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SEVERE POISONINGS IN SWEDEN

–DEMOGRAPHY, INTENSIVE CARE, AND DEATH

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Thesis for Doctoral Degree (Ph. D)

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Popular science summary of thesis

A case of poisoning can be many things. It can for example be a young woman with depression taking too many antidepressants as a means of self-harm or suicide, a person raised in another country eating the wrong mushroom from the Swedish forest, a young man with substance abuse disorder taking heroin, or an older person forgetting to put out a candle before going to sleep and then being poisoned by fire smoke inhalation. Bits of information about these patients are found here and there but no national or uniform reporting currently exists.

This thesis consists of four register-based studies describing the "who", "what", and "how did it go" of the severe poisonings in Sweden: and includes patients who need intensive care, who suffer an out-of-hospital cardiac arrest, or die due to poisoning. The first two studies describe patients treated in the intensive care unit and what happens to them afterwards. The results show that every tenth intensive care admission is due to a poisoning, in mostly young men and women, and almost half of those admitted had a previous hospitalisation for poisoning. Few died in the intensive care unit, but death was a little overrepresented among older men with no previously known poisoning. The number who have died one year after intensive care due to poisoning is higher than for comparable people without poisoning. Younger patients are more likely die from a new poisoning. The third study describes patients with an out-of-hospital cardiac arrest caused by poisoning, and showed these patients to be younger and have less favourable factors for surviving than cardiac arrest from other causes., but to still have a higher survival. The fourth study describe patients who died due to poisoning, and show that illicit drug use is the most common cause of death and that the victims often are men in their 40-50s. Also, time trends from this study reflected the famous opioid-boom in and around 2014-2017.

The conclusions drawn from this thesis are that poisoning is a common cause of intensive care unit-admission, non-medical out-of-hospital cardiac arrest, and death in Sweden. Patients are mostly young and have often already shown signs of being at risk for disease or death, marking themselves for the health care as a group for intense observation and treatment. It may be possible to do more to prevent these deaths. The best ways to prevent poisonings and death by poisoning is probably to limit access to poison and to continue to improve treatment for patients with mental health problems or substance abuse disease.

Abstract

Background: Poisonings are common and diverse in their origins, clinical presentations, and outcomes. Poisoning accounts for a substantial number of hospital admissions with need for a higher level of care. The hospital mortality is low but never the less around 1,000 people die from poisoning each year in Sweden. Patients suffering from the most severe poisonings are treated in the intensive care unit and may suffer a cardiac arrests prior to admission or during hospitalisation. A significant proportion of patients dies outside of hospital. Robust information regarding these patients is scares.

Aim: The overall aim of the thesis was to increase knowledge about patients suffering from severe poisoning in Sweden. The specific aims were to describe national data for characteristics, short and long-term mortality for patients treated in the intensive care unit (ICU) due to poisoning, to compare key characteristics and outcomes between out-of-hospital cardiac arrest caused by poisoning vs. other causes, and to describe the national patient population deceased due to poisoning including toxicology results.

Methods and results: Four epidemiological studies are included in the thesis. Study I and II were cohort studies based on three national registers, the Swedish intensive care register, the national patient register, and the cause of death register. Variables were collected for all adult patients treated in a Swedish ICU during 2010-2011, with 8,155 registered ICU admissions. Patients had a median age of 38 years and men and women were equally represented. Almost half of the patients had a previous hospitalisation due to poisoning. Approximately 30% were unconscious on admission to the ICU and 14.6% were mechanically ventilated during their stay. The in-hospital mortality was 1.9% and the subgroup with the highest mortality was older men without a previously known poisoning. The population's one-year mortality was 4.5% and also here it was higher for older men. The whole population had a nine-fold increased risk of death during the year following ICU admission compared to population based controls. The highest mortality was found in women between 19-39 years, with a 50 times higher mortality compared to controls and the clear majority of deaths after hospital discharge (94%) was caused by suicide and/or accidents.

Study III was a cohort study based on the Swedish register for cardiopulmonary resuscitation, the national patient register, and the cause of death register. All adult patients with an out-of-hospital cardiac arrest (OHCA) during 2007-2021 were included. In total, 66,261 OHCA patients were included, of whom 5.2% were found to receive a diagnosis of poisoning. Poisoned OHCA patients had a median age of 43 years (compared to 73 of the whole group) and included more men. The cardiac arrests due to poisoning were less likely to be witnessed and less likely to have a shockable first rhythm. Despite this, they had a somewhat lower mortality than the other cardiac arrests groups (84% vs 88%).

Study IV was a cohort study which included all adult patients who died from poisoning between 2000-2021, according to the cause of death register. Variables were also added from the national forensic database. The results showed that 1.3% of annual deaths in Sweden were caused by poisoning (n poisoning deaths=27,057/n deaths=2,018,495). Patients who died due to poisoning had a median age of 53 years and 70% were men. In total, 87% of these deaths underwent some sort of forensic examination. Drugs (synthetic narcotics and opioids) caused 46% of deaths and alcohols caused 33%. Positive toxicologic tests were found in 83% of patients. Temporal trends show an increase in opioids, antidepressants/neuroleptics, and sedative/antiepileptic substances in femoral blood of patients who died around 2014-2017.

Conclusion: Poisoning is a common cause of ICU admission, non-medical OHCA, and death in Sweden. Many patients have a previous history of poisoning before ICU admission, and a mix of substances is the most common poisoning. The ICU-mortality is low but the long-term mortality is high for these often young patients, and death is in many cases caused by a new poisoning. Patients with OHCA due to poisoning are younger than patients with OHCA of other causes and have better survival. Deaths out of hospital are often due to illicit drug use.

List of scientific papers

I. **Lindqvist E**, Edman G, Hollenberg J, Nordberg P, Ösby U, Forsberg S. Intensive care admissions due to poisoning. Acta Anaesthesiol Scand. 2017 Nov;61(10):1296-1304.

II. **Lindqvist E,** Edman G, Hollenberg J, Nordberg P, Forsberg S. Long-term mortality and cause of death for patients treated in Intensive Care Units due to poisoning. Acta Anaesthesiol Scand. 2019 Apr;63(4):500-505.

III. **Lindqvist E**, Hollenberg J, Ringh M, Nordberg P, Forsberg S. Out-of-hospital cardiac arrest caused by poisoning – a Swedish nationwide study over 15 years. Resuscitation. 2023 Dec 1;193:110012.

IV. **Lindqvist E**, Hollenberg J, Ringh M, Nordberg P, Svensson L, Druid H, Forsberg S. Death and forensic toxicology in Swedish poisonings. *Manuscript submitted.*

Contents

List of abbreviations

ATC	anatomical therapeutic chemical classification
CA	cardiac arrest
CDR	cause of death register
CI	confidence interval
CPR	cardiopulmonary resuscitation
CRRT	continuous renal replacement therapy
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EMS	emergency medical service
GCS	glasgow coma scale
ICD	international classification of disease
ICU	intensive care unit
IQR	interquartile range
MAO	monoamine oxidase
NFD	national forensic database
NPR	national patient register
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
RLS	reaction level scale
SAPS	simplified acute physiology score
SSRI	selective serotonin reuptake inhibitor
WHO	world health organisation

1 Introduction

1.1 Definition

Everything is poison! The Swiss 16th century physician Paracelsus, known as the "father of toxicology", is famous for the phrase: "What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison.".[1] This is still one of the basic principles of modern pharmacology and toxicology. Alfred Swaine Taylor, a 19th century toxicologist, noted "A poison in a small dose is a medicine, and a medicine in a large dose is poison."[2] The World Health Organization (WHO) definition is that a poisoning occurs when an individual is exposed to a hazardous substance that might inflict harm or death to the individual.[3,4]

The word poison originates from the Old French word "puison", meaning a (medical) drink[5], and has been used since the 11th century. The use of the verb form "to poison" dates to the 14th century. The word toxin originates from the Greek word "toxon" meaning bow or arc, implying the use of poisoned arrows to hunt.[1]

Poisonings are in many aspects very heterogeneous. The poison may be ingested, inhaled, injected, radiated, or dermally transmitted and can be in the form of gas, liquid, or solid. It can originate in toxins (produced by an organism) from food, plants, animals, chemicals, or drugs (pharmaceutical or illicit). There are 1,200 species of poisonous marine organisms, and also 700 species of fish, 400 species of snakes, 60 species of ticks, 75 species of scorpions, 200 species of spiders, and 750 other poisons in more than 1,000 types of plants.[1] The number of chemicals, pharmaceutical, or illicit drugs is countless and constantly increasing. Furthermore, a poisoning can be acute or chronic, deliberate or non-deliberate. Causes of deliberate poisoning can vary from self-harm or to achieve death to intoxication. Intoxication is here defined as a voluntary self-inflicted action caused by alcohol or narcotics for recreational purposes and not synonymous to poisoning, but is included in the concept. An adverse drug reaction also differs from poisoning, and is here defined as an unintended potentially harmful or unpleasant reaction to the prescribed use of a pharmaceutical drug, but can of course transition into a poisoning.

1.2 Symptoms

The great number of potentially poisonous substances from toxins, chemicals, or drugs makes it impossible to separate symptom descriptions for each substance. More commonly used are the *toxidromes*, which are constellations of signs and symptoms characteristic to the class of substance or mechanism of actions of the substance group. The most common ones are anticholinergic, cholinergic, opioid, sympathomimetic[6], serotonergic, and hypnosedative. The toxidromes can guide the clinician's initial treatment until toxicology testing is completed.

1.3 Treatment

Treatment of the poisoned patient differs between cases, depending on the patient and the poisoning substance(s). There are however some general treatment guidelines, both overall and more specific. Airway management, hemodynamic support, stabilisation of vital parameters, and treatment of metabolic derangements always come first followed by more specific poisoning treatments. The specific treatments for poisoning are to decrease the uptake of the poisonous substance by using activated charcoal ingestion, gastric lavage, gastroscopy, or whole-bowel-irrigation. Acceleration of the elimination of poisonous substances can in some cases be achieved through forced or alkalinised diuresis, or hemodialysis. In some cases treatment with antidotes is possible, and in some cases treatment is purely symptomatic until the poison has been metabolised by the body. There are also specific treatment options if the patient develops seizures, circulatory instability, or arrythmias. Examples of these treatments are benzodiazepines or chemically induced coma for seizures. In addition, magnesium, sodium bicarbonate, and antiarrhythmic medications may be indicated for treatment of arrhythmias. Cardiovascular instability might be treated with intravenous fluid therapy, vasoactive medications, or inotropic medications such as dobutamine, methylene blue, or the combination of high dose insulin and glucose infusion.

1.4 History of poisoning

Poisoning has been a concept throughout human history. For example in hunting, murder, suicide, execution, pest-control, and warfare. Historians have found signs of poison use in Europe as far back as 12,500-8500 B.C.[1] One such sign is grooves in hunting tools, capable of retaining toxins from plants or animals. Grooves in arrows and spears used for poison have also been found in Africa and Asia.[1] Perhaps the most famous plant toxin used in this setting is curare, an alkaloid that paralyses the muscles of the victim making it immobile and unable to breathe, thus causing death within minutes.

The first documented knowledge of poison was in the Egyptian Eber Papyrus (1550 B.C.) and in the Vedic books from India (1500 B.C.). The Eber Papyrus is a 20 meter long scroll with over 900 formulae for medical remedies and descriptions of poisons from animals, plants, and minerals.[1,7]

With a less nomadic lifestyle and more residential living in larger groups, and with the development of religion the areas of use for poison expanded. It was used for recreational purposes with hallucinogenic substances, magical therapy, religious ceremonies, remedies for ailments, and murder.[1] Murder by poisoning dates back to ancient times, for example in the Roman empire poison was often used for murdering enemies, spouses, or competitive heirs. The roman emperors had a specific court poisoners to perform murders on his order and also a professional taster for his own food and drinks. Substances used were mainly toxins from animals or plants (for example opium, belladonna, hemlock, and aconite), and minerals such as mercury and arsenic.[1]

In late medieval Europe (12th-14th century), there was an increase in poisonings with the development of 'apothecaries', and the absence of methods for detection and thus low risk of legal punishment. The apothecaries held stocks of classic poisons such as hemlock, nightshade, aconite, opium, strychnine, cyanide, arsenic, and mercury. These substances were sold as medicines, pesticides, and beauty products.[1] During the European renaissance (around 13th-16th century), in

France, Spain, and Italy murder by poison was still very common and often reported among nobles, royalties, and popes who wanted to eliminate enemies. During this time many scientists started to study poisons and their antidotes, and the knowledge of the subject advanced substantially.

Since the renaissance, chemical science has continued to develop and the increased knowledge in detection of substances has led to a decrease in poisoning as a method for murder, presumably because evidence could be produced and legal penalties followed.[8] With an increase in the panorama of substances, toxicology developed into its own scientific discipline during the 19th century. Later on, during the two world wars, a new area of application was discovered: chemical warfare. On the battlefields of the first World War gases such as chlorine, phosgene, and sulphur mustard were used to kill and injure a large number of people. During the second World War further developments had been made and even more lethal nerve agents were used to kill millions, and poison was a common method of suicide among German Nazi leaders to avoid legal punishments for war crimes.[9] Chemical warfare is still used today[10], despite it being prohibited by international law.

1.5 Epidemiology

In the present, many poisonous substances are used in pest control, food preservation, building material, manufacturing, and household cleaning. Poisonings are now, besides the occasional political assassination or spousal homicide, mainly associated with accidents, suicides, or overdoses and constitute a significant part of emergency and critical care medicine.

1.5.1 Emergency departments and in-hospital

Of about 600,000 annual hospital admissions from Swedish emergency departments (ED) approximately 15,000 are because of poisoning (2.5%).[11,12] International studies report that 0.7-2.1% of all ED visits are because of poisoning, which is similar to the Swedish experience.[13-16] The number of ED visits and patient characteristics are fairly similar in western countries with the typical patient being a woman between 20-40 years with a poly-substance poisoning with sedatives, psychoactive, or analgesic drugs, often in combination with alcohol.[13-21] Most admitted patients do not receive treatment other than solely observation. Antidotes may be given continuously as treatment, the more common use is as a diagnostic test to elucidate the main effects of the poisoning.[22,23] The in-hospital mortality for poisonings in Sweden is low, about 0.5-0.6%.[12] Other countries report hospital mortality rates of between 0.4-2.1% for these patients.[16,18,21,22,24] Patients with worse prognosis are those who are unconscious at presentation, and those of higher age. [22,25,26]

1.5.2 Intensive care

The most severe poisonings are usually treated in the ICU. A recent large Swedish study showed that poisoning is the most common cause for ICU admission, representing 19% of admissions.[27] About 8.1-49% of poisoned patients in the ED are admitted to the ICU in European studies, and this is mainly because of the need for observation.[15,19,21-23,27-31] The large difference in frequency of admitted patients might be related to different availability of ICU care, local routines, and inclusion or exclusion of high-dependency units in the statistics. A Dutch study identified respiratory failure, male sex, age over 55 years, impaired GCS, and poisoning with antihypertensive or antipsychotic substances as predictors for ICU admission.[32] The same study showed that only 6.5% of ICU-admitted patients developed a need for intensive care interventions, such as mechanical ventilation, during their stay.[32]

Characteristics of patients admitted to Swedish ICUs because of poisoning are not known. In other countries there are as many women as men admitted to the ICU because of poisoning. This population is somewhat older than the general poisoning population and most often present with a poly-substance poisoning of opioids, antidepressants, or sedatives, and often in combination with alcohol.[28,30,15,33,31,34] Their median length of stay is reported to be 0.7 to 3 days.[28,31,35,33,36] Treatment of poisoned patients differs substantially between countries, in both method and frequency. Some studies show that specific treatment was provided in up to 83% of the cases and consisted of antidote (35-38%), activated charcoal (16-74%), and/or gastric lavage (9-82%).[23,31] Many patients are treated with mechanical ventilation (69-84%), receive inotropic drugs (6-27.5%), or continuous renal replacement therapy (CRRT; 1-14%).[22,28,35] When opioids are involved both inotropes and CRRT are more frequently needed.[36]

ICU-mortality for poisoned patients is reported as being between 2-8% in Europe, but is unknown for Sweden.[28,37] The rate in Europe is lower than for many other ICU diagnoses.[33] The factors shown to be most strongly associated with higher mortality are respiratory failure, renal failure, and hypotension.[37]

1.6 Near fatal poisonings

A severe or late phase poisoning can present as a cardiac arrest, due to several mechanisms such as respiratory failure and primary cardiac effects. In Sweden there are approximately 5,000 annual OHCA patients in whom cardiopulmonary resuscitation (CPR) is attempted by the emergency medical service (EMS).[38] Poisoning as cause of OHCA is reported as ranging between 0.3-13% of the non-cardiac etiologies.[39-42] The fraction of OHCA caused by poisoning is not known for the Swedish population. The non-cardiac OHCA are in general more often unwitnessed, more rarely have an initial shockable rhythm (ventricular tachycardia or ventricular fibrillation), affects younger patients, and have lower survival rate compared to OHCA due to cardiac causes.[39,43] However, some studies report a higher survival with good neurological outcome in OHCA due to poisoning.[41,44] This suggests that there might be a rather large group of young people with cardiac arrest due to poisoning with potentially good outcome if treated swiftly and correctly. In the sections on “special circumstances”, the European Resuscitation Council and the American Heart Association recommend considering other treatment options for cardiac arrest due to poisoning, such as prolonged CPR, specific antidote treatment, and extra corporeal membrane oxygenation (ECMO), which makes it important to identify these patients.[45,46]

1.7 Fatal poisonings

There are approximately 90,000 annual deaths in Sweden and poisoning accounts for almost 1% according to reports.[17,47] A report from 2014 states that 45% of these deaths are accidental and mainly occur in men with illicit drug abuse problems, while 30% are stated as suicides and 25% with unclear intent.[17] Of the 1,100-1,500 suicides each year in Sweden, poisoning is the most common method among women and it is also globally the most common method of self-harm.[20,48-50]

Of the annual deaths in Sweden about 6% (c:a 5,000-6,000) undergo a forensic autopsy.[51] According to Swedish law a forensic autopsy must be performed in cases of unexpected, violent, or unnatural deaths such as accidents, suspected homicide/suicide, ongoing drug or alcohol abuse, or in cases when the identification of the deceased is difficult.[52] A forensic examination almost always includes toxicology testing. The accuracy in clinical diagnosis when later compared to autopsy results differs. A systematic review showed that the prevalence of misdiagnosis ranged between 5.5-100% in 31 studies of 5863 autopsied patients (clinical and forensic) in the ICU.[53] The autopsy frequency among patients who die due to poisoning is unknown in Sweden. One study showed that of patients forensically autopsied in Sweden 1992-2002, 12-13% died due to poisoning.[51] An average of 3.5-4.1 substances per deceased patient was found. Ethanol was detected in 43% of the patients, of whom 32% had toxic concentrations. These data are however over 20 years old and the panorama of poisonous substances, especially illicit drugs, evolves fast.

1.8 Long-term prognosis

When long-term follow ups of poisoned patients in the ICU are conducted, an increased mortality can be seen compared to aged-matched controls. Whether any specific subgroup has a higher mortality and the specific causes of death are not known.[25,48]. Of patients with Glasgow coma scale (GCS) less than 10 treated for poisoning in two Swedish ICUs, a one-year mortality of 10.9% was found, which is 100 times the one-year mortality of age-matched controls. The two-year mortality was 13.7%.[25] A Dutch study showed that mortality 1, 12, and 24 months after ICU admission was 2.8%, 6.5%, and 9.3%, respectively.[24] In Australia the one-year mortality has been reported to be 1.8% and the four-year mortality 3.4%.[30] There is an apparent increased risk of suicide even after the poisoning event itself. Most suicides occur long after the index poisoning, emphasising the importance of long-term follow up and continuous psychiatric treatment.[48] Studies predicting suicide following self-harm found male sex, low socioeconomic status, drug abuse, suicidal intent, physical health problems, and previous self-harm to be risk factors.[24,54,55] The long-term mortality of patients who have been treated in a Swedish ICU due to poisoning is unknown.

1.9 Rationale

Some information regarding patients suffering from poisoning is known, but this information is fragmented and incomplete. To facilitate treatment and preventive work for this high-risk group of often younger individuals more and uniform information about characteristics, poisoning substances, and outcomes are needed.

2 Research aims

The overall aim of the thesis was to increase knowledge about patients suffering from severe poisoning in Sweden.

Study specific aims:

Study I

To describe national data for characteristics and mortality of patients treated in the ICU due to poisoning.

Study II

To describe the one and two-year mortality including cause of death for patients previously treated in the ICU for any type of poisoning.

Study III

To compare key characteristics and outcomes between OHCA caused by poisoning vs. other causes.

Study IV

To describe the patient population with poisoning as the cause of death, including forensic toxicology analysis.

3 Materials and methods

3.1 Ethical considerations

The first three studies were approved by the Swedish Ethical Review Authority, which however did not consider such approval necessary for the fourth study since the study method did not include elements covered by the § 3-4 in the Ethical Review Act.

The ethical problems are similar for all studies in this thesis, mainly that sensitive personal information is used. Sweden has a long tradition of collecting register data from patients without individual informed consent but instead a more general information to the public that data associated with hospital care could be saved and used in research in the future. To mitigate the individual risk without compromising research results the Swedish Ethical Review Authority carefully considers whether to provide data from Swedish registries to researchers who apply. All four studies in this thesis used pseudonymised data which prevents many ethical problems. The pseudonymised data cannot be identified without a code key, which is generally destroyed three months after data collection. All results were based on group analyses of historical data and did not affect or identify the individual patient. No individual benefit for the included patients existed but a significant public benefit exists which has been assessed to outweigh the minimal risks for the individuals included in these studies. The information gained from these studies could be important in treatment and preventive work for patients with acute poisoning.

3.2 Registers

3.2.1 National Patient Register (NPR)

The national patient register is a national register administered by the Swedish National Board of Health and Welfare. It has been mandatory for all county councils to participate since 1987 and its aims are to follow the health development of the population, improve possibilities to prevent and treat diseases, facilitate development, and improve the quality of healthcare in

Sweden. It contains information on inpatient and outpatients care, information regarding emergency care, and information about compulsory psychiatric treatment for each patients seeking medical care in Sweden. Data loss is considered to be less than 1% for the most frequent variables (main diagnosis, external causes for main diagnosis, personal identification number) and loss of data in all other variables is considered negligible.[56]

3.2.2 Cause of Death Register (CDR)

The cause of death register is a national register administered by the Swedish National Board of Health and Welfare with mandatory recording of all deaths in Sweden since 1961 (excluding stillborns, but including deaths of patients without civil registration in Sweden since 2012). The aims of the register are to document patterns of death over time, regional differences, and help identify potential preventable causes of death. The registered cause of death is based on either autopsy or clinical assessment based on symptoms, patient history, laboratory results, and medical or surgical examinations. The register includes information on patient characteristics, date and place of death, ICD-code for cause of death, autopsy status, and nationality.[57] It has been validated and is considered to have high quality and nearly a 100% coverage.[58]

3.2.3 Swedish Intensive Care Register (SIR)

The Swedish intensive care register is a non-profit national register started in 2001, and aims to monitor and improve the quality of intensive care and facilitate intensive care research in Sweden. It is based on data reported from almost all ICUs in Sweden and includes data on patient characteristics, treating ICU, dates and length of stay, cause of admission, mortality, ICD-diagnosis, and quality of life after discharge.[59] In 2011 the register covered 91% of all intensive care admissions, and in 2022 all Swedish ICUs reported data to SIR.[60]

3.2.4 Swedish Register for Cardiopulmonary Resuscitation (SRCR)

The Swedish register for cardiopulmonary resuscitation is a non-profit register including all cardiac arrests (CA) in Sweden where CPR has been started.

Registration of OHCA started in 1990 and since 2006 in-hospital cardiac arrests are also included. The stated aim of the register is to document and investigate progress in improving the CA-treatment and to increase survival after CA. The register includes information, according to the Utstein template, on patient characteristics and much detailed information regarding the CA, including time, place, if witnessed, suspected cause, times to different treatments and execution thereof, rhythm on electrocardiogram (ECG), hospital treatment, and mortality.[61] Compliance has varied but currently 100% of EMS-providers report to the register, but when validated up to 25% of OHCA are missed in the register and those reported differ from those not reported.[38,62] Patients not reported to the register are often older, have a higher frequency of bystander-CPR, and a higher survival rate.[62]

3.2.5 National Forensic Database (NFD)

The National Board of Forensic Medicine is an expert authority within the Swedish judicial system. Forensic autopsies are performed at six centers in Sweden but toxicological analysis only at one laboratory, the Department of Forensic Chemistry in Linköping. The NFD includes information on all cases handled by the department since 1992. Subdivisions include forensic chemistry/toxicology, forensic autopsy, forensic genetics and forensic psychiatry.[63]

3.3 ICD-classification

The International Statistical Classification of Diseases (ICD) and Related Health Problems is WHO's system used for classification of diseases, health problems, and causes of death worldwide since the 1940's. It is based on 22 chapters with subsections and categories ending in a code with one letter and two following numbers for a specific disease. It is the same worldwide and is the basis for major international statistics on health issues and causes of death. It has recently been revised for the 11th time, ICD-11. The version currently used in Sweden is ICD-10(-SE), and it has been in use since 1997.[64,65] In ICD-10, poisoning is coded as: T36–T65, T96, T97, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, X20-X29, X40–X49, X60–X69, X76, or Y10–19.[65]

3.4 Study specific methods

Table 1. Description of study methods for study I-IV.

	Study I	Study II	Study III	Study IV
Design	Observational cohort study	Observational cohort study	Observational cohort study	Observational cohort study
Data sources	NPR CDR SIR	NPR CDR SIR	SRCR NPR CDR	CDR NFD
Study period	1 jan 2010 – 31 dec 2011	1 jan 2010 - 31 dec 2011	1 jan 2007 - 31 dec 2021	1 jan 2000 - 31 dec 2021
Number of patients	8155	6730	71,895	27,057
Exposure	Intensive care caused by poisoning.	Intensive care caused by poisoning.	OHCA caused by poisoning.	Death caused by poisoning.
Outcome	Characteristics, mortality.	Long-term mortality and cause of death.	Characteristics, mortality.	Characteristics, cause of death.
Statistical analyses	Descriptive statistics. ANOVA, χ^2. Logistic regression.	Descriptive statistics. χ^2. Kaplan-Meier.	Descriptive statistics. Kruskal-Wallis, χ^2. Logistic regression.	Descriptive statistics. $\chi^{2.}$ Wilcoxon.

3.4.1 Study I + II

Both studies were observational cohort studies based on the same population. All adult patients with poisoning as primary or secondary discharge ICD-10 diagnosis in the NPR were collected and matched with admissions with the same date in the SIR to select only ICU treated poisonings. Patients were also matched to previous admissions caused by poisoning in the NPR back to 1987, and to the CDR up until 31 December 2013 for date of eventual death. ICD 10-codes used in the study were T36-T65, F10.0, F11.0, F12.0, F13.0, F14.0, F15.0, F16.0, F17.0, F18.0, F19.0 and ICD 9-codes used were 9600-9899, 2914, 2922. The study period was from 1th January 2010 to 31th December 2011. Variables collected were number of overall admissions and specific admissions for poisoning, age, sex, admission and discharge time, level of consciousness according to GCS or Reaction Level Scale (RLS), organ supportive treatment (dialysis or invasive ventilation), discharge diagnosis, SAPS 3, ATC-code, and cause and date of death. Patients were for one analysis divided into to nine different groups according to main substance and this was based primarily on ICD-codes, and then secondly pharmaceutical code (ATC-code). If none of these specified the substance the patients were categorised as unspecified.

Descriptive data was presented as median, interquartile range (IQR), counts, or percentage. ANOVA or χ^2-tests were used to compare groups. A p-value of ≤0.05 was considered significant. A logistic regression analysis for mortality was performed, which included age, sex, invasive ventilation, previous hospital admission due to poisoning, and unconsciousness and was presented as odds ratios (OR) and confidence intervals (CI). A Kaplan-Meier curve was used to present overall survival.

3.4.2 Study III

All adult patients with an OHCA in the SRCR between 1th January 2007 and 31th December 2021 were included as study population. All were matched, via personal identification number, with the CDR and ICD-10 codes registered ±1 day of the OHCA were included. The study population was also matched to the NPR. In both CDR and NPR, if the main diagnosis was unspecific the 1-3 secondary diagnosis was used for classification. In addition, hospital admissions ±2 days were used to include erroneous registrations and events close to midnight.

The study population was divided into three groups based on the cause of OHCA: medical, non-medical (excluding poisonings), or poisoning. This was primarily based on the CDR diagnosis and secondary on the NPR diagnosis. The ICD-10 codes used for the different groups were: *Poisoning* T36-T65, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, X20-29, X40-49, X60-69, X76, Y10-19; *Non-medical* S00-T35, T66-T98, V01-Y98; *Medical* A00-R99. The ICD-10 codes used for the different subdivision according to substance were: *Drugs (pharmaceutical or illicit)* T36-49, X60-64, Y10-13, X40-43, F11-17; *Alcohols* F10, X65, T51, Y15, X45; *Solvents, pesticides, corrosive substances, detergent* T52-57, T60, X66, X68, Y18, X46, X48, F18; *Smoke/carbon monoxide* T58-59, X67, Y17, X47, X76; *Animals, plants, food* T61-64, X20-29; *Unspecified* T50, T65, X69, Y14, Y19, X44, X49, F19.

Descriptive data were presented as median, IQR, count, or proportions. Comparative analysis was performed with a Kruskal-Wallis' and Pearson's χ^2 -tests. A p-value of ≤0.05 was considered significant. A logistic regression analysis for mortality was performed, which included sex, cause of OHCA, location of OHCA, witness status, initial rhythm, and bystander-CPR with OR and CI presented in a forest plot.

3.4.3 Study IV

Adult patients with an ICD-10-code for poisoning (T36-T65 + F10, 11, 12, 13, 14, 15, 16, 17, 18, 19, T96-T97, X20-29, X40-X49, X60-X69, X76, Y10-19) as primary cause of death in the CDR between 1th January 2000 to 31th December 2021 were included. Patients were matched to the NFD for additional information. Variables collected were age, sex, date of death, place of death, autopsy type, ICD-10 codes in the CDR, and results from forensic examination and toxicological testing including substances and concentrations. The ICD-10 codes used for the different groups were: *Poisoning* T36-T65, F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, X20-29, X40-49, X60-69, X76, Y10-19. The ICD-10 codes used for the different subdivision according to substance were: *Drugs (pharmaceutical or illicit)* T36-49, X60-64, Y10-13, X40-43, F11-17; *Alcohols* F10, X65, T51, Y15, X45; *Solvents, pesticides, corrosive substances, detergent* T52-57, T60, X66, X68, Y18, X46, X48, F18; *Smoke/carbon monoxide* T58-59, X67, Y17, X47, X76; *Animals, plants, food* T61-64, X20-29; *Unspecified* T50, T65, X69, Y14, Y19, X44, X49, F19.

Descriptive data were presented as median, IQR, count, or proportions. Comparative analyses were made with χ^2 and Wilcoxon's tests. A p-value of ≤0.05 was considered significant.

4 Results

4.1 Study I

During the two-year study period 8,155 ICU admissions of 6,730 unique patients were registered. They constituted 21% of all patients seeking medical care in the ED and 10.5% of all ICU admissions. The study population's median age was 38 years, there was an equal number of men and women and 46.5% of them had a previous hospital admission due to poisoning, see Table 2.

There were 30.5% classified as unconscious upon arrival to the ICU (GCS 8 or lower/RLS 4 or higher), 14.6% received invasive ventilation with a median treatment time of 13h, 1.2% received dialysis with a median time of 42:15h, and their median length of stay (LOS) was 14:30h, see Table 2. A combination of multiple drugs was most commonly used by the patients (29.7%). Unspecified (16.5%), sedatives/hypnotics/ antiepileptics (16.2%), and ethanol (15%) were also common, see Table 3.

Table 2. Description of the 8,155 cases of ICU admitted poisonings.

Variable	**% (n)**
Age, median *(IQR)*	38 *(26-51)*
Female	49.4 (4030)
Previous known poisoning	46.5 (3790)
Unconscious on arrival to ICU*	30.5 (2490)
Invasive ventilation	14.6 (1194)
Dialysis	1.2 (99)
Electroencephalogram	0.9 (71)
LOS ICU, median hh:mm *(IQR)*	14:30 *(9:00-22:45)*
SAPS3**, median *(IQR)*	40 *(34–49)*
In-hospital mortality	1.6 (128)
30-day mortality	2.7 (222)

*GCS 8 or below, RLS 4 or above.
**Simplified Acute Physiology Score

Table 3. Categorisation of suspected poisoning substances among the 8,155 cases.

Group of poisoning substance		**% (n)**
Antidepressants/antipsychotics/neuroleptics		3.4 (283)
Alcohols	Ethanol	15 (1221)
	Other toxic alcohols	0.4 (29)
	Unspecified	1.6 (127)
Sedatives/hypnotics/antiepileptics		16.2 (1318)
Analgesics, non-opioid		2.3 (186)
Narcotics		8.0 (652)
Substances with non-medical use (food, animals, others)		4.1 (336)
Miscellaneous*		2.9 (235)
Mixed substances from two or more categorie		29.7 (2424)
Unspecified		16.5 (1344)

*Include all drugs not included in the other categories, e.g., insulin, anticoagulation, and allergy medicines.

The in-hospital mortality was 1.9% and among the deceased the median age was 61 years and there were significantly more men (67.1%) (p <0.01). For 78.3% of the deceased this was their first recorded admission due to poisoning. The 30-day mortality was 2.7% and also included significantly more men (65.3%) (p <0.01). Variables most associated with in-hospital mortality were invasive ventilation, age >40 years, and no previous registered poisoning. See Table 4.

Table 4. Association between in-hospital mortality and five clinical variables.

Variable	**p**	**OR**	**95% CI**
Invasive ventilation	<0.001	6.91	4.59-10.42
Age >40 years	<0.001	4.54	2.86-7.21
No previous poisoning	<0.001	3.23	2.06-5.07
Unconsciousness	0.016	1.66	1.10-2.53
Male sex	0.008	1.68	1.15-2.47

4.2 Study II

Study II included the same population as study I, but only unique patients were included (N=6,730). Their one-year mortality was 4.5%, with a median age of 54 years and there were significantly more men (59.1%) (p <0.002), at their ICU admission time. The study population had nine times higher one-year mortality compared to the general public at the time, when age-adjusted the largest difference was seen among women aged 19-39 years. The women between 19-39 years had a 50 times higher one-year mortality compared to the general population of the same age at the time. See Table 5.

Table 5. **Mortality** *and age-matched mortality for men/women among different age groups.*

Age group	**Mortality** *(Age matched mortality), %*		
	Total	Women	Men
19-39	**2.4** *(0.05)*	**1.5** *(0.03)*	**3.1** *(0.07)*
40-59	**4.2** *(0.21)*	**2.7** *(0.17)*	**5.6** *(0.25)*
60-79	**10.4** *(1.40)*	**10.2** *(1.14)*	**10.4** *(1.66)*
80-	**23.***1 (8.95)*	**24.3** *(8.09)*	**20.8** *(10.15)*
Total	**4.5** *(0.48)*	**3.8** *(0.48)*	**5.2** *(0.49)*

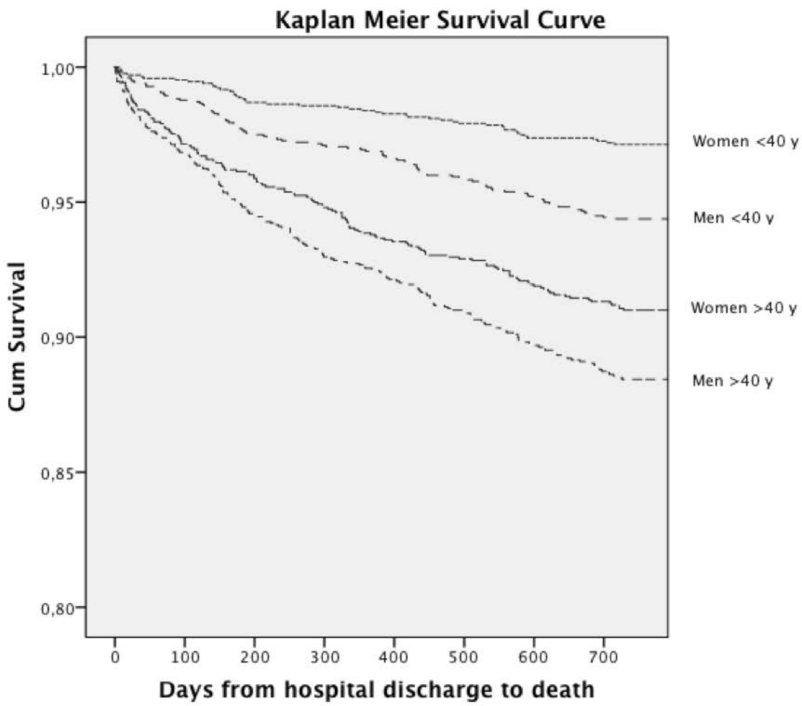

Figure 1. Kaplan Meier survival curve from hospital discharge.

The most common cause of death within one year from hospital discharge was "suicide and/or accident" (50.5%). There was an apparent difference between age groups with the older patients' deaths more often classified as cardiovascular whilst i.e., in the group 19-39 years "suicide/accident" caused 94% of the deaths of which 70% were due to a new poisoning, see Table 6. The two-year mortality was 7.2%, and successively increasing for older men. See Figure 1.

Table 6. Cause of death among all deceased patients within one year from hospital discharge.

Category	**Age group, % (n)**				
	19-39	**40-59**	**60-79**	**80-**	**Total**
Suicide/accident *-poisoning* *-hanging/drowning/ traffic/weapon*	97.0 (78) *-69.9 (58)* *-24.1 (20)*	61.0 (58) *-44.2 (42)* *16.8 (16)*	18.2 (16) *-12.5 (11)* *-5.7 (5)*	2.7 (1) *-2.7 (1)* *-0 (0)*	50.5 (153) *-37.0 (112)* *-13.5 (41)*
Cardiovascular	1.2 (1)	7.4 (7)	28.4 (25)	43.2 (16)	16.2 (49)
Respiratory	0 (0)	2.1 (2)	14.8 (13)	2.7 (1)	5.3 (16)
Infection	1.2 (1)	7.4 (7)	11.4 (10)	10.8 (4)	7.3 (22)
Neurological	0 (0)	1.0 (1)	0 (0)	0 (0)	0.3 (1)
Abdominal	0 (0)	11.6 (11)	11.4 (10)	13.5 (5)	8.6 (26)
Other/multiple	1.2 (1)	3.2 (3)	11.4 (10)	16.2 (6)	6.6 (20)
Unspecific	2.4 (2)	6.3 (6)	4.5 (4)	10.8 (4)	5.3 (16)

4.3 Study III

There were 71,895 OHCA in SRCR during the study period and of them 66,261 patients had a valid personal identification number and a hospital admission and/or a cause of death registered. Of these 89% were classified as medical and 11% as non-medical OHCA. Of the non-medical OHCA, 47% were considered to be caused by poisoning, which represents 5.2% of all OHCA.

All the included OHCA had a median age of 73 years and 65.8% were men. The patients with an OHCA caused by poisoning had a median age of 43 years, significantly lower than the other groups, and 67% were men, see Table 7. The OHCA caused by either poisoning or medical cause occurred significantly more often at home than non-medical OHCA. OHCA caused by poisoning had the lowest frequency of witnessed CA and shockable rhythm, shown in Table 7.

Table 7. Description of patients and out of hospital cardiac arrest caused by medical-, non-medical- or poisoning cause.

Characteristic	Poisoning, N = 3,453[1]	Non-Medical, N = 3,882[1]	Medical, N = 58,926[1]	p-value[2]
Age				<0.001
Median (IQR)	43 (30, 57)	56 (37, 72)	75 (66, 83)	
Missing	313	115	4,203	
Sex				<0.001
Men	2,311, (67%)	2,767, (71%)	38,548, (66%)	
Women	1,136, (33%)	1,103, (29%)	20,224, (34%)	
Missing	6	12	154	
Location				<0.001
Home	2,440, (74%)	1,680, (45%)	41,303, (74%)	
Public	400, (12%)	1,554, (42%)	8,107, (14%)	
Other	455, (14%)	490, (13%)	6,592, (12%)	
Missing	158	158	2,924	
Witnessed				<0.001
Yes	1,032, (32%)	1,497, (41%)	38,963, (68%)	
Missing	182	234	2,038	
Rhythm				<0.001
VT/VF	409, (14%)	711, (21%)	22,487, (43%)	
PEA/Asystole	2,499, (86%)	2,614, (79%)	29,294, (57%)	
Missing	545	557	7,145	
BystanderCPR				<0.001
Yes	1,847, (57%)	1,888, (52%)	29,982, (54%)	
Missing	215	222	3,787	
Mortality				<0.001
Alive	563, (16%)	242, (6.2%)	7,082, (12%)	
Dead	2,890, (84%)	3,640, (94%)	51,844, (88%)	
Missing	0	0	0	

[1] n, (%)

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Of the OHCA caused by poisoning 22% had a single-substance poisoning and when considering only the first registered poisoning-diagnosis in the registers, the most common substance was drugs (pharmaceutical or illicit), see Table 8.

Table 8. Poisoning population subdivided by substance.

Category	**% (n)**
Drugs (pharmaceutical or illicit)	51 (1751)
Alcohols	15 (531)
Solvents, pesticides, corrosive substances, detergent	3 (114)
Smoke/carbon monoxide	4 (150)
Animal, plants, food	1 (29)
Unspecified	25 (878)

The crude 30-day mortality for OHCA caused by poisoning was 84%, lower than the corresponding mortality in the medical and non-medical groups of OHCA. In the adjusted analyses female sex, bystander-CPR, non-shockable rhythms (compared to shockable), medical or non-medical cause (compared to poisoning) were associated with higher mortality, shown in Figure 2.

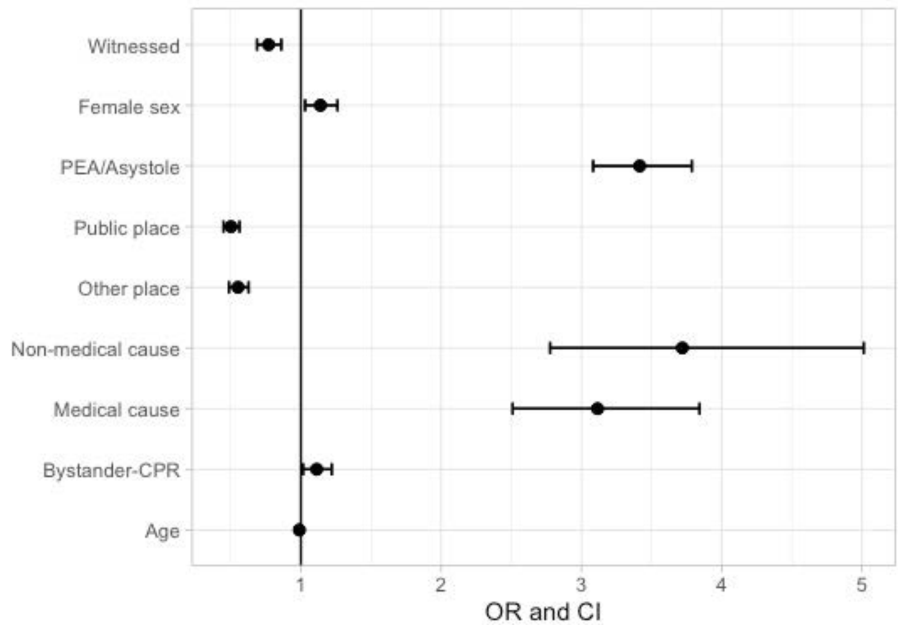

Figure 2. Forest plot of adjusted odds ratios with confidence intervals for 30-day mortality, comparing key variables in OHCA including cause (poisoning vs. medical or non-medical).

4.4 Study IV

There were 27,057 deaths due to poisoning in Sweden during the 22-year long study period, making it in average of 1230 per year. During this time 2,018,495 people died in Sweden, making poisoning the cause for 1.3% of annual deaths. The median age of those who died due to poisoning was 53 years and 70% were men. The majority (52%) died in a private home and 87% underwent some sort of clinical or forensic post-mortem examination. See Table 9.

Table 9. Characteristics of patients deceased by poisoning.

Characteristic	**Overall**, N = 27,057[1]	**Men**, N = 18,838[1]	**Women**, N = 8,219[1]	**p-value**[2]
Age	53 (18, 103)	52 (18, 99)	55 (18, 103)	<0.001
Place				<0.001
Hospital	11%	10%	12%	
Service home	5.1%	5.5%	4.2%	
Private home	52%	51%	55%	
Other	8.2%	9.1%	6.1%	
Unknown	24%	24%	23%	
Autopsy				<0.001
Clinical	1.3%	1.4%	1.1%	
Extensive forensic	0.6%	0.5%	0.7%	
Forensic	85%	84%	87%	
None	13%	14%	12%	

[1]Median (Range); %

[2]Wilcoxon rank sum test; Pearson's Chi-squared test

The most common causes of death were drugs (pharmaceutical or illicit) or alcohol. According to the ICD-10-codes synthetic narcotics, opioids, or heroin caused most deaths, followed by acute alcohol use. Shown in Table 10.

Table 10. ICD-10-codes for cause of death.

Poisoning group	% (n)	Most common ICD-10-codes, % (n)		
Drugs (pharmaceutical or illicit)	46 (12,448)	**T40.4** 15.5 (1,927)	**T40.2** 11.4 (1,416)	**T40.1** 9.4 (1,176)
Alcohols	33.4 (9,056)	**F10.2** 46.2 (4,188)	**T51.0** 22.6 (2,048)	**F10.1** 15.3 (1,390)
Solvent, pesticides, corrosive substances, detergent	0.4 (98)	**T52.8** 53.1 (52)	**T57.3** 10.2 (10)	**T52.0** 8.2 (8)
Smoke/carbon monoxide	3.8 (1,015)	**T58.0** 92.8 (942)	**T59.8** 3.4 (35)	**T30.0** 2.2 (22)
Animals, plants, food	0.1 (26)	**T63.4** 96.1 (25)	**T63.8** 3.9 (1)	
Unspecified	16.3 (4,414)	**T40.2** 20.2 (892)	**T40.4** 17.6 (779)	**T50.9** 10.9 (483)

For 83% (n=22,550) of the patients toxicologic test results were available. The analysis found 396 unique substances in 100,984 positive tests of the deceased patient's femoral blood. The patients had between 1-21 substances, median 4. The most common substances were ethanol, zopiclone, and nordazepam. When grouping the substances found, the most common were sedative/antiepileptics (35.2%) followed by antidepressant/neuroleptic (17.9%) and opioid (17.1%). See Table 11 and 12.

Table 11. The 20 most common substances (and metabolites) and their min-max and median concentration found per gram femoral blood.

Substance	Found in % (n) of patients	Median concentration	Min-max concentration
Ethanol	50.4 (11,368)	1.8 ‰	0.1-2323 ‰
Diazepam *Nordazepam*	17.1 (3858) (453) *(3405)*	0.12 µg *0.15 µg*	0.03-13 µg *0.03-7 µg*
Zopiclone	15.4 (3479)	0.13 µg	0.01-19 µg
Morphine *Etylmorphine*	14.6 (3291) (3063) *(228)*	0.14 µg *0.265 µg*	0.005-36 µg *0.005-3.5 µg*
Paracetamol	14.5 (3263)	13 µg	1.0-1650 µg
Propiomazine *Dihydropropiomazine*	12.8 (2892) (14) *(2878)*	0.1 µg *0.17 µg*	0.03-96 µg/ *0.03-47 µg*
Alprazolam	12.4 (2786)	0.04 µg	0.002-7.5 µg
Codeine *Dihydrocodeine*	12.0 (2701) (2695) *(6)*	0.03 µg *0.009 µg*	0.005-46 µg *0.005-31.0 µg*
Alimemazine *Desmethylalimemazine*	11.0 (2477) (911) *(1566)*	0.4 µg *0.3 µg*	0.02-39 µg *0.05-14 µg*
Citalopram *Desmethylcitalopram*	8.8 (1975) (593) *(1382)*	0.4 µg *0.1 µg*	0.05-46 µg *0.02-8 µg*
Carbon monoxide	8.7 (1970)	59 %	0.5-87 %
Mirtazapine *Desmetylmirtazapine*	8.2 (1847) (609) *(1238)*	0.19 µg *0.08 µg*	0.01-46 µg *0.01-6.4 µg*
Amphetamine	8.2 (1843)	0.4 µg	0.02-98 µg
Tramadol *O-desmethyltramadol*	7.6 (1715) (515) *(1200)*	1.8 µg *0.4 µg*	0.05-119 µg *0.02-18.0 µg*
Pregabalin	7.5 (1694)	7.5 µg	0.55-559 µg
Clonazepam *7-amino-clonazepam*	7.5 (1692) (1) *(1691)*	0.01 µg *0.09 µg*	0.005-0.5 µg *0.005-4.8 µg*
Methadone	6.0 (1343)	0.4 µg	0.05-10.0 µg
Oxycodone	5.7 (1293)	0.2 µg	0.005-83.0 µg
Tetrahydrocannabinol *Tetrahydrocannabinol acid*	5.7 (1281) (1273) *(8)*	0.001 µg *0.003* µg	0.0003-0.25 µg *0.001-0.006 µg*
Zolpidem	5.6 (1275)	0.25 µg	0.02-15.0 µg

Table 12. The most common groups of substances found in deceased patients.

Group	**Found in % of samples (of 100,984)**
Sedative/antiepileptic	35.2
Antidepressant/neuroleptic	17.9
Opioid	17.1
Alcohols	11.7
Illicit drugs	5.0
Other	4.8
Analgesics	3.8
Cardiovascular	2.6
Carbon monoxide	2.0

Figures 3-7 shows the median age to have been between 50-56 years during the 22-year study period. Men have always been more frequently represented in deaths due to poisoning, with a peak during 2014-2020. Forensic autopsies have always been the most common type of autopsy in deaths by poison. The number of substances found in post-mortem femoral blood has generally increased during the study period and the presence of opioids, antidepressant/neuroleptic, and sedative/antiepileptic has increased substantially in recent years.

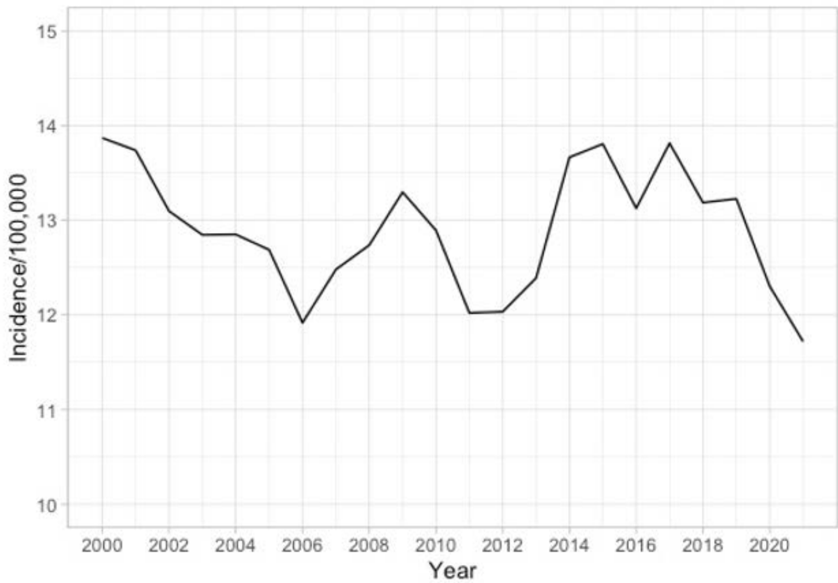

Figure 3. Incidence of poisonous deaths per year.

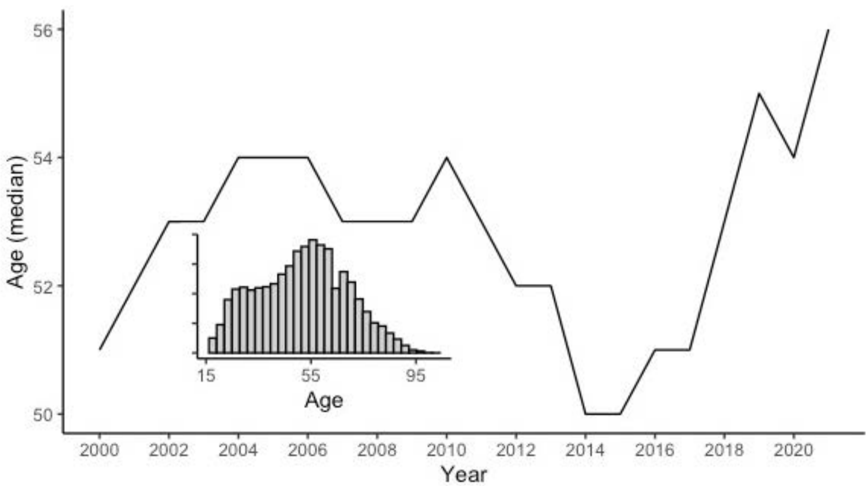

Figure 4. Median age over time and inset of distribution of ages across study period.

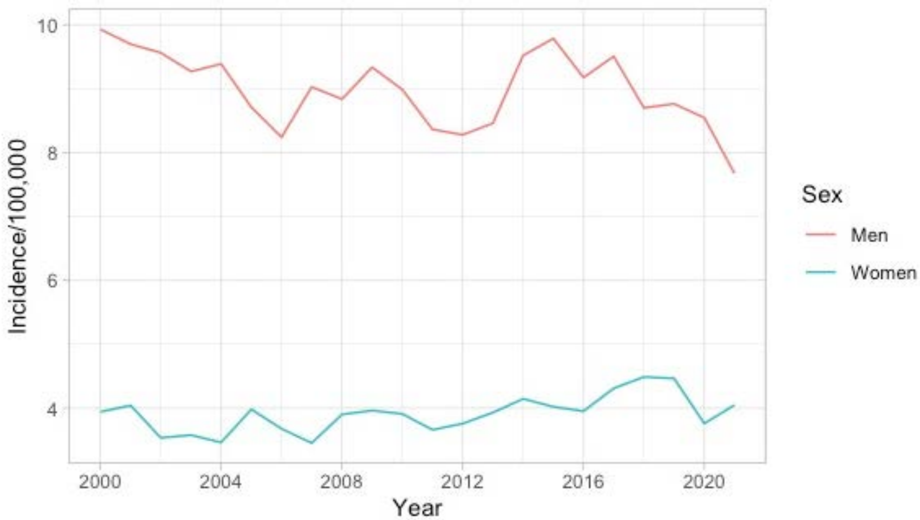

Figure 5. Incidence of sex per year.

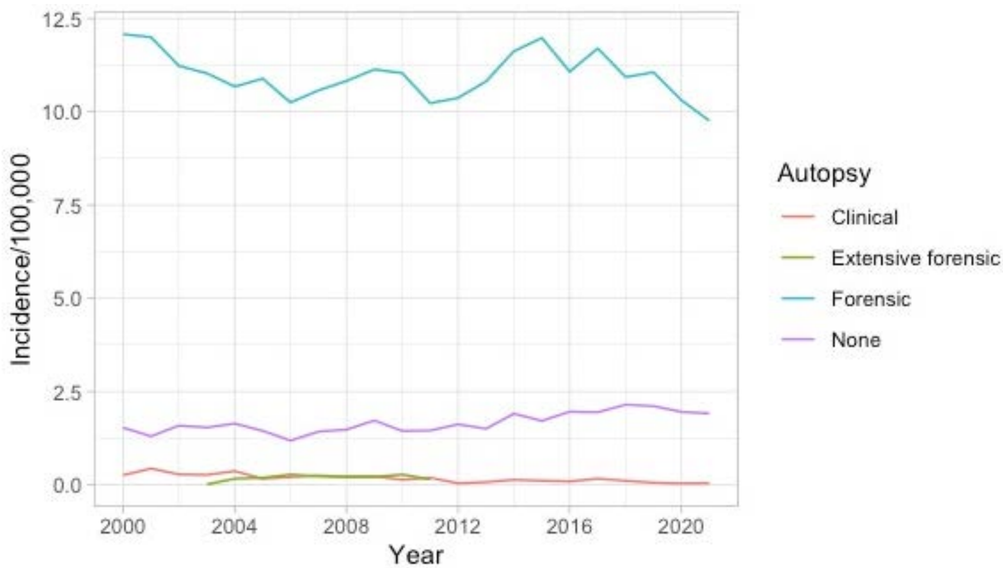

Figure 6. Incidence of autopsy type per year.

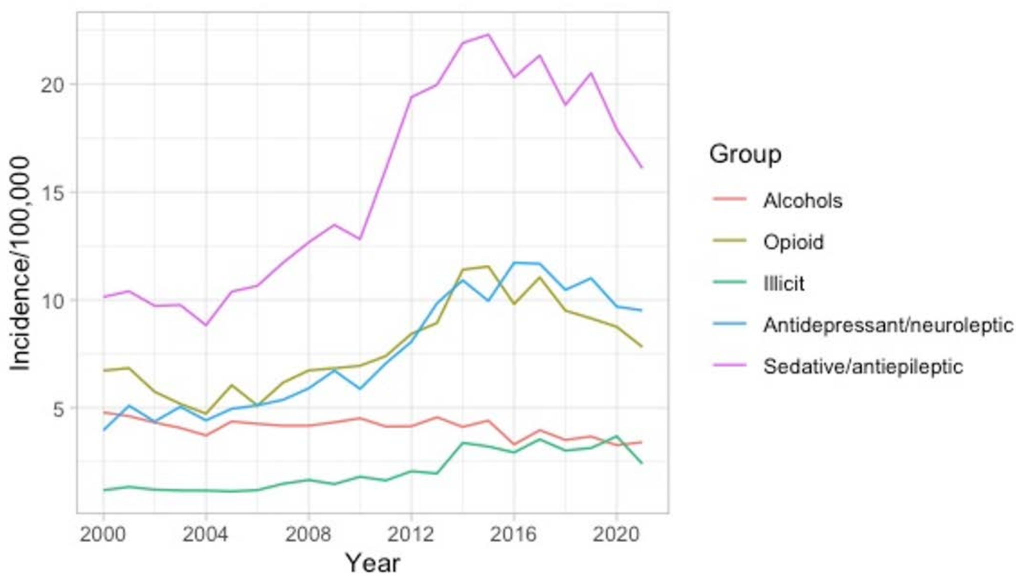

Figure 7. Incidence of substances found in femoral blood of deceased patients over time.

5 Discussion

5.1 Register based research

Register based research is widely used nowadays. In the Nordic countries the increase in the field started in the 1960s with the expansion of a more secure unique personal identification number.[79] There are several strengths with register based research, the volume of data being one large advantage which increases the likelihood of a diverse study population with less bias and higher internal and external validity.[78,79] The ability to link registers via the personal identification numbers has enabled even wider datasets and given rise to the possibility of tracing individuals over a long period of time and with different aspects.[80] The use of register data is also very time and cost-effective compared with researchers repeatedly collecting data themselves.[78,79] The possibility of using registers in research is limited by some circumstances, and the major limitation to a register is the quality of data in it. Some registers are lacking data or have incomplete data.[78] The data is often manually registered and done so by different people in different parts of the country, potentially creating risk for errors or incoherent registrations, and differential misclassifications. Another limitation is that not all variables needed for a specific study might be available because data is pre-collected, making it potentially hard to adjust for some confounders. Additionally, only associations can be found within register based observational data and not causality.[79] The validity of a register might be assessed by completeness and quality of variables included, that is, if all and correct information is registered for an individual in the register.

The registers used in this thesis are presented in the method section, and include NPR, CDR, SIR, SRCR, and NFD. In summary, the NPR and CDR are national mandatory registers since 1987 and 1961. Both are considered to have near 100% coverage, few missing data, and high quality.[58,60] SIR is a non-profit national register that has had a minimum of 91% coverage of all Swedish ICU admissions when study I and II were performed, and now almost 100% coverage. For the most common intensive care treatments, mechanical respiratory support and dialysis, the coverage is over 90%.[81] SRCR is also a non-profit national register and 100% of EMS-providers report to the register. When validated however, up to 25% of OHCA are missed, and some selection bias is likely to be found.[62] Also, the quality of the variables varies since there are many variables to report and these are collected in a stressful situation by the EMS personnel and registered afterwards.[63] The NFD collects all information on forensic examinations since 1992 and since a forensic examination follows a predetermined protocol and the same variables are collected from each examination, the missing values could be low but exact numbers are not reported.

The data disclosed from registers held by the Swedish National Board of Health and Welfare, SIR, and SRCR are handled by statisticians, which is likely to minimise mistakes in disclosure. The main concern for registers used in the thesis is the registration of data into the register. For SIR and SRCR, data input is carried out by different people, with different education and experiences, all over the country. For NPR and CDR variables can be collected automatically from patients' electronic health records at hospitals (for example admission times and discharge diagnosis) and from cause of death certificates, often based on clinical assessment instead of autopsy. Coding errors and manual mistakes might have affected the results of studies included in the thesis since the included populations are selected from ICD-10 codes often registered by clinicians or medical secretaries.

5.2 Intensive care

Intensive care requires a lot of resources in the healthcare system, due to the high level of competent and adequate staffing, along with expensive technical equipment. In Sweden, intensive care is estimated to cost between 50,000-80,000 SEK per day per patient.[66] In Europe the availability of ICU and high-dependency unit beds is on average 11.5 per 100,000 inhabitants. Sweden has the second lowest number of ICU beds per 100,000 inhabitants in Europe (5.8). Only Portugal has fewer, and Germany has five times more beds per capita than Sweden.[67] According to study I in the thesis, every tenth patient in the ICU is admitted due to poisoning which implies the admission of approximately 4,000 patients each year with a median LOS of 14,5h - thereby representing a cost of around 120-190 million SEK per year.

The most common reason for ICU admission for patients admitted due to poisoning is observation, mainly of the airway/breathing and circulatory system including blood pressure, heart rate, and ECG.[27,28] In study I 30.5% of patients were assessed to be unconscious, upon arrival 14.6% received mechanical ventilation, and 1.2% dialysis. Accordingly, almost 2/3 admitted patients did not have nor developed a real indication for intensive care. According to an Australian study, only 8% of patients admitted due to poisoning who did not have a specific intensive care treatment ongoing upon arrival developed the need for ICU treatment during their stay[28], and in the Netherlands only 6.5% of ICU admitted poisoned patients developed a need for intensive care specific treatment.[32] In summary, Sweden has a very low availability of ICU beds and a high frequency of poisoned patients that may not need intensive care. There is an urgent need for a safe prediction model for development of the need for intensive care specific treatments for poisoned patients to optimise resource utilisation.

5.3 Death, autopsy, and long-term prognosis

A finding in study IV was that approximately 1,200 people die each year in Sweden because of a poisoning, and the excess long-term mortality of patients previously treated for poisoning in the ICU was shown in study II, where women aged 19-39 years had a 50 times increased one-year mortality compared to the general population. These women most often died from suicide or accident rather than somatic illness. Furthermore, study III showed that over 5% of OHCA are caused by poisoning. These are young patients with higher survival rates than other OHCA's. The increased long-term mortality is corroborated by a study from Norway where increased long-term mortality was seen for patients with previous poisoning for up to 20 years, and those with the highest risk of death were under 30 years at discharge, belonged to a lower social group, had a history of illicit drug abuse, and presented with a lower level of consciousness upon hospital arrival.[55] A Swedish study of poisoned patients admitted due to poisoning and presenting unconscious (GCS <10) to the ED found a 100 times increased one-year mortality compared to the general population of the same age.[26] Other studies have also shown that patients hospitalised due to poisoning who had taken illicit "street drugs" had the highest two-year mortality, and that all-cause mortality after poisoning increased significantly, especially for accidents and suicides.[24,68] The patients previously treated in the ICU for poisoning accounts for a substantial part of preventable deaths in young people, and should perhaps be the target population for more intensive suicide prevention and psychiatric treatment.

A clear majority of patients who died due to poisoning were autopsied (87%). This number should however probably be close to 100% since the Swedish law states that all unnatural deaths (suspected to be caused by suicide, homicide, or accident) should be reported to the police who decides if a forensic examination is to be performed[58], in other cases there should at least be a regular autopsy. There is a large difference between the clinically suspected diagnosis when compared to autopsy results, in part due to the fact that the panorama of, especially illicit, substances used in poisoning is changing rapidly. In addition, the fact that a lot of poisoning symptoms could be masked as other diseases implies that the use of toxicology testing should possibly be further extended in death investigations.[69-71]

5.4 Preventive measures

Study IV showed that heroin, other opioids, and synthetic narcotics were the most common causes of death in patients who died due to poisoning, and also that ethanol was found in the blood of 50% of these patients. The way to lower the number of poisonings (and death by poisoning) is to limit access to poison, comparable to the situation where limiting access to firearms decreases suicide by firearm[72] or speed control lowering traffic accidents. A very clear example of success in this area is the restriction of import and sales of some of the most toxic organophosphates in Sri Lanka in 1995, which has substantially decreased the number of deadly poisonings in the country. Importantly, these measures were not associated with an increase in other methods of suicide.[72,73] A number of preventive measures have successfully been made in Sweden as well: tricyclic antidepressant and MAO-inhibitors have largely been replaced with the less toxic SSRI, benzodiazepines have replaced barbiturates, toxic malaria medicines are less common, and the opioid dextropropoxyphene involved in many deaths was banned in 2011. There have also been other successful methods in access reduction, such as both the improvement in car catalytic converters and the switch from coal gas to natural gas as means to reduce carbon monoxide content.[72]

Some poisonous substances are despite posing a substantial threat to public health and causing significant morbidity and mortality still easily available to the public, such as paracetamol and ethanol. Ethanol consumption is linked to over 200 diseases and health issues, such as hypertension, several types of cancer, mental health issues including increased risk of suicide, accidents, and crime.[74] Regulation of availability, pricing, legal drinking age, and advertisement have decreased the alcohol consumption but much can still be done to reduce access to this poison.[74] Paracetamol poisoning is a major cause of liver transplants in western countries, and this substance is sold prescription free at pharmacies.[75] The balance between availability and restriction of hazardous substances has been a long standing debate in the society, with considerations taken to both use of common community assets (such as healthcare resources) and the individual's right to choose what to put in his or her body.

Another way to reduce poisonings is to improve treatment of mental health diseases and alcohol or drug misuse.[73] Education among those who meet and treat most patients, for example those who work in primary care, certain medical and surgical specialties, to increase diagnostics and thereby treatment have for example had good results.[72,76] More intense and targeted suicide prevention might be indicated for patients who have required hospital or ICU treatment for a poisoning. Community efforts targeting drug abusers may also be effective in reducing deaths due to poisoning, special injection facilities where drug users can use drugs supervised under more safe and hygienic conditions are available in several European countries.[72] The take-home-Naloxone programs, where drug addicts and friends and families are trained in overdose symptom recognition and usage of the opioid antidote Naloxone, aim to prevent out-of-hospital poisoning deaths.[72] And, although leakage from the medical-assisted treatment of opioid addiction is the main source of illegally distributed methadone and buprenorphine, the programs have been shown to reduce morbidity and mortality among opioid addicts.[77-79]

5.5 Future research

This thesis has increased knowledge about victims of poisoning in Sweden, but has also highlighted several areas that need further research. One main area is prediction of which patients suffering from poisoning will develop a need for intensive care versus those who will be fine in a more observational setting. There is an ongoing large multicenter study conducted from the poisoning center in the Netherlands, which Sweden is participating in, which aims to create a prediction model of need for intensive care specific interventions among patients admitted due to poisoning. The study is called “INTOXICATE” and the investigators have just finished the data collection phase.

Treatment studies of patients admitted due to poisoning are difficult since controlled exposure is highly unethical, the effects and treatment of different poisoning substances will continue to be mainly observational. Studies concerning more accurate diagnosis could however be relevant, both in-hospital and post-mortem. There are perhaps more deaths caused by clinically unnoticed poisoning, or perhaps iatrogenic in-hospital poisonings than previously known. The toxicological testing could be further developed and the frequency of autopsies increase. Another main area for continued research is in the psychiatric field, regarding poisonings this concerns most suicide/self-harm prevention research.

To further gather information on these patients, to increase knowledge, and to increase the opportunity to perform research to benefit the population a national poisoning register could possibly benefit these patients. No such register exists at the moment, the closest thing is perhaps the information the Swedish Poisons Information Center (Giftinformationscentralen) saves on cases they are involved in, this could however be combined with registration from in-hospital care to form a more complete register of Swedish poisonings.

6 Conclusions

This thesis, comprised of four national register based cohort studies, aimed to increase knowledge about patients suffering from severe poisoning in Sweden and from the studies included the following conclusions are drawn:

- Every fifth patient seeking medical care for poisoning in Sweden is admitted to an ICU. A mix of several substances is the most common poisoning agent, and almost half of the patients had a previous hospitalisation for poisoning. The ICU-mortality is low (1.9%) and correlated to invasive ventilation, age >40 years, male sex, and no previous hospitalisation for poisoning.

- After discharge from an ICU treated non fatal poisoning the long-term mortality (one and two years) is markedly increased. Patients between 19-39 years have an almost 50 times increased one-year mortality compared to age matched controls, and a clear majority died from a new poisoning.

- OHCA caused by poisoning is very common among non-medical cardiac arrests. These patients are younger, more often male, and more often have several unfavorable factors for survival yet still have higher 30-day survival than OHCA by other causes.

- Poisoning causes 1.3% of all deaths in Sweden. Men in their fifties are the most common victims and their deaths are often caused by synthetic narcotics, other opioids, or alcohol. The forensic autopsy frequency is lower than expected for poisonous deaths. Temporal trends show an increase in opioids, antidepressants/neuroleptics, and sedative/antiepileptic substances in patients who died around 2014-2017.

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8 References

1. Charitos IA, Gagliano-Candela R, Santacroce L, Bottalico L. Venoms and Poisonings during the Centuries: A Narrative Review. *Endocr Metab Immune Disord Drug Targets*. 2022;22(6):558-570.

2. Neal M. Nature's Toxic Gifts: The Deadly Story of Poison. Accessed 2024: https://www.popularmechanics.com/science/health/a34100092/history-of-poison/

3. WHO. Poisoning. Accessed 2024: https://www.who.int/environmental_health_emergencies/poisoning/en/

4. NHS UK. Health A to Z. Accessed 2024: https://www.nhs.uk/conditions/poisoning/

5. Online etymology dictionary. Poison. Accessed 2024: https://www.etymonline.com/word/poison

6. Holstege CP, Borek HA. Toxidromes. *Crit Care Clin*. Oct 2012;28(4):479-98.

7. Nepovimova E, Kuca K. The history of poisoning: from ancient times until modern ERA. *Arch Toxicol*. Jan 2019;93(1):11-24.

8. Watson KD. Poisoning Crimes and Forensic Toxicology Since the 18th Century. *Acad Forensic Pathol*. Mar 2020;10(1):35-46.

9. Szinicz L. History of chemical and biological warfare agents. *Toxicology*. Oct 30 2005;214(3):167-81.

10. Ciottone GR. Toxidrome Recognition in Chemical-Weapons Attacks. *N Engl J Med*. Apr 26 2018;378(17):1611-1620.

11. The National Board of Health and Welfare. Statistics on emergency department, waiting periods and visits 2022. Accessed 2024: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2023-9-8704.pdf

12. The Swedish Poisons Information Center. "About Swedish poisons information centre". Accessed 2024: https://giftinformation.se/om-giftinformationscentralen-avd/om-giftinformationscentralen/

13. Hendrix L, Verelst S, Desruelles D, Gillet JB. Deliberate self-poisoning: characteristics of patients and impact on the emergency department of a large university hospital. *Emerg Med J*. Jan 2013;30(1):e9.

14. Yaylaci S, Genc AB, Demir MV, Cinemre H, Tamer A. Retrospective evaluation of patients at follow-up with acute poisoning in Intensive Care Unit. *Niger J Clin Pract*. Mar-Apr 2016;19(2):223-6. doi:10.4103/1119-3077.164340

15. Beaune S, Juvin P, Beauchet A, Casalino E, Megarbane B. Deliberate drug poisonings admitted to an emergency department in Paris area - a descriptive study and assessment of risk factors for intensive care admission. *Eur Rev Med Pharmacol Sci*. 2016;20(6):1174-9.

16. Cook R, Allcock R, Johnston M. Self-poisoning: current trends and practice in a U.K. teaching hospital. *Clin Med (Lond)*. Feb 2008;8(1):37-40.

17. The Swedish Civil Contingency Agency. Förgiftningar 2014. Accessed 2024: https://www.msb.se/RibData/Filer/pdf/27456.pdf

18. Avsarogullari L, Senol V, Akdur O, Akin A, Durukan P, Ozkan S. Characteristics of acute adult poisonings in a university hospital emergency department in central Turkey: a three-year analysis. *J Pak Med Assoc*. Feb 2012;62(2):129-33.

19. Kristinsson J, Palsson R, Gudjonsdottir GA, Blondal M, Gudmundsson S, Snook CP. Acute poisonings in Iceland: a prospective nationwide study. *Clin Toxicol (Phila)*. Feb 2008;46(2):126-32.

20. Hawton K, Bergen H, Casey D, et al. Self-harm in England: a tale of three cities. Multicentre study of self-harm. *Soc Psychiatry Psychiatr Epidemiol*. Jul 2007;42(7):513-21.

21. Buckley NA, Whyte IM, Dawson AH, Isbister GK. A prospective cohort study of trends in self-poisoning, Newcastle, Australia, 1987-2012: plus ça change, plus c'est la même chose. *Med J Aust*. May 4 2015;202(8):438-42.

22. Heyerdahl F, Bjornas MA, Hovda KE, et al. Acute poisonings treated in hospitals in Oslo: a one-year prospective study (II): clinical outcome. *Clin Toxicol (Phila)*. Jan 2008;46(1):42-9.

23. Lund C, Drottning P, Stiksrud B, et al. A one-year observational study of all hospitalized acute poisonings in Oslo: complications, treatment and sequelae. *Scand J Trauma Resusc Emerg Med*. Jul 24 2012;20:49.

24. Brandenburg R, Brinkman S, de Keizer NF, Meulenbelt J, de Lange DW. In-hospital mortality and long-term survival of patients with acute intoxication admitted to the ICU. *Crit Care Med*. Jun 2014;42(6):1471-9.

25. Forsberg S, Hojer J, Ludwigs U. Prognosis in patients presenting with non-traumatic coma. *J Emerg Med*. Mar 2012;42(3):249-53.

26. Forsberg S, Hojer J, Ludwigs U. Hospital mortality among poisoned patients presenting unconscious. *Clin Toxicol (Phila)*. Apr 2012;50(4):254-7.

27. Wilhelms SB, Wilhelms DB. Emergency department admissions to the intensive care unit - a national retrospective study. *BMC Emerg Med*. Oct 23 2021;21(1):122.

28. Athavale V, Green C, Lim KZ, Wong C, Tiruvoipati R. Characteristics and outcomes of patients with drug overdose requiring admission to Intensive Care Unit. *Australas Psychiatry*. Oct 2017;25(5):489-493.

29. Maignan M, Pommier P, Clot S, et al. Deliberate drug poisoning with slight symptoms on admission: are there predictive factors for intensive care unit referral? A three-year retrospective study. *Basic Clin Pharmacol Toxicol*. Mar 2014;114(3):281-7.

30. Savage M, Kung R, Green C, Thia B, Perera D, Tiruvoipati R. Predictors of ICU admission and long-term outcomes in overdose presentations to Emergency Department. *Australas Psychiatry*. Feb 2020;28(1):75-79.

31. Novack V, Jotkowitz A, Delgado J, et al. General characteristics of hospitalized patients after deliberate self-poisoning and risk factors for intensive care admission. *Eur J Intern Med*. Nov 2006;17(7):485-9.

32. Brandenburg R, Brinkman S, de Keizer NF, Kesecioglu J, Meulenbelt J, de Lange DW. The need for ICU admission in intoxicated patients: a prediction model. *Clin Toxicol (Phila)*. Jan 2017;55(1):4-11.

33. Fernando SM, Reardon PM, Ball IM, et al. Outcomes and Costs of Patients Admitted to the Intensive Care Unit Due to Accidental or Intentional Poisoning. *J Intensive Care Med*. Apr 2020;35(4):386-393.

34. Orsini J, Din N, Elahi E, et al. Clinical and epidemiological characteristics of patients with acute drug intoxication admitted to ICU. *J Community Hosp Intern Med Perspect*. Oct 2017;7(4):202-207.

35. Clark D, Murray D, Ray D. Epidemiology and Outcomes of Patients Admitted to Critical Care after Self-Poisoning. *Journal of the Intensive Care Society*. 2011;12(4):268-273.

36. McMahon A, Brohan J, Donnelly M, Fitzpatrick GJ. Characteristics of patients admitted to the intensive care unit following self-poisoning and their impact on resource utilisation. *Ir J Med Sci*. Sep 2014;183(3):391-5.

37. Liisanantti JH, Ohtonen P, Kiviniemi O, Laurila JJ, Ala-Kokko TI. Risk factors for prolonged intensive care unit stay and hospital mortality in acute drug-

poisoned patients: an evaluation of the physiologic and laboratory parameters on admission. *J Crit Care*. Apr 2011;26(2):160-5.

38. The Swedish CPR council. The Swedish Cardiopulmonary Resuscitation Register Yearly Report 2017. Accessed 2024: https://www.hlr.nu/wp-content/uploads/2018/02/Svenska-HLR-registret-%C3%A5rsrapport-2017.pdf2018.

39. Engdahl J, Bang A, Karlson BW, Lindqvist J, Herlitz J. Characteristics and outcome among patients suffering from out of hospital cardiac arrest of non-cardiac aetiology. *Resuscitation*. Apr 2003;57(1):33-41.

40. Ro YS, Shin SD, Song KJ, et al. A comparison of outcomes of out-of-hospital cardiac arrest with non-cardiac etiology between emergency departments with low- and high-resuscitation case volume. *Resuscitation*. Jul 2012;83(7):855-61.

41. Hawkes C, Booth S, Ji C, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. *Resuscitation*. Jan 2017;110:133-140.

42. Hess EP, Campbell RL, White RD. Epidemiology, trends, and outcome of out-of-hospital cardiac arrest of non-cardiac origin. *Resuscitation*. Feb 2007;72(2):200-6.

43. Yogeswaran V, Drucker C, Kume K, et al. Presentation and Outcomes of Adults With Overdose-Related Out-of-Hospital Cardiac Arrest. *JAMA Netw Open*. Nov 1 2023;6(11):e2341921.

44. Gässler H, Fischer M, Wnent J, Seewald S, Helm M. Outcome after pre-hospital cardiac arrest in accordance with underlying cause. *Resuscitation*. May 2019;138:36-41.

45. Lott C, Truhlář A, Alfonzo A, et al. European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstances. *Resuscitation*. Apr 2021;161:152-219.

46. Lavonas EJ, Akpunonu PD, Arens AM, et al. 2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. Oct 17 2023;148(16):e149-e184.

47. The National Board of Health and Welfare. Causes of death 2019. Accessed 2024: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2020-6-6798.pdf

48. Finkelstein Y, Macdonald EM, Hollands S, et al. Risk of Suicide Following Deliberate Self-poisoning. *JAMA Psychiatry*. Jun 2015;72(6):570-5.

49. Sorge M, Weidhase L, Bernhard M, Gries A, Petros S. Self-poisoning in the acute care medicine 2005-2012. *Anaesthesist*. Jun 2015;64(6):456-62.

50. Fisher LB, Overholser JC, Dieter L. Methods of committing suicide among 2,347 people in Ohio. *Death Stud*. Jan-Jun 2015;39(1-5):39-43.

51. Jönsson A, Holmgren P, Ahlner J. Fatal intoxications in a Swedish forensic autopsy material during 1992-2002. *Forensic Sci Int*. Jun 30 2004;143(1):53-9.

52. Ministry of Health and Social Affairs. Swedish code of status, law on autopsy (1995:832). Accessed 2024: https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-1995832-om-obduktion-mm_sfs-1995-832

53. Winters B, Custer J, Galvagno SM, Jr., et al. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. *BMJ Qual Saf*. Nov 2012;21(11):894-902.

54. Chan MK, Bhatti H, Meader N, et al. Predicting suicide following self-harm: systematic review of risk factors and risk scales. *Br J Psychiatry*. Oct 2016;209(4):277-283.

55. Bjornaas MA, Jacobsen D, Haldorsen T, Ekeberg O. Mortality and causes of death after hospital-treated self-poisoning in Oslo: a 20-year follow-up. *Clin Toxicol (Phila)*. Feb 2009;47(2):116-23.

56. The National Board of Health and Welfare. The National Patient register. Accessed 2024: https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/patientregistret/

57. The National Board of Health and Welfare. The Cause of Death Register. Accessed 2024: https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/dodsorsaksregistret/

58. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. Sep 2017;32(9):765-773.

59. The Swedish Intensive Care Register. About SIR. Accessed 2024: http://www.icuregswe.org/sv/Om-SIR/

60. The Swedish Intensive Care Register. Year Report 2022. Accessed 2024: https://www.icuregswe.org/globalassets/arsrapporter/arsrapport_2022_final.pdf

61. The Swedish Cardiopulmonary Register. About register. Accessed 2024: https://shlr.registercentrum.se/om-registret/om-svenska-hjaert-lungraeddningsregistret/p/rkNbvekfW

62. Strömsöe A, Svensson L, Axelsson Å B, Göransson K, Todorova L, Herlitz J. Validity of reported data in the Swedish Cardiac Arrest Register in selected parts in Sweden. *Resuscitation*. Jul 2013;84(7):952-6.

63. The National Board of Forensic Medicine. Statistics. Accessed 2024: https://www.rmv.se/om-oss/forskning/statistik/

64. The National Board of Health and Welfare. ICD-10. 2016. Accessed 2024: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/klassifikationer-och-koder/icd10se-inledning-till-icd10se-utdrag-fran-del1-2016.pdf

65. WHO. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Accessed 2024: https://icd.who.int/browse10/2019/en

66. The Swedish Intensive Care Register. *Year report*. 2018. Accessed 2024: https://www.icuregswe.org/globalassets/arsrapporter/analyserande_arsrapport_2018.pdf

67. Rhodes A, Ferdinande P, Flaatten H, Guidet B, Metnitz PG, Moreno RP. The variability of critical care bed numbers in Europe. *Intensive Care Med*. Oct 2012;38(10):1647-53.

68. Karasouli E, Owens D, Abbott RL, Hurst KM, Dennis M. All-cause mortality after non-fatal self-poisoning: a cohort study. *Soc Psychiatry Psychiatr Epidemiol*. Jun 2011;46(6):455-62.

69. Tejerina EE, Padilla R, Abril E, et al. Autopsy-detected diagnostic errors over time in the intensive care unit. *Hum Pathol*. Jun 2018;76:85-90.

70. Rusu S, Lavis P, Domingues Salgado V, et al. Comparison of antemortem clinical diagnosis and post-mortem findings in intensive care unit patients. *Virchows Arch*. Feb 13 2021.

71. Combes A, Mokhtari M, Couvelard A, et al. Clinical and autopsy diagnoses in the intensive care unit: a prospective study. *Arch Intern Med*. Feb 23 2004;164(4):389-92.

72. Mann JJ, Michel CA, Auerbach RP. Improving Suicide Prevention Through Evidence-Based Strategies: A Systematic Review. *Am J Psychiatry*. Jul 2021;178(7):611-624.

73. Gunnell D, Fernando R, Hewagama M, Priyangika WD, Konradsen F, Eddleston M. The impact of pesticide regulations on suicide in Sri Lanka. *Int J Epidemiol*. Dec 2007;36(6):1235-42.

74. WHO. SAFER: Preventing and Reducing Alcohol- Related Harms. Accessed 2024: https://www.who.int/docs/default-source/alcohol/safer-framework.pdf

75. Brune K, Renner B, Tiegs G. Acetaminophen/paracetamol: A history of errors, failures and false decisions. *Eur J Pain*. Aug 2015;19(7):953-65.

76. Zalsman G, Hawton K, Wasserman D, et al. Suicide prevention strategies revisited: 10-year systematic review. *Lancet Psychiatry*. Jul 2016;3(7):646-59.

77. Fugelstad A. The Swedish opioid crisis. 2023. Accessed 2024: https://arenaide.se/rapporter/den-svenska-opioidkrisen/

78. Fairley M, Humphreys K, Joyce VR, et al. Cost-effectiveness of Treatments for Opioid Use Disorder. *JAMA Psychiatry*. Jul 1 2021;78(7):767-777.

79. Hoffmann O, Ljungberg T. [Methadone and buprenorphine maintenance therapy of opioid dependence - 10 years of experience]. *Lakartidningen*. Apr 27 2021;118LARO med buprenorfin/metadon – en säker och effektiv behandling.