the hallucinogen groups in 2006, while they did not have a significantly higher OR to be at work or to have an income above the median in 1990 and 2006.

In a logistic multivariate regression analysis including the same risk and protective factors as in the previous analysis, drug users with a hospitalization with a drug diagnosis (diagnoses in Appendix) during the follow-up (n=98) in 1990 had an OR of 0.67 (95% CI 0.37–1.21) to have an education of ≥12 years while for other drug users (n=3,482), the OR was 1.62 (95% CI 1.47–1.77) compared with the NDUG. Both drug groups had lower probability to be at work (OR 0.11, 95% CI 0.07–0.17, and OR 0.78, 95% CI 0.67–0.89, respectively). Only those with a drug diagnosis had a significantly lower probability to have a disposable income above the median. In 2006, only subjects with a drug-related hospitalization during the follow-up had a significantly lower OR for the different outcomes compared with the NDUG.

Separate multivariate analyses of the DUGs and the NDUG adjusting for risk and protective factors showed only small differences between the two in the probability for favourable outcomes. Having a father from social group I and speaking with parents about leisure time remained associated with a higher OR of having an education ≥12 years and a disposable income above the median both in 1990 and in 2006. Intellectual ability remained associated with a higher OR for all outcomes except that of being at work in 1990 for the DUGs. In both the DUG and NDUG groups, having behavioural problems (contact with the juvenile authorities/police) was significantly associated with lower probability for all three favourable outcomes in 1990 and 2006.

Analyses of ORs for favourable socio-economic outcomes among drug users with different number of risk and protective factors showed that the OR increased with the number of protective factors. Subjects with 0–1 risk factors and 3–6 protective factors had an OR of 8.9 to have an education ≥12 years in 1990, compared with subjects with 3–6 risk factors and 0–1 protective factors.
Severe drug users with a drug frequency of >50 times or an experience of drug injecting before conscription with 0–2 risk factors (n=328) and 2–6 protective factors (n=222) in 1990 had about five times higher OR (OR 4.94, 95% CI 3.00–8.15) to have an education ≥12 years compared with those with 3–6 risk factors and 0–1 protective factors. In the same year, only subjects with 0–2 risk factors and 2–6 protective factors had a significantly higher OR to be at work (OR 4.84, 95% CI 1.84–12.76) and to have a disposable income above the median (OR 2.81, 95% CI 1.76–4.48). Interaction analyses in 1990 indicated that increased protection and decreased risk and decreased protection increased the probability of being at work (p=0.0006) and of having a disposable income above the median (p=0.0022).

### 5.2 METHADONE MAINTENANCE TREATMENT COHORTS

#### 5.2.1 Study III

Of all 204 MMT patients, about 30% were women. Seventy-five per cent of the patients were unemployed. The patients had a mean number of 11 years of intravenous opiate use. The mean observation time was 2.5 years for all patients. At the end of the follow-up, 120 patients were still in treatment and had a mean time of 3 years in treatment while discharged patients had a mean time of 1.5 years in treatment. The 1-year retention rate was 84% and the 2-year retention was about 65% in both the individual and the group counselling groups. Of all 231,073 drug analyses, 3% were positive for an illicit drug. On the other hand, the great majority (91%) of subjects in MMT had at least one positive test. Discharged patients had significantly higher rates of positive urine samples (21% v. 9%) than those who remained in treatment. Discharged patients had more relapse periods per person and year during the first 6 months and during each following year. Relapse to opiates was negatively associated with the last adjusted methadone dose and discharged patients had a lower mean

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### Table 2. Odds ratio (OR) for favourable socio-economic outcomes among drug users with a different number of risk- and protective factors (n=3,580).

<table>
<thead>
<tr>
<th>Protective factors</th>
<th>Risk factors</th>
<th>0–1 n=1,881</th>
<th>2 n=942</th>
<th>3–6 n=757</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education ≥12 yrs</td>
<td>1990</td>
<td>2.09 (1.65-2.64)</td>
<td>3.79 (2.85-5.04)</td>
<td>2.60 (1.90-3.54)</td>
</tr>
<tr>
<td>0–1 n=1,442</td>
<td></td>
<td>1.36 (1.07-1.74)</td>
<td>7.34 (5.23-10.30)</td>
<td>5.04 (3.33-7.63)</td>
</tr>
<tr>
<td>2 n=1,104</td>
<td></td>
<td>1.36 (0.95-1.96)</td>
<td>0.86 (0.62-1.20)</td>
<td>1.0</td>
</tr>
<tr>
<td>3–6 n=757</td>
<td></td>
<td>1.99 (1.26-3.15)</td>
<td>1.86 (1.12-3.09)</td>
<td>0.84 (0.54-1.31)</td>
</tr>
<tr>
<td>At work</td>
<td></td>
<td>2.40 (1.48-3.91)</td>
<td>1.96 (1.09-3.54)</td>
<td>1.41 (0.71-2.80)</td>
</tr>
<tr>
<td>0–1 n=0–2</td>
<td></td>
<td>2.51 (1.96-3.29)</td>
<td>2.25 (1.71-2.96)</td>
<td>0.92 (0.67-1.27)</td>
</tr>
<tr>
<td>2 n=1,162</td>
<td></td>
<td>1.99 (1.03-3.59)</td>
<td>2.06 (1.16-3.08)</td>
<td>2.13 (1.45-3.20)</td>
</tr>
<tr>
<td>Disposable income &gt; the median</td>
<td>0–1 n=0–2</td>
<td>1.65 (1.32-2.07)</td>
<td>1.25 (0.99-1.57)</td>
<td>1.0</td>
</tr>
<tr>
<td>2 n=951</td>
<td></td>
<td>2.56 (1.99-3.29)</td>
<td>2.25 (1.71-2.96)</td>
<td>0.92 (0.67-1.27)</td>
</tr>
<tr>
<td>3–6 n=757</td>
<td></td>
<td>5.60 (2.79-4.26)</td>
<td>2.26 (1.46-3.08)</td>
<td>2.15 (1.45-3.20)</td>
</tr>
<tr>
<td>Education ≥12 yrs</td>
<td>2006</td>
<td>2.07 (1.64-2.60)</td>
<td>1.44 (1.14-1.83)</td>
<td>1.0</td>
</tr>
<tr>
<td>0–1 n=0–2</td>
<td></td>
<td>4.51 (3.48-5.85)</td>
<td>3.97 (2.91-5.15)</td>
<td>2.70 (1.98-3.67)</td>
</tr>
<tr>
<td>2 n=1,104</td>
<td></td>
<td>9.33 (7.01-12.41)</td>
<td>7.79 (5.90-11.02)</td>
<td>5.61 (3.80-8.42)</td>
</tr>
<tr>
<td>Disposable income &gt; the median</td>
<td>0–1 n=0–2</td>
<td>2.07 (1.58-2.71)</td>
<td>1.32 (1.03-1.70)</td>
<td>1.0</td>
</tr>
<tr>
<td>2 n=951</td>
<td></td>
<td>3.48 (2.45-4.96)</td>
<td>1.84 (1.32-2.57)</td>
<td>1.46 (1.03-2.08)</td>
</tr>
<tr>
<td>3–6 n=757</td>
<td></td>
<td>3.44 (2.43-4.89)</td>
<td>2.74 (1.79-4.18)</td>
<td>1.50 (0.94-2.41)</td>
</tr>
<tr>
<td>At work</td>
<td></td>
<td>1.99 (1.58-2.49)</td>
<td>1.41 (1.12-1.78)</td>
<td>1.0</td>
</tr>
<tr>
<td>Disposable income &gt; the median</td>
<td>0–1 n=0–2</td>
<td>3.00 (2.33-3.87)</td>
<td>2.08 (1.58-2.75)</td>
<td>1.32 (0.97-1.81)</td>
</tr>
<tr>
<td>2 n=942</td>
<td></td>
<td>4.58 (3.53-5.98)</td>
<td>3.04 (2.23-4.16)</td>
<td>2.49 (1.87-3.11)</td>
</tr>
<tr>
<td>3–6 n=757</td>
<td></td>
<td>3.60 (2.79-4.65)</td>
<td>2.26 (1.46-3.08)</td>
<td>2.15 (1.45-3.20)</td>
</tr>
</tbody>
</table>
methadone dose than those who remained in treatment. The 131 patients (29% women) who were admitted to the “Old Team” had significantly more relapse periods per person and year during the first 2 years of treatment and the methadone dose was significantly higher in the “New Team”. The most common reason for involuntary discharge was illicit drug use, most frequently in combination with other reasons.

5.2.2 Study IV

Of all 157 patients, 27% were women and 49% (n=77) were HIV-seropositive. At the end of the follow-up, December 31, 2003, 71 (45 %) had died and 52 (73 %) of those were HIV-seropositive. Fifty percent of the men and one third of the women had died.

During MMT, death was caused by HIV-related causes or by other drug- or alcohol-related diseases, while after discharge from MMT, death was caused by opiates or other drugs, intoxication by alcohol or drugs and AIDS- and HIV-related diagnoses. In multivariate analyses, being HIV-seropositive (HR 3.8, 95% CI 2.23–6.49), being a lodger (HR 1.9, 95% CI 1.05–3.50) and having a prison sentence during the 4 years preceding first MMT (HR 1.7, 95% CI 1.03–2.68) was associated with significantly higher hazard to die. About 70% of living subjects were in mainly out-patient care MMT each year, while the proportion who were hospitalized, who received social assistance, who were convicted or who were coerced into treatment decreased during the observation period. A higher frequency of convictions, poly-drug use, prison sentences, and age between 17 and 20 years at first conviction predicted criminality during the first MMT while a higher methadone dose was associated with a lower risk. Psychiatric diagnosis predicted retention in MMT at the end of the follow-up. Patients who remained in the first MMT (n=25) had low annual incidences of in-patient care, of in-patient care with opiate diagnoses or other drug diagnoses, and of convictions, and no prison sentence after admission to MMT. The proportion of subjects with prison sentences remained fairly stable. Patients who did not re-enter MMT after discharge and patients who were discharged from the second MMT had a significantly higher incidence of convictions during the 4 years prior to MMT. Patients discharged from the second MMT had the least favourable situation, with incidence rates about the same, 2 years after discharge as during the 4 years before first MMT. Discharged patients who did not re-enter MMT had been in MMT about 70% of the time and patients who were in their second, or had been discharged from the second, MMT had been in MMT about 50% of the time.
6 DISCUSSION

6.1 CONSCRIPTION STUDIES

The accuracy of data in a longitudinal study using several data sources is important. The two conscription studies in this thesis work are studies of male conscripts considered representative of males in the general population born in 1949–1951. The conscripts were asked to voluntarily answer two questionnaires and participate in different psychological assessments performed by health professionals and psychologists specially trained for these tasks. Response to the questionnaire was voluntary and the conscripts were assured that their answers would not influence their position within the military.

The response rate was very high, possibly influenced by the special conscription situation. Self-reported data on drug use for the conscripts have been considered valid after verification with in-patient records (Benson and Holmberg 1985). Also, self-reported drug use at conscription was associated with in-patient care and drug and alcohol-related death, i.e. there was high predictive validity. However, the non-anonymous questionnaires may have introduced some bias, resulting in under-reporting of use of illicit drugs, e.g. due to social desirability. This situation may also have influenced answers to questions by indicating less problematic situations, especially with regard to family problems or intrapersonal problems. There is no reason to believe that this was a greater problem in our study than in other, similar studies. Underreporting of drug use would lead to attenuation of increased true relative hazards and risks, as some drug users with increased risk for adverse outcome would be categorized as non-drug users. It is also probable that some drug users stopped drug use after conscription while others started later, which would have a similar impact on calculated risk and hazards. It is a limitation that we lack information about drug use after conscription, except for data about hospitalizations and death from a drug-related cause.

Of all subjects, 1,374 subjects did not answer any drug question and were excluded from the studies. Severe drug use was probably more common in this group, as a higher proportion of deaths in this group were caused by alcohol and drugs than in the NDUG. But this does not mean that the studied associations should be different among these 1,374 subjects. The registers used in the studies are considered to have good validity and reliability and very high coverage. One limitation was that we lacked data on education, income and work situation before 1990.

Study II included only living subjects, which probably contributes to an underrepresentation of individuals with more advanced drug use. However, this does not necessarily mean that associations would be different in this group.

Study I is, to the best of our knowledge, the first major study of the association between various kinds of drug use before or during late adolescence in the general population and mortality during such a long follow-up period. Drug experience before conscription was associated with an increased hazard to die (HR 1.6). However, among drug groups, the association remained only significantly increased for the stimulant group after adjusting for early risk factors and drug diagnosis and convictions during follow-up, which may partly be due to more subjects reporting amphetamine use than use of opiates and hallucinogens. However, the reported dominant group at conscription may
not correspond to the dominant group later, among those who continued drug use. It is likely that some turned to opiates as the dominant, or complementary, drug when heroin was introduced into Sweden in the early 1970s. Heavy drug use was dominated by stimulants, with 63% of drug users in the national case-finding study in 1967 being heavy drug users. (SOU 1969:53) higher than the figure for the later surveys in 1979 and 1992 (48 %) and in 1998 (32 %) (CAN 2009). This means that we should be cautious in interpreting the effects of different drugs. Drug users with a drug-related hospitalization had an adjusted HR of 4.2 to die, which approached the higher hazard to die in clinical samples. On the other hand, the remaining 94% of all conscripts with drug experience and no such hospitalization did not have significantly increased mortality risk (HR 1.08, 95% CI 0.96–1.22). This probably indicates that the majority of men had less severe and/or occasional drug use. Moreover, drug use usually declines after the twenties, especially among those with low frequency (Chen and Kandel 1995). In this study, drug injection at conscription, principally among stimulant and opioid users, was associated with an increased mortality risk after adjusting for early risk factors, which is in agreement with other studies (Bird, Hutchinson, Goldberg. 2003; Copeland et al. 2004). Cannabis use of >50 times predicted mortality and is an indicator for more severe drug use (Fergusson and Horwood 2000; Fuller et al. 2001) as well as, frequently, use of other drugs (Degenhardt, Hall, Lynskey 2001). The association between one drug experience using opiates, stimulants or hallucinogens and mortality may indicate easier access and involvement in environments with more severe drug use and a more rapid progression to more severe drug use (Byqvist 1996). An alcohol diagnosis was more frequent as underlying or contributory cause of death among drug groups than among the non-drug users, which corresponds with other longitudinal studies on mortality among drug users. Several familial, behavioural, social, intellectual and psychiatric risk factors measured at conscription were independently associated with mortality. Earlier mortality studies of this cohort with shorter follow-up periods have reported similar results. Study I shows that the negative impact of these factors, and of drug use generally, is long-lasting. This is the main result of study I.

Study II includes only men who were alive and 55–57 years old at the end of the follow-up. The results show that those with self-reported drug experience in late adolescence had lower probability of being at work and of having a disposable income above the median in younger and older middle age compared with those with no drug use, but higher probability to have an education ≥12 years in 1990 and 2006. The cannabis and hallucinogen users had higher ORs to attain 12 years or more of education, had higher intellectual ability and more frequently came from social group I. In this study the majority of men had used drugs fewer than ten times. In previous studies, it has been reported that those with low frequency of drug use in late adolescence may not progress to severe drug use (Chen and Kandel 1995). Continued drug use, as evidenced by hospitalization with a drug diagnosis, predicted lower probability for favourable outcome in 2006 than in 1990, while no difference was found between other drug users and the NDUG in 2006. This indicates chronicity and a problematic life course for severe drug users, in agreement with other longitudinal studies of drug users (Hser et al. 2001; Stenbacka, Leifman, Romelsjö 2010). Some presumed protective factors in research for drug use were associated with a favourable socio-economic outcome. They included having a father from social group I, speaking with one’s parents about leisure time activities, having good communication with one’s school teacher(s), and having high intellectual ability. These factors have been associated with reduced risk for various adverse outcomes in other studies (Melchior et al. 2007; Hawkins, Catalano, Miller 1992; Brook and Brook 1990; Colman et al. 2009; Masten and Coatsworth 1998). The accumulation of protective factors increased the
probability of favourable outcomes within the drug group, as has been shown in earlier research about drug use (Kliewer and Murrelle 2007; Newcomb and Felix-Ortiz 1992).

6.2 METHADONE MAINTENANCE TREATMENT STUDIES

The two MMT studies are based on two different cohorts of MMT patients with no-one lost until the end of follow-up. In study III, urine analyses had high sensitivity and specificity. Data about methadone dose and about personal background were taken from the medical records. While the information about methadone dose and reasons for discharge probably is accurate and has a high coverage in the specialized MMT units some information about personal background is probably missing. This information is used only for description of the subjects, and not in statistical analyses. We do not know whether we should have found more illicit drug use through more frequent urine testing or complementary self-reports, especially among those with longer treatment periods and lower frequency of urine analyses. However, the rate of urine testing at the time was very high in Sweden and especially in Stockholm, compared with treatment programmes in other countries.

In study IV, the subjects were followed in national registers with almost 100% coverage. Data from all addiction units in the out-patient register in Stockholm County has a similar coverage for out-patient visits, which we used. The organization and policy in the MMTP was based on a restrictive policy and following Dole and Nyswander’s original treatment model which must be taken into account when comparing results with other studies from MMTP with harm reduction oriented policy. The results showed that retention rates corresponded to other Swedish studies, while it was much higher than in most MMT in other countries. The higher methadone doses, the high number of personnel per patient, the stress on social and psychological support and the collaboration with the social welfare may contribute to the higher retention. However, on the other hand, the strict discharge policy and the time period with no possible readmission contributed to a return to high risk for drug use and mortality.

To the best of our knowledge, study III is the only study of illicit drug use during MMT with an observation period ranging from 6 months to 6 years, with results from urine analyses for all 204 patients during their time in MMT. Almost all patients had at least one positive urine sample and one of these was positive for opiates. Several patients, both among those who remained in treatment and among those who were discharged, had several positive urine tests. This shows that a positive urine test was seen as just one indicator for discharge. The percentage of positive urine samples (13%) was lower in this MMT study than in a study by Saxon et al (1996) although the methadone dose was higher in our study. In studies from other countries it is common that at least 30% of patients leave treatment within 3 months (Hubbard et al. 1989; Peles, Schreiber, Adelson 2005), while only two patients in our study left treatment so soon. Patients with most frequent drug use were discharged first and this was also seen in the study by Morral et al. (1999). Patients were discharged following the rules mentioned in section 1.5.2. The discharged patients had more use of benzodiazepines, which is more common among those with a dysfunctional life (Darke 1998), and may be used to enhance the effect of opiates (Keen and Oliver 2004), and may indicate benzodiazepine dependence (Ross and Darke 2000). Use of both amphetamine and cannabis was more frequent in the discharge group. In Stockholm these drugs have been found to be the most frequent second-hand drugs among opiate users (Bykvist 1997). Low methadone dose predicted discharge as in other studies (Ball and Ross 1991). A low methadone dose may for some be the result of illicit drug use because of withdrawal, which may have delayed the increase of the dose. The relapse rate was lower in the psychosocial
team with group counselling than for those with individual counselling. Whether the difference in risk of discharge is mainly due to the higher methadone dose in the New Team, or to other treatment factors cannot be determined from current data.

Study IV is one of the few longitudinal MMT studies that follow the study population during, after and between MMT periods with regard to criminality, social assistance, in-patient care and mortality simultaneously. The 157 subjects had used opiates intravenously during at least the previous 10 years, and almost half were HIV-sero positive. After first admission to MMT, about 70% of all living subjects were in MMT each year. In-patient care decreased, probably partly because of MMT but possibly also because of the new Highly Active Anti-Retroviral Treatment (HAART) medication for HIV-sero positive subjects available from the mid-1990s (Nosyk et al. 2006) as well as a general reduction in available in-patient care in Stockholm County (Burström et al. 2007). About 40% (of 87 living subjects) received social assistance at the end of the follow-up, but only a few had contact with the labour market. Other studies have also shown that heavy drug users have little contact with the labour market (Olsson et al. 2001) and that heroin-dependent subjects have worse living conditions than other drug users (Svensson 2000). As in other studies (Darke, Degenhardt, Mattick 2007), the mortality was high, and higher among men than among women (Darke, Degenhardt, Mattick 2007). Although the mortality also was high within the MMT, the mortality there was caused principally by drug-related diseases, while outside MMT it was mainly caused by drug use-related causes (Fugelstad et al. 2007). Seropositivity for HIV was the strongest predictor for mortality as three out of four of all deceased subjects were HIV-seropositive. Since not all of these died by HIV or AIDS as underlying cause of death, this poses the question whether they had a more risky or problematic life situation than those who were not HIV-seropositive (Darke, Degenhardt, Mattick. 2007). Being a lodger predicted mortality and may indicate that an unstable social and living condition is a sign of a low psychosocial functioning and risky life situations. In a study by Gossop et al. (2002), homelessness increased the risk for mortality. The 53 subjects with prison sentences during the 4 years before MMT had significantly higher hazard to die. A non-significant relationship between recent severe criminal involvement and risky behaviour was found in a study by Hser et al. The division of the population into subgroups with different experience of MMT made it possible to show that patients who remained in MMT had a lower level of convictions, compared with other subgroups, and had often undergone in-patient care already before the first MMT while the subgroup who were discharged from the second MMT had the highest incidence of convictions and in-patient care. This indicates that already before MMT, we can use information about of in-patient care and criminality among patients and therefore probably provide more targeted treatment interventions specific for patients’ needs.
7 GENERAL DISCUSSION

The aim of this thesis work was to analyse the association between drug use in adolescence and later life outcomes in the general population and the impact of MMT on opiate dependents’ future life course. Consequently we studied drug users covering the whole spectrum of drug use, with a focus on the opposite ends of the drug-using spectrum.

The results of the general population studies indicate that drug use during adolescence is associated both with increased mortality and with less favourable socio-economic outcomes, with the exception of educational level, compared with non-drug users, especially among those with documented continued drug use after conscription. However, the increased mortality was limited to those who had used stimulants and those 6% of the drug users who had been hospitalized with a drug diagnosis, with an HR of 4.19 (95% CI 3.35–5.24) to die after adjustment for other factors. The majority of drug users had no increased hazard to die (HR 1.08, 95% CI 0.96–1.22), which may be explained by low frequency of use and interruption or a continued, less severe drug use (Kandel and Logan 1984). This may also be the result of less exposure to different risks, and some may have had a greater resilience, with superior physiological and psychological coping capacities (Rutter, Kim-Cohen, Maughan 2006). The association between other risk factors and mortality may indicate that during the life course, those who are exposed to several risk factors are at greatest risk for severe drug use in adolescence, and for severe drug use and mortality later in life. Another study of this cohort has shown that these risk factors were common among those drug users who continued intravenous drug use and were arrested (Stenbacka, Allebeck, Romelsjö 1992).

Of those who still were alive at about 55-57 years of age, the majority had used drugs less than ten times at conscription and a large majority had used cannabis. More cannabis users than non-drug users had a father from social group I and high intellectual ability. In the multivariate analysis, both these factors acted as protective factors for favourable socio-economic outcomes. Other studies have shown that drug use is more frequent in the higher social groups while severe drug use is more frequent in the lower social group (Kandel 1978; Grant 1996; Guttormsson, Andersson, Hibell 2004). At 55-57 years of age, the drug users in our study who were not hospitalized with a drug diagnosis during follow-up did not have a significantly different socio-economic outcome compared with the non-drug users, while those with a hospitalization had a worse outcome than at about 40 years of age. This indicates the importance of targeted interventions as the heterogeneity among young men with drug use is important. These results are from studies of a 1949–1951 birth cohort. In recent studies of cannabis use among youth, it seems that the use persists until older age, which may contribute to increased health risks (Merline et al 2004; Perkonigg et al. 2008). Overall, the results do not provide support for a less restrictive drug policy, as several negative consequences are linked to cannabis use, as well as other risky health behaviour (Fergusson et al. 2007).

The MMT became a turning point for most of the opiate-dependent subjects and may be seen as a life-long treatment. For the majority of the subjects, MMT became an important part of life. The changes in, e.g., drug use and criminality during and after MMT differed between subjects. The results show that although treatment contributes to positive outcomes in different domains, a majority had difficulties to remain in treatment despite very high retention rates.
8 SAMMANFATTNING

De två övergripande syftena med denna avhandling var att 1) studera det långsiktiga sambandet mellan drog användning upptill 18-20 års ålder och dödlighet och socio-ekonomisk situation samt 2) betydelsen av metadonbehandling för opiatberoendes framtidiga livssituation.


Resultat från värnpliktstudierna visar att stimulantia, cannabis och ospecificerad droganvändning hade samband med död efter kontroll av riskfaktorer. Efter att hänsyn tagits till droginjektion, lagföring och sluten vård med drogdiaagnos under uppföljningsperioden så hade enbart stimulantiabruk samband med död (HR 1.82, 95 % CI 1.002-3.31). Droganvändarna med sluten vård med drogdiaagnos under uppföljningen hade cirka 4 gånger högre risk att dö än ide som ej var droganvändare vid mönstringen (4.19 (95 % CI 3.35-5.24), medan övriga droganvändare vid mönstringen inte hade högre risk (HR 1.08, 95 % CI 0.96-1.22). Flera riskfaktorer hade samband med död, t.ex. låg intellektuell kapacitet, socialgrupp 3, rökning och låg emotionell kontroll. Hos värnpliktiga som var i livet den sista december 2006 (cirka 55-57 år) hade de flesta värnpliktiga med droganvändning brukat droger tio gånger eller mindre och majoriteten hade brukat cannabis. Efter att hänsyn tagits till protektiva och risk faktorer hade de som främst använt cannabis eller hallucinogenen signifikant högre sannolikhet att ha uppnått utbildning på 12 år eller mer, men inte för att vara i arbete eller ha en inkomst över medianen år 1990 och 2006. Droganvändare med sjukhusinläggning med drog diagnos fick en försämrad socio-ekonomisk situation från 1990 till 2006 medan ingen skillnad framkom mellan övriga och icke-droganvändarna år 2006. Vissa (protektiva) faktorer ökade sannolikheten för en gynnsam socio-ekonomisk situation och en ackumulering av dessa ökade sannolikheten, mest bland de med få riskfaktorer. Hög intellektuell kapacitet, en far från social grupp 1 och att samtala med föräldrar om fritiden var viktiga protektiva faktorer för en gynnsam socio-ekonomisk situation.
Nästan alla patienter i metadonbehandling återföll minst en gång i drogbruk. Patienter som blev utskrivna från behandlingen hade fler återfallsperioder, brukade mer amfetamin, cannabis och bensodiazepiner och hade lägre metadon-dos. Patienterna som deltog i den strukturerade grupp behandlingen hade lägre incidens av återfallsperioder än de i individuell behandling, men ett- och två års retentionen var densamma. 18-års-uppföljningen av 157 metadonpatienter visade att kriminalitet, slutet vård, LVM, antal lagföringar och fängelsedomar var lägre under metadonbehandling. Skillnader förekom mellan patienter som kvarblev i behandling, de som skrevs ut och ej återkom i behandling, de som var i en andra behandling och de som hade skrivits ut från den andra behandlingen. Resultaten indikerar att det är viktigt att anpassa både förebyggande och behandlande insatser till den heterogenitet som förekommer bland dels ungdomar med droganvändning, dels hos metadonpatienter. Faktorer som hade visat sig skyddande för droganvändning visade sig också vara öka sannolikheten för att uppnå en gynnsam social situation. En ackumulering av risk faktorer hos de med allvarligt droganvändande och ett fortsatt livsförlopp med fortsatt drogmissbruk bidrog till död och en sämre socio-ekonomisk situation i 55-57 års ålder än i 40 års ålder.
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10 REFERENCES


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Appendix

Hospitalisations with a drug diagnosis include the following diagnoses:

ICD-8 1965 years version of the ICD,
304.00 Opium, opii alcaloïdes et derivata ex iis
304.10 Analgetica synthetica cum effectu simili morphino
304.20 Barbhuraturn
304.30 Alia hypnotica et sedativa sive»tranquillizers»
304.40 Cocainum
304.50 Cannabis sativa
304.60 Alia psychostimulantia
304.70 Hallucinogenes
304.88 Alia definita
304.99 NUD
965.00 Analgetika av morfintyp
968.5
969.6, 969.7

ICD-9 The Swedish version of the International Classification of Diseases, Ninth Revision (ICD-9)...
304 Drogberoende
965A Förgiftning med smärtstillande och febernedsättande medel samt antireumatiska medel
Opiater och närbesläktade narkotiska medel
968F Förgiftning med medel med hämmande inverkan på centrala nervsystemet.
Förgiftning med psykotropa medel
969G Psykodysleptika (hallucinogen)er
969H Psykostimulantia

F11.0-6 Psykiska störningar och beteendestörningar orsakade av opiate
F12.0-6 Cannabis
F13.0-6 Sedativa, hypnotika
F14 0-6 Kokain
F15.0-6 Stimulantia, koffein
F16.0-6 Hallucinogen gener
F18.0-6 Flyktiga läsningsmedel
F19.0-6 flera droger i kombination
O35.5 Vård av blivande moder för (misstänkt) skada på fostret av läkemedel.
P04.4 Foster och nyfödd som påverkats av bruk av tillvägajande droger hos moder
T40.0-3 Förgiftning med narkotiska och psykodysleptiska medel (hallucinogen)en, T40.0 Opium, T40.1 Heroin, T40.2 Andra opiate, T40.3 Metadon
T40.5 Kokain, T40.6 andra icke specificerade narkotiska medel, T40.7 Cannabis och dess derivat
T40.8 Lysergid (LSD), T40.9 Andra och icke specificerade psykodysleptiska (hallucinogen)gener
T43.6 Förgiftning med psykotropa läkemedel som ej klassificeras anorrstädess psykostimulantia med missbruksrisk
Z71.5 Kontakt med hälso- och sjukvården för medicinsk och annan rådgivning som ej klassificeras anorrstädess. Rådgivning och kontroll vid drogmissbruk.
Diagnosis of harmful use and dependence of psychoactive drugs

There are two systems of classification of diseases, the International Classification of Diseases (ICD) by the World Health Organization (WHO), and the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition (DSM-IV), published by the American Psychiatric Association (APA). In this thesis, we use the ICD codes since we have used patient records and records from the death register with ICD codes.

The definitions for harmful use and dependence syndrome in ICD-10 are as follow:

**ICD-10 WHO.**

**ICD 10 F1x.1 Harmful use**

The diagnosis requires that actual damage should have been caused to the mental or physical health of the user.

Harmful patterns of use are often criticized by others and frequently associated with adverse social consequences of various kinds. The fact that a pattern of use or a particular substance is disapproved of by another person or by the culture, or may have led to socially negative consequences such as arrest or marital arguments, is not in itself evidence of harmful use.

**ICD 10 F1x.2 Dependence syndrome**

A definite diagnosis of dependence should usually be made only if three or more of the following have been present together at some time during the previous year:

(a) a strong desire or sense of compulsion to take the substance;
(b) difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
(c) a physiological withdrawal state (see F1x.3 and F1x.4) when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
(d) evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users);
(e) progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance.
or to recover from its effects;
(f) persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm. (WHO, ICD 10)