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Åhman, Ada

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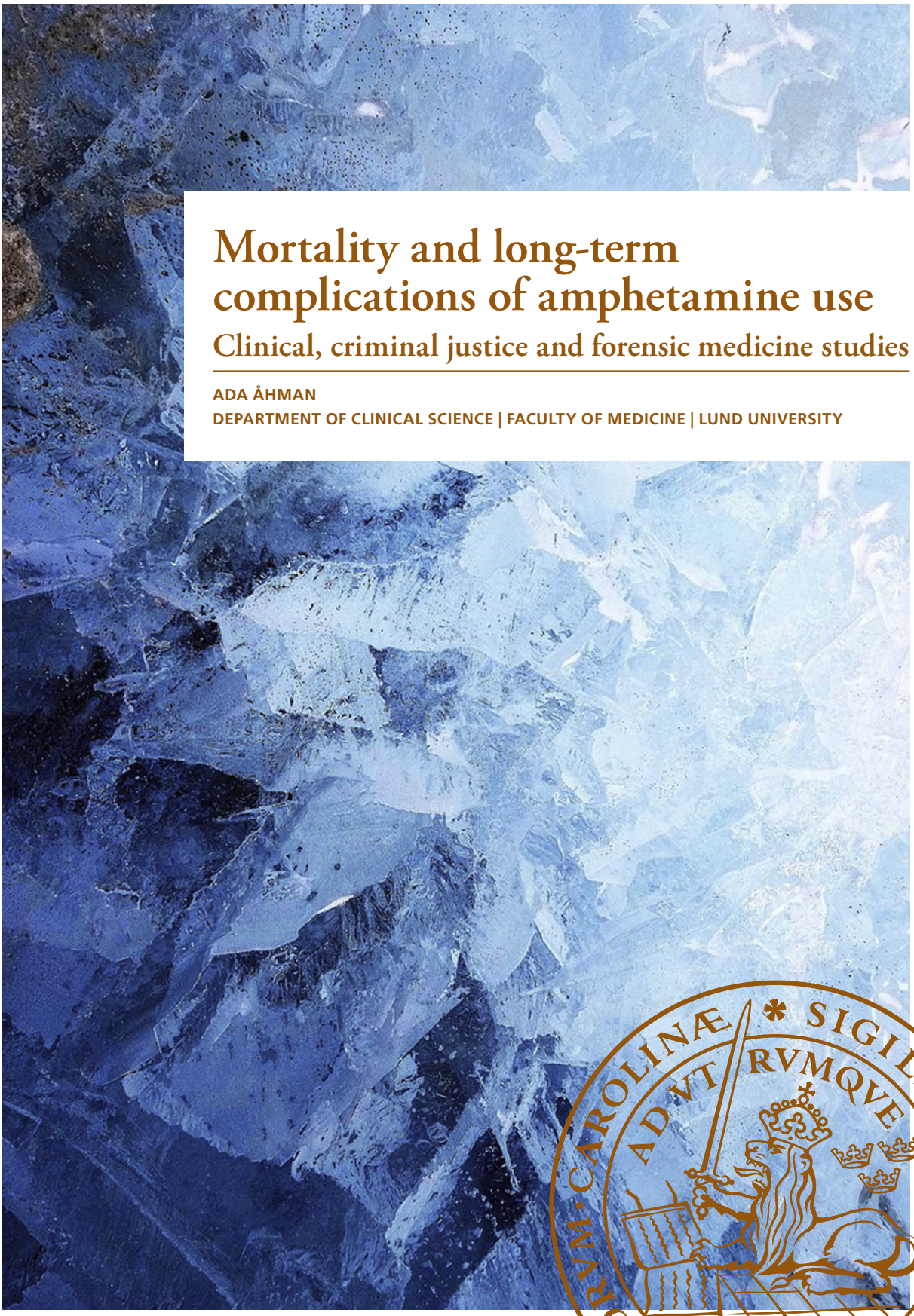

Mortality and long-term complications of amphetamine use

Clinical, criminal justice and forensic medicine studies

ADA ÅHMAN
DEPARTMENT OF CLINICAL SCIENCE | FACULTY OF MEDICINE | LUND UNIVERSITY

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The use of amphetamines is a global problem that appears to be increasing in many parts of the world. In Sweden, amphetamine has long been a central substance in the context of drug use, and while the short-term negative effects have been well-known, knowledge about the long-term effects of amphetamine use has been limited. This thesis examines mortality, causes of death, and risk factors for death among individuals who use amphetamines in Sweden. A deeper understanding of the long-term effects of amphetamine use could contribute to improving the care offered to people who use amphetamines, especially concerning preventive and harm-reducing efforts.

ADA ÅHMAN is a medical doctor working in addiction medicine healthcare in Stockholm, Sweden, and is interested in both somatic and psychiatric complications of substance use.

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Ada Åhman

LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine at Lund University, Sweden. To be publicly defended on May 24th, 2024, at 1.00 pm in Konferensrum 12, Baravägen 1, Lund.

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Norwegian Centre for Addiction Research, University of Oslo, Norway

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Assistant supervisor: Associate Professor Jonas Berge

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Title and subtitle: Mortality and long-term complications of amphetamine use – clinical, criminal justice and forensic medicine studies

Abstract:

Background: The use of amphetamines is a global issue, and in Sweden, amphetamine is one of the most common drugs to use and the most common drug to inject. Amphetamine use is associated with a range of acute consequences. However, there has been limited research on the long-term effects, and studies examining mortality and causes of death among amphetamine users in Sweden have been scarce.

Aim and methods: The overarching aim of this thesis is to explore mortality and long-term complications associated with amphetamine use in a Swedish context using various registry data. Study I investigates mortality and causes of death among individuals who inject amphetamines (N=2,019) recruited from a Swedish needle exchange program and compares it to the general Swedish population. Study II examines fatalities (N=2,734) where stimulants, opioids, or both were detected during forensic autopsy and compares them to each other. In Study III, morbidity, mortality, and causes of death within a national cohort of individuals (N=5,018) who use amphetamine-type stimulants (ATS) were analysed. Study IV investigates the risk of cardiovascular disease (CVD) or cerebrovascular disease (CBD) events (death or diagnosis) among individuals who inject different primary substances (N=2,422), using data from the criminal justice system. Risk factors for all-cause death (Study I and Study III) and CVD or CBD related events (Study IV) was identified using Cox regression.

Results: In Study I, common causes of death were external causes (38%) and diseases of the circulatory system (16%). The all-cause and cause-specific mortality were significantly elevated compared to the general population. In Study II, the most common cause of death in the stimulant group was suicide (26.8%), a higher proportion compared to the opioid group (20.8%, p=0.017). Death by transport accidents was also significantly associated with the stimulant group (p<0.001) as well as death by other accidents (p=0.016). In Study III, the most common cause of death was overdose (28.9%). Multiple drug use, anxiety disorder, viral hepatitis and liver disease were found to be risk factors of all-cause mortality. In Study IV, the adjusted Cox regression analysis did not yield sufficient evidence to conclude any differences in the risk of CVD or CBD events between the substance-using groups.

Conclusions: Individuals who use amphetamine in Sweden exhibit elevated mortality rates. Common causes of deaths among this population include somatic causes and external causes - particularly accidental drug overdosing, other accidents, and suicides. Multiple drug use and anxiety disorders appear to be psychiatric risk factors for all-cause mortality among people who use amphetamine in Sweden. Furthermore, viral hepatitis and liver diseases appear to be somatic risk factors for all-cause mortality within this population. There is not enough evidence to conclude any differences in the risk of CVD or CBD events among criminal justice clients who inject amphetamine compared to clients injecting opioids or multiple substances, and further research is warranted.

Key words: Amphetamine, stimulants, ATS, mortality, causes of death, long-term complications, comorbidity, Sweden, needle exchange program, criminal justice clients, autopsy

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To Lena and Dick

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Populärvetenskaplig sammanfattning

Användningen av amfetamin är ett stort problem i världen och den tycks ha ökat i många länder under det senaste decenniet. I Sverige har amfetamin historiskt haft en framträdande roll, både inom medicinen och som illegalt använd drog, och är än idag en av de vanligaste drogerna att använda och den vanligaste drogen att injicera. Användningen av amfetamin är förknippat med flertalet akuta konsekvenser, exempelvis blodtrycks- och pulsstegring, ökad kroppstemperatur och psykos, och drogen har visat sig ha en rad skadliga effekter på kroppens organ. Det saknas idag effektiv läkemedelsbehandling för personer som använder amfetamin och en stor del av vården för dessa personer syftar till att hantera de akuta komplikationerna samt erbjuda olika former av samtalsbehandling.

Med tanke på den omfattande användningen av amfetamin både globalt och i Sverige och på drogens kända negativa effekter, har det länge funnits förvånansvärt lite forskning om dödligheten och långtidskomplikationerna hos personer som använder amfetamin. Antalet internationella studier på ämnet har dock ökat senaste åren, och dödligheten bland individer som använder amfetamin tycks vara lägre än bland personer som använder opioider men avsevärt högre än hos den allmänna befolkningen. Dock är antalet studier alltjämt begränsat, särskilt jämfört med den kunskapsbas som finns kring dödlighet och komplikationer hos personer som använder opioider. Det övergripande syftet med denna avhandling var därför att utforska dödligheten och långtidskomplikationerna bland personer som använder amfetamin i Sverige genom att använda data från olika register.

I avhandlingens första studie undersöktes dödlighet och dödsorsaker bland 2019 personer som injicerar amfetamin och går på en Sprututbytesmottagning i Malmö. Dödligheten bland individerna i studien jämförs med dödligheten hos den allmänna svenska befolkningen. I den andra studien undersöktes 2733 dödsfall där centralstimulerande droger (såsom amfetamin), opioider eller där droger från någon av dessa båda drogklasser upptäckts under rättsmedicinsk obduktion. Dödsfallen jämförs med varandra med avseende på flera olika faktorer så som ålder, kön, dödsorsak och andra förkommande droger. I avhandlingens tredje studie analyserades sjuklighet, dödlighet och dödsorsaker bland alla vuxna individer i Sverige som fått en diagnos relaterad till amfetaminanvändning under två års tid, vilket totalt omfattade 5018 individer. I den fjärde studien undersöktes risken för att drabbas eller dö av hjärt-, hjärn- eller kärlsjukdom bland 2422 personer som injicerade amfetamin, opioider eller flera olika droger och befann sig inom kriminalvården. Dessutom undersöktes i studie I och III vilka faktorer som ökade risken för att dö av alla tänkbara orsaker bland personer som använder amfetamin.

I studie I var onaturliga orsaker till död, exempelvis olyckor och självmord, vanliga, liksom död till följd av kroppsliga sjukdomar, framför allt hjärt- hjärn- och kärlsjukdom. Dödligheten bland personerna som injicerade amfetamin i studien

visade sig vara påtagligt förhöjd jämfört med den generella svenska befolkning – både när det gällde den totala dödligheten och när man granskade enskilda dödsorsak var för sig. I studie II var självmord den vanligaste dödsorsaken i gruppen som vid obduktion hade centralstimulerande droger i kroppen, vilket visade sig vara en högre andel självmord jämfört med andelen självmord i gruppen med opioider i kroppen. Död till följd av transportolyckor var även det förknippat med att ha centralstimulerande droger i kroppen, liksom död till följd av andra olyckor. I den tredje studien var den vanligaste dödsorsaken överdos. Att ha en diagnos relaterad till blandsubstansbruk (dvs en diagnos som beskriver att man använder flera droger) och att ha en ångestsyndrom-diagnos, visade sig vara psykiatriska riskfaktorer för död. Inflammationssjukdom i levern på grund av virusinfektion (viral hepatit) och andra leversjukdomar visade sig även vara riskfaktorer för död bland individerna i den tredje studien. I den fjärde studien gick det inte att slå fast några skillnader i risk för att insjukna i eller dö av hjärt-, hjärn- och kärlrelaterade diagnoser när man jämförde personerna som injicerade amfetamin med personer som injicerade opioider eller som injicerade flera droger.

Denna avhandling har kunnat visa att vuxna individer som använder amfetamin i Sverige har en påtagligt förhöjd dödlighet och att amfetaminanvändning verkar vara förknippat med både psykiatrisk och kroppslig samsjuklighet. Vanliga dödsorsaker bland personer som använder amfetamin i Sverige inkluderar både kroppsliga sjukdomar och yttre orsaker - särskilt överdoser, andra olyckor och självmord. Användning av flera droger verkar vara vanligt förekommande i denna grupp. Att använda av flera droger och att ha en ångestproblematik verkar vara psykiatriska riskfaktorer för död bland personer som använder amfetamin i Sverige. Dessutom verkar inflammation i levern till följd av virusinfektion och andra leversjukdomar vara kroppsliga riskfaktorer för död i denna grupp. Det finns inte tillräckligt med bevis för att dra slutsatser om några skillnader i risken för drabbas av hjärt-, hjärn- och kärlrelaterade sjukdom eller dödsfall bland personer som injicerar amfetamin jämfört med personer som injicerar andra droger – i alla fall inte när man undersökte individer inom kriminalvården, och ytterligare forskning behövs.

Sammanfattningsvis är förhoppningen att insikterna från denna avhandling kan bidra till att förbättra vården för personer som använder amfetamin i Sverige. Kunskaperna skulle kunna öka incitamenten för att genomföra insatser för att minska både psykiatriskt lidande och kroppsliga sjukdomar hos personer som använder amfetamin, och i bästa fall på sikt, bidra till att minska den höga dödligheten i denna grupp.

List of Papers

I. **Mortality and causes of death among people who inject amphetamine: A long-term follow-up cohort study from a needle exchange program in Sweden**

Åhman A., Jerkeman A., Alanko Blomé M., Björkman P., Håkansson A.
Drug and Alcohol Dependence 2018;188
http://doi.org/10.1016/j.drugalcdep.2018.03.053

II. **Causes and circumstances of death in stimulant and opioid use – a comparative study**

Åhman A**.**, Wingren CJ., Håkansson A.
PLoS One 2024;19
https://doi.org/10.1371/journal.pone.0297838

III. **Mortality, morbidity, and predictors of death among amphetamine-type stimulant users - A longitudinal, nationwide register study**

Åhman A., Karlsson A., Berge J., Håkansson A.
(In review) 2024

IV. **Is cardiovascular or cerebrovascular mortality and morbidity predicted by amphetamine use? A longitudinal cohort study of criminal justice clients.**

Åhman A., Berge J., Håkansson A.
(Submitted) 2024

Abbreviations

ASI	Addiction Severity Index
ADHD	Attention deficit hyperactivity disorder
ADD	Attention deficit disorder
ATS	A category of synthetic stimulants controlled under the United Nations Convention on Psychotropic Substances of 1971. Includes amphetamine, methamphetamine, methcathinone, 3,4-methylenedioxymethamphetamine (MDMA) and its analogues.
CAN	Centralförbundet för alkohol- och narkotikaupplysning (The Swedish Council for Information on Alcohol and Other Drugs)
CBD	Cerebrovascular disease
CBT	Cognitive Behavioral Therapy
CDR	The Causes of Death Register
CI	Confidence interval
CMR	Crude mortality rate
CVD	Cardiovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile range
MNEP	Malmö Needle Exchange Program
NPR	The National Patient Register
SMR	Standardised mortality rate
Stimulants	Substances having a stimulating effect on the brain. Synonymous with the terms *central nervous system stimulants*, *central stimulants*, and *psychostimulants*.
WHO	World Health Organisation

Introduction

Definitions

Stimulants (also called *central nervous system stimulants* or *psychostimulants*) include substances having a stimulating effect on the brain generating symptoms such as alertness, improved mood, and increased energy (1). The term stimulants include a wide range of substances such as all *amphetamine-type stimulants* (ATS) and cocaine. ATS represent a category of substances comprised of synthetic stimulants controlled under the United Nations Convention on Psychotropic Substances of 1971 (2). This group encompasses amphetamine, methamphetamine, methcathinone, and substances belonging to the "ecstasy" category, such as 3,4-methylenedioxymethamphetamine (MDMA) and its analogues. In this thesis ATS also includes prescribed medications such as methylphenidate. Amphetamines is a group of amphetamine-type stimulants where the most common ones are amphetamine and methamphetamine.

Two of the included studies in this thesis investigate individuals using amphetamine as primary drug (Paper I and IV), which is the most common stimulant in the context of Swedish substance use (3). One of the included studies examines individuals using stimulants (Paper II), which is the broadest inclusive term, also encompassing cocaine. Lastly, one paper explores individuals using ATS (Paper III). Hence, all the substances included in the studies have a stimulating effect on the central nervous system and share many features with each other. Although there are also some differences between them, it often makes sense to investigate and talk about stimulants as a group. However, amphetamine is present in all studies and is assumed to be the predominant substance, which is why the focus throughout this thesis will be on amphetamine.

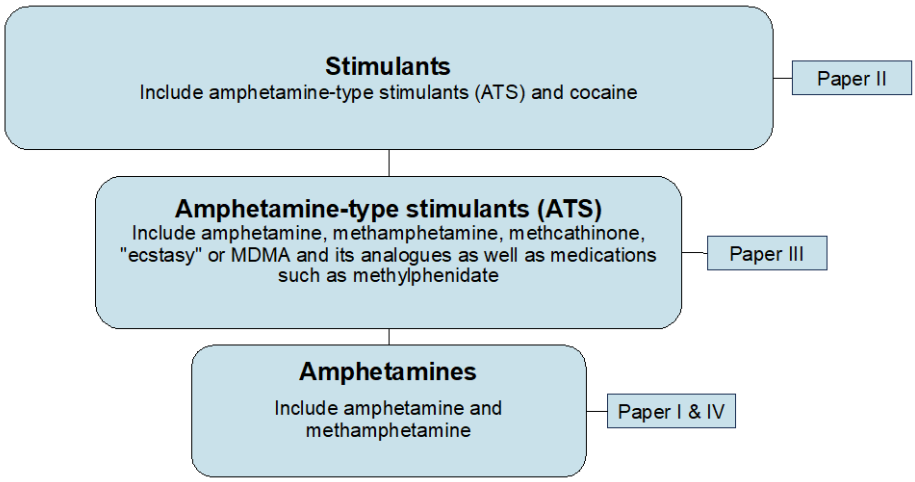

Figure 1. Definition of central concepts.

Amphetamine in a historical context

Amphetamine is considered to have been first synthesised in 1887 in Germany by the Romanian chemist Lazăr Edeleanu. The description of the stimulating effects of amphetamine is however commonly attributed to the American chemist Gordon Allen in 1927 (4). Allen conducted the first human trial with amphetamine in 1929, by injecting himself with 50 mg of amphetamine. During the intoxication he wrote (5):

"Nose cleared-dry"
"Feeling of well-being—palpitation"
"Rather sleepless night. Mind seemed to run from one subject to another."

Following Allen's discovery, amphetamine began to be sold in the 1930s as a decongestant for nasal congestion. However, its applications quickly expanded, and the drug was launched as a treatment for various conditions such as depression, schizophrenia, narcolepsy, seasickness, opioid dependence, as well as a weight loss medication (4,5).

Although originally intended for medical purposes, the substance found use in the military due to its stimulating effect, aiding soldiers in overcoming exhaustion (4). During World War II, its use was widespread among the combatants. In the early 1940s, the German military used over 10 million 3 mg methamphetamine tablets per month, equivalent to approximately 10 tablets per soldier per month (5).

In the 1950s, the use of the substance for psychiatric and psychosocial conditions became prevalent, and in the 1960s, its use for recreational purposes also increased (6). The knowledge of the nature and prevalence of medical amphetamine consumption around 1960 is derived from studies conducted in the United Kingdom. During that period, approximately one third of amphetamine prescriptions were intended for weight loss, another third for defined psychiatric conditions such as depression and anxiety, and the remaining third for vague, predominantly psychiatric, and psychosomatic issues like fatigue. The predominant age group among medical users was between 36 and 45 years, with women constituting 85% of all amphetamine using patients (6).

The negative consequences of the drug became more apparent, and proof accumulated that amphetamine had potential addictive properties (6). Case reports of abuse and psychosis among American patients regularly medicating with amphetamine had already emerged in the 1930s (5). Still, many oral amphetamine products in the United States were, in the 1960s, subject to loose regulation, and 80% to 90% of the amphetamines confiscated on the streets were pills produced by pharmaceutical companies in the United States (6). It would take until 1971 for amphetamines to be subjected to stricter regulations in the United States (6) and international regulation through a convention developed by the United Nations (7).

Sweden

Amphetamine was introduced to the Swedish market in 1938 and quickly gained popularity (7). Despite the requirement for prescription in 1939, consumption levels of amphetamine were high. In 1942, 6 million tablets were sold, and the estimated number of people who used amphetamine was 200,000, constituting 3 percent of the adult population. In 1944, amphetamine became subject to the provisions of parts of the Narcotics Act (Narkotikakungörelsen), which served as the drug legislation at the time. Prescription rights for amphetamines were regulated, but import, export, manufacturing, and possession was not covered by the legislation at this time (7).

Amphetamine gained prominent attention as a performance-enhancing agent in Sweden during the 1940s. In the 1950s and 1960s, amphetamine was primarily emphasised as a weight-loss medication. The illegal use also became increasingly common. The legislation was further regulated in 1958, classifying more stimulants as narcotics and imposing stricter penalties for violations of the law (7). The legislation subsequently underwent additional changes during the 1960s and 1970s (8).

In other European countries and in the United States during 1950-1965, substance use was dominated by morphine and heroin. However, in Sweden during the same period, the use of these substances was low, and instead, amphetamine became the

primary substance of abuse (7). Why did amphetamine use become so widespread in Sweden during this time? Research on the historical use of narcotics in Sweden from a sociological perspective suggests several interrelated factors: broad and diffuse indications for the use of these agents, reports from physicians highlighting positive medical effects and an absence of significant side effects, and nearly non-existent pharmaceutical control at the time. This coincided with the growth of the pharmaceutical industry and the development of marketing methods, all of which could be interacting factors (7).

Amphetamine has thus historically played an important role as a substance in medicine, in the military and as a general performance-enhancing agent as well as drug of abuse - both internationally and in Sweden. In contrast to numerous other nations, amphetamine has held a notably central position in Sweden, and, as we will observe, amphetamine persists as a significant factor in the context of Swedish substance use.

Amphetamine use today

Globally

In 2021, the United Nations estimated the global number of past-year users of amphetamine to be 36 million and the use of amphetamine has increased in most countries in the world in the past decade (3). Among amphetamines, the major use of amphetamine is observed in Western and Central Europe, South America, and North Africa. In contrast, methamphetamine predominates in North America, Australia, New Zealand, East and South-East Asia, as well as Southern Africa. Methamphetamine constitutes the primary substance in ATS seizures globally, while amphetamine predominates in Western, Central, and South-Eastern Europe, as well as in the Middle East (3).

In Sweden

Today, amphetamine remains the dominant drug among people who inject drugs in Sweden (9). The prominence of amphetamine can also be seen in Swedish seizure statistics, where it ranks as the second most frequently encountered drug after cannabis (10).

The use of stimulants in Sweden has historically been dominated by amphetamine, which according to the United Nations remains the most commonly used stimulant in Sweden in terms of the number of users (3). Methamphetamine's prevalence in seizure statistics grew significantly during the 2000s, with its portion rising to 28%

of all amphetamine seizures by 2011. However, since then, there has been a subsequent decline, with methamphetamine's share of all amphetamine seizures decreasing to 3% by 2017 (10). The use of cocaine in the Swedish population appears to have increased between the years 2013-2017, albeit from low levels (11). The use of cocaine in 2021 is estimated to be at approximately the same level as in 2017 (12); however, the number of cocaine-related diagnoses seems to have increased from 2013-2021 (13).

Estimating the percentage of the total population using amphetamines poses challenges. According to a 2021 report from Centralförbundet för alkohol- och narkotikaupplysning (CAN) (12), relying on survey responses, the estimated proportion of the Swedish population (ages 17–84) who used amphetamine in the past 12 months was 0.6%. Additionally, the percentage of those who used stimulating drugs without a doctor's prescription was reported to be 0.8%. It is important to note that the study is based on self-reported data, and there is a possibility that it may underestimate the actual prevalence.

Societal cost

There is no specific statistical data on the cost of amphetamine use to Swedish society. In 2022, the Institute for Health and Care Economics released a report attempting to estimate the societal cost of overall drug use in the year 2020 (14). The estimation encompassed both direct costs, such as expenses related to healthcare, treatment, and the legal system, and indirect costs, including productivity losses due to premature deaths and unemployment. The report also incorporated so-called intangible costs, referring to the value of lost quality of life among individuals using drugs and their close associates. This cost constituted the highest component in the estimation. The total societal cost for the year 2020 was estimated to amount to 38.5 billion Swedish kronor (14).

What is stimulant use disorder?

Today there are two prevailing diagnostic systems in psychiatry that define stimulant use related disorders. One is the Diagnostic and Statistical Manual of Mental Disorders (DSM), currently on its 5th edition (DSM-5), published by the American Psychiatric Association (15). The other diagnostic system is the International Classification of Diseases (ICD), developed and maintained by the World Health Organisation (WHO) (16). The ICD is revised periodically and is currently on the 11th revision (ICD-11). ICD-11 is presently being implemented in Sweden, but is not yet widely used, instead, the 10th revision (ICD-10) is used. In Swedish clinical practice, both the DSM and ICD diagnostic systems are used

during the diagnostic process, although the diagnosis finally is determined and recorded according to the ICD in the medical records. In Swedish registers with statistics on causes of death, diseases, and other health problems, the ICD is the most common.

DSM-5

In DSM-5, the diagnosis related to stimulant use is referred to as *stimulant use disorder,* indicating whether it involves amphetamine/amphetamine-like substances, cocaine, or other unspecified stimulants by using a specific code. The diagnosis is also specified along a continuum of mild, moderate, or severe, and is based on the number of present criteria. A mild stimulant use disorder consists of the presence of 2 or 3 criteria, a moderate of 4 or 5 criteria, and in the case of severe stimulant use disorder, there 6 or more criteria are present.

ICD-10

In ICD-10, the most common ICD version in Swedish clinical use and in Swedish registers, the diagnosis related to stimulant use is referred to as *Mental and behavioural disorders due to use of other stimulants, including caffeine* and described by two separate patterns of drug use - *harmful drug* use or *dependence*.

Next is the definition of stimulant use disorder according to DSM-5 and ICD-10.

DSM-5 Basic Diagnostic Criteria for Stimulant Use Disorders (15):

A problematic usage pattern of stimulants resulting in significant clinical impairment or distress, as indicated by the presence of at least two of the following criteria within a 12-month period:

1. Stimulants are often taken in larger amounts or over a longer period than intended.
2. Persistent desire or failed efforts to cut down or control the stimulant use.
3. A significant deal of time is spent obtaining, using, or recovering from the effects of stimulants.
4. Craving or a strong desire to use stimulants.
5. Repeated stimulant use resulting in failure to fulfil major responsibilities at work, school, or home.
6. Continued stimulant use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of stimulants.

7. Important social, occupational, or recreational activities are given up or reduced due to stimulant use.
8. Recurrent stimulant use in situations where it is physically harmful.
9. Stimulant use persists despite awareness of experiencing persistent or recurrent physical or psychological problems likely caused or worsened by stimulant consumption.
10. Tolerance, as defined by either of the following:
    a. A significant increase in the amount of stimulants required to achieve intoxication or the desired effect.
    b. A notable decrease in the effect experienced despite continued use of the same amount of stimulants.
11. Withdrawal, manifested by either of the following:
    a. Characteristic withdrawal syndrome for stimulants.
    b. Stimulants are taken to relieve or avoid withdrawal symptoms.

ICD-10 Diagnostic Criteria for Mental and behavioural disorders due to use of other stimulants, including caffeine (15):

Harmful use

A pattern of stimulant use that is causing damage to health. The damage may be physical (as in cases of hepatitis from the self-administration of injected stimulants) or mental (e.g. episodes of depressive disorder secondary to heavy stimulant use). The following criteria must be fulfilled:

1. There must be clear evidence that the use of the stimulant has caused (or contributed to) physical or mental harm, including impaired judgment or dysfunctional behaviour, or has had a negative impact on interpersonal relationships.
2. The nature of the harm should be clearly defined (and specified).
3. The pattern of use has been persistent for at least one month or has occurred repeatedly over a 12-month period.
4. The disorder does not meet the criteria for any other mental disorder or behavioural disorder related to the same substance during the same time period (except for acute intoxication).

Dependence syndrome

A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated stimulant use. Three out of the following six criteria must have occurred simultaneously for a period of at least one month, or occurred simultaneously and recurrently over a 12-month period:

1. A strong desire to take the stimulant.
2. Difficulties in controlling its use.
3. Persisting in its use despite harmful consequences.
5. A higher priority given to stimulant use than to other activities and obligations.
6. Increased tolerance.
7. Physical withdrawal state.

Etiology

Why do some individuals become addicted to substances? A simple answer to this question is that it is not known. There are numerous theories, which have gained varying degrees of prominence in different eras and contexts. Psychological personality theories attempt to delineate the characteristics associated with addiction (17,18). Significant resources have been invested in genetic research to identify genes and epigenetic mechanisms that could potentially play a role in the development of addiction (19,20). Research in neurobiology and neuroimaging has highlighted biological theories, presenting evidence that supports the involvement of reward-related neural pathways, particularly those associated with the neurotransmitter dopamine (21–24).

The reward system

The brain's reward system is commonly described as comprising neuronal pathways located in various brain regions, such as the ventral tegmental area, nucleus accumbens, frontal cortex, and amygdala (24). The dopaminergic pathways are usually highlighted as central to the reward system, but several other neurotransmitters are also thought to be involved (23). Different stimuli induce an increase in activity in these dopaminergic pathways, resulting in a rewarding sensation. The reward system serves essential physiological functions. For instance, it is activated when we eat or engage in sexual activities (1).

All addictive substances are considered to, in one way or another, increase the amount of available dopamine in the brain's mesolimbic system, particularly in the

nucleus accumbens (1). Amphetamine binds to a transport protein and inhibits its ability to transport the dopamine back into the presynaptic nerve cell (25). By inhibiting the transporter, the amount of freely available dopamine in the synaptic cleft increases, allowing dopamine to exert its effects more intensely and for a longer duration. Amphetamine is also thought to cause an increase in dopamine through various other mechanisms, such as dopamine transporter-mediated reverse transport (25) as well as a non-dopamine transporter-mediated mechanism involving norepinephrine and the prefrontal cortex (26).

This results in the rewarding effect or what can be described as the "high" in the context of drug use. Amphetamine induces a substantial increase in dopamine concentration in the synaptic cleft. For example, food and sex may increase dopamine levels by a factor of two, while amphetamine can elevate levels by a factor of ten, depending on the dosage (1).

The role of dopamine in various stages of addiction development is debated (27,28). The rewarding effects of addictive substances seem also to be mediated and regulated by other neurotransmitters such as endogenous opioids and cannabinoids, GABA, serotonin, and glutamate (23).

Progression to addiction

With repeated intake of the addictive substance, the rewarding effects decrease, leading to a phenomenon known as desensitisation or tolerance (1). An effect of this is that a larger quantity of the substance must be consumed to achieve the same rewarding effect as before. A paradoxical process may also occur where there is an increased sensitivity to other effects of the substance instead. For instance, an amphetamine user may develop tolerance to the euphoric effects but elevated sensitivity to the motor effects of the substance, potentially resulting in a significant impact on motor patterns (sometimes referred to as Choreoathetosis) at an increased dosage (1,29).

With repeated intake of addictive substances, a series of neurobiological changes occur in the brain progressively. For instance, there is a decreased sensitivity of neuron receptors, which can also be completely inactivated or downregulated in number. The gene-regulating systems can also be influenced by addictive substances, resulting in reduced synthesis of proteins that make up the receptors, thereby decreasing their number. A new homeostatic balance can be said to have emerged (1). This balance is disrupted when the addictive substance is suddenly discontinued, leading to what is known as withdrawal symptoms. Common symptoms during amphetamine withdrawal include fatigue, weakness, slow movements, low mood, anxiety, sleep disturbances, and difficulty concentrating (30). To restore homeostasis, the substance needs to be ingested again, and a cycle occurs of craving, intoxication, tolerance, and withdrawal - characteristics of addiction.

This is a simplified but common explanatory model today for the development of addiction. However, why some individuals become addicted relatively quickly while others can use an addictive substance for a longer time without developing an addiction remains uncertain. Likely, several individual and context-related factors influence who develops an addiction. Examples of such factors include previous experiences, the presence of other illnesses, as well as genetic, social, and environmental factors.

Psychiatric comorbidity in amphetamine use disorder

Psychiatric comorbidity is prevalent in individuals who use amphetamines (31). Psychiatric symptoms and conditions have been reported both during acute intoxication, with prolonged use, and after the individual has ceased use.

Depression and anxiety

In a systematic review and meta-analysis conducted in 2019, it was demonstrated that any use of amphetamines was associated with double the odds of depression (32). Individuals seeking treatment for stimulant dependence commonly exhibit depressive symptoms (33). Withdrawal from heavy stimulant use can also include symptoms of depression (30). The mood-enhancing effects of stimulant intoxication could potentially contribute to a cycle involving the self-medication of depressive symptoms. While evidence for an association between amphetamine use and anxiety is limited (32), experiences of panic can occur during acute intoxication, possibly due to amphetamine's potential to cause hyperarousal (31). Furthermore, anxiety is a stimulant withdrawal symptom (30).

Violent behaviour

A correlation between the use of stimulants and violent behaviour (often defined as behavioural measures of violence, e.g. self-reported interpersonal violence and scales of hostility) has been identified (32). However, the relationship is complex and other factors such as personality traits, polysubstance use or other contextual factors may contribute. One plausible explanation for a connection is that stimulants elevate sympathetic arousal (31), potentially intensifying aggression. Prolonged exposure to amphetamines may also enhance the risk of aggression by impairing mood regulation (34) and impulse inhibition (35). Another possible explanation is that amphetamine use increases the risk of psychosis, which in turn is suggested to increase the risk of violence (36).

Psychosis

The relationship between amphetamine use and psychosis can be considered one of the more extensively researched relationships (32,37–40). Any use of amphetamines as well as having an amphetamine use disorder has been shown to be associated with psychosis (32). According to a systematic review from 2018, the factors most consistently associated with psychosis in individuals using methamphetamine were the frequency and quantity of use, along with the severity of dependence and polydrug use (37). Stimulants have also been shown to have the potential to worsen and trigger psychotic episodes in individuals diagnosed with schizophrenia (38,40).

Suicidality

The evidence regarding amphetamine use and suicidality is mostly based on cross-sectional studies (41,42). In the systematic review and meta-analysis from 2019 (32), any amphetamine use as well as having an amphetamine use disorder was associated with increased likelihood of suicidality (defined as either high suicide risk, suicidal ideation, suicide attempt or completed suicide, but not other forms of self-harm). When adjusting for demographics, other substance use, and premorbid factors in the included studies, these associations diminished but remained statistically significant (32).

Concomitant substance use

It is documented that concurrent use of multiple drugs is prevalent among people who use amphetamine (43–45). Common concomitant problems are high alcohol consumption (46–50) and cannabis use (31,47). In an Australian study where people who use amphetamine sought treatment, nearly half of the treatment episodes (45%) involved clients expressing concerns related to concurrent cannabis use, and 21% involved clients with concurrent alcohol-related issues (51). A Swedish study examining patterns of drug use among individuals engaging in illicit substance use revealed that cannabis was the most used companion substance among people who use stimulants (54%), followed by alcohol (44%) (52).

Somatic comorbidity in amphetamine use disorder

Amphetamine use is associated with a variety of somatic complications. Cardiovascular and cerebrovascular complications are some of the more well-known. This connection is often attributed to amphetamine's ability to increase the release of endogenous catecholamines such as norepinephrine and adrenaline, causing a rapid elevation in heart rate and blood pressure (25,31). Nevertheless,

amphetamine is also associated with direct toxic effects on blood vessels, as demonstrated by an accelerated development of atherosclerosis in people who use amphetamine (53,54). Furthermore, a high proportion of people who use amphetamine are smokers (49), which likely contributes to the somatic comorbidity.

Cardiovascular morbidity

It has long been known that amphetamine use could lead to acute myocardial infarction (55–59). Two reviews from 2007 and 2008 further recognised a heightened risk of various cardiovascular pathologies among people who use methamphetamine, including arrythmias and acute aortic dissection (31,53). Subsequent studies, primarily based on autopsy findings, have consistently verified the link between amphetamine use and diverse cardiovascular problems, including coronary artery atherosclerosis and hypertension (54,60,61). The connection to acute myocardial infarction has also been confirmed in a later retrospective cohort study (62), stating individuals using methamphetamine to be more likely to develop acute myocardial infarction compared to matched controls. Additionally, there is evidence connecting amphetamine use to cardiomyopathy (60,63,64).

Cerebrovascular morbidity

Moreover, there is substantial evidence supporting a correlation with cerebrovascular pathology. An Australian study (54) examined methamphetamine-related fatalities in Australia from 2000 to 2005, discovering cerebrovascular pathology in 20% of the cases, particularly cerebral hemorrhage and hypoxia. Various other studies (65–68), including a 2017 review (69), confirm the association between amphetamine use and hemorrhagic stroke. Furthermore, a systematic review conducted in 2018 (70) indicated that prescribed amphetamine-type stimulants may elevate the risk of stroke, albeit based on a restricted number of studies.

The primary pathophysiological mechanisms underlying ischemic stroke linked with amphetamine use are suggested to include vasoconstriction, arrythmia, embolism originating from the heart, and vasculitis leading to decreased blood supply and hypoxia (71). Conversely, the main mechanisms contributing to haemorrhagic strokes in individuals using amphetamines are thought to involve acute hypertension, as well as the formation and rupture of aneurysms (71).

Neurocognitive impairment

There are also studies that indicate a link between amphetamine use and Parkinson's disease (72–75), as well as the development of dementia (76). Potential explanations include the blood pressure-elevating effect of amphetamines, direct harm to

dopaminergic neurons and related comorbidities such as alcohol use disorder and psychosis.

Bloodborne infections

Given the fact that amphetamine is the most common drug among people who inject drugs in Sweden, it is worth mentioning something about bloodborne infections. Viral hepatitis, and especially viral hepatitis C (HCV), is prevalent within this group (9). The proportion of people who use amphetamine in Sweden receiving treatment for HCV infection has previously been reported to be low (48). However, the proportion has likely increased in recent years, with an increasing number of needle exchange programs since 2017 following a change in the law and expanded opportunities to provide treatment for HCV in such programs (77). HIV infection is another known injection-related condition, but Sweden has a low prevalence of HIV (78). Other injection-related infections are endocarditis and soft tissue infections (79).

Mortality in people with amphetamine use disorder

Given the harmful effects of amphetamine and the extensive use globally, there has historically been little research on the mortality of people who use amphetamine. Older studies have reported mortality rates among individuals using amphetamines to be lower than those among individuals using opioids (80–83), yet substantially higher than in the general population (82–84).

Two systematic review articles, one in 2009 (85) and one in 2019 (86) which also included a meta-analysis, have compiled the existing evidence regarding mortality among people who use amphetamine. Singleton et al.'s systematic review (85) included only eight studies and provided mortality estimates as crude mortality rates (CMR) per 100 person-years of follow-up. CMR from the included studies ranged from 0 to 2.95. Only one study in the review reported standardised mortality ratios (SMR) for people who use stimulants, revealing an overall SMR of 6.22 (87). Stockings et al. (86) found 25 cohorts 10 years later and data from 23 cohorts were included in the pooled analysis of CMR, yielding a rate of 1.14 per 100 person-years (95% confidence interval [CI] = 0.92–1.42). The highest CMR was observed in studies conducted in Southeast Asia and Western Europe (including Sweden). The reported pooled all-cause SMR from 23 cohorts was 6.83 (95% CI [5.27-8.84]).

There has thus been an increase in the number of studies on the mortality of people who use amphetamine in recent years, and it is becoming increasingly evident that this is a group with an elevated mortality. However, there is still a limited volume of research investigating cause-specific mortality with detailed descriptions of how

the cause of death was ascertained and including specific ICD codes for each cause of death (86). Moreover, studies characterised by extensive follow-up periods, along with investigations comparing individuals using amphetamines to those using other substances, remain scarce.

Causes of death in people with amphetamine use disorder

People who use amphetamine often die from external causes (66,81,88). In an Australian study from 2017 examining methamphetamine-related deaths, 77.8% of deaths were classified as external (66). Accidental poisoning is commonly reported as the leading external cause of death in this group (54,66,89). However, other accidents are also frequently observed among the external causes of death. Traffic accidents seem to be particularly prevalent in this group, with some studies suggesting an association between amphetamine use and compromised driving abilities (90–93). Another common external cause of death among people who use amphetamine is suicide. The proportion of suicides has been reported to vary between 11-32.3% in different studies (54,66,88,94,95). Finally, homicide also occurs as an external cause of death in previous studies, although to a somewhat lesser extent, with a reported proportion of 1.5-6% of the cases (66,81,88).

The proportion of somatic causes of death has varied in different studies, ranging from 14% (88), 22.3% (66), 36.9% (94), to 45% (95). Among these, cardiovascular diseases are reported to be the most common. The overall proportion of people who use amphetamine who die from cardiovascular diseases has been reported to be between 10-19% (66,94,95).

In Stocking et al.'s systematic review and meta-analysis (86) of 25 cohorts, the most common causes of death were drug poisoning, accidental injury, suicide and cardiovascular disease. Compared to the general population, individuals with regular or problematic amphetamine use exhibited significantly higher rates of death from drug poisoning, homicide, suicide, cardiovascular disease and accidental injury (86).

Treatment

Currently, there is no established pharmacological treatment for amphetamine use disorder. Numerous reviews and systematic reviews (96–99) and several meta-analyses (100–104) have been conducted without yielding any conclusive evidence on pharmacological treatment. A recent review and meta-analysis (100) generated

pooled results from ten randomised placebo-controlled trials (RCTs) to evaluate the efficacy of prescription stimulants for ATS substance use disorder. In the main analysis, they found prescription stimulants to be effective in reducing endpoint ATS craving compared to placebo. However, no significant effects were found in other outcome measures, including urine analysis, self-reported ATS use, retention in treatment, dropout following adverse events, early-stage craving, withdrawal, or depressive symptoms. A sensitivity analysis, excluding certain studies from the analysis, revealed a reduction in positive urine tests; however, the clinical significance of this finding remains unclear (100).

Consequently, the emphasis in treating amphetamine use disorder has been on social and psychotherapeutic interventions. Among these, Contingency Management, potentially combined with the Community Reinforcement Approach, stands out as the interventions demonstrating best efficacy (105,106). Conversely, other interventions, such as Cognitive Behavioural Therapy (CBT), exhibit limited effectiveness or were not examined by enough studies to establish the efficacy of the treatment (47,107).

Treatment in Sweden

In Sweden, the National Board of Health and Welfare has developed national guidelines for the treatment of individuals with central stimulant dependence, which have been formulated by the authority based on prevailing evidence and proven clinical experience (108). In these guidelines, it is stated that healthcare and social services (who share a joint responsibility for the care of individuals with substance use disorders) *should* offer (priority 3) one of the following psychotherapeutic interventions: Twelve-Step Facilitation, the MATRIX Program (a treatment program that combines twelve-step facilitation and relapse prevention with social network support and regular urine testing), Community Reinforcement Approach with the addition of Contingency Management. Relapse prevention or CBT *may* be offered (priority 4) (108).

Regarding pharmacological treatment, the healthcare *may* offer (priority 4) individuals with amphetamine dependence treatment with naltrexone - a specific opioid antagonist (108). Treatment with methylphenidate for amphetamine dependence is only recommended as a measure to be used within research and development since the scientific evidence is insufficient. Extended-release methylphenidate as a treatment for amphetamine dependence with concurrent ADHD is only recommended as a measure within research and development, also due to insufficient scientific evidence. Treatment with methylphenidate is not recommended for cocaine dependence as it appears to lack efficacy in reducing cocaine use, achieving drug abstinence, and retention in treatment (108).

In clinical practice in Sweden, there are also harm reduction measures, especially for people who inject amphetamine, such as needle exchange programs (109). Another important harm reduction intervention is access to substitution treatment, particularly when combined with needle exchange programs (110). This treatment involves participation in specialised outpatient care, where additional preventive and health-promoting measures can be offered (109). Since there is no substitution treatment available for individuals using amphetamines, there is also no comparable specialised outpatient care. Additionally, there is uncertainty about which preventive measures are most effective for people who use amphetamine, partly due to limited research on the morbidity and mortality of individuals in this group.

Aims

The overarching aim of the thesis is to explore the mortality and long-term complications of amphetamine use in a Swedish context using various registry data to describe the population of people who use amphetamine as accurately as possible.

Paper I

To investigate mortality and causes of death among people who inject amphetamine recruited from a Swedish needle exchange program, and to compare to the general Swedish population.

Paper II

To examine fatalities that were subject to a forensic autopsy where stimulants, opioids or stimulants *and* opioids were detected in the bodies of the deceased. Specifically, the aim was to 1) investigate characteristics and circumstances around the deaths, 2) examine the causes of death, and 3) examine how fatalities of individuals with stimulants detected in their system differ from those with opioids alone or those with a combination of opioids and stimulants?

Paper III

To assess the morbidity, mortality, and causes of death within a national cohort of people who use ATS and assess potential predictors of all-cause mortality within this population.

Paper IV

To investigate the risk of being affected by or dying of cardiovascular or cerebrovascular pathology for people who inject drugs with different substances as the primary drug, using data from the criminal justice system.

Methods

Study design

All studies in this thesis are based on adult individuals using amphetamine, ATS, or stimulants in Sweden. Furthermore, all studies are quantitative and based on register data. Studies I, III, and IV are longitudinal and follow cohorts over time. Study II is a cross-sectional study where each participant is grouped according to the substance detected in forensic toxicology, and where the constructed groups are compared in terms of cause of death and circumstances surrounding the death. Table 1 gives a brief outline of the methodological characteristics of the included studies.

Table 1. Methodological characteristics of the four studies included in the thesis (N = number of participants in the study, SMR = Standardised mortality ratio).

Study	Methodology	Sample	Follow-up time	N	Analyses
I	Quantitative register study, longitudinal	Cohort of people who inject amphetamine during 1987-2011	Mean 13.7 years	2,019	Descriptive statistics SMR calculations Cox regression
II	Quantitative register study, cross-sectional design	Group of individuals with substances detected in forensic toxicological analysis during 2000-2018	-	2,734	Descriptive statistics Chi square test Fisher's exact test Mann-Whitney U test
III	Quantitative register study, longitudinal	Nationwide cohort of all individuals >18 years with a F15 diagnosis during 2013-2014	Median 4.1 years	5,018	Descriptive statistics Cox regression
IV	Quantitative register study, longitudinal	Cohort of criminal justice clients with injection substance use problems during 2001-2006	Median 10.3 years	2,422	Descriptive statistics Fisher's exact test Mann-Whitney U test Cox regression

Setting

Study I was based on participants in the Malmö Needle Exchange Program (MNEP). Study II included individuals who underwent forensic autopsies in Lund's catchment area, identified in the case registry of the Swedish National Board of Forensic Medicine (Rättsmedicinalverket). Study III and Study IV were based on register

data from two registers held by the Swedish National Board of Health and Welfare (Socialstyrelsen) – the Swedish National Patient Register (NPR) and the Swedish Cause of Death Register (CDR). Study IV was also based on data from a database held by the Swedish Prison and Probation Service (Kriminalvården) - the Addiction Severity Index interview database (ASI database). Each register and database used in this thesis are described below.

The Malmö Needle Exchange Program

The MNEP is a part of the Department of Infectious Diseases at Skåne University Hospital located in Malmö, and it opened in 1987. Approximately 70% of all the people who inject drugs in the catchment area were estimated to be included in the program in 1998 (111). At the time when the participants in Study I were enrolled in the program, the criteria included being 20 years of age or older, demonstrating physical indicators of ongoing substance injection use such as injection marks, and consenting to regular HIV testing (111). The participants were requested to declare their primary (predominant) substance of injection use upon enrolment. The percentage of participants for whom the Swedish national identity number was not recorded by the MNEP gradually declined from 1987 to 2006, and since 2006, it has been compulsory to register the national identity number for all participants.

The Swedish National Patient Register

The NPR (112) covers physicians' documentation of patients' diagnoses upon hospital discharges and outpatient care appointments, including emergency visits. The registry consists of two components: an in-patient care part and an out-patient care part. The diagnoses are registered according to ICD. Both primary and secondary diagnoses, along with registration dates, are provided (113,114). The register is estimated to contain 99% of all somatic and psychiatric hospital discharges and approximately 80% of all specialised outpatient care (114). Diagnoses from both public and private health care are included, but diagnoses from primary healthcare are not incorporated into the NPR. The reduced coverage of outpatient care is likely attributed to missing data from private healthcare providers and certain psychiatric outpatient treatment facilities (113).

In this dissertation, no distinction has been made between primary and secondary diagnoses. The determination of which diagnosis is assigned as primary or secondary often depends on the healthcare context in which the patient is treated. Below is a fictitious example:

Primary and secondary diagnosis

For example, a patient may visit their primary care physician for a urinary tract infection, while also suffering from hypertension and amphetamine use disorder. None of these diagnoses would be found in the NPR as primary care visits are not included. However, if the patient were to seek treatment at an emergency department for urinary tract symptoms, the attending physician would likely register urinary tract infection as the primary diagnosis, with hypertension and amphetamine use disorder as secondary diagnoses. All of these diagnoses would be recorded in the NPR for that particular healthcare visit. Alternatively, if the patient went to an appointment with the patient's psychiatrist, the psychiatrist would likely register amphetamine use disorder as the primary diagnosis, with urinary tract symptoms and hypertension as secondary diagnoses.

Thus, whether a diagnosis is labelled as primary or secondary reflects more about the healthcare encounter itself than about which diagnosis is most relevant for the patient. Also, considering the aim of the dissertation, which was to investigate the long-term effects of amphetamine use, it is not meaningful to differentiate between these categories.

The Swedish Cause of Death Register

Data on dates and causes of death were obtained from the CDR (115). The register is based on information from death certificates issued by physicians. It includes both the underlying cause of death and any number of contributing causes according to ICD. The cause of death was determined according to the ninth revision of the ICD (ICD-9) from 1987 to 1996, while the tenth revision (ICD-10) has been utilised from 1997 and onwards (116). Before 2012, the register encompassed all deceased individuals within a calendar year who were registered in the Swedish Population Register at the time of death (regardless of whether the death occurred within or outside the country). Since 2012, the register has also included individuals not registered in the Swedish Population Register (hence, all persons who died during their stay in Sweden). Since 2013, the register covers over 99% of deaths in Sweden (117).

The WHO defines the underlying cause of death as the disease or injury that triggers a sequence of pathological events ultimately resulting in death (or alternatively, the circumstances surrounding the accident or act of violence that caused the fatal injury) (118). Contributing causes of death refer to additional significant conditions that contributed to the fatal outcome yet were not directly related to the disease or

condition causing death. However, the assessments may differ between different physicians. Below is a fictitious example:

> *Underlying and contributing causes of death*
>
> A patient diagnosed with cancer experienced an embolic stroke, which led to an epileptic seizure ultimately resulting in death. Additionally, the patient had pre-existing hypertension and diabetes mellitus. In this case, cancer could be stated as the underlying cause of death, with hypertension and diabetes mellitus as contributing causes. However, another doctor might consider the diabetes mellitus as the underlying cause that triggered the sequence of pathological events (embolic stroke and then epileptic seizure) leading to death and consider the hypertension and the cancer as contributing causes.

When examining all-cause mortality, it is often reasonable to investigate the underlying cause of death. However, in the context of drug-related mortality, it is often relevant to also study contributing causes of death to obtain a more comprehensive understanding of the consequences of drug use and extend the analysis beyond solely focusing on instances of overdose.

The case registry of the Swedish National Board of Forensic Medicine

The case registry (119) maintained by the Swedish National Board of Forensic Medicine includes data on all forensic autopsies conducted in Sweden since 1994. Approximately 6% of the over 90,000 deaths that occur annually in Sweden undergo forensic autopsy. When a physician suspects an unnatural death or where the circumstances surrounding death are unclear, they are obligated to report the death to the police. For most of these instances, a forensic autopsy will be requested by the police (120). The findings from the autopsy, together with background information (such as a police report), forms the basis for the forensic medical report. In this report, the forensic pathologist determines the most probable underlying and contributing cause of death (121).

The registry comprises information extracted from forensic medical reports, containing details concerning age and gender of the deceased, the causes and manner of death (according to ICD-9 or ICD-10), the circumstances surrounding the death and autopsy findings including organ weights and toxicological analyses (illicit drugs and other identified substances). In 90% of forensic autopsies conducted in Sweden, a comprehensive analysis of alcohols, pharmaceuticals, and illicit drugs is undertaken (120).

The Addiction Severity Index interview database

The Addiction Severity Index interview database is held by the Prison and Probation Service Services in Sweden (122). The database contains information from a standardised and semi-structured interview instrument, the Addiction Severity Index (ASI), used in the criminal justice system (123). The interview is also used in the social service as well as in clinical settings, both globally and in Sweden. For instance, close to 90 percent of Sweden's municipalities utilise the ASI (124). The interview instrument was initially introduced into the Swedish Prison and Probation Service in 2001 (125). The ASI interview was administered to individuals with known or suspected substance use problems. The purpose was to evaluate alcohol- and drug-related issues in order to guide the individuals toward appropriate treatment facilities (126). The interview covers various domains, including substance use, medical and psychiatric history, as well as social and legal issues (123,125). All the answers are documented in the database. In Paper IV, the ASI version ASI-X (127) was utilised, representing an adapted iteration of the European standard version recognised as EuropASI (128).

Participants and study procedure

Paper I

The study sample in Paper I consisted of participants in the MNEP program from 1987 to 2011, whose Swedish national identity number was recorded by the MNEP and who identified amphetamine (including methamphetamine) as their primary substance of injection use upon registration.

The unique national identity numbers facilitated linkage with the CDR, and data on mortality and causes of death were retrieved from the CDR. From 1987 to 1996 ICD-9 was in use, while from 1997 to 2011, the ICD-10 was utilised. In this study, ICD-9 codes (n = 47) were translated to ICD-10 to ensure consistency. The underlying cause of death was retrieved. The linkage of the subjects in the cohort to the CDR was conducted in 2013. The outcome variable was all-cause mortality and cause-specific mortality. The covariates were age and gender.

Paper II

In Paper II, the study sample included individuals who died between 2000 and 2018 and underwent forensic autopsy at Forensic Medicine in Lund, Skåne County, Sweden. The geographic coverage of Forensic Medicine in Lund's catchment area underwent minor changes after 2016. Therefore, only individuals from the same geographic area during the study period were encompassed. Included in the study

were individuals aged 18 years and above who tested positive for stimulants, opioids, or a combination of both substances (irrespective of concentration) in forensic toxicology.

The study population was categorised into three groups as follows:

The opioid group - Comprising individuals whose forensic toxicological analysis revealed the presence of opioids, without detection of stimulants. However, other substances such as benzodiazepines and tetrahydrocannabinol (THC) may have been detected. Opioids were specifically defined as heroin (6-monoacetylmorphine), methadone, buprenorphine, morphine, oxycodone, fentanyl (including fentanyl analogues), or tramadol.

The stimulant group - Consisting of individuals who tested positive for stimulants in forensic chemical analysis, without the presence of opioids (but with possible presence of other substances). Similar to the opioid group, other substances such as benzodiazepines and THC might have been detected. Stimulants encompassed amphetamine, methamphetamine, derivatives of stimulant drugs (such as lisdexamphetamine, methylphenidate, dexamphetamine sulfate, modafinil), MDMA, and cocaine.

The polysubstance group - Comprising individuals with positive results for both opioids and stimulants (and with possible presence of additional substances) in forensic chemical analysis, alongside the potential detection of other substances like benzodiazepines and THC.

The three groups were evaluated based on various variables: gender, age, place of death, body mass index (BMI), other substances detected in forensic toxicological analysis, organ weights, underlying causes of death, and contributing causes of death. Unless otherwise specified, all variables were binary with values "yes" and "no." The BMI variable was categorised into four groups: Underweight (BMI < 18.50), Normal weight (BMI = 18.50 - <25), Overweight (BMI = 25.00 - <30), and Obesity (BMI ≥ 30.00).

Additional substances, apart from stimulants and opioids, identified in forensic chemical analysis and included in the study were: alcohol (only cases with a blood alcohol concentration of > 0.1‰ were considered in order to avoid including cases of postmortem alcohol production), benzodiazepines (diazepam, clonazepam, lorazepam, midazolam, nitrazepam, flunitrazepam, oxazepam, alprazolam, triazolam), Z-drugs (zolpidem or zopiclone), gabapentin, pregabalin, and THC. Materials for forensic chemical analysis were restricted to blood, urine, muscle, or eye fluid, with all analyses conducted at the same national laboratory.

The underlying cause of death was mainly investigated. Most of the individuals in the study had their cause of death recorded according to ICD-9. However, for 27 individuals, the cause of death was recorded according to ICD-10. In such cases, a corresponding cause of death were reassigned according to ICD-9 after a review.

Furthermore, the Swedish version of ICD-9 includes the code "E859" for "accidents due to poisoning," which is not present in the international version of ICD-9. Initially, 297 individuals were attributed the code "E859" as the primary cause of death; however, this was substituted with the most appropriate corresponding code in the international version of ICD-9 - the code "E858" for "accidental poisoning by other drugs."

Paper III

The study sample in Paper III covers all individuals aged 18 years or older residing in Sweden with a documented diagnosis of ATS use (as defined by the ICD-10 diagnosis F15, "Mental and behavioural disorders due to use of other stimulants, including caffeine"), as a primary or secondary diagnosis in the NPR, between January 1, 2013, and December 31, 2014.

Information regarding age at inclusion, gender, and selected comorbid diagnoses recorded up to two years preceding the ATS diagnosis, were extracted from the NPR. Age was categorised into four groups: <30 years, 30-44 years, 45-59 years, and >59 years, with the <30 years category serving as the reference. The comorbid diagnoses included other substance use disorders, psychiatric disorders, and somatic conditions previously linked to ATS use, alongside self-harm and accidental poisoning (32,48,50,53).

Data obtained from the NPR were linked via personal identity numbers to the CDR to access information on death dates and underlying causes of death during the follow-up period.

Paper IV

Participants in Paper IV were retrieved from the ASI database of adult criminal justice clients. The ASI interviews were conducted within the Swedish Prison and Probation Service between January 2001 and August 2006. Participation in the ASI interview was not mandatory. Past studies have shown that approximately 6% of clients approached for an ASI interview declined to participate (30). Only clients who spoke Swedish were assessed. Fifty individuals were interviewed prior to admission to the criminal justice facility, with a median of 10 days before admission. Among the remaining 2,372 clients, the mean duration between admission and interview was 55 days (median 27 days; 98% were interviewed within the first year) (29). A total of 2,608 participants (82%) underwent interviews while in custody or prison (median incarceration time 4.8 months [range 0-166.5 months]).

The study's inclusion criteria encompassed self-reported regular injection of primary amphetamine, heroin, or polysubstance use. The primary drug was defined as the

substance identified by the interviewed subject as their main issue. Polysubstance use was characterised by the presence of two or more primary drugs, with at least one being an illicit substance. Regular injection use was characterised by any injection drug use for a duration of at least six months preceding admittance to the criminal justice facility.

The covariates were extracted from the ASI database, with the primary ones being self-reported injection drug use (amphetamine, heroin, or polysubstance use), with amphetamine as the reference variable. Control variables included age, gender, tobacco use, and incarceration (defined as the duration of time in days spent in prison or custody).

The individuals in the ASI database were linked to the NPR and the CDR by the Prison and Probation Service and the Swedish National Board of Health and Welfare through national identification numbers. Follow-up data on cardiovascular disease (CVD) and cerebrovascular disease (CBD) outcomes were obtained from the NPR and the CDR. Outcome variables included time to the first CVD event and time to the first CBD event, defined as the initial occurrence of ICD-10 coded diagnoses I20-I25 (CVD events) or I60-I69 (CBD events) in the NPR or CDR. Both primary and secondary diagnoses were taken into account in the NPR, along with underlying and contributory causes of death in the CDR. The observational period was completed at the occurrence of a CVD or CBD related diagnosis or death, or on December 31, 2014, whichever happened first. The ASI data used in Paper IV has been the focal point of several longitudinal investigations (49,79,129–131).

Below is a summary table of the design, setting and participants of the included studies.

Table 2. Design, setting and participants of the four studies included in the thesis (ICD-10 = International Classification of Diseases 10th edition, ICD-9 = International Classification of Diseases 9th edition, MNEP = Malmö Needle Exchange Program, CVD = cardiovascular disease, CBD = cerebrovascular disease).

	Study I	Study II	Study III	Study IV
Study inclusion	MNEP participants ≥18 years between 1987-2011 who self-reported amphetamine as their main substance of injection use at registration in MNEP	Individuals ≥ 18 years who underwent a forensic autopsy at Forensic Medicine in Lund between 2000–2018 and with stimulants, opioids or both stimulants and opioids in forensic toxicology	All Swedish residents ≥18 years with a registered ICD-10 diagnosis F15 either as primary or secondary diagnosis between 2013-2014	Criminal justice clients ≥18 years who self-reported regular injection use with amphetamine, heroin, or polysubstance use as the main problem between Jan 2001 and Aug 2006
Study censoring	Date of death, or December 31, 2011	-	Date of death or December 31, 2017	CVD or CBD event (diagnosis or death), or December 31, 2014
Comparison	The Swedish general population, study participants	Study participants	Study participants	Study participants
The Swedish Cause of Death Register	The main and contributing causes of death according to ICD-9 and ICD-10, and date of death	-	The main and contributing causes of death according to ICD-10, and date of death	CVD or CBD as main or contributing cause of death according to ICD-10, and date of death
The Swedish National Patient Register	-	-	Date of F15 diagnosis, age at inclusion, gender, and a selection of comorbid diagnoses (primary and secondary diagnosis according to ICD-10) registered up to two years prior the F15 diagnosis	First occurrence of a CVD or CBD diagnosis as primary or secondary diagnosis according to ICD-10 and date of the diagnosis
The case registry of the Swedish National Board of Forensic Medicine	-	Causes and manner of death according to ICD-9 and ICD-10, autopsy findings, toxicological analysis and circumstances surrounding the death	-	-
The Addiction Severity Index interview database	-	-	-	Age at inclusion, gender, self-reported injection drug, tobacco use, and time in prison or custody

Statistical Methods

Below follows a description of the statistical models that have been important in the dissertation work. Then, each paper is discussed separately with regard to the statistical analyses used.

Incidence rate & Crude mortality rate

The incidence rate is calculated as the number of new incident cases (such as disease or death) occurring during the study follow-up divided by the total person-time at risk over the follow-up period (132).

Incidence rate = number of new cases/total person-time at risk

Person-time represents the total observed time-at-risk of experiencing an event in the study, typically measured in years, months, or days. Participants may be observed for varying durations, as some remain free from the event of interest for longer periods than others. A participant is eligible to contribute person-time to the study only as long as they have not yet experienced the event of interest and are still at risk of experiencing it. Incidence rate is often expressed as "number of new cases per 1,000 person-years" (132).

The crude mortality rate (CMR) refers to an incidence rate of the total study population and specifically encompassing fatalities. The CMR was calculated as follows (132):

CMR= the observed number of deaths in the cohort/
the number of person-years of follow up

The Standardised Mortality Ratio

In epidemiology, the Standardised Mortality Ratio (SMR) is used to compare the mortality rates of a study cohort with those of a reference population, typically the general population from the same geographic area, standardised by gender, age, and potentially other variables (133). Hence, the SMR is a ratio that quantifies the increase or decrease in mortality for the study cohort in relation to the reference population. The method can also be used to compare deaths due to specific causes of death in the cohort to the cause specific deaths in the reference population. The SMR is calculated as follows:

$$SMR = O/E$$

O = The observed number of deaths in the cohort
E = The expected number of deaths (the total number of deaths per person and year in the reference population multiplied by the number of person-years in the cohort)

In Paper I, the reference population was the Swedish general population. The data of the reference population were retrieved from a database on official statistics on mortality in the general population, presented by the Swedish National Board of Health and Welfare and available to the public on their website (134). The data on mortality rates from the database were stratified based on gender and age categories with 10-year intervals, to which the specific rates of the corresponding strata in the cohort were compared. The number of cases expected in each stratum if the general population had the same sample size, gender and age composition as the cohort was then obtained.

A confidence interval (CI) should be calculated and presented along with each estimate of the SMR. The 95% CI was calculated according to a standard formula (135):

$$95\%\ CI = \bar{x} \pm c \cdot SE(\bar{x}) = SMR \pm 1.96 \cdot SE(SMR)$$

$\bar{x}$ = point estimate
c = constant, for a 95% confidence interval in a normal distribution (z-distribution), the critical z-value is 1.96
SE = standard error

The Cox proportional hazards model

Regression is a statistical tool often used in medical research to assess relationships between different variables and to identify and quantify risk factors (136).

Cox proportional hazards model, or Cox regression model, was proposed by David Cox in 1972 (137). It is a type of regression analysis where the main metric of interest is *time to event*, or until the end of follow-up (censoring), if the event of interest has not yet occurred at the end of follow-up. The model is considered a semi-parametric model, meaning that the baseline hazard function is unspecified, and the model only estimates the relative change in rate of the hazards (138).

The hazard function in the model estimates the rate at which events occur at a given time point. The hazard ratio (HR) describes the ratio between the hazard function in one group (e.g., individuals using amphetamines) and the hazard function in a comparison group (e.g., individuals using opioids). If the null hypothesis holds, the hazard function is the same in both groups, and the HR is 1. When HR > 1 in one group, it indicates that at any given time point, there is a higher likelihood of an event occurring for a person in this group compared to a person in the comparison group (138).

In the Cox proportional hazards model, like in other statistical models, some assumptions must be fulfilled for the model to be valid. Two central assumptions in the model are:

1. *Assumption of proportional hazards.* The fundamental assumption in the Cox model is that the hazards are proportional, which means that the hazard ratio, the ratio between the hazard functions, should be constant over the entire observation period. This assumption can be assessed in various ways, for example graphically by plotting Kaplan Meier curves for every predictor respectively or statistically by using scaled Schoenfeld residuals.

2. *Censoring in the data is independent.* This means that individuals that are censored at a certain time are assumed to have the same probability of experiencing a subsequent event as individuals that remain in the study at the same time. This assumption cannot be tested statistically (139).

In Paper IV, the age of the study participants was applied as the time scale, which is considered preferable to using time-on-study with age as a covariate in observational studies when the influence of age is not the primary focus (139). Using age as the time scale allows for comparisons between subjects of the same age, rather than those with the same time on study. Furthermore, age as a covariate in Cox regressions often violates the assumption of proportionality, a complication that can be avoided by employing age as the time scale.

Study I

SMRs with 95% CI were calculated for all-cause mortality as well as specific causes of mortality following the ICD-10 main diagnostic categories. SMRs were also calculated separately for males and females within each 10-year interval from 20 to 59 years.

The mortality incidence rate was calculated and reported as number of deaths per 100 person-years.

Potential predictors of death were explored using Cox regression, with all-cause and specific causes of death serving as the dependent variable. The independent variables included in the analysis were age (at registration in the MNEP) and gender. Time-at-risk was defined as the duration from registration in the MNEP until death, emigration, or December 31, 2011, whichever event occurred first. HR along with their corresponding 95% CI were reported.

SMR and incidence rate calculations were performed in Microsoft Excel (140) and the other analyses were carried out in IBM Statistical Package for Social Sciences (SPSS) (141) version 23.

Study II

The data were analysed through frequency and proportion calculations, cross-tabulations, and comparisons of medians between the substance groups. To assess differences in variable distribution between groups, statistical testing was conducted using Pearson's chi-square test and Fisher's exact test. Additionally, the Mann-Whitney U test was used to compare medians across groups. In the pairwise comparisons between substance groups, opioids, which were identified as the most common drug among the deceased, were set as the reference value. P-values below 0.05 were considered statistically significant and 95% CIs were reported. Medians were presented along with the interquartile range (IQR) - defined as the range between the first and the third quartile of the data. Statistical analyses were carried out in IBM SPSS version 27 and 28.

Study III

Cox regression was utilised to examine the relationship between comorbid diagnoses and mortality. Initially, the mortality event was regressed against individual comorbid diagnoses, while controlling for age at inclusion and gender. Subsequently, another analysis was conducted adjusting for age, gender, and all comorbid diagnoses. Time-at-risk was defined from the inclusion date (occurrence of an F15 diagnosis in the NPR between 2013-2014) until either death or the end of follow-up on December 31, 2017, whichever came first. HR with corresponding 95% CIs were reported, with statistical significance set at p-values below 0.05. Median age and median follow-up time were reported alongside their corresponding IQR.

The CMR was calculated and expressed as number of events per 1,000 person-years.

The proportionality assumption was assessed using scaled Schoenfeld residuals (139). When testing multiple variables there is always a risk of achieving statistically significant results by random. The Benjamini-Hochberg method (142) was therefore used to obtain corrected p-values accounting for the risk of a false discovery rate at 5% among the 21 Cox regression analyses in the multivariable model.

Data preparation was conducted using R version 4.0.2, while the statistical analysis was performed using IBM SPSS version 29.

Study IV

Bivariate analyses were conducted. Dichotomous variables were presented as absolute and relative frequencies, and group comparisons were made using Fisher's Exact test. Differences in median age were evaluated using the Mann-Whitney U test. Medians were reported alongside the IQR.

Incidence rate of first CVD or CBD event (diagnosis or death) were reported as number of events per 1,000 person-years.

Extended Cox regression models were utilised to examine the time to the first CVD or CBD event during the observational period. The age of the study participants was used as the time scale. Incarceration, including time spent in custody, was treated as a time-varying variable due to the inclusion of follow-up data both during and after prison release, until the occurrence of the first event. In the unadjusted model, each variable was tested separately, while in the adjusted model, all variables were simultaneously controlled for one another. HR with corresponding 95% CIs were reported, with statistical significance considered at p-values below 0.05.

Robust estimates of standard errors were obtained using the Huber Sandwich Estimator (143) to account for the multiple observations of some study participants. Variance inflation factors (144) were calculated to test for multicollinearity, and all were found to be below 1.1 for every variable studied.

Statistical analyses were conducted using R version 3.3.2 and IBM SPSS versions 25 and 29.

Ethical considerations

Adherence to legal frameworks and international agreements

All studies received ethical approval from either the Regional Ethical Review Board in Lund, Sweden (file numbers: Study I: 2012/142, Study III: 2018/147, Study IV: 2014/478), or from the Swedish Ethical Review Authority (file number Study II: 2019-04759). This was due to a change in the organisation of the responsibility for ethical review of research in Sweden in 2019, transitioning from a regional to a national level (145).

Informed consent was not obtained in the included studies due to the nature of the studies' design. However, Study I was announced through advertisements in a local free-of-charge newspaper, as well as in the MNEP. An opt-out strategy was implemented, where individuals could choose not to participate by contacting the provided contact details, but no opt-out requests were received. In Study IV, the planned research was announced in a free-of-charge newspaper in the major cities

of Sweden (Stockholm, Gothenburg, and Malmö), offering participants the opportunity to decline participation. However, no individuals opted out.

Both our internal assessment and evaluation by the Ethical Review Board concluded that the included studies posed minimal risk of harm to the participants, leading to the decision that retrospective consent was not necessary.

Integrity and stigmatisation

The research material in the four included studies did not contain any personal identifiers such as names or social security numbers when accessed by the researchers to enable integrity of the study subjects. Furthermore, we presented the data on a group level to ensure maximum confidentiality, aiming to prevent study participants or their relatives from identifying them within the studies.

Individuals who use drugs represent a vulnerable part of the society, facing stigmatisation, which contributes to negative health outcomes (146–148). There is a hypothetical risk that research on this group's mortality and comorbidity could contribute to further stigmatisation. This consideration was taken into account when we evaluated the risk-benefit balance of our research. It was our belief that this research project would ultimately benefit individuals with amphetamine use disorder. Given the limited research on this group and the significant suffering caused by the disorder, there is an urgent need to gain a deeper understanding of the long-term effects and risks associated with it. The hope is that such knowledge will ultimately contribute to better treatment measures for individuals using amphetamine. Additionally, we tried to use inclusive language and avoid stigmatising words and phrases such as "amphetamine addicts". However, the term "misuse of drugs" is used (Study II) when such phrasing has appeared on the death certificates (which have been issued based on ICD-9 where such expressions occur), in order to accurately reflect these.

Main Results

Study I

Between 1987 and 2011, a total of 4,494 individuals were enrolled in the MNEP. Among them, 2,475 individuals were excluded due to various reasons: absence of a registered national identity number (n = 903), duplicate entries (n = 7), incomplete baseline information (n = 3), registration in the program after the reported date of death (n = 6), and primary drug use other than amphetamine (n = 1,556). The cohort ultimately comprised the remaining 2,019 individuals.

Characteristics

Of the cohort, 23% were women and 77% were men. The median age at baseline was 33 years, ranging from 16 to 77 years. The mean follow-up time for the entire cohort was 13.7 years (range 0.02–24.2 years).

Mortality, causes of death and standardised mortality ratios

Throughout the follow-up period, 448 individuals (22%) died. The average age at the time of death was 48 years, ranging from 21.4 to 93.0 years. The mortality incidence was 1.6 per 100 person-years.

Somatic causes accounted for the majority of the fatalities (n=252, 56%, unknown causes of death not included) with diseases of the circulatory system being the most common cause of death (n=67, 16%). External causes accounted for 38% of the fatalities (n=162). Within the category of external causes, accidents (n=64) and events of undetermined intent (n=62) were the most prevalent, with poisonings constituting most of the cases of undetermined intent (n=60/62) as well as most of the accidents (n=29/64). Traffic accidents were also a prevalent accidental cause (n=16/64). Intentional harm accounted for 6% of the total fatalities (n=27).

The SMRs were significantly elevated for the entire cohort, with an SMR of 8.3 (95% [CI 7.5–9.1]), as well as for each specific cause of death. The highest SMR was observed for infectious diseases, at 38.3 (95% CI [23.8–52.7]). Across all gender and age groups, the SMR was significantly elevated, except for women aged 50-59.

The causes of death and SMR of the cohort's fatalities are presented in table 3.

Table 3. Study I. Underlying causes of death according to ICD-10 and standardised mortality ratios (SMR) among 428 individuals age 20–59 who inject amphetamine.

Causes of death (ICD-10 code)	n	%	SMR	95% CI
Certain infectious and parasitic diseases (A00-B99)	28	7	38.3	23.8-52.7
Neoplasms (C00-D48)	48	11	3.2	2.3-4.1
Endocrine, nutritional and metabolic diseases (E00-E90)	7	2	4.7	0.9-8.4
Diseases of the nervous system (G00-G99)	8	2	5.5	1.7-9.3
Diseases of the circulatory system (I00-I99)	67	16	5.4	4.1-6.8
Diseases of the respiratory system (J00-J99)	17	4	12.7	6.7-18.7
Diseases of the digestive system (K00-K93)	24	6	10.0	6.0-14.0
Diseases of the skin and subcutaneous tissue (L00-L99)	1	0.2	-	-
Mental and behavioral disorders (F00-F99)	52	12	31.2	22.7-39.7
Unknown causes of death (R00-R99)	14	3	9.4	4.5-14.3
External causes of morbidity and mortality (V01-Y99)	162	38	12.7	10.8-14.7
- **Intentional self-harm (X60-X84)**			5.3	3.3-7.3
- **Poisoning, accidental or of undetermined intent (X40-X49 or Y10-Y19)**			32.0	25.4-38.6
- **Transport accidents (V01-V99)**			8.0	6.8-14.5
Total	428	100.0	8.3	7.5-9.1

Predictors of mortality

In the Cox regression analysis, age at inclusion and male gender were both significant predictors of all-cause mortality. The HR were 1.06 for age (95% CI [1.05–1.07], $p < 0.001$) and 1.58 for male gender (95% CI [1.21-2.07], $p = 0.001$), respectively. Male gender emerged as a significant predictor of deaths with mental and behavioural disorders as the underlying cause of death (HR 5.04, 95% CI [1.57-16.21], $p = 0.007$), deaths resulting from external causes of morbidity and mortality (HR 1.71, 95% CI [1.11–2.65], $p = 0.016$), and deaths due to poisoning (HR 2.18, 95% CI [1.16-4.12], $p = 0.016$).

Study II

Initially, the dataset consisted of 2,746 individuals. However, twelve individuals were excluded due to insufficient information on gender (n = 8), age (n = 3), and detected substances (n = 1). Consequently, the final dataset comprised 2,734 individuals.

Characteristics

The majority of individuals were identified in the opioid group (74.6%), followed by 11.3% in the stimulant group and 14.1% in the polysubstance group. A significant portion of the deceased were men (73.2%). The median age at death was 45.5 years (IQR 32–60). Besides opioids and stimulants, benzodiazepines were the most common drug detected, present in 47.9% of the deceased, followed by alcohol > 0.1‰ (26.0%). The characteristics, forensic and substance-related data are shown in table 4. Women were predominantly found in the opioid group, with women comprising 30.2% of the opioid group compared to 17.1% in the stimulant group and 16.4% in the polysubstance group ($p<0.001$ for both). The stimulant and polysubstance groups exhibited significantly lower median ages at death compared to the opioid group: 40 years (IQR 28.8–51) and 35 years (IQR 26–43) versus 50 years (IQR 34–64), respectively ($p < 0.001$ for both).

The occurrence of benzodiazepines was significantly lower in the stimulant group and significantly higher in the polysubstance group ($p<0.001$ for both). THC presence was notably more common in both the stimulant group ($p<0.001$) and the polysubstance group ($p<0.001$) compared to the opioid group.

Table 4. Study II. Characteristics, forensic and substance-related data among the study population. Opioids were set as the reference group for Chi-square comparisons between the substance groups. Numbers are presented as percentages (absolute number) if otherwise is not stated.

	Total, n=2,734	Opioids (and no stimulants), n=2,039	Stimulants (and no opioids), n=310	P-value	Polysubstance group (stimulants + opioids), n=385	P-value
Age at death, median years (IQR)[a]	45.5 (32–60)	50 (34–64)	40 (28.8–51)	<0.001*	35 (26–43)	<0.001*
Male gender, % (n)	73.2 (2,002)	69.8 (1,423)	82.9 (257)	<0.001*	86.3 (322)	<0.001*
Place of death, % (n)						
Hospital	13.4 (366)	14.3 (276)	13.4 (39)	0.675	13.8 (51)	0.801
Other health care facility	2.8 (76)	2.4 (47)	3.1 (9)	0.508	5.4 (20)	0.002*
Private housing	51.6 (1,412)	57.3 (1,105)	43.3 (126)	<0.001*	49.1 (181)	0.003*
Other/unknown, not in healthcare	26.8 (733)	26.0 (499)	40.2 (117)	<0.001*	31.7 (117)	0.021*
Missing[b]	5.4 (147)	5.5 (112)	6.1 (19)	-	4.2 (16)	-
BMI, % (n)						
Underweight	5.9 (160)	6.1 (123)	7.4 (22)	0.379	3.9 (15)	0.097
Normal weight	42.2 (1,155)	40.3 (814)	53.5 (159)	<0.001	47.6 (182)	0.007*
Overweight	31.6 (865)	33.2 (672)	28.0 (83)	0.069	28.8 (110)	0.089
Obesity	19.1 (521)	20.4 (413)	11.1 (33)	<0.001*	19.6 (75)	0.724
Missing[b]	1.2 (33)	0.8 (17)	4.2 (13)	-	0.8 (3)	-
Other substances, % (n)						
Alcohol (>0.1‰)[c]	26.0 (708)	27.1 (553)	29.0 (90)	0.482	17.0 (65)	<0.001*
Benzodiazepines	47.9 (1310)	46.9 (957)	34.2 (106)	<0.001*	64.2 (247)	<0.001*
Z-drugs	15.9 (436)	18.2 (372)	5.8 (18)	<0.001*	11.9 (46)	0.003*
Gabapentin, Pregabalin	9.2 (251)	8.6 (176)	3.2 (10)	0.001*	16.9 (65)	<0.001*
THC	14.7 (402)	10.6 (217)	25.8 (80)	<0.001*	27.3 (105)	<0.001*

* p-value of <0.05 considered statistically significant
[a] Mann-Whitney U test used to compare medians between groups
[b] Proportion missing relative to the total number of participants
[c] Analyses carried out exclusively on blood

Causes of death

The underlying causes of death are summarised in table 5. In the stimulant group, somatic causes of death accounted for 21%, and 13% of the total fatalities were due to cardiovascular disease and 2.3% were due to mental and behavioural disorders. The leading cause of death in the stimulant group was suicide, accounting for 26.8% of the fatalities, which was significantly higher compared to the opioid group, where suicides constituted 20.8% of deaths.

The most common cause of death in the polysubstance group was accidental poisoning (38.2%), a higher proportion compared to the opioid group (18.0%) ($p<0.001$).

Homicides were more prevalent in both the stimulant group (3.5%, $p = 0.004$) and the polysubstance group (3.9%, $p<0.001$) compared to the opioid group (1.2%). Death resulting from transport accidents was significantly associated with the stimulant group ($p<0.001$), as was death resulting from other accidents ($p = 0.016$). Drug dependence or misuse of drugs mentioned somewhere on the death certificate (including both underlying and contributing causes of death) were more common in the stimulant group compared to the opioid group ($p<0.001$).

Table 5. Study II. Underlying causes of death according to ICD-9 with external causes of death specified. Opioids were set as the reference for Chi-square comparisons between the substance groups. Percentages (absolute number).

	Total, n=2,734	Opioids (and no stimulants), n=2,039	Stimulants (and no opioids), n = 310	P-value	Polysubstance group (opioids + stimulants), n=385	P-value
Somatic causes of death	22.5 (615)	25.4 (518)	21.0 (65)	0.092	8.3 (32)	<0.001*
External causes of death	77.5 (2,119)	74.6 (1,521)	79.0 (245)	0.092	91.7 (353)	<0.001*
Transport accident (E800-E845)	4.2 (116)	2.8 (58)	13.5 (42)	<0.001*	4.2 (16)	0.170
Accidental poisoning (E850-E869)	20.4 (558)	18.0 (368)	13.9 (43)	0.071	38.2 (147)	<0.001*
Other accidents (E880-E928)	4.6 (125)	4.6 (93)	7.7 (24)	0.016*	2.1 (8)	0.025*
Suicide and self-inflicted injury (E950-E959)	19.6 (537)	20.8 (424)	26.8 (83)	0.017*	7.8 (30)	<0.001*
Homicide and injury purposely inflicted by other persons (E960-E969)	1.8 (50)	1.2 (24)	3.5 (11)[a]	0.004*	3.9 (15)	<0.001*
Injury undetermined whether accidentally or purposely inflicted (E980-E989)	26.4 (722)	26.7 (545)	13.5 (42)	<0.001*	35.1 (135)	<0.001*
External cause of death but no E-code (ICD-9 codes 800–999)[b]	0.3 (8)	0.3 (6)	0	-	0.5 (2)	-
Other diagnosis	3	3	0	-	0	-

* p-value of <0.05 considered statistically significant
[a] Fisher's exact test used due to small sample sizes
[b] Individuals with an external cause of death but no E-code

Study III

In Sweden, a total of 5,018 individuals (N=5,018) aged 18 or older were diagnosed with an ATS use disorder during the years 2013-2014 and all of these were included in the study.

Characteristics

The follow-up period lasted a maximum of five years, with a median follow-up time of 4.1 years (IQR 3.5 - 4.6). The median age upon inclusion was 36.6 years (IQR 27.4 - 48.1). The majority of the cohort were men, accounting for 70.5%.

Comorbidity

Alcohol use disorder was the most prevalent single substance use disorder in the cohort, affecting 31.6% of individuals, followed by opioid use disorder at 14.3%. A total of 44.7% of the cohort exhibited multiple drug use disorder. Additionally, 28.7% were diagnosed with attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD). A total of 21.9% experienced anxiety disorder, and 15.8% had depressive disorder. Moreover, 12.3% of the cohort had a history of intentional self-harm, and 4.7% had experienced overdose. Among somatic disorders, viral hepatitis was the most prevalent, observed in 19.3% of the cohort.

The study characteristics and the comorbid diagnosis data of the cohort are summarised in table 6.

Table 6. Study III. Comorbid diagnosis data two years prior to study inclusion for both the total study population and for the deceased. Inclusion during 2013-2014. Abbreviations: attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD), human immunodeficiency virus (HIV), International Classification of Diseases 10th Revision (ICD-10)

Variables (ICD-10)	Total, N = 5,018 N (%)	Deceased, N = 484 N (%)
Female gender	1,478 (29.5)	103 (21.3)
Age groups at study start		
<30	1,636 (32.6)	120 (24.8)
30-44	1,778 (35.44)	137 (28.3)
45-59	1,382 (27.5)	161 (33.3)
>59	222 (4.4)	66 (13.6)
Time in person-years observed, median (IQR)	4.1 (3.5-4.6)	1.6 (0.63-2.8)
Alcohol use disorder (F10)	1,587 (31.6)	182 (37.6)
Opioid use disorder (F11)	720 (14.3)	107 (22.1)
Cannabis use disorder (F12)	663 (13.2)	56 (11.6)
Sedatives use disorder (F13)	681 (13.6)	99 (20.5)
Cocaine use disorder (F14)	136 (2.7)	14 (2.9)
Multiple drug use (F19)	2,242 (44.7)	278 (57.4)
Depressive disorder (F32-F33)	792 (15.8)	80 (16.5)
Anxiety disorder (F41)	1,098 (21.9)	133 (27.5)
Psychotic disorder (F20-F29)	742 (14.8)	80 (16.5)
ADHD/ADD (F90)	1,440 (28.7)	136 (28.1)
Self-harm (X60-X84)	616 (12.3)	81 (16.7)
Accidental poisoning (X40-X49)	236 (4.7)	38 (7.9)
Hypertension (I10-I15)	154 (3.1)	36 (7.4)
Ischemia (I20-I25)	60 (1.2)	23 (4.8)
HIV (B20-B24)	51 (1.0)	12 (2.5)
Viral hepatitis (B15-B19)	967 (19.3)	184 (38.0)
Liver disease (K70-K77)	61 (1.2)	23 (4.8)

Mortality and causes of death

During the follow-up period, a total of 484 participants died. The CMR was 24.6 per 1,000 person-years (95% CI [22.5-26.9]). The median age at death was 43.0 years (IQR 30.0-55.7). Somatic causes of mortality accounted for 40.9% of the fatalities, and external causes accounted for the majority of deaths at 59.1%.

Accidental drug poisoning was the most frequent cause of death, accounting for 28.9% of all fatalities. Deaths attributed to diseases of the circulatory system accounted for 13.8%, followed by deaths due to events of undetermined intent (12.8%) and intentional self-harm (12.4%). Accidents (poisoning accidents excluded) accounted for 4.5% of all fatalities and deaths classified as resulting from mental and behavioural disorders accounted for 2.7%.

Predictors of all-cause mortality

Age at inclusion above 59 years, compared to age below 30 years at inclusion, significantly predicted all-cause mortality (HR 3.51, 95% CI [2.52-4.89], p=0.004). Additionally, multiple drug use disorder (HR 1.39, 95% CI [1.14-1.70], p=0.004), anxiety disorder (HR 1.39, 95% CI [1.11-1.72], p=0.014), viral hepatitis (HR 1.85, 95% CI [1.50-2.29], p=0.004), and liver disease (HR 2.41, 95% CI [1.55-3.74], p=0.004) were also identified as predictors of all-cause mortality. Female gender showed a negative association with death (HR 0.65, 95% CI [0.52-0.82], p=0.004).

Study IV

During the study period, interviews were conducted with a total of 7,085 individuals. Exclusion of 50 individuals was due to multiple reasons, outlined as follows: misinterpretation of questions, inability to comprehend, refusal to participate, incapacity to conduct or interruption of the interview. Additionally, 4,588 individuals did not meet the inclusion criteria of at least 6 months of injection use with the main drug being heroin, amphetamine, or polysubstance use, and were therefore excluded. Consequently, the cohort consisted of 2,447 clients. Among these, three subjects were interviewed using the Adolescent Drug Abuse Diagnosis (ADAD) instrument (149) instead of a full ASI interview and were subsequently excluded. Furthermore, eight individuals were excluded from the analysis due to missing age information. Finally, 14 individuals experienced an event before the ASI interview was conducted and were excluded from the study. Ultimately, the analysis was conducted using data from 2,422 clients.

Characteristics and incidence of first episode of CVD and CBD event

In the cohort, 339 were women (14%) with a median age of 36 years (IQR 29-43 years), and 2,083 were men (86%) with a median age of 36 years (IQR 28-43 years). Self-reported main drug was amphetamine in 51.5%, polysubstance use in 33%, and heroin in 15.5% of the cohort.

The total observational time for the entire cohort amounted to 23,911 person-years, with a median duration of 10.3 years (IQR 9.3-11.2 years). The total observational time for the CVD event outcome variable was 23,679 person-years, with a median duration of 10.3 years (IQR 9.2-11.2 years). Similarly, for the CBD event, the total observational time was 23,767 person-years, with a median duration of 10.3 years (IQR 9.2-11.2 years).

The total count of CVD events was 57, including 9 CVD-related deaths. Similarly, there were 41 CBD events, with 9 being CBD-related deaths. The person-time incidence rates for the first episode of a CVD and CBD events are presented in table 7.

Table 7. Study IV. Incidence of first CVD and CBD event (diagnosis or death), expressed as person-time incidence (number of events per 1,000 person-years) during the observational time 2001-2014. Data retrieved from the National Patient Register and the Causes of Death Register. Abbreviations: cardiovascular disease (CVD), cerebrovascular disease (CBD)

	Study participants (n)	Total CVD events (n)	Total CBD events (n)	CVD events (n events per 1,000 person-years)	CBD events (n events per 1,000 person-years)
Total sample	2,422	57	41	2.41	1.73
Main drug amphetamine	1,247	37	26	2.99	2.09
Main drug heroin	376	4	2	1.14	0.57
Polysubstance use	799	16	13	2.05	1.66

Bivariate analyses

Bivariate analyses revealed some significant findings. The median age among individuals who experienced an event (CVD or CBD) was significantly higher than among those who did not experience an event. Specifically, the median age for those who experienced an event was 44 years (IQR 39-50) and 45 years (IQR 38-50) respectively, compared to 36 years (IQR 28-43) for those who did not experience an event ($p<0.001$). Women had a significantly lower proportion of CVD events compared to men, with 0.6% versus 2.6% ($p=0.019$). A higher percentage of individuals who used amphetamine experienced a CVD event compared to individuals who used other substances, with rates of 3% compared to 1.7% ($p<0.044$). However, no significant differences emerged in the proportions of CVD or CBD events between tobacco users and non-users, nor between individuals serving time in prison or custody compared to those who were not.

Predictors of CVD and CBD events

Female gender was associated with reduced risk of experiencing a CVD event (HR 0.21 [95% CI 0.05-0.87], $p=0.032$) in the unadjusted model. However, no other variable demonstrated a significant association with either CVD or CBD events. Upon conducting an adjusted Cox regression analysis, none of the variables including main drug (heroin or polysubstance use) showed significant associations with the outcome variables CVD or CBD events when compared to amphetamine use. Notably, female gender remained significantly associated with a lower risk of experiencing a CVD event (HR 0.21 [95% CI 0.05-0.87], $p=0.032$).

Discussion

Methodological considerations

Capturing the amphetamine-using population

There are challenges associated with capturing the amphetamine-using population in Sweden. Partly, this is due to the responsibility for the care of individuals with substance use resting with two different entities – healthcare and social services (150). The healthcare, managed at the regional level, is responsible for managing acute complications of substance use such as intoxication, psychosis, and withdrawal, but also for outpatient follow-up and treatment. The outpatient addiction care includes both pharmacological treatment and psychotherapeutic interventions. Social services, managed at the municipal level, handle social support but also provide therapeutic interventions and are responsible for long-term care in treatment centres. As previously mentioned, there is currently no pharmacological substitution treatment available for amphetamine use disorders (108). This likely contributes to individuals using amphetamine being less prevalent in addiction outpatient care compared to individuals using opioids and individuals using alcohol, for whom there are well-established pharmacological treatment options (108). In healthcare, individuals using amphetamines primarily appear in emergency departments, for example, due to acute psychosis, or are encountered at needle exchange programs if they inject amphetamines.

It is crucial to consider this when aiming to study the population of people who use amphetamine based on diagnostic data. A diagnosis is only obtained through contact with healthcare. An amphetamine user who only interacts with social services will never receive an amphetamine use-related diagnosis and thus will not be included, for example, in the NPR and therefore will not be represented in research based on NPR data. However, one could argue that it is likely that an amphetamine-using individual who interacts with social services for their amphetamine use will probably have some form of healthcare contact, such as an emergency department visit due to acute intoxication, at least if examining a longer timeframe, such as one to two years.

It has thus been important in this thesis to identify the amphetamine-using group in various types of registry materials, not only those based on diagnostic data, to provide as accurate a description as possible of this population. In Paper I, a cohort

of individuals with self-reported injection use of amphetamine who attend a needle exchange program is investigated. In Paper II, forensic material is examined, and individuals who died with amphetamine in their bodies are compared with those who died with other substances in their bodies. In Paper III, a national dataset of individuals diagnosed with amphetamine use-related diagnoses over a two-year period is examined. Finally, in Paper IV, criminal justice material is analysed, comparing individuals with self-reported injection drug use of amphetamine with those with self-reported injection drug use of other substances. The utilisation of diverse registry materials is a strength of this thesis. However, it can also pose challenges regarding generalisability, as we will outline below.

Controls

In Paper I, mortality rates among individuals injecting amphetamines and attending the MNEP are compared with the general population in Sweden. When examining all-cause mortality and cause-specific mortality, the study population was matched with the general population based on gender and age (grouped in 10-year intervals). The broad age groups result in somewhat rough estimations, which must be considered when interpreting the results. In Papers II, III, and IV, individuals in the study are compared with each other. In Papers II and IV, the comparison between groups is based on substances detected in forensic toxicology analysis (Paper II) and self-reported primary injection drug (Paper IV). In Paper III, participants are compared with each other by investigating the impact of the participants' various baseline variables on the outcome of overall mortality.

External and internal validity

External validity is defined as the extent to which a result in a specific study can be assumed to apply to other contexts and times (151). Internal validity in a quantitative study refers to the extent to which the study accurately measures or assesses what it claims to measure or assess (151). The external validity of the studies in this thesis will be discussed in the light of their *generalisability*. Furthermore, the internal validity of these studies will be considered in terms of various biases, including *selection bias*, *non-response bias* and *representativeness*, *type I* and *type II errors* and *confounding*.

Generalisability

The populations studied in the various papers included in this thesis differ in several aspects, which are discussed below.

In Paper I and IV, the population consisted of individuals who inject amphetamine. Injection practice carries specific risks (9,79) and the results of the studies cannot

be generalised to individuals who administer amphetamine in other ways than injecting.

In Paper I, which investigated people who inject amphetamine at MNEP, there is a risk of potential *selection bias*. Individuals who inject drugs and participate in needle exchange programs have been shown to have poorer health than individuals who inject drugs but do not participate in such programs (152). At the same time, amphetamine is the most common drug among individuals who inject drugs in Sweden (9), and it is predominantly within needle exchange programs that this group is encountered within outpatient healthcare settings. Consequently, there is rationale for utilising data from needle exchange programs to study the amphetamine using population. Moreover, it is estimated that approximately 70% of all individuals who injected drugs within the catchment area at the time of the study were included in the MNEP (111). However, our results might not be applicable to the remaining 30% of the population of individuals injecting amphetamine in Malmö.

In Paper IV, the population consisted of criminal justice clients who inject drugs, without distinction based on participation in needle exchange programs. Consequently, from that perspective, the findings may be considered applicable to other populations of amphetamine-injecting individuals. However, being a criminal justice client may be presumed to entail specific effects and risks; for instance, there is data suggesting generally poorer psychiatric and somatic health among incarcerated clients (153), thus rendering the generalisation of the results to the broader population of people who inject amphetamine challenging. On the other hand, a substantial body of research (154–156) indicates a high prevalence of substance use disorders among criminal justice clients. This, along with the previously mentioned challenges in capturing the amphetamine-using population within healthcare settings, justifies the use of data from the criminal justice system to study the amphetamine using population.

In Paper II, the study population comprises forensic material, with participants defined based on substances detected in forensic toxicology analyses conducted alongside forensic autopsies. The findings of this paper cannot be straightforwardly extrapolated to individuals with amphetamine dependence. Instead, the study describes and compares causes of death and autopsy findings within an unselected cohort of individuals who use drugs. Specifically, the population included all individuals undergoing forensic autopsies between 2000 and 2018 in the catchment area of Forensic Medicine in Lund, where opioids or stimulants were identified during forensic toxicology analyses, constituting a heterogeneous population in a real-world setting. This utilisation of 'real-world data' enables the examination of deaths among individuals who use substances, irrespective of prior healthcare contacts or previous identification as individuals with amphetamine use problems. Despite issues regarding the generalisability of this study due to the selection of the study population, the study is nonetheless justified given the limited availability of

data concerning the amphetamine-using population and the challenges in accurately capturing this population through diagnostic data.

In Paper III, individuals with a diagnosis of amphetamine use disorder were included, which in the paper is defined as all diagnoses within the ICD-10 F15 category. Here, a broad spectrum of people who use amphetamine is encompassed – potentially including individuals who regularly inject amphetamines, as well as those who have only intoxicated themselves with amphetamines on a single occasion and have appeared in a healthcare context for some reason where an F15 diagnosis has been assigned. The material is nationally comprehensive over two years, and thus individuals with varying degrees of issues related to their amphetamine use are likely included, allowing for generalisation to the broader population of people who use amphetamine in general.

When considering generalisability, it is pertinent to mention the geographical context of the respective studies. Paper I recruited participants from a needle exchange program located in Malmö, the third largest city in Sweden, while Paper II included individuals who underwent forensic autopsies at Forensic Medicine in Lund, thus capturing deaths occurring within the catchment area of Forensic Medicine in Lund. Conversely, Paper III and IV (although from the criminal justice system in Paper IV), involved the recruitment of study participants at a national level. These variations in recruitment settings could impact generalisability. For instance, previous research suggests that CMR estimates tend to be notably lower in studies utilising national-level data compared to those using subnational or city-level recruitment (86).

Selection bias

As previously mentioned, Paper I is at risk of containing selection bias, as individuals injecting drugs and participating in needle exchange programs may have poorer health than individuals who inject drugs but do not participate in such programs (152). Similarly, Paper II could be argued to risk a form of selection bias, as deaths subject to forensic autopsy are typically those suspected of external causes of death. Therefore, external deaths may be overrepresented in such a study population. However, it is also true that deaths among individuals who use drugs should be subject to forensic autopsy (120), which suggests that the risk of such selection bias may be lower among individuals who use drugs undergoing forensic autopsy. In Paper III, all individuals in Sweden diagnosed with an F15 disorder over a two-year period were included, and the risk of selection bias should be lower. In Paper IV, interviewed criminal justice clients who self-reported injection drug use of amphetamine were included. Potential selection bias here could be that those who agreed to the ASI interview were individuals with milder substance-related problems, possibly due to the stigma associated with substance use (146–148). This issue is also described in the next section through what is known as non-response bias.

Non-response bias and representativeness

Non-response bias refers to the participants in the study not being representative due to a high proportion of missing data or refusal to participate in the study. In all four included papers, the sample sizes were large, and the prevalence of missing data was low. In Paper I, where it was possible to decline participation in the study, no one chose to opt out. In Paper IV, it was also possible to decline participation in the study, but no one chose to do so. Furthermore, it was possible to decline participation in the ASI interview. However, a questionnaire administered to the ASI interviewers revealed that only approximately six percent of clients approached for the ASI interview declined to participate (130).

The representativeness of the study samples can be discussed in the light of the exclusion criteria in each study. In Paper I, a smaller proportion (n=16) was excluded due to duplicate entries, incomplete baseline information, and registration in the MNEP after the reported date of death. However, 903 out of the 4,494 participants in the MNEP were excluded due to the absence of personal identification numbers. This was because a personal identification number was required to identify the study participants in the cause of death register. There was no structured analysis of these excluded individuals, which is a limitation. However, in a previous study including participants from the MNEP, which excluded individuals lacking a personal identity number, only marginal and non-significant distinctions in baseline variables between the two groups were observed (111).

In Paper II, only a small number of individuals (n=12) were excluded due to insufficient information on gender, age, and detected substances. In Paper III, all individuals with age 18 years or more with an ICD-10 F15 diagnosis in the NPR over a two-year period were included, and none were excluded. In Paper IV, 75 individuals were excluded for various reasons (shown in the method section), which is a low proportion of the total number of individuals in the ASI database (n=7,085).

Prior research on the same material from the ASI database as we used in Paper IV, has demonstrated that the present material is an oversampling of prisoners, female clients, and clients involved in a drug crime or an acquisitive crime (not unexpected given the primary purpose of the ASI interview to identify clients with substance use problems) (157). While this may limit the generalisability of the sample to the broader criminal justice population, it may still be representative of the population of individuals using substances in the criminal justice system (157).

Type I and type II errors

The foundation for statistical tests is to conduct hypothesis testing (158). In doing so, a null hypothesis, H0, is formulated, which in the studies included in this thesis generally can be expressed as "There is no true difference between the groups." The opposite of the null hypothesis is the alternative hypothesis, H1, which states "There is a true difference between the groups." It is the null hypothesis that statistical tests

are designed to either reject or fail to reject; if the result of a statistical test reaches statistical significance (often defined as a p-value below 0.05), the null hypothesis is rejected, and the alternative hypothesis is accepted (158). During hypothesis testing, various errors may arise, and there are numerous methods to mitigate the risks of such errors. However, despite endeavours to minimise the risks, it is impossible to entirely compensate for such errors.

A *type I error* is defined as rejecting the null hypothesis when the null hypothesis is actually true (158). In this thesis, we have attempted to reduce the risk of type I errors by limiting the predictor variables in Cox regressions and only including predictor variables with at least approximately 10 events (159). We have also taken into account the risk of randomly significant results in multiple testing in Paper III, by correcting the p-values using the Benjamini-Hochberg procedure (142). In Paper IV, we utilised the Huber Sandwich Estimator to compute robust estimates of standard errors (143). This was done in order to account for the multiple observations of some study participants (i.e. those who spent time both in and outside of prison). Not accounting for multiple observations violates the assumptions of the statistical model, resulting in inaccurate standard errors and an increased risk of type I errors (160).

A *type II error* is defined as failing to reject the null hypothesis when the null hypothesis is actually false (158). We have attempted to limit the risk of type II errors by using large datasets in all four included papers to achieve good statistical power. Large datasets were achieved through the use of nationwide samples (Papers III and IV) and inclusion of individuals over a long time span (Papers I and II). Another way to reduce the risk of type II errors in Paper IV was efforts to discover strong multicollinearity (referring to a substantial level of linear intercorrelation among predictor variables in a multiple regression model), as it can increase the risk of false non-significant results. This was done by calculating variance inflation factors for each variable studied (144).

Confounding

In statistical analysis aiming to suggest potential causal relationships, a confounder is a variable that is associated with both the exposure and the outcome, and it should not serve as a mediator variable in the causal pathway between the exposure and the outcome (161). Addressing a confounder statistically is commonly referred to as "controlling for" or "adjusting for." Identifying a confounder can sometimes be straightforward, but often it can be challenging to discern whether a variable is indeed a confounder, a mediator, or a collider (variable that is directly affected by two or more other variables) (161). For instance, in Paper IV, one might argue that smoking is a confounder, as it is associated with amphetamine use (the exposure) as well as cardiovascular and cerebrovascular disease (the outcome). However, it could also be argued that the effect of amphetamine use on CVD and CBD events is in

fact mediated through smoking, in which case smoking should not be considered a confounder but rather a mediator. Nevertheless, we have chosen to account for factors of significant importance to the outcome, even if they may also have mediating potential. When controlling for factors that could act as mediators, the overall effect of the exposure variable on the outcome is attenuated, and instead, a more direct effect of the exposure on the outcome is examined (161).

Furthermore, achieving complete control over all potential confounding variables in a study is inherently unattainable. Consequently, all observational studies must be interpreted within this context.

Data type and sources

The cause of death data

The accuracy of cause-of-death data relies on several factors, including the extent of the investigation performed (i.e. autopsy or just external examination of the body, investigation of medical records or interviews with relatives and health care professionals who had interactions with the deceased) and how well physicians document the causes of death on the death certificate. The accuracy of the data also depends on the subsequent coding, classification, and review by the National Board of Health and Welfare which enters the data from the death certificate into the CDR (116). For instance, it is not unusual for death certificates of hospital deaths to rely solely on an external examination of the body conducted by the attending physician at the time of death. It has been suggested that the greatest uncertainty regarding cause-of-death data originates from nursing homes, where elderly patients with multiple comorbidities reside and where the autopsy rate is particularly low (162).

Autopsy is considered the most reliable way to determine the cause of death (163–165) and forensic autopsy is a complete autopsy often including toxicology and histology analyses and taking circumstances surrounding the deaths into account. Swedish legislation mandates deaths related to drug use (including suspected overdoses and all deaths of individuals with a known or suspected substance use disorder) to undergo forensic autopsy, wherein the forensic pathologist determines the cause of death according to ICD and completes the death certificate (120). It can therefore be assumed that the causes of death for a majority of the participants included in the studies incorporated in this thesis are established through forensic autopsy and thus have a high reliability.

Despite the uncertainty factors in the cause of death data, The National Board of Health and Welfare asserts that the overall reliability of the CDR is high – with a high coverage and registered causes of death corresponding to what the responsible physician deemed as the basis for the death (117). The reliability of the registered cause of death was externally examined in a study from 2009 (166). Causes of death recorded in the CDR for the year 1995 were compared with case summaries from

for the patient's final hospitalisation, revealing agreement in 77% of cases. Accuracy was notably higher among younger patients, reaching 98% for individuals between 15-44 years of age and 91% for those aged 45-64 (166).

The diagnosis data

The diagnostic data utilised in Paper III and IV are retrieved from the Swedish NPR, comprising of two segments: the in-patient and out-patient parts (112). A prior study has assessed the validity of the in-patient segment of the NPR registry, reporting a positive predictive value ranging between 85% and 95% for in-patient register diagnoses (114). However, the out-patient segment of the registry has not undergone external validation. In both Paper III and IV, there was no differentiation made between diagnoses originating from the two segments of the registry. While the coverage of the out-patient part is inferior to that of the in-patient part, the proportion of missing primary diagnoses in the out-patient care has decreased over time, reaching approximately 2% in 2021 (113). The rationale behind using diagnoses from both segments of the registry was to encompass all instances featuring a recorded diagnosis of interest, not exclusively acute conditions (i.e., subjects admitted for in-patient care).

The self-reported data

Paper I and Paper IV relies on self-reported data and in such cases, consideration must be given to *recall bias*. Recall bias stems from variations in the accuracy or completeness of remembering past events, potentially resulting in misclassification of the exposure (167). However, previous studies have demonstrated satisfactory reliability and validity when individuals who inject drugs report their history of drug use (168). In Paper I, participants were asked to specify their primary drug upon enrolment in the MNEP. However, in Paper IV, which utilised ASI data, there may have been a longer period between intake in the criminal justice system and the actual ASI interview, potentially increasing the risk of recall bias. Nonetheless, previous research has indicated that ASI data exhibit high reliability (169,170).

Other considerations

Participants in Papers I, III, and IV may have changed their main drug after inclusion in their respective studies, which is important to keep in mind. Nonetheless, a previous study suggests that individuals who inject drugs in Sweden, at least historically, primarily used either heroin or amphetamine (49). Additionally, it is possible that some of the participants discontinued their drug use during the follow-up period, which we have not been able to control for.

International consensus on the definition of drug-related mortality is lacking. Definitions vary across countries, each carrying its own set of limitations (171).

Plausible mechanisms linking substance use to death encompass a wide spectrum, including acute poisoning, chronic organ damage caused by drugs, and accidents during intoxication. When examining all-cause mortality, as we did in Papers I-III, one could be considered to employ a broader definition of drug-related mortality. This approach is justified when studying people who use amphetamine, as compared to opioids, amphetamines have several organ-toxic effects (31) that may contribute to long-term disease development, thus necessitating an examination of mortality beyond short-term drug-related fatalities such as poisonings. In Paper IV, we aimed to specifically investigate mortality related to CVD and CBD, which entails a narrower definition. In Papers I, III and IV we examined people already identified as having amphetamine use problems. In Paper II, our aim was to investigate a more unselected population of individuals who use drugs, not exclusively focusing on those who received a substance-related diagnosis. To achieve this, we identified cases based on toxicological findings in forensic autopsy cases. We categorised any death in which opioids or stimulants were detected during postmortem toxicology analysis as potentially related to the use of these substances.

In each paper, we lack information regarding the duration and extent of the participants' substance use careers. Additionally, in all included papers, except for Paper III, we lack information on the individuals' psychiatric and somatic medical history. However, the causes of death, particularly as determined by the forensic pathologist, likely reflect pre-existing pathological conditions that are deemed to contribute to the death, thus, in that regard, constituting part of the study findings. In all the included papers we lack information on the participants' prescribed medications. Even with access to such data, confirming whether the medication was used as prescribed would remain unattainable.

Paper III included information regarding participants' comorbidity. It is crucial to acknowledge that the baseline diagnoses presented in this paper represent *a subset* of diagnoses which were documented up to two years prior to the individuals receiving their amphetamine use diagnosis. Therefore, we lack information regarding the occurrence of comorbidity further back in time or following the establishment of the amphetamine use diagnosis.

Lastly, it is imperative to bear in mind that the findings presented in each paper depict associations, and that not all variables potentially influencing the outcome are accounted for. Therefore, the results should not be interpreted as causal relationships.

Interpretation of main findings

Contributions from each study

Papers I and Paper III describe the mortality among people who use amphetamine in Sweden using CMR. Papers I-III contribute with knowledge regarding prevalence of different causes of death among people who use amphetamine. Furthermore, findings from Paper I contribute with knowledge on SMRs in all-cause and specific causes of death as well as risk factors for all-cause mortality. Paper II compares fatalities and causes of death among people who use stimulants with fatalities and causes of deaths among people who use opioids. Paper III describes comorbidities in a national sample of people who use amphetamine and identifies risk factors for all-cause mortality in a national cohort of people using amphetamine. Paper IV is a subsequent study to the findings in Paper I which identified a substantial number of deaths attributed to somatic diseases, particularly cardiovascular and cerebrovascular diseases, among individuals who injected amphetamines. Paper IV explores if amphetamine use could predict CVD and CBD outcomes in comparison to other substance use. The main findings of the four papers are discussed below.

Elevated mortality among people who use amphetamine

The findings from both Paper I and Paper II support the notion that individuals who use amphetamine in Sweden encounter increased levels of mortality both in terms of CMR and SMR.

The mortality incidence in Paper I was 16 per 1,000 person-years and in Paper III 24.6 per 1,000 person-years. A previous review from 2009 (85) on the subject has shown varying CMR among people who use amphetamine ranging from 0 to 29.5 per 1,000 person-years in different settings, and in a subsequent review and meta-analysis from 2019 on mortality among people who use amphetamine (86), encompassing 25 cohorts, a pooled CMR of 11.4 per 1,000 person-years was reported.

Several factors could account for the comparatively high CMR observed in our studies. In Study I, exclusively individuals who *inject* amphetamine were examined, a subgroup known to typically have higher CMR (172). In a previous study on individuals recruited from the MNEP, but with reported injection use with primary opioids, the CMR was 23.7 per 1,000 person-years (173). Findings from international studies of mortality rates among people who use opioids and amphetamine, have shown that people who use opioids frequently exhibit higher mortality rates (80–82,84).

However, in Paper II, which relied on national-level data of people who use amphetamine, the CMR was notably high - 24.6 per 1,000 person-years. This figure

is in the same range as mortality rates among people who use opioids (174), which is an interesting finding. This result also stands out since CMR estimates tend to be notably lower in studies utilising national-level data compared to those using subnational or city-level recruitment methods (86). The higher rate in Paper III could partly be attributed to a notable portion of individuals injecting amphetamines within this national dataset, but it was not feasible to control the actual proportion. However, we do know that amphetamine is the most common drug among individuals who inject drugs in Sweden (9), making it likely that the dataset contains a significant proportion of individuals who inject amphetamine. We also do not know the proportion of individuals receiving treatment for their amphetamine use in this national dataset - it is possible that this study captures a larger portion of people who use amphetamine who are not receiving treatment compared to Paper I, where individuals were recruited from a needle exchange program. Furthermore, in Paper III, the prevalence of polysubstance use was high, and this factor could also contribute to the elevated mortality rate.

Standardised mortality

In Study I, the mortality of people who use amphetamine was compared to that of the general Swedish population using the measure SMR. The all-cause SMR was significantly elevated, with an SMR of 8.3 (95% CI [7.5-9.1]). International studies investigating excess mortality among individuals who use stimulants have reported varying SMRs, for example ranging from 6 to 9.6 (83,84,87). Three earlier Swedish studies that have investigated standardised mortality ratios (SMRs) among people who use amphetamine have reported varying figures: an SMR of 2.5 was documented in an earlier Swedish study involving exclusively male participants (82), an SMR of 4.1 was observed among participants aged 20-64 in a study conducted on criminal justice clients (88), and an SMR of 9.1 was reported in a study focusing on hospitalised individuals who use amphetamine (175). In Stocking's meta-analysis from 2019 (86), the pooled all-cause SMR reported for people who use amphetamine was 6.8 (95% CI [5.27-8.84]). The SMR of study I is at a comparable level to most previous studies but falls within the higher range observed.

In terms of SMR across various age groups in Study I, all were significantly elevated except for women aged 50–59 years. Individuals in the 30-39 age group, regardless of gender, exhibited the highest SMR, with a tendency towards higher SMR among women (25.5 vs. 19.6 for men). A notable excess mortality has earlier been observed in females who use amphetamine compared with the general population (83,95). While this could reflect the lower mortality rates among females compared to males in the general population, it may also suggest that females are particularly susceptible to the adverse effects of amphetamine use.

Paper I also demonstrates that the SMRs in the investigated cohort of people who injected amphetamine were elevated in almost every cause of death category, respectively, and some of these cause-specific SMRs are discussed below together with the demonstrated causes of death as well as other relevant findings.

External causes of death and psychiatric comorbidity

External causes of death

Deaths due to external causes are common among people who use amphetamine in Sweden, which is shown in Papers I-III where it accounts for 38%, 79% and 59.1% of the total deaths respectively. This is consistent with prior research over time highlighting a notable prevalence of external causes of death among individuals who use amphetamines (66,81,88,95).

Among the external causes in Papers I-III, accidents are being particularly prevalent. In Paper I, accidents accounted for 15% of all deaths, and in Paper II and Paper III the numbers were 35.2% and 33.4% respectively. Among the accidental fatalities, two distinct types emerge – poisonings (often referred to as "overdoses"), and traffic accidents.

Poisoning deaths and polysubstance use

The accidents in all three papers primarily consisted of poisoning accidents. The overall proportion of poisoning accidents were 7% (Paper I), 13.9 % (Paper II) and 28.9% (Paper III). It should be noted that the proportions may be even higher, as a significant portion of deaths categorised as events of undetermined intent could be poisonings (as in the case in Paper I), and poisoning deaths with undetermined intent among people who use drugs are suggested to share more similarities with accidental poisoning deaths than with suicides (176).

In Paper I, the SMR for poisoning deaths, accidental or of undetermined intent, was notably high at 32. This is an important finding along with the findings on comorbidity in this group from Paper III, where 44.7% of the participants who all had an amphetamine use disorder diagnosis (F15), also had been diagnosed with a Multiple drug use diagnosis (F19) up to two years prior to the F15 diagnosis. Additionally, alcohol use disorder was the predominant single substance use disorder in the national cohort of people who use amphetamine in Paper III, occurring in 31.6% of the cohort, followed by opioid use disorder at 14.3%. Several earlier studies have demonstrated that polydrug use is prevalent among individuals who use amphetamines (43–45,54).

Findings from Paper II also support the notion that polysubstance use is common among people who use stimulants in Sweden. In Paper II, both accidental poisoning deaths and poisoning with an undetermined intent (mentioned anywhere on the

death certificate) were significantly more prevalent in the polysubstance group, comprising individuals with both stimulants and opioids detected in forensic toxicology analysis, compared to the opioid-only group. Previous research has also indicated that concurrent use of opioids and stimulants is associated with an elevated risk of overdose compared to opioid use alone (177). The mechanism underlying fatal opioid overdose involves respiratory depression, a process that could be exacerbated by the concurrent intoxication of other substances, thereby placing additional strain on the cardiovascular and respiratory systems (178).

Furthermore, in Paper II, when comparing the stimulant group to the opioid group, a higher proportion of deaths in the stimulant group involved the simultaneous presence of THC in forensic toxicology analysis, and a similar proportion of cases involved alcohol, higher than in the opioid group, although the difference was not significantly assured. A co-use of alcohol and cannabis among people who use stimulants is common (31,51,179,180). Concomitant use of cannabis and alcohol among individuals in Sweden who use amphetamine has been shown in a prior study (52). As mentioned in the introduction, an earlier Australian study (180) showed that individuals who used heroin demonstrated a greater propensity for benzodiazepine use, while those who used amphetamine displayed a higher likelihood of consuming cannabis and alcohol, as well as hallucinogens, cocaine, and inhalants. Our findings in Paper II align with this pattern, although the disparity in alcohol prevalence between the opioid and stimulant groups did not reach statistical significance.

In summary, concurrent use of other substances seems to be widespread among people who use amphetamine in Sweden and might serve as an important contributing factor to increased rates of poisoning deaths in this population.

Other accidents and risk-taking behaviour

Among the accident-related deaths, traffic/transport accidents emerged as a prevalent cause and constituted 25% of the accidents in Paper I and 38.5% of the accidents in Paper II. In Paper II, the stimulant group had a significantly higher overall proportion of deaths in traffic accidents compared to the opioid group (13.5% and 2.8%, respectively), as well as in other types of accidents (7.7% vs 4.6%). This result may be indicative of a lifestyle characterised by significant risk-taking behaviour among people who use amphetamine. Our findings regarding traffic accidents also align with previous studies suggesting an association between amphetamine use and compromised driving abilities (90–93). Whether this association could be related to intoxication or withdrawal, where fatigue can be central after prolonged wakefulness, is not established, but regardless, it indicates further reasons for enhanced measures to treat amphetamine use disorder.

Psychiatric comorbidity and suicide deaths

Suicides were a common cause of death in Paper II and Paper III, accounting for 26.8% (Paper II) and 12.4% (Paper III) of the total fatalities. In Paper I, 6% of the fatalities were due to suicides. Previous studies have reported figures of 12–32% suicides among people who use amphetamine (54,66,88,94,95). The higher number in Paper II is probably due to the study inclusion of forensic autopsied individuals. Furthermore, distinguishing between suicides and accidental overdoses among people who use drugs may pose challenges (181). In Paper I, where the proportion of suicides was lower (6%), 15% of all deaths were attributed to self-inflicted events with undetermined intent. Therefore, it is possible that the actual rate of suicides in Paper I was higher. In Paper II, the proportion of suicides in the stimulant group (26.8%) were significantly higher compared to the opioid group (20.8%), which is an interesting finding that could be a subject for future studies to further investigate. Also when comparing to the general Swedish population in Paper I, the proportion of suicides was elevated – demonstrating a SMR for suicides of 5.3.

A high prevalence of psychiatric comorbidity among people who use stimulants has been documented earlier (31). In the systematic review and meta-analysis from 2019 (32) the authors found that any use of amphetamines was associated with psychosis, violence, suicidality, and depression. In our investigation of the comorbidity of people who use amphetamine in Paper III, the most prevalent psychiatric comorbid diagnosis, apart from substance use disorders, was ADHD/ADD, detected in 29% of cases. This finding aligns with previous research indicating that ADHD/ADD diagnoses are commonly encountered among individuals with substance use disorders (182). Anxiety diagnoses were present in 21.9% of the cohort, and depression diagnoses in 15.8%, which are notably higher compared to the estimated one-year prevalence rates in the general population (estimated in the European Union 2010) of around 14% for anxiety and 7% for depression, respectively (183). The causal pathway between amphetamine use and psychiatric comorbidity remains unknown. Longitudinal studies that control for various factors such as socioeconomics and other comorbidity are needed in order to further explore this relationship.

Hence, it appears that people who use amphetamine in Sweden exhibit a considerable psychiatric comorbidity. Also, given the elevated suicide rates demonstrated, this underscores the importance of enhancing screening for mental health outcomes and suicidality, as well as expanding treatment options for this population.

Psychiatric risk factors for all-cause death

In Paper III, multiple drug use disorder and anxiety disorder emerged as the only psychiatric comorbidities that retained significance as predictors of all-cause mortality in the multivariable adjusted analysis.

Multiple drug use disorder as a risk factor for all-cause death among a national cohort of people who use amphetamine in Sweden is an important finding, especially in combination with the fact that poisoning was the predominant cause of death (28.9%) and multiple drug use disorders, as well as additional single substance disorders, were common comorbid diagnoses among the participants. The role of polydrug use in amphetamine toxicity is not completely clear and multiple drugs are typically reported in fatal opioid overdose (44). A potential mechanism is that amphetamines elevate oxygen demand by releasing catecholamines which exert pressure on the cardiovascular system (25,31), whereas the intake of opioids, sedatives, and alcohol can contribute to reduced oxygen supply through respiratory depression (44,178). The combination of stimulants and respiratory depressants may therefore increase the risk of overdose (44). Additionally, as mentioned earlier, concurrent use of stimulants alongside opioids has been linked to a heightened risk of overdose compared to opioid use alone (177). A multiple drug use disorder diagnosis may also indicate a more severe and uncontrolled substance use, as well as entail several other factors that increase the risk of death, which we have not controlled for in the study.

Nevertheless, multiple drug use as a risk factor for all-cause death is an important finding in this national cohort of people who use amphetamine in Sweden. This, coupled with the observation that polysubstance use as well as poisoning deaths seem to be prevalent among people who use amphetamine in Swedish, emphasises a critical need to address and manage polysubstance use within the Swedish amphetamine-using population.

Somewhat unexpectedly, anxiety disorder was identified as a predictor of mortality in Paper III. Acute effects of amphetamine use may include panic and anxiety (31), while withdrawal from heavy amphetamine use has been shown to potentially exacerbate or initiate anxiety issues (30). Consequently, anxiety disorder in this cohort may partly signify a more severe substance use pattern. Additionally, it is plausible that anxiety disorders could lead to an increased prescription of benzodiazepines, potentially heightening the risk of overdose. Nonetheless, our findings highlight the importance of addressing anxiety issues among people who use amphetamine and investigating any underlying or associated concerns. Further studies, controlling for various confounding factors and longitudinal monitoring of the conditions, are warranted.

Somatic causes of death and somatic comorbidity

The somatic comorbidity among people who use amphetamine in Sweden was indirectly examined in Papers I-III through the various somatic causes of death, but also directly investigated in Paper III through diagnostic data. These results will be discussed in an integrated manner.

Somatic causes of death

Somatic causes of death constituted 58.9% (unknown causes excluded) in Paper I, 21% in Paper II and 40.9% in Paper III. The proportion of somatic causes of death has varied in previous studies, ranging from 14-45 (66,88,94,95). The proportions reported in Paper I are notably higher compared to previously reported figures, while the proportion in Paper III falls within the higher range of previously reported values. In Paper I, this could partly be due to the study participants being exclusively individuals *injecting* amphetamine. Injection drug use has been associated with an elevated risk of injection-related infectious diseases (184–186). Additionally, individuals who inject drugs have been found to exhibit an increased incidence of certain malignancies (111), potentially due to the risk of repeated exposure to various carcinogens, including toxic substances present in injected drugs, as well as blood-borne viruses, which may predispose individuals to carcinogenesis (31,187).

Another potential explanation for the higher rates of somatic causes of death could be that our studies analyse all-cause mortality among people who use amphetamine, encompassing not only direct substance-related causes. Furthermore, the elevated rate of somatic causes in Paper I could also be due to the long follow-up time, enabling the identification of deaths caused by somatic disorders that manifest with advancing age. Moreover, somatic diseases related to amphetamine use, which can lead to fatal consequences, may manifest over a prolonged period, even after discontinuation of drug use. For instance, infection with the hepatitis C virus could lead to end-stage liver disease after several decades (187). The long duration of follow-up allows for the identification of causes of death beyond short-term and acutely drug-related mortality such as poisonings.

Cardiovascular disease

Among the somatic causes documented in Papers I-III, cardiovascular diseases emerge as the most prevalent, accounting for 16% (Paper I), 12.6% (Paper II), and 13.8% (Paper III) of the total number of fatalities in their respective cohorts. This aligns with findings from prior studies examining fatalities among people who use amphetamine, where deaths attributed to cardiovascular diseases have been documented to range between 10-19% (66,94,95). This notion is further supported by the findings of Paper I, where the mortality rate from cardiovascular diseases among people who inject amphetamine was 5.4 times higher than in the general population, adjusted for age and gender. The figure is comparable to the pooled SMR of cardiovascular disease in the meta-analysis from 2019 on mortality among people who use amphetamine, reported to be 5.1.

People who use amphetamine in Sweden thus seem to experience elevated rates of cardiovascular disease. There is an established association between amphetamine use and both acute and chronic cardiovascular diseases (53,60,62,63,188) and the impact of amphetamine on catecholamine levels in the peripheral nervous system

likely contributes to this association (53). Additionally, smoking is common among people who use amphetamine (49), which is likely to exacerbate cardiovascular disease and contribute to excess cardiovascular mortality.

In Paper IV, the specific risk of cardiovascular and cerebrovascular morbidity and mortality among people who use amphetamine were examined in comparison to people who use other substances. This study was designed considering the findings from Paper I, where somatic causes of death, particularly cardiovascular and cerebrovascular diseases, were found to constitute a significant portion of fatalities.

In the bivariate analyses in Paper IV, participants who used amphetamine exhibited a higher percentage of CVD events compared to participants who used other substances, with rates of 3% versus 1.7% ($p<0.044$). This finding aligns with the above described evidence demonstrating a correlation between amphetamine use and diverse cardiovascular pathologies (53,60,62,63). Furthermore, it is congruent with the observations made by Turner et al. (188), suggesting that fatalities associated with stimulant use were more frequently attributed to cardiovascular causes than those associated with opioids.

Subjects reporting amphetamine as their primary drug also appeared to exhibit the highest incidence rates of both CVD and CBD events. Amphetamines, being exogenous catecholamines, exert characteristic effects including an immediate elevation in heart rate and blood pressure (31). This, coupled with an accelerated progression of atherosclerosis (53,54) may contribute to a heightened incidence of cardiac pathology among people who use amphetamine.

In the extended Cox regression analysis in Paper IV, neither heroin nor polysubstance use showed significant associations with CVD or CBD events compared to amphetamine use. Female gender was the only significant association, indicating a lower risk of CVD events, consistent with previous evidence (189). This finding may be attributed to the study sample size not being sufficient to detect a difference between the groups. As per previous literature (159), approximately 10 events were estimated to be needed for each included predictor variable. However, this estimate was derived from the literature, and it is conceivable that a larger number of study participants may have been necessary in this instance.

Moreover, within this particular cohort of substance users, distinctions between the groups may be relatively small. Over a median follow-up period of 10.3 years, there were fewer CVD and CBD events than anticipated. Most deaths among released prisoners, not exclusively individuals who use drugs, are due to external causes, particularly homicide, suicide, and drug overdose (190), with suicide being the leading cause (153). It is possible that amphetamine-using individuals in this study may be more prone to external causes of death before experiencing a CVD or CBD-related event, suggesting that lifestyle and personality traits associated with criminal justice clients may overshadow the impact of amphetamine use thereby minimising any potential group differences.

Additionally, certain studies propose that incarceration might act as a health-promoting factor, especially for somatic diseases (191,192), potentially attributed to enhanced access to healthcare compared to the community (193). Imprisonment may also lead to a decrease in drug usage. This could imply that any group differences in cardiovascular and cerebrovascular morbidity and mortality among individuals who use different substances in the prison environment become less evident.

To summarise, Paper IV did not yield sufficient evidence to reject the null hypothesis, namely, that there is no difference between substance-using groups regarding cardiovascular and cerebrovascular mortality and morbidity. Further studies are warranted, examining amphetamine-using groups outside the criminal justice system and including a larger number of study participants.

Infectious diseases and liver diseases

In Paper III, viral hepatitis emerged as the most prevalent somatic diagnosis investigated among the individuals who used amphetamine, identified in 19.3% of the individuals within the national cohort. This observation may be associated with injection drug use, as viral hepatitis, particularly HCV infection, is prevalent among people who inject drugs, and amphetamine is the most frequently used drug among people who inject drugs in Sweden (9). HIV infection is also recognised as an injection-related condition, but Sweden has a low prevalence of HIV (78) and only 1% of the investigated cohort in Paper III received such a diagnosis.

The notably high SMR of 38.3 for infectious diseases in Paper I, could also be attributed to intravenous drug use, particularly resulting in viral hepatitis but also skin and soft-tissue infections, sepsis, and endocarditis (184–186). The heightened SMR for diseases of the digestive system could be associated with liver complications (such as cirrhosis) from multiple drug use or excessive alcohol consumption (194,195).

Viral hepatitis and liver disease were the only assessed somatic co-morbidities that predicted all-cause death in the national cohort in Paper III. Untreated HCV infection can progress to end-stage liver cirrhosis and hepatic failure, and the proportion of people who use amphetamine with treated HCV infection in Sweden has been reported to be low (48) although the proportion has likely increased in recent years. Individuals using amphetamines may engage less with healthcare providers than those using opioids, primarily because of the lack of substitution treatment, potentially leading to diminished access to antiviral therapy. Another potential factor that may contribute is problematic alcohol consumption (46–50) and other concomitant drug use (43–45) among individuals who use amphetamines. This may exacerbate the development of liver complications (194,195) and impact the effectiveness of HCV treatment. Furthermore, impaired liver function may also lead

to higher drug concentrations in the blood and increasing toxic effects, potentially enhancing the risk of overdose.

The findings taken together from Paper I-III, suggest that screening and treating hepatitis infection and liver diseases, as well as addressing associated conditions like alcohol and multiple drug use disorders, could potentially reduce mortality among people who use amphetamine.

Further considerations

Worth noting is that 12% of fatalities in Paper I were classified as fatalities linked to mental and behavioural disorders and categorised as a somatic cause of death. In Paper II the same number was 2.3% (supplementary table 2 in Paper II) and in Paper III 2.7%. Within this category, it could be presumed that several deaths resulted from external causes, such as drug-related causes, although our methodology in respective papers did not facilitate detailed examinations of these cases. However, it highlights a problem with the cause of death-data. Likewise, the high rates of additional single drug use diagnoses in Paper III apart from the F15 diagnosis, as well as the high rate of the Multiple drug use diagnosis (F19), may also signal a difference in how these diagnoses are interpreted and used (196). Moreover, this raises questions on how to interpret the concurrent presence of multiple psychiatric diagnoses and in a wider sense the validity of psychiatric diagnoses in general (197,198). However, this topic is beyond the scope of this thesis.

Lastly, in both Paper I and III, male gender was identified as a risk factor for all-cause mortality, consistent with prior research (44,88). Additionally, higher age at inclusion emerged as a risk factor for all-cause mortality in both papers, aligning with previous findings (44). Advanced age independently elevates the risk of death, yet in the amphetamine-using population, older age may also reflect a longer duration of amphetamine use. Our study designs did not allow for differentiation between these two explanatory factors, but age should nevertheless be a significant factor to consider in a clinical setting when encountering people who use amphetamine.

General conclusions

From the four studies included in this thesis, we have been able to demonstrate that adult individuals who use amphetamines in Sweden exhibit high mortality rates, and that amphetamine use, in the settings investigated in this thesis, appears to be associated with both psychiatric and somatic comorbidity. More specifically, the conclusions of this thesis can be summarised as follows:

Comorbidity

- People who use amphetamine in Sweden exhibit high rates of both psychiatric and somatic comorbidities.
- Multiple drug use appears common in the Swedish amphetamine using population.

Mortality and causes of death

- People who inject amphetamine in Sweden have significantly elevated mortality rates compared to the general Swedish population. This applies to fatalities due to both external and somatic causes of death.
- Common causes of deaths among the Swedish amphetamine-using population include somatic causes - notably cardiovascular and cerebrovascular diseases - and external causes - particularly accidental drug overdosing, other accidents, and suicides.
- Individuals with the detection of stimulants, and no opioids, during forensic autopsy, died to a higher extent from suicide, transport accidents and other accidents, when compared to individuals with opioids, and no stimulants, detected at forensic autopsy.

Risk factors for mortality and morbidity

- High age and male gender appear to be risk factors for all-cause mortality among people who use amphetamine in Sweden.
- Multiple drug use and anxiety disorders appear to be psychiatric risk factors for all-cause mortality among people who use amphetamine in Sweden.

- Viral hepatitis and liver diseases appear to be somatic risk factors for all-cause mortality within this population.
- There is not enough evidence to conclude any differences in the risk of CVD or CBD events among criminal justice clients who inject amphetamine in comparison to clients injecting opioids or multiple drugs. Further research is warranted to investigate whether amphetamine use presents a risk factor for CVD or CBD when compared to other substance use, and to differentiate substance-specific pathology from the influence of other harmful lifestyle factors prevalent among individuals with substance use disorders.

Implications

The use of amphetamines is a major concern, both globally and in Sweden. While the association between amphetamine use and predominantly acute serious somatic and psychiatric complications has been recognised, research on the long-term effects of amphetamine use has been relatively limited, especially considering the known organ toxic effects of the substances. One approach to exploring long-term effects involves examining mortality rates and causes of death. Despite a recent increase in the number of international studies investigating mortality among amphetamine users, the existing evidence remains limited. Notably, there has been a lack of studies with extensive follow-up periods reporting cause-specific mortality and detailing how the cause of death was determined, including the specific ICD codes for each cause of death, as well as investigations comparing individuals using amphetamines with those using other substances.

Given the longstanding central role of amphetamines in Sweden, individuals using amphetamines in the Swedish context have received relatively little attention, both in research and clinical settings, especially compared to efforts aimed at individuals using opioids. This discrepancy is likely attributed in part to the link between opioid use and the risk of fatal overdose, as well as the availability of evidence-based substitution treatment for opioid dependence, which has become a primary focus for healthcare provision — a resource lacking for individuals using amphetamines.

Amphetamine remains the most common drug among injecting drug users in Sweden, thus making it a significant factor in the Swedish substance use context. While waiting for evidence-based pharmacological treatment alternatives, there is an imperative to gain a deeper understanding of the population of individuals using amphetamines in Sweden, to improve the current care.

This thesis has demonstrated a considerable suffering and an increased mortality experienced by individuals who use amphetamines in Sweden, stemming from both somatic ailments and unnatural causes such as overdoses, suicides, and accidents. Polydrug use also appears prevalent in this population, highlighting the importance of identifying and addressing such patterns among individuals using amphetamines. Many established harm reduction interventions used in opioid dependence could potentially be beneficial for individuals with amphetamine use disorders as well, including overdose prevention counselling and naloxone distribution. Furthermore,

the findings suggest a need to intensify efforts in identifying psychiatric comorbidities and potentially associated suicidality within this group.

Moreover, our research has underscored the prevalence of somatic diseases among individuals using amphetamines in Sweden, particularly cardiovascular and cerebrovascular disease, liver disease, and hepatitis, thus emphasising the need for heightened attention for these conditions in the health care settings treating people who use amphetamine. This could for instance be achieved through expanded needle exchange programs and within standard addiction outpatient care, if clinicians are attentive to these associated conditions when encountering individuals using amphetamines.

In summary, the hope is that the insights from this thesis can contribute to improved care for individuals using amphetamines in Sweden. The insights can enhance incentives to implement initiatives aimed at reducing suffering among individuals who use amphetamines, thus ultimately contributing to the reduction of the high mortality rate in this population.

Future Aspects

There are many unanswered questions regarding the long-term effects of amphetamine use, as well as several new questions that have arisen from the results of the studies in this thesis.

First, there is a need for more studies on people who use amphetamines, with long-term follow-up which also controls for additional relevant covariates, such as socioeconomic status, previous comorbidities, as well as comparisons with individuals with other substance use disorders, to better understand the risks specifically linked to amphetamine use. Exploring individuals who use amphetamines and maintain predominant contact with social services would also be interesting to explore.

Based on the results in Paper I and Paper IV, a further research question would be how individuals who inject amphetamines and participate in needle exchange programs differ from those who inject other primary drugs, in terms of causes of death and comorbidity. In Paper IV, no such differences were found concerning cardiovascular and cerebrovascular outcomes among criminal justice clients injecting different substances, but the result might have been different if the study included individuals recruited from another setting.

Paper II provides insights into several new research questions. It would be interesting to combine forensic data with additional data from other authorities and institutions to gain comprehensive insights into the group differences highlighted in the study. This could include information from social services regarding previous contacts and treatments, as well as data from medical records or registers containing diagnoses and treatment details. Moreover, in Study II, access to tissue samples was unavailable, which could have offered additional insights into chronic organ damage among individuals who use amphetamines. Integrating such data into future studies could enhance the comprehension of the long-term health effects of amphetamine use.

Papers I-III enlightened challenges in determining the cause of death, even in forensic autopsies. For example, the evaluation of accidental or suicidal poisoning is multifaceted, relying not only on autopsy findings but also on past medical history and the circumstances surrounding the death. Future studies on mortality and causes of death among people who use drugs would benefit from a thorough investigation into the circumstances and medical history of each death. Working with this thesis

has also emphasised the importance of considering the definition of drug-related mortality, as well as the advantages and disadvantages associated with the selected definition.

It would be interesting to further investigate polydrug use among individuals who use amphetamines in Sweden. Is it as common among individuals who inject amphetamines as among those who administer amphetamines in other ways? And how is polydrug use best identified and treated in this patient group?

Considering the significantly increased diagnosis and prescription of ADHD medications in recent years (199), a topic for future research could also be to investigate the long-term effects of treatment with central stimulant ADHD medications.

Furthermore, what interventions are most effective in reducing mortality and comorbidity in this patient group? How could addiction outpatient care be organised with this in mind? For example, could collaboration with primary care be improved? Would more harm reduction interventions need to be implemented in regular outpatient services encountering people who use amphetamine? These questions, along with several others, remain to be answered.

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