From the Department of Physiology and Pharmacology
Section of Anesthesiology and Intensive Care
Karolinska Institutet, Stockholm, Sweden

LONG-TERM OUTCOMES AFTER TRAUMA AND INTENSIVE CARE

Erik von Oelreich M.D.

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LONG-TERM OUTCOMES AFTER TRAUMA AND INTENSIVE CARE
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By

Erik von Oelreich M.D.

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Principal Supervisor:
Professor Anders Oldner
Karolinska Institutet
Department of Physiology and Pharmacology
Section of Anesthesiology and Intensive Care

Co-supervisors:
Associate professor Emma Larsson
Karolinska Institutet
Department of Physiology and Pharmacology
Section of Anesthesiology and Intensive Care

Dr. Mikael Eriksson
Karolinska Institutet
Department of Physiology and Pharmacology
Section of Anesthesiology and Intensive Care

Opponent:
Professor Markus Skrifvars
University of Helsinki and
Helsinki University Hospital
Department of Emergency Care and Services

Examination Board:
Professor Anders Enocson
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Trauma, Acute Surgery and Orthopaedics

Associate professor Pelle Gustafson
Lunds University
Faculty of Medicine
Department of Clinical Sciences, Lund

Professor Therese Djärv
Karolinska Institutet
Department of Medicine
Division of Clinical Medicine

To Nina, Alexander and Eugen

POPULAR SCIENCE SUMMARY OF THE THESIS

Trauma is a major cause of mortality and morbidity and the leading cause of death in Sweden for individuals under 45 years of age. The young age of this patient group causes significant losses to society in terms of lives, disability and costs. In trauma research, mortality has been the most common endpoint, while on the contrary long-term morbidity is not fully investigated and sometimes hard to measure. The Swedish national demographic and health registries with detailed information and minimal loss to follow-up provide invaluable resources for epidemiological research. Combining this information with a large trauma registry or data from the Swedish Intensive Care Registry yield internationally unique datasets for short and long-term studies of outcomes.

In the first study sick leave functioned as a proxy for long-term morbidity and the extent of, and risk factors for prolonged sick leave after trauma were investigated. Compared with a control group, trauma patients had more sick leave both before and after trauma. High age, low level of education, psychiatric disease, serious injury and staying longer in the hospital were among the factors associated with more sick leave one year after trauma. In the second study, two separate prediction models were developed to predict sustained morbidity measured as sick leave after trauma. Factors related both to the trauma *per se* as well as host factors were important predictors for long-term sick leave.

Both trauma patients and patients admitted to critical care often experience pain in response to injuries or as a result of their treatment. Opioids are part of the first-line treatment for moderate to severe pain, but some patients become dependent on opioids after discharge. In the third and fourth study, opioid use before and after trauma and intensive care were investigated. Trauma patients used more opioids compared to controls and among patients admitted to critical care, opioid use was substantial both before and after admission. Risk factors for chronic opioid use included high age, pre-existing medical conditions and pre-injury opioid use. In the trauma cohort, injury severity also influenced post-injury opioid use and among patients admitted to critical care the duration of critical care was important. In both groups long-term opioid usage was associated with an increased risk of mortality.

To conclude, both injury and non-injury related factors impact long-term morbidity after trauma and sick leave might be used as a proxy for post-trauma morbidity. Prediction models may identify groups of patients at risk of sick leave following trauma and helpful when allocating resources for rehabilitation. Furthermore, chronic opioid use is substantial both before and after trauma and intensive care and is associated with an increased risk of death.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Trauma är en vanlig orsak till död och sjuklighet och är den vanligaste dödsorsaken i Sverige för personer under 45 år. Den unga åldern för den här patientgruppen leder till omfattande skador både för individen och för samhället i stort i form av exempelvis förlorade liv, kvarvarande långtidssjuklighet och stora kostnader. Många tidigare studier har tittat på död som utfallsmått, men långtidssjuklighet är bristfälligt undersökt, svårt att mäta och kvantifiera. De svenska hälsoregistren innehåller högupplöst och detaljerad information och är bra verktyg för epidemiologiska studier inom det här fältet. Att kombinera information från nationella register med antingen ett lokalt traumaregister eller med ett nationellt intensivvårdsregister skapar bra underlag för att genomföra studier om exempelvis långtidssjuklighet för den här patientgruppen.

I den första studien användes sjukskrivning som ett alternativt sätt att mäta långtidssjuklighet efter trauma. Traumapatienter var mer sjukskrivna jämfört med en kontrollgrupp både före och efter skadetillfället. Hög ålder, låg utbildningsnivå, psykisk sjukdom, svåra skador och längre tid på sjukhus var alla faktorer som var associerade med heltidssjukskrivning ett år efter trauma. I den andra studien utvecklades två olika prediktionsmodeller som användes för att predicera långtidssjuklighet uttryckt som sjukskrivning. Både faktorer relaterade direkt till traumat och bakgrundsfaktorer som till exempel utbildningsnivå var viktiga prediktorer för höga sjukskrivningstal.

Patienter som vårdas för skador orsakade av trauma eller som är inlagda på en intensivvårdsavdelning upplever ofta smärta på grund av deras skador eller som ett resultat av den behandling de genomgår. Opioider används ofta för behandling av smärta, men en del patienter fortsätter att använda de här läkemedlen under lång tid och blir beroende av dem. Hur vanligt långtidsbruk av opioider efter trauma och intensivvård är har inte studerats i någon större omfattning, inte heller de faktorer som bidrar till detta bruk. I den tredje och fjärde studien undersöktes opioidanvändning före och efter trauma och intensivvård. Traumapatienter använde mer opioider jämfört med en kontrollgrupp både före och efter trauma och bland patienter som skrevs in på en intensivvårdsavdelning var opioidanvändningen också betydande både före och efter vårdtillfället. Riskfaktorer för kronisk användning av opioider inkluderade i båda studierna hög ålder, samsjuklighet och tidigare opioidanvändning. Bland traumapatienterna påverkades opioidanvändningen även av hur svårt skadad patienten var och bland intensivvårdspatienterna av hur lång vårdtid de hade. I båda grupperna var kronisk opioidanvändning associerat med en ökad risk för död.

Sammanfattningsvis lider traumapatienter i hög grad av långtidssjuklighet som i stor utsträckning påverkas av faktorer som inte är relaterade till skadan i sig. Sjukskriving skulle kunna användas som ett sätt att kvantifiera långtidssjuklighet efter trauma och en prediktionsmodell för långtidssjukskrivning kan fungera som ett verktyg för att identifiera patientgrupper med hög risk för sjukfrånvaro och i behov av mer uppföljningsresurser. Vidare är kroniskt bruk av opioider både före och efter trauma och intensivvård vanligt och förenat med en ökad risk för död.

ABSTRACT

The goals of trauma and critical care are twofold: to prevent short- and long-term mortality and to return the patient to an independent life. With the development of modern trauma care including technical advancements and generalized concepts, outcome has been improving steadily. However, trauma is still a major cause of mortality in the 1–45 years old age groups and treating these patients is a challenging task consuming significant resources. In strive for improved results in trauma care it is highly important to study factors that may influence outcomes. Apparent determinants such as injury severity, shock and bleeding have been intensively studied over the last decades. There are, however, several less apparent factors including socioeconomic factors, that may influence long-term outcomes.

Management of trauma patients continue to evolve, and many previous open surgical procedures are being replaced by nonoperative approaches shifting part of the trauma management to the ICU. Hence, trauma and intensive care are closely connected and improvement on either depends on improvement on both. The aim with this thesis was to increase knowledge of long-term morbidity and outcomes of trauma patients and patients surviving intensive care using national and regional registers in four epidemiological studies.

Significant morbidity can be measured as delayed return to work, an entity that causes considerable suffering for trauma victims and significant costs for society. In study I we explored the extent of, and risk factors for delayed return to work after major trauma in a cohort study with matched controls using sick leave as a proxy for long-term morbidity. Compared with controls, trauma patients had more sick leave both before and after trauma. High age, psychiatric disorders, low educational level, serious injury, spinal injury, reduced consciousness at admission, not being discharged directly home, and hospital length of stay for more than seven days were associated with full time sick leave one year after trauma. In study II two separate prediction models, one comprehensive and one simplified, were developed to predict trauma patients at risk of long-term sick leave. Factors related both to the trauma per se as well as host factors were important predictors. Both models were internally validated, accurate and showed high precision. Sick leave after trauma might serve to quantify long-term morbidity and predictive modelling could be valuable when targeting use of scarce follow-up resources.

Severe trauma and treatment in the intensive care unit typically involves significant pain rendering treatment with potent analgesics. Commonly the situation resolves, and the drugs can be tapered. It is, however, noted in pain clinics that subgroups of patients become dependent on chronic opioid-treatment for a long time after trauma. This prolonged use or misuse of opioids is obviously influenced by the nature of the injury per se but also by several less well characterized factors. The precise magnitude of this problem is not known, neither are all the associated factors. The wide-spread use of opioids is currently questioned, and prolonged use of opioids is associated with worse outcomes. In study III and IV opioid use before and after trauma and intensive care were investigated. Trauma patients used more opioids compared to matched controls both before and after trauma and among patients

admitted to critical care opioid use was also substantial before and after admission. In the trauma cohort, exposure to trauma was associated with long-term opioid usage. High age, comorbidities, increasing injury severity and pre-injury opioid use were some of the factors associated with chronic post-traumatic opioid use. Among patients admitted to critical care, increasing age, female sex, comorbidities, ICU length of stay and pre-admission opioid use were among the factors associated with long-term opioid use. Both among trauma patients and ICU patients, long-term opioid use was associated with increased risk of death 6-18 months after trauma and ICU admission respectively. In both studies the same results applied for patients not using opioids before trauma or admission to critical care. These studies highlight the risks with long-term opioid treatment following trauma or intensive care.

To conclude, trauma patients suffer from significant long-term morbidity influenced by non-trauma related factors. Sick leave might be used as a proxy for post-trauma morbidity and prediction models may identify groups of patients at risk of sick leave following trauma and useful when allocating resources for rehabilitation. Furthermore, chronic opioid use is substantial both before and after trauma and intensive care and is associated with an increased risk of death.

LIST OF SCIENTIFIC PAPERS

I. **Post-trauma morbidity, measured as sick leave, is substantial and influenced by factors unrelated to injury: a retrospective matched observational cohort study**
von Oelreich E, Eriksson M, Brattström O, Discacciati A, Strömmer L, Oldner A, Larsson E
Scand J Trauma Resusc Emerg Med. 2017 Oct 13;25(1):100

II. **Predicting prolonged sick leave among trauma survivors**
von Oelreich E, Eriksson M, Brattström O, Discacciati A, Strömmer L, Oldner A, Larsson E
Sci Rep. 2019 Jan 11;9(1):58

III. **Risk factors and outcomes of chronic opioid use following trauma**
von Oelreich E, Eriksson M, Brattström O, Sjölund KF, Discacciati A, Larsson E, Oldner A
Br J Surg. 2020 Mar;107(4):413-421

IV. **Opioid use after intensive care: a nationwide cohort study**
von Oelreich E, Eriksson M, Sjölund KF, Discacciati A, Larsson E, Oldner A
Crit Care Med. 2021 Mar 1;49(3):462-471

CONTENTS

LIST OF ABBREVIATIONS

AIS	Abbreviated injury scale
AUC	Area under the curve
CCI	Charlson comorbidity index
CI	Confidence interval
GEE	Generalized estimating equation
HR	Hazard ratio
ICD	International classification of diseases
ICU	Intensive care unit
ISS	Injury severity score
IQR	Interquartile range
LISA	Longitudinal integration database for health insurance and labour market studies
MG	Milligram
NBHW	National board of health and welfare (Sw. Socialstyrelsen)
OR	Odds ratio
P-value	Probability value
SAP	Systolic arterial blood pressure
SCB	Statistics Sweden (Sw. Statistiska Centralbyrån)

1 INTRODUCTION

Trauma is a global health concern and predominantly affects younger individuals. Each year, injuries kill more than five million people worldwide and for every person who dies, several more are injured, many of them with permanent sequelae[1]. Trauma care is challenging and expensive for health care systems and decreasing the global burden of traumatic injuries is one of the main challenges for public health. Many seriously injured trauma patients present to the intensive care unit requiring a level of care involving close monitoring, higher staffing levels and advanced treatment.

Multiple factors affect recovery after injury including age, preexisting medical conditions, the severity of injury and access and response to treatment and rehabilitation. Recovery is not one dimensional and whom is to fully recover and whom is not is hard to predict. In the literature, outcome is measured in several ways ranging from mortality to various scales, making comparisons between studies difficult[2]. However, trauma survivors and survivors after critical illness, are likely more focused on long-term outcomes including an independent life, return to work and reintegration into society.

This thesis is based on four studies that address several aspects of trauma and intensive care. The aim was to illustrate factors contributing to increased long-term morbidity and mortality. In study I and II sick leave is used as a proxy for long-term morbidity describing how injury and non-injury-related factors affect the long-term effects of injury. Two prediction models were developed to assess how individuals at risk of long-term sick leave may be identified already at discharge from a trauma unit. Study III and IV aimed to elucidate whether chronic opioid use could worsen the already poor prognosis of trauma patients and intensive care unit (ICU) survivors.

2 LITERATURE REVIEW

2.1 Epidemiology

In Sweden, trauma is the leading cause of death among individuals younger than 45 years[3]. However, the cumulative burden of trauma including long-term disability is likely to be higher and for every trauma death, between three and four patients survive with a serious or permanent disability[4]. Hence, trauma is not just a temporary physiological setback to an individual but affects health and quality of life for many years. Common injury mechanisms are motor vehicle collisions, intentional injuries and injuries from falls[5]. Considerable differences exist between countries, in low-income countries the risk of dying from road traffic injuries is three times higher than in high-income countries[6].

Following improvement in first aid, emergency room and operative management, more injured patients survive to admission to the ICU[7]. For patients admitted to critical care long-term morbidity is significant and quality of life is often reduced[8]. Sweden has a publicly funded health care system Sweden and around 40,000 episodes of ICU care every year[9].

2.2 Trauma scoring systems

Severity scales in traumatology designed for classification and characterization of injuries are important adjuncts to trauma care and can aid in predicting survival or benchmarking trauma centers. There is a wide variety of scoring systems available based on anatomical descriptions of injuries, physiological parameters or both. There is no consensus on the ideal scoring system and no system is completely accurate in any setting. The Abbreviated Injury Scale (AIS) is an anatomical scoring system used to assess trauma patients and every injury is assigned a code based on anatomical site, nature and severity (1=minor and 6=maximal)[10]. Injury Severity Score (ISS) is a commonly used scoring system in trauma literature derived from the AIS and provides an anatomical description of injuries that is designed to assess the combined effects in multiply injured patients. ISS is defined as the sum of squares of the highest AIS grade in the three most severely injured body regions. ISS ranges from 1-75 where ISS of 75 indicates that an injury is unsurvivable and is also assigned anyone with any AIS body region score of 6. The body regions are divided into (1) head or neck, (2) face, (3) chest (thorax), (4) abdominal or pelvic contents, (5) extremities or pelvic girdle and (6) external[11]. Major trauma is commonly defined using ISS of 15 as a threshold[12].

2.3 Trauma mortality

Mortality after multiple trauma has decreased over the last decades due to effective pre-hospital care, implementation of modern trauma systems and improvements in post-traumatic care[13, 14]. With a decreasing number of deaths, lethal injuries account for a smaller fraction of the combined impact of trauma on society. Instead, more essential are the large number of non-fatal injuries of a young trauma population resulting in substantial morbidity and high costs.

Historically, but still widely taught in the trauma literature, the distribution of trauma deaths has been described as trimodal with immediate deaths at the scene (usually unpreventable e.g. high spinal or brain injury, catastrophic hemorrhage), early deaths (within hours, typically hemorrhage-related) and days to weeks after trauma (multi-organ failure or sepsis)[15]. This concept has been questioned and other alternative patterns have been suggested such as quadrimodal distributions or an early peak followed by a continuous decline of deaths[16]. Apart from expected age-dependent causes of death, another trauma or self-inflicted injuries are more common causes of death among patients with previous trauma[17].

2.4 ICU mortality

Mortality rates are high for patients requiring critical care, but has decreased over the past decades and vary depending on admission diagnosis[18]. For example, trauma patients have experienced a better prognosis over time[19], whereas survival rates for sepsis patients are unchanged[20]. In Sweden, 30-day mortality for ICU patients is around 17 %[21] which is low compared with previous ICU studies[22, 23].

2.5 Long-term outcomes

Traditionally, outcome studies of trauma are limited to in-hospital or 30-day mortality, endpoints also recommended in trauma research[24]. Later studies report increased risk of death for several years following trauma and more recent reports include longer follow-up periods[25, 26]. Given the effective injury-prevention strategies and improved trauma care, attention of today is increasingly focusing on improving the quality of survival and reducing long-term morbidity after nonfatal injuries. Patients surviving trauma experience long periods of intensive care, interventions and rehabilitation leading to subsequent long-term morbidity, and several factors other than injury severity seem to influence the final total degree of morbidity. Compared to matched comparison groups, trauma patients seem to have an excess mortality for many years after trauma[26, 27]. The same holds true for ICU patients where in-hospital mortality is significantly lower than more accurate long-term measures since many ICU patients similarly have an increased risk of mortality for many years after discharge[28]. Physical impairment is common for ICU survivors, for example after acute respiratory distress syndrome[29], but how to best assess outcome of these patients is not clear and there are more than 26 reported functional outcome measures[30].

2.6 Trauma and employment

2.6.1 Sick leave in Sweden

The Swedish Social Insurance Agency provides paid sickness absence for individuals aged over 16 living in Sweden with income (from work, unemployment or parental leave) if the disease or injury has led to reduction of work capacity. The first day of a sick-leave period is not reimbursed and mental health disorders is the most common reason for sickness absence in Sweden.[31].

Prescribing sick leave is a common practice in health care but is widely questioned since it is suggested that sick leave instead may have overall negative effects for many patients. A number of studies have shown that the longer the period of work absence lasts, the more likely that the individual never returns to work[32, 33] and one study indicated that individuals on disability pension had increased mortality rates[34]. This underlines the importance of identifying individuals at risk of sick leave at an early stage and concentrate on reintegration to working life.

2.6.2 Return to work after trauma

In a long-term perspective, the goal with trauma care is reintegration into previous level of activity and to an independent life. Post-traumatic return to work could serve as a proxy for long-term functional outcome and a measure of performance for trauma or ICU care[35]. It has been suggested that return to work should be measured in trauma follow-up, and studies have shown that survivors after trauma do not return to pre-injury employment level for many years[36, 37]. Other recommended measurements are injury severity scores or outcome scores such as Glasgow Outcome Scale (GOS)[38, 39]. However, they have proven to be poor when trying to predict long-term outcomes and level of future employment after trauma, and other instruments and measurements are needed[40].

Predicting future duration of sickness absence is complex and dependent on several different factors such as injury severity, personal and psychosocial factors and design of the sickness insurance system[41, 42]. Already in the late 80s, MacKenzie studied factors influencing return to work and functional outcome one year after trauma and concluded that spinal injury was the single most important factor for not returning to work[43]. Later studies report widely divergent proportions of returning to work one year after trauma varying from 28 % [44] to 70 % [45]. Possible explanations for these variations are differences in case mix or varying definitions of return to work. In the literature, factors influencing return to work rates are both demographic (age, educational level, income) and injury-related (injury severity, injury localization). However, different studies conclude with different factors associated with return to work and there is no consensus on what factors are most important. In addition, many studies focus on a specific injury type or localization limiting the generalizability to other trauma populations[46, 47].

An important reason to identify individuals with a possible poor outcome is to be able to tailor rehabilitation or other preventive measures for these patients. How to identify patients most suitable for rehabilitation is not clear but is important since it is a limited and expensive resource to be used on patients most likely to benefit from it[48].

2.7 Pain management after trauma and intensive care

2.7.1 Long-term opioid use

Opioids are potent and effective pain relievers and therefore play an important role as first line-treatment of moderate to severe pain[49]. However, use of opioids entails risks including addiction and physical dependence[50] and prolonged use can lead to higher doses due to tolerance[51]. Prescription opioids used incorrectly is a serious issue in global health and contributes to the global disease burden[52]. In the light of escalating opioid use, treatment of acute and chronic pain has emerged as a growing challenge in modern medicine[53].

There are several definitions of prolonged opioid therapy, but a common definition is treatment longer than three months[54-56]. Several factors are associated with long-term use of opioids in previous studies; the amount prescribed early after injury[57], level of inpatient use[58], orthopedic injuries[59] and pre-injury opioid use[60]. Other possible predictors include history of illicit drug and alcohol abuse[61] and comorbid mental health disorders[62, 63]. Overall, opioid prescribing seems to follow a pattern in which patients with high probability of unfavorable outcomes following opioid treatment also are more likely to be prescribed large amounts of opioids.

2.7.2 Opioid use for chronic pain

The evidence for long-term opioid usage is weak[64] and using opioids to treat chronic pain is very much in question[65, 66]. In addition, opioids carry a dose-dependent risk for health-related harms when used for long-term treatments[64] and unintentional overdose injury has been shown to be related to the prescribed opioid's duration[67]. Patients are often given standard doses not based on individual pain response, but instead based on expectations on a group level. Furthermore, chronic opioid treatment is associated with adverse effects including increased probability of vehicle crashes[68], risk of myocardial infarction[69] and increased risk of death[70] and in one study 80 % of first time heroin users initially misused prescription opioids[71]. In the U.S. an estimated 20–30 % of the population suffers from chronic pain, which is similar to findings in Europe, Canada and Australia[72].

2.7.3 The U.S. opioid epidemic

Most current studies on opioids are performed in the U.S. where a majority of prescribed opioids are consumed[73]. Addiction from opioids is not a new phenomenon, during the Civil War in the United States the Union army consumed large amounts of opium tincture and opium pills with the consequence of a high rate of addiction among soldiers[74]. However, the origin of the current opioid epidemic started in the 1990s with the idea of pain as the fifth vital sign and increased prescription of opioids lead to widespread misuse[75]. In the U.S. more than 30 % of the adult population use prescription opioids[76] and in 2019 there were more than 70,000 drug overdose deaths[77]. Today, prescription opioids together with heroin account for a majority of all drug overdose fatalities[78] and a majority of fatalities originate from opioids prescribed within the guidelines[79].

2.7.4 Opioids after trauma

An important aspect of trauma care is pain management, and more than 50 % experience pain for many years following injury[80]. The proportion of trauma victims who become long-term users of opioids following injury is not known, but most likely has increased. Pain at the time of discharge has been found a predictor of pain six months after orthopedic injury[81], and discomfort at three months a predictor of pain up to seven years after trauma[82, 83]. In the U.S., more than 39 million individuals are injured every year and opioid-treatment is common among these individuals[84]. One Canadian study found that 35 % in a trauma cohort used prescription opioids four months after injury[85] and another U.S. study reported a smaller proportion of chronic opioid use after trauma around 15 %[86]. These differences are possibly explained by different study endpoints and varying definitions of chronic opioid use. Furthermore, longitudinal follow-up is important, one study found that out of patients that continue to use opioids for more than six months after trauma, more than a third continued to use opioids for more than twelve months[87]. The proportions of persistent opioid users also differ between countries with lower numbers in European countries. In a Danish study, seven % of a trauma population were persistent opioid users six months after trauma[88]. In addition, trauma victims have a high prevalence of established controlled substance abuse use adding to the risk of post-injury opioid use[89].

Many studies on surgery and opioids are related to orthopedic surgery, perhaps because pain management after orthopedic surgery continues to be opioid-centric[90] and orthopedic surgeons prescribe high quantities of opioids[91]. In addition, orthopedic patients are more likely compared with the general population to use prescription opioids already before the injury[59].

2.7.5 Opioids after intensive care

Most ICU patients are exposed to opioids as pain management or for sedation. The magnitude of chronic opioid use after ICU care is not fully investigated, but theories that continuous infusions of opioids for longer time periods during ICU care might drive chronic use after discharge has not been supported in previous studies[92, 93]. In addition, many patients experience pain for several years after discharge from ICU and opioids are commonly used also in this setting despite absence of evidence for any benefit of chronic opioid use[64]. Since opioid prescriptions have increased over time, older studies might not reflect current prescription patterns making findings hard to interpret[94]. In a more recent Canadian study only 2.6 % of the included ICU patients requiring invasive mechanical ventilation met criteria for chronic opioid use after discharge from hospital[95]. An important limitation of previous studies is the inability to measure any doses or reason for opioid treatment during the ICU stay, thus little is known if or how opioid use during the ICU stay possibly drives a subsequent chronic opioid use[96].

3 RESEARCH AIMS

To investigate the magnitude of sick leave before and after trauma

To identify factors associated with full time sick leave one year after trauma

To develop prediction models for prolonged sick leave after trauma and validate their predictive performances

To analyze if trauma is associated with chronic opioid use

To investigate the magnitude of opioid use before and after trauma

To describe factors associated with chronic opioid use following trauma

To investigate if chronic opioid use following trauma is associated with increased risk of death and identify causes of mortality

To examine the magnitude of and factors associated with chronic opioid use after admission to intensive care

To analyze if chronic opioid use following admission to intensive care is associated with increased risk of death

4 MATERIALS AND METHODS

4.1 Ethical considerations

The Regional Ethical Review Board in Stockholm, Sweden, approved studies I-IV. All studies were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All studies were retrospective observational studies and waived requirement for informed consent. However, data included in the studies are sensitive personal data and the Personal Data Act applies. All data were retrieved from existing registries and the datasets were processed and anonymized by the National Board of Health and Welfare (NBHW) before delivery to the research group. Thus, there was no access to any information that enabled identification of individual patients.

4.2 National registries

All Swedish citizens have a unique personal identity number that allows linkage of patient data to different registries[97].

4.2.1 The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA)

The LISA database was launched as a tool to investigate changes in the labor market and contains data on education, occupation, income, social welfare, work of absence benefits due to injury, disease or rehabilitation. LISA includes information on individuals aged 16 or older since 1990 making it a useful tool for various medical research purposes[98].

4.2.2 The National Patient Register

The Swedish National Patient Register, managed by the NBHW, contains information on all inpatient care episodes in psychiatric care since 1973 and in somatic care since 1987. Outpatient care, not classified as primary care, is included from 2001. Each care episode, diagnosis of which one is principal, is classified according to the International Classification of Diseases (ICD-10). ICD version 10 has been used in Sweden since 1997. The coverage of the register is > 95 %[99, 100].

4.2.3 The Swedish Cause of Death Register

The Swedish Cause of Death Register is managed by the NBHW and comprises data on all deaths of people registered in Sweden, and from 2012 also deaths that occurred in Sweden even if the deceased was not a registered citizen[101]. Originating from the decision in the Swedish parliament in 1749 to document cause of death statistics, the Cause of Death Register is virtually complete and contains electronically available data from 1952 and onwards. Certifying a death includes the physician submitting a death certificate to the NBHW filling out underlying cause of death defined as “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury”[102]. The register is of high quality with < 1 % loss of death certificates. Misclassifications of the underlying cause of death have been estimated to approximately 20 % overall but vary with diagnosis and age with lower numbers among younger individuals and in patients with violent causes of death, malignancies and ischemic heart disease[103].

4.2.4 Swedish Intensive Care Registry (SIR)

SIR collects individual data from Swedish ICUs with an increasing completeness (2011: 91 %; 2019: 99 %)[104]. SIR contains data on diagnoses, interventions and follow-up and operates within the legal framework of the Swedish National Quality Registries[105] and does not require written informed consent from the patients. However, patients may withdraw their data from the registry at any time.

4.2.5 The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register includes individual level data on dispensed prescription drugs in Sweden and is managed by the NBHW. On 1 July 2005, the register was expanded to include personal identity numbers allowing linkage between drug dispensing data and other registers[106]. The register contains detailed information on drugs, dispensed amounts and information about the patient and the prescriber. The register does not include data on medication used in hospitals and nursing homes and only partially covers drugs used in day-care such as TNF-alfa-inhibitors[107]

4.2.6 The Total Population Register

The Total Population Register managed by Statistics Sweden (SCB) includes information about the population and its changes and is available for every year from 1968 onwards. The register serves as a database which can supply supplementary data to other registers and surveys and includes population by sex, age, marital status etc[108].

4.3 Regional registries

4.3.1 Trauma Registry Karolinska

All patients admitted through the trauma unit, regardless of ISS, as well as patients admitted without involvement of the trauma team, but afterwards found to have an ISS > 9 are included in the trauma registry of the Karolinska University Hospital. Patients with isolated fractures of the upper or lower extremity, drowning, chronic subdural hematomas, severe burns or hypothermia without concomitant trauma are not included in the registry. From 2013 data is registered according to the Utstein Template and reported to the Swedish Trauma Register (SweTrau)[24].

4.4 Definitions

Education was categorized as low, medium or high corresponding to 9 years or less, 10-12 years, and more than 12 years of school. Income was classified as low, medium or high corresponding to < 50 %, 50-200 % or > 200 % of the median income in Sweden the year preceding ICU admission (Paper IV). Somatic comorbidity was assessed up to eight years prior to trauma (Paper I-III) and up to five years prior to ICU admission (Paper IV) and defined as presence of any somatic diagnosis included in the Charlson comorbidity index (CCI) coded to ICD-10[109, 110]. Psychiatric comorbidity was defined as presence of any ICD-10 codes F20-99 and substance abuse as presence of diagnoses found in F10-19. Injury severity was classified according to the ISS, based on the AIS 1990 edition for year 2005-2006 and AIS 2005 edition from 2007 (Paper I-III). Serious injury to an AIS-region was defined as AIS score more than 2 (Paper I and III). Serious injury in general was defined as ISS > 15 (Paper I). Chronic opioid use after trauma was equal to filling at least one prescription during 91–180 days following trauma, or corresponding index date for controls (Paper III). Chronic opioid use after admission to critical care was defined as dispensed opioid prescription both during day 1–90 and day 91–180 following ICU admission (Paper IV). Individuals not filling any opioid prescription during 6 months before trauma and 12 months before ICU admission were considered opioid naïve (Paper III and IV).

4.5 Statistics

Categorical data are presented as proportions and percentages and continuous data with median and interquartile range (IQR) (Paper I-IV) except for days spent on sick leave which are presented as means (Paper 1). Crude comparisons of proportions were performed using chi-square tests.

Generalized Estimating Equation (GEE) regression models were used to estimate differences in days spent on sick leave over time for trauma patients compared to controls (Paper I). Estimated mean differences were expressed in terms of Cohen's d. GEE regression models were also used to analyze differences in opioid consumption among injured patients and controls before and after trauma (Paper III) and before and after ICU admission (Paper IV).

Logistic regression models were used to estimate odds ratios (OR) with 95 % confidence intervals (CI) for the association between traumatic injury per se and chronic opioid use (Paper III), and factors potentially associated with post-traumatic sick leave (Paper I) and chronic opioid use after trauma or intensive care (Paper III and IV). Cox regression models were used to investigate the association between chronic opioid use and all-cause mortality after trauma and ICU admission respectively (Paper III and IV). Results were presented as hazard ratios (HR) with corresponding 95 % CI. Schoenfeld residuals was used to test model performance (Paper III).

As a sensitivity analysis, probability weights were used in the logistic regression model to account for dropout from the study due to death (Paper I, III and IV). Multiple imputation was used to account for missing data (Paper III). Logistic regression models were also used to develop two different prognostic models used to predict prolonged sick leave based on candidate predictors (Paper II). The predictor variables were selected using a backward selection algorithm and discrimination and calibration were internally validated using 10-fold cross-validation.

A P value less than 0.05 was considered statistically significant; all tests were two-tailed. IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA), Stata/SE 14.2 (StataCorp, College Station, TX, USA) and GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA, USA) were used for statistical analyses.

4.6 Study design and outcome measures

Study design and outcome measures are summarized in Table 1.

Table 1. Study design and outcome measures.

Study	**I**	**II**	**III**	**IV**
Design	Matched cohort study	Cohort study	Matched cohort study	Cohort study
Study population	Trauma cohort 2005-2010	Trauma cohort 2005-2010	Trauma cohort 2006-2015	ICU cohort 2010-2018
Sample size	Patients 4712 Controls 25 013	4458	Patients 13 309 Controls 70 621	265 496
Register used	Trauma Register Cause of Death Register Total Population Register National Patient Register LISA	Trauma Register Cause of Death Register National Patient Register LISA	Trauma Register Cause of Death Register Total Population Register National Patient Register LISA Prescribed Drug Register	Swedish Intensive Care Register Cause of Death Register National Patient Register LISA Prescribed Drug Register
Outcome measures	Sick leave before and after trauma, risk factors for full-time sick leave one year after trauma	Full-time sick leave one year after trauma	Chronic opioid use after trauma, opioid use before and after trauma, all-cause mortality 6-18 months after trauma, causes of death for chronic opioid users	Chronic opioid use after ICU admission, all-cause mortality 6-18 months after ICU admission

4.6.1 Study I

In a cohort study, injured patients from the Karolinska Trauma Register 2005-2010 were matched by age, gender and municipality in a 1:5 ratio with uninjured controls from the Register of Total Population. Patients were linked to LISA and the Patient Register for assessment of level of education, comorbidities and rates of sick leave. GEE models were used to estimate crude differences in mean number of days spent on sick leave for trauma patients and controls. Logistic regression models were used to identify factors associated with sick leave one year after trauma.

4.6.2 Study II

Patients from the Karolinska Trauma Register 2005–2010 were extracted and included in a cohort study. After linkage to the Patient Register and LISA, information on comorbidities and level of education was provided. By using logistic regression models and stepwise backward elimination for variable selection, two prediction models were developed for assessment of full-time sick leave one year after trauma. Potential predictors were chosen based on physiological plausibility and data availability.

4.6.3 Study III

Injured patients from the Karolinska Trauma Register 2006–2015 were matched in a 1:5 ratio with uninjured controls from the Register of Total Population. By linkage to LISA and the Patient Register, level of education and comorbidities were investigated. Causes of death were explored by linkage to the Cause of Death Register. In addition, patients were linked to the Prescribed Drug Register to define opioid use before and after trauma. GEE models were used to assess opioid use before and after trauma and logistic regression models to explore risk factors for chronic opioid use after trauma. Cox regression models were used to assess risk of mortality for chronic opioid users. A subset of trauma patients not using opioids during the six months preceding injury was explored separately.

4.6.4 Study IV

In this cohort study all patients included in the Swedish Intensive Care Registry (SIR) from January 2010 to December 2018 were included and followed for two years. Primary outcome was chronic opioid use after ICU admission and secondary outcome risk of death 6–18 months after ICU admission. Socio-economic variables and comorbidities were assessed after linkage to the Patient Register and LISA. Patients were also linked to the Prescribed Drug Register to explore opioid use before and after ICU admission using GEE models. Among ICU patients, logistic regression models were used to investigate factors associated with chronic opioid use. A Cox regression model was employed to study excess risk of mortality.

5 RESULTS

5.1 Study I

4712 trauma patients and 25 013 controls were included in the study with a median age of 36 years in the trauma cohort. 72 % were male and median ISS was 5 with 21 % seriously injured (ISS > 15).

Trauma patients had more sick leave before trauma compared to controls (0.9 days vs. 0.4 mean days/month, P < 0.001), a difference that was markedly larger following trauma (Figure 1). The difference in sick leave decreased but was still significant in the follow-up period 13 to 36 months after trauma (2.7 days/month, P < 0.001).

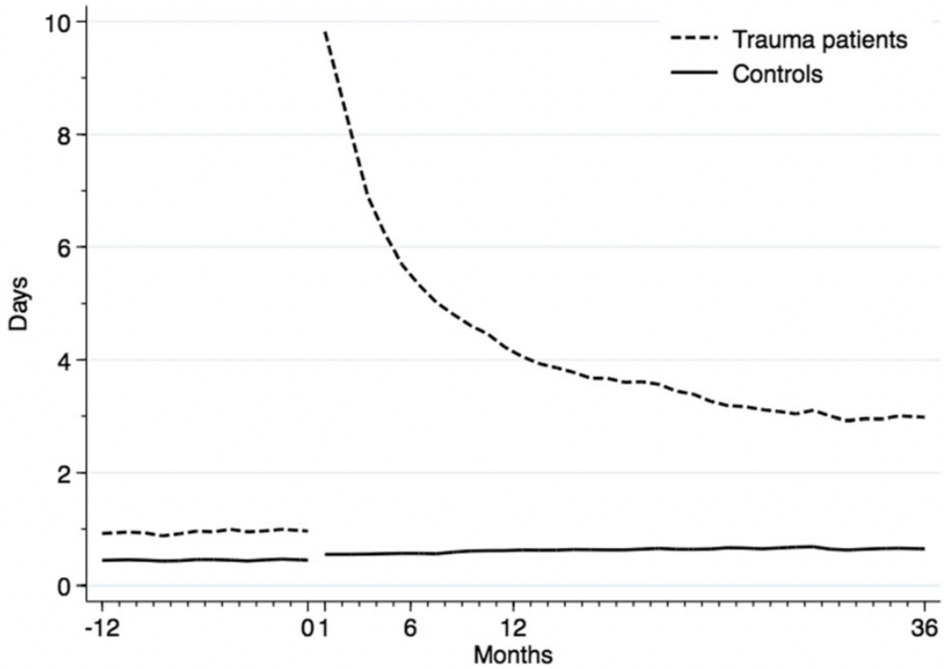

Figure 1. Characteristics of sick leave pre- and post-trauma. Sick leave over time measured as mean number of days per month in trauma patients and controls. Time of trauma depicted by time 0 on the x-axis

Different patterns of sick leave for subgroups of age, sex, level of education and injury severity are presented in Figure 2. Following trauma, sick leave rates were higher among older patients, more serious injuries and lower education.

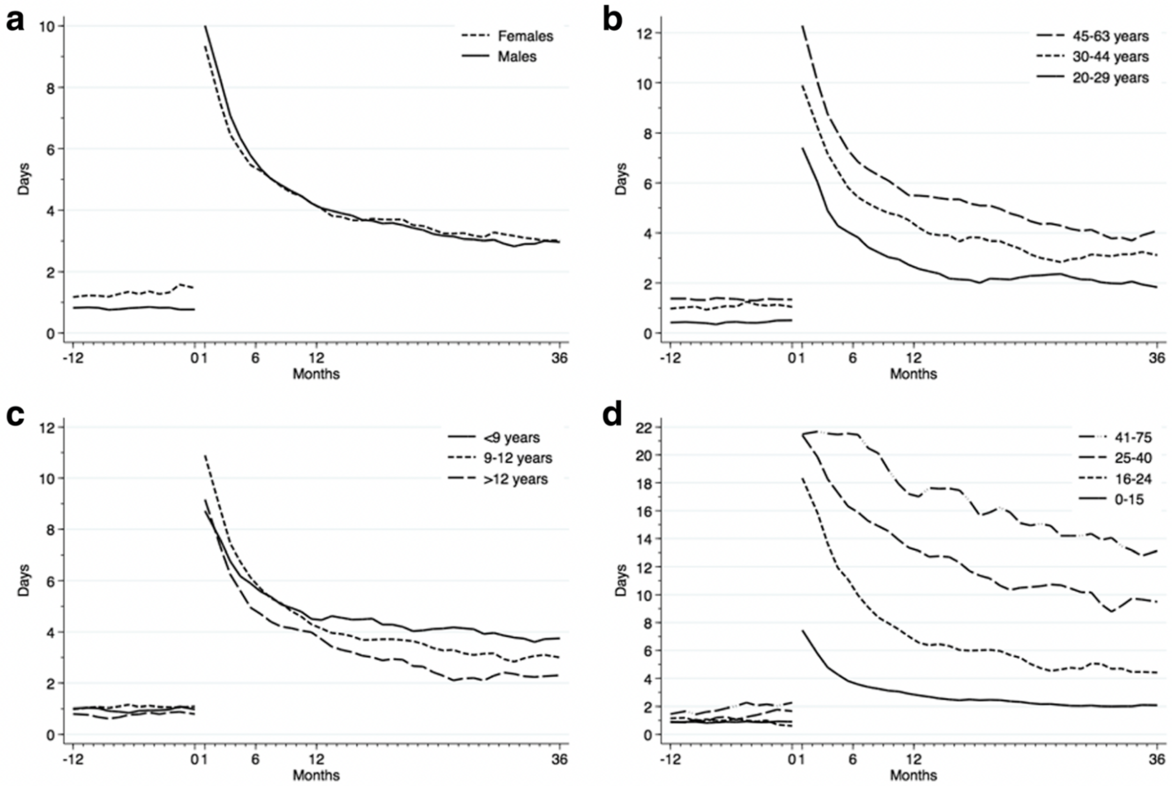

Figure 2. Mean number of days of sick leave in subgroups pre- and post-trauma. Sick leave over time measured as mean number of days per month pre- and post-trauma in subgroups of sex (**a**), age (**b**), years of education (**c**) and Injury Severity Score (**d**) among trauma patients. Time of trauma depicted by time 0 on the x-axis

495 patients had full time sick leave one year after trauma. In the multivariable logistic regression model being older, fewer years of education, psychiatric comorbidity, sick leave before trauma, ISS 25–40, serious spinal injury, GCS at admission < 14, being discharged anywhere else but home and LOS in hospital for more than seven days were all independent risk factors for sick leave one year after trauma. The strongest risk factor was pre-injury sick leave with an OR of 7.72 (5.30–11.23) for part-time and OR of 11.98 (7.04–20.39) for full-time sick leave the month before trauma

5.2 Study II

After excluding individuals who died during the first year following trauma, 4458 patients were included in the analysis of which 488 had full-time sick leave one year after trauma. Patients with full-time sick leave had more sick leave already before the trauma, were older, had more comorbidities and were also more seriously injured.

In Figure 3 the model building is graphically visualized with seven patient-related and seven trauma-related potential predictors in the comprehensive model compared with a total of eleven potential predictors in the simplified model. After variable selection, nine predictors remained in the comprehensive model compared with seven in the simplified version. For the comprehensive model the area under the curve (AUC) was 0.81 and a discrimination regarded as excellent and calibration as very good. For the simplified version the discrimination was still excellent, and the calibration was regarded as good.

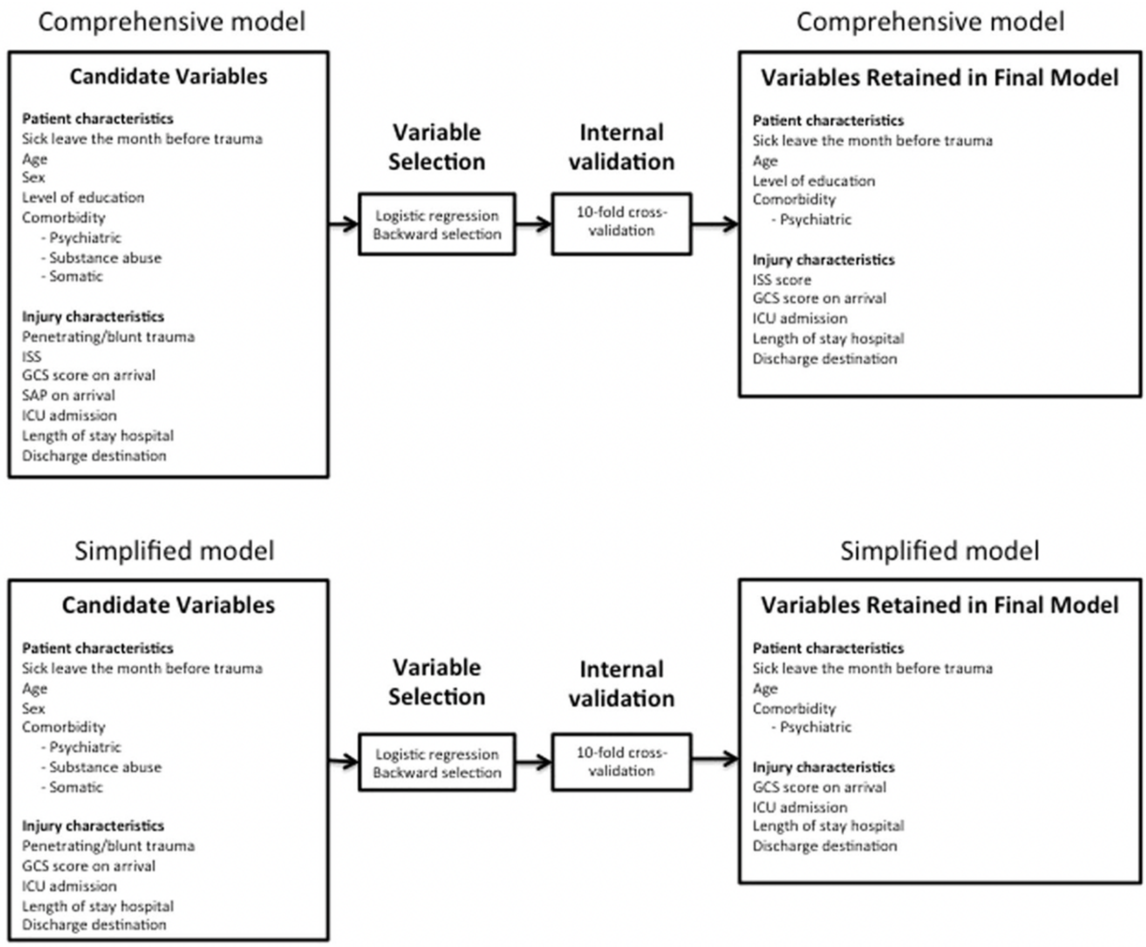

Figure 3. Model building for the comprehensive and the simplified model.

5.3 Study III

In this cohort study, 13 309 trauma patients and 70 621 matched controls were included. Compared to controls, fewer injured patients had achieved university level of education. In addition, trauma patients had more comorbidities (somatic, psychiatric and substance abuse) and a greater proportion used opioids preceding trauma (9.4 vs. 5.0 %). In univariate regression analysis, exposure to trauma was associated with chronic opioid use, OR 3.28 (3.70, 95 % CI 3.46–3.97, P < 0.001). In the adjusted model, this finding was still significant (Table 2).

Table 2. Associations between exposure to trauma and chronic opioid use among trauma patients and controls, presented as OR (95 % CI).

	Odds ratio	P value
Unadjusted	3.70 (3.46-3.97)	< 0.001
Restricted model*	4.04 (3.77-4.33)	< 0.001
Full model**	3.28 (3.02-3.55)	< 0.001

Values in parentheses are 95 % confidence intervals. *Adjusted for age and sex (variables used in matching). **In addition to restricted model, adjusted for education, somatic comorbidity, psychiatric comorbidity, substance abuse and pretrauma opioid use.

Mean opioid use for injured patients compared with controls was increased both before and after trauma (Figure 4). Furthermore, trauma patients had an increased mean opioid use after injury compared with their pretrauma opioid use, an increase that was statistically significant for the first three calendar quarters after injury. Chronic opioid users after trauma compared with non-users were older with lower level of education, less likely to be male and had more comorbidities including substance abuse in more than one fifth of the patients. In addition, chronic opioid users were more seriously injured, more likely to be admitted to ICU and 30 % used opioids already before the trauma.

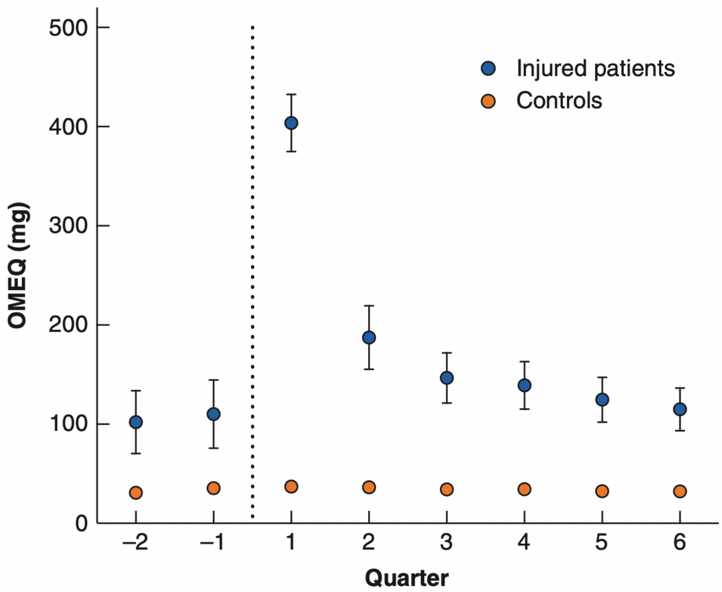

Figure 4. Opioid prescription before and after trauma in injured patients and in controls. Values show mean oral morphine equivalents (OMEQ) as milligrams per person per quarter for all trauma patients (including subjects with and without previous opioid exposure) and controls. The dashed line indicates the time of the index trauma.

In the multivariable model exploring factors associated with chronic opioid use following trauma, all variables except pre-existing substance abuse, severe abdominal injury and injury to upper extremity as well as shock and low GCS on arrival remained independent risk factors (Table 3). In the multivariable Cox regression analysis, the adjusted HR for all-cause death 6–18 months after trauma for trauma patients with chronic opioid use was significantly increased (HR 1.82, 95 % CI 1.34–2.48, P < 0.001). 205 patients died of whom 59 were chronic opioid users. Causes of death for chronic opioid users included external causes (12 %), psychiatric disease (10 %), respiratory problem (10 %), circulatory problem (32 %), neoplasm (12 %) and other (24 %).

In a subset of patients without previous opioid exposure findings were similar including baseline characteristics of chronic opioid users, risk factors for chronic opioid use and association with long-term mortality (HR 1.85, 95 % CI 1.26–2.72, P = 0.002).

Table 3. Univariable and multivariable logistic regression analysis of associations with chronic opioid use in injured patients presented as OR (95 % CI).

	Univariate	P value	Multivariable	P value
Age (years)				
15-44	Ref.	Ref.	Ref.	Ref.
45-54	1.41 (1.21-1.64)	< 0.001	1.07 (0.90-1.27)	0.43
55-64	1.57 (1.33-1.85)	< 0.001	1.15 (0.95-1.38)	0.16
65-74	1.73 (1.42-2.10)	< 0.001	1.08 (0.85-1.36)	0.54
75-84	2.34 (1.86-2.95)	< 0.001	1.49 (1.12-1.99)	0.007
≥ 85	3.08 (2.33-4.07)	< 0.001	2.19 (1.52-3.15)	< 0.001
Male sex	0.82 (0.73-0.91)	< 0.001	0.87 (0.76-0.99)	0.038
Educational level				
Low	Ref.	Ref.	Ref.	Ref.
Medium	0.95 (0.84-1.08)	0.428	0.97 (0.84-1.12)	0.67
High	0.74 (0.63-0.86)	< 0.001	0.83 (0.70-0.99)	0.038
CCI score				
CCI 0	Ref.	Ref.	Ref.	Ref.
CCI 1	1.75 (1.49-2.06)	< 0.001	1.21 (1.00-1.45)	0.049
CCI > 1	2.73 (2.34-3.19)	< 0.001	1.73 (1.42-2.11)	< 0.001
Psychiatric comorbidity	1.96 (1.73-2.22)	< 0.001	1.51 (1.29-1.76)	< 0.001
Substance abuse	1.67 (1.46-1.90)	< 0.001	1.09 (0.92-1.28)	0.34
Pretrauma opioid use	8.99 (7.89-10.24)	< 0.001	8.38 (7.26-9.67)	< 0.001
Severe head injury*	1.03 (0.88-1.20)	0.72	-	
Severe thoracic injury*	1.75 (1.52-2.01)	< 0.001	1.46 (1.23-1.73)	< 0.001
Severe abdominal injury*	1.50 (1.16-1.95)	0.002	1.12 (0.83-1.53)	0.45
Severe spinal injury*	2.80 (2.29-3.42)	< 0.001	2.78 (2.21-3.50)	< 0.001
Severe injury lower extremity*	3.25 (2.79-3.78)	< 0.001	3.37 (2.82-4.02)	< 0.001
Severe injury upper extremity*	1.83 (1.20-2.80)	0.005	1.43 (0.87-2.34)	0.16
Penetrating trauma	0.89 (0.72-1.10)	0.264	-	
Shock on arrival**	1.93 (1.39-2.69)	< 0.001	1.00 (0.67-1.48)	0.99
GCS				
13-15	Ref.	Ref.	Ref.	Ref.
9-12	1.36 (1.06-1.74)	0.016	1.07 (0.80-1.43)	0.65
3-8	1.30 (1.05-1.60)	0.014	0.80 (0.61-1.04)	0.090
ICU admission	1.73 (1.53-1.96)	< 0.001	1.32 (1.11-1.58)	0.002

*Values in parentheses are 95 per cent confidence intervals. *Severe injury equal to Abbreviated Injury Scale score above 2; **shock on arrival equal to systolic arterial pressure below 90 mmHg on arrival in trauma unit. CCI, Charlson comorbidity index; GCS, Glasgow Coma Scale; ICU, Intensive Care Unit*

5.4 Study IV

After exclusion of individuals not surviving the first two quarters after ICU admission as well as patients using methadone or buprenorphine, 204 402 individuals were included in the study. Median age was 63, 59 % were male, 23 % used opioids the year before ICU admission and median length of ICU stay was 1.5 days. Opioid usage for the study cohort and for individuals not using opioids the year before ICU admission is shown in Figure 5. After 24 months (eight quarters), the mean opioid consumption was still increased compared with baseline use (equaling 9-12 months before admission). The same pattern was noted for individuals not using opioids before ICU admission.

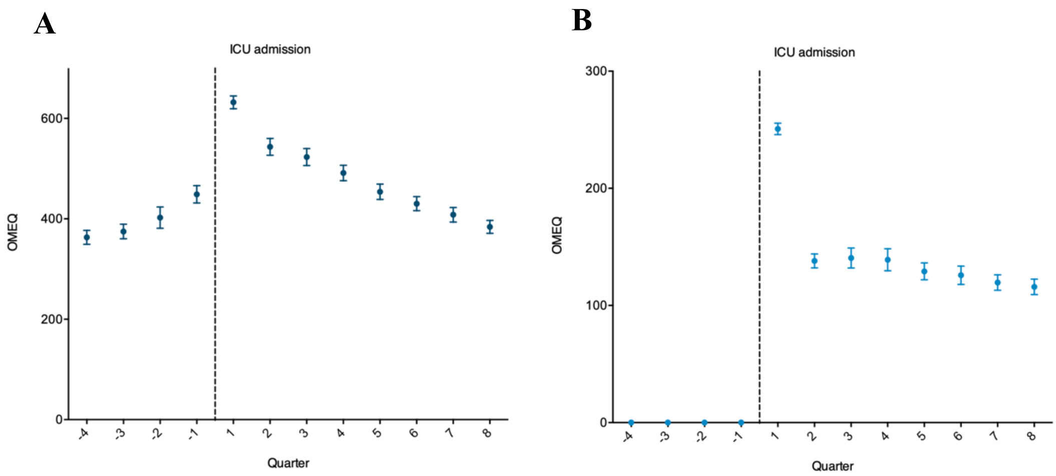

Figure 5. Opioid prescription pre- and post ICU care for the entire study cohort (n = 204 402) (**A**) and for a subset of patients without opioid exposure 12 months prior to ICU admission (n = 157 925) (**B**).

Chronic opioid users compared to non-users were older, less likely to be male, had more comorbid conditions and used opioids before ICU admission to a greater degree. In the multivariable logistic regression model being older, female sex, a low socioeconomic position, comorbidities (somatic, psychiatric), pre-ICU opioid exposure, low EMR, longer ICU stay, and earlier year of ICU admission were factors associated with higher odds of chronic opioid use following ICU admission (Figure 6). In the Cox regression analysis, chronic opioid use was associated with increased risk of death both unadjusted HR 2.2 (95 % CI, 2.2–2.3, P < 0.001) and after adjustment for age, sex, somatic and psychiatric comorbidities, substance abuse, EMR and ICU LOS, HR 1.7 (95 % CI, 1.6–1.7, P < 0.001). In the subset of patients without previous opioid exposure findings were similar with an adjusted HR of 1.9 (95 % CI, 1.8–2.1, P < 0.001).

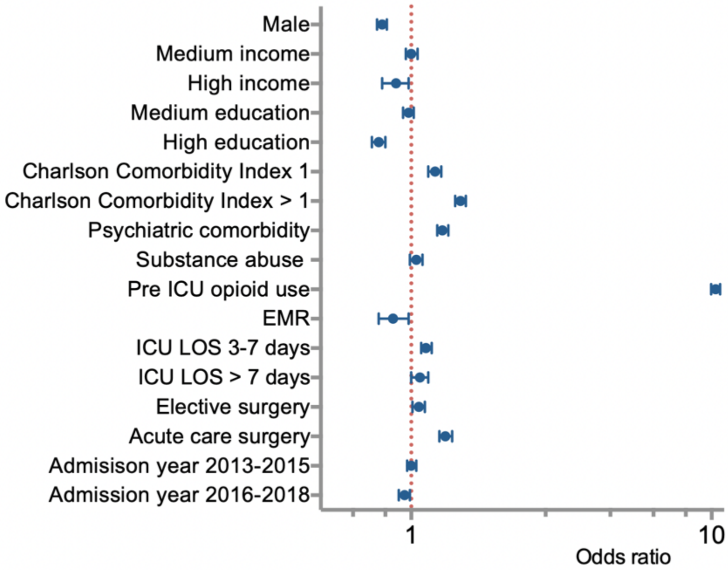

Figure 6. Odds ratios with corresponding 95 % confidence intervals. Multivariable logistic regression analysis. Estimated Mortality Rate (EMR), Intensive Care Unit (ICU), Length of Stay (LOS).

6 DISCUSSION

6.1 Methodological considerations

6.1.1 Study design

Optimal study design is fundamental to attaining valid results and to be able to answer a research question. In this thesis, all studies are retrospective observational cohort studies, where study I and III are matched cohort studies. Observational studies are often criticized for being vulnerable to bias and unpredictable confounding, but well executed they can be very powerful and perform similar conclusions as RCTs and can also complement RCTs in hypothesis generation[111, 112].

Cohort studies usually follow two separate groups recruited from the same source population, but with different exposure, in this case trauma or intensive care. In study I-III the source population is the greater Stockholm area for patients and controls and in Study IV the country of Sweden for included ICU patients. After exposure to trauma or intensive care, outcomes were followed prospectively and both local and national registers were used. In all four studies the cohort design allowed us to examine large populations over an extended time period. Study IV would have been better with matched controls, but the number required would need to be very high to be enough and that was not feasible.

In study I-III trauma patients were identified in a local trauma register. An alternative approach would have been to identify trauma patients from ICD-coding[113, 114]. This however would include patients less severely injured and with other mechanisms of injury such as isolated fractures[14]. Using patients from a trauma register also enabled comparisons with other studies.

6.1.2 Generalizability

One cause for concern in epidemiological studies is generalizability from the study sample to the population at large. In paper I-III, trauma patients and controls are included from the greater Stockholm area raising concerns about trauma patients originating from countries with different health care systems. However, patients baseline characteristics were similar to studies from other centers making inference also in other settings possible[115-117].

In study I and II sick leave functioned as a surrogate for long-term morbidity. Sickness benefits covering short- and long-term illness are complicated and differ widely across countries. However, all Nordic countries have highly developed hospital services with taxation-based health care with every citizen having equal access to services including trauma and intensive care. Furthermore, similar strategies are used to reduce sickness absence making an extrapolation of the results of study I and II to other Nordic countries possible. Social policies across Europe are generally much more generous than in the U.S. but with considerable variation across different countries. With that in mind, sick leave as a proxy for long-term morbidity still might be an adequate measure within a country, but making comparisons with other countries more difficult, hence reducing generalizability.

Study I-III were single center studies where generalizability is limited by size. In study IV the cohort was obtained from SIR, a large database covering more than 90 % of the Swedish ICU population at the time, and thus generalizability was considered good.

Inclusion and exclusion criteria set the boundaries for the research question and are important when trying to extrapolate results to other contexts. In study I-IV only adults were studied. In study I and II sick leave was the primary outcome which makes age boundaries reasonable. In trauma studies injury severity is important, and in study I median ISS was fairly low. However, restricting the patients to only ISS > 15 did not change the results. In study III and IV individuals not surviving 180 days were excluded since they were not able to fulfill the primary outcome of long-term mortality. However, including these patients in the sensitivity analyses did not change the results. In addition, patients using methadone and buprenorphine were excluded since they are used predominantly for individuals with problematic drug use.

In study II we developed two prediction models using data from the study population and then internally validated the model. However, external validation in another population is needed to confirm the generalizability.

6.1.3 Misclassification

All measurements are prone to error and understanding common errors and the means to reduce them is important and improves the precision of estimates. Misclassification of exposure or outcome is a form of systematic error and refers to the classification of an individual, a value or an attribute into a category other than that to which it should be assigned. This might arise because the information collected from study subjects is erroneous and is also known as information bias.

6.1.3.1 Misclassification of exposure

In all the included studies national health registers are used to collect information on socioeconomic factors and classification of comorbidities. LISA has a high validity[98], but in the data collected there was missing data on education. However, given the large number of individuals included this was not considered a problem in any of the studies. In paper I and II information on sick leave was collected from LISA. Since the employer pays for the first fourteen days, data on sick leave for day 1-30 after trauma were not complete and for this reason excluded in paper I. The National Patient Register has a high validity[99], but primary care is not included, neither is the information on outpatient care complete for the first years. However, it is unlikely that different definitions of comorbidities would influence estimates of interest for the included studies.

In study III and IV the definition of opioid use is important. In study III chronic opioid use was defined as any prescription in the second calendar quarter following trauma, and in study

IV chronic opioid use was equal to repeated prescriptions both in the first and the second calendar quarter following ICU admission. In study III we cannot be sure to what extent individuals in fact were chronic users since we accepted one prescription in the second calendar quarter to be classified as chronic users. The reason for this, was to avoid misclassification of individuals with prolonged hospital stay during the first three months, and we chose to censor all prescriptions in the first quarter following trauma. Moreover, there is no consensus on how to define chronic opioid use, but a common definition is treatment longer than three months[54-56]. In paper III a sensitivity analysis was performed including weaker opioids, but this did not change the results. In study III and IV some degree of misclassification cannot be excluded since some individuals receiving one prescription of opioids in the second calendar quarter could have received this for another event not connected with trauma or ICU admission. In study III and IV there is no data available on whether the individuals consumed the opioids prescribed, but previous studies of opioid use suggest fair to moderate agreement between self-reported data on medicine use and prescription records[118].

6.1.3.2 Misclassification of outcome

In study I and II sick leave was the primary outcome, but to minimize selection bias individuals receiving disability pension were included. Students and unemployed are also entitled to sickness benefits, and for this reason included further reducing bias. In study III and IV the primary outcome was death 6-18 months after trauma and ICU admission respectively. The Swedish Cause of Death register has around 99 % coverage regarding death, but only around 80 % correct for underlying cause of death[103]. Studies in Sweden and other countries show that validity varies regarding accuracy with age and different diagnoses.

6.1.4 Confounding

Confounding is the distortion of the association between an exposure and an outcome by a third variable. Confounders introduce a bias since an observed effect could be attributed to the confounder rather than the independent variable studied. Accounting for confounders is important and randomization, restriction or matching are ways to reduce the risk of confounding when designing a study. When analyzing data, confounders can also be assessed using for example regression models or stratification.

6.1.4.1 Study I

In the first study trauma patients and the control group were matched on age, sex and municipality. Matching is applied when there is a potential difference in occurrence of potential confounders between exposed and unexposed individuals. In addition, stratified analyses based on age, sex, education and injury severity were performed. Furthermore, the study cohort was restricted with respect to age and logistic regression models were used to analyze risk factors for prolonged sick leave.

6.1.4.2 Study II

Candidate variables were selected based on etiological knowledge, physiological plausibility and data availability and selected into the model using a backward selection algorithm based on their predictive value[119].

6.1.4.3 Study III

Trauma patients and the control group were matched on age, sex and municipality. Patients were restricted with respect to hospital admission for more than 180 days and dying during the first 180 days. A sensitivity analysis addressing non-random dropout from the study owing to death was performed but did not change the results. Stratified analyses based on a subset of trauma patients without opioid exposure six months preceding injury were performed. Missing data was addressed with multiple imputation.

6.1.4.4 Study IV

Similar to study III, patients were restricted with respect to hospital admission for more than 180 days and dying during the first 180 days and the same sensitivity analysis was performed. Equally, patients not using opioids before ICU admission were analyzed in a stratified analysis. There was some missing data but given the large number of patients this was considered not to affect the outcome.

However, unmeasured confounders and residual confounding may still remain despite the above-mentioned methods used to adjust for confounders. In addition, there is no consensus in how to include variables when building regression models or how to best adjust for different factors.

6.1.5 Random errors

All data contain random errors – no measurement system is perfect. A study population is a small sample of the entire population and a principal assumption in epidemiology is that we by using a study population can draw an inference on the source population. However, chance may affect the results and produce an estimate different from the true value. The uncertainty in using a sample to estimate for the larger population can be quantified with p-values and CI. The CI reflects the interval which were a study repeated infinitely often, would contain the true mean 95 % of the times. CI are affected by sample size and spread of the data. The p-value is the probability that results seen could have occurred by chance alone assuming that there is in fact no difference between groups (null hypothesis). The lower the p-value, the more we can be sure that the difference is not just random sampling error with no real underlying difference. P-values cannot tell you if there is bias in the study and does not determine if the effect is clinically significant, a small effect in a study with large sample size can have a very small p-value.

The large sample sizes in study I, III and IV and the generally narrow CI reduce the likelihood for random errors. In study I to IV the significance level was set to 0.05, meaning that we have chosen to accept a 5 % risk of type I error (null hypothesis is incorrectly rejected leading to a falsely positive finding). In study II the sample size was smaller introducing risk for type II error, incorrectly retaining the null hypothesis equaling not seeing a difference even when there was a true difference.

6.2 Interpretation of findings

6.2.1 Sick leave and pharmacological treatment following trauma and critical care

The goal of trauma and critical care is apart from reducing short-term morbidity and mortality rates, also to reduce disability and enhance personal autonomy and productivity. In the literature, in-hospital or 30-day mortality have long been primary endpoints and only more recent studies address long-term outcomes and morbidity. Trauma and critical care are closely connected since many of the previous open surgical procedures following severe trauma are being replaced by nonoperative approaches shifting part of the trauma care management to the ICU.

Our approach to identify individuals at risk of long-term morbidity was to use sick leave as a combined measure of somatic, psychological and social functioning originating from the idea that also factors not related to the injury per se are important when evaluating long-term outcomes. A recent multi-center study concluded that sociodemographic factors are central and suggests that social support systems might be even more relevant than for example trauma severity[120]. This strengthens our idea of sick leave as a feasible proxy and summary measure of long-term morbidity after trauma.

Another aspect of long-term outcomes is potential negative side effects of pharmacological treatment commonly used in trauma care or critical care. Severe trauma as well as patients admitted to the ICU typically involves significant pain rendering treatment with potent analgesics where opioids are part of the first-line treatment for moderate to severe pain. However, it has been suggested that high cumulative doses or taking opioids over a long period of time could lead to dependence, addiction as well as hormone and immune system changes. Furthermore, the misuse of and addiction to opioids has turned into a crisis in several countries affecting public and economic health. With improved survival rates after trauma and critical care patients, long-term effects such as opioid dependence affecting long-term outcomes has become increasingly important.

6.2.2 Sick leave after trauma – magnitude and prediction

Patients surviving traumatic injury and critical care often show impairments that affect functional capacity, and more than half of patients report physical limitations on long-term follow up[120]. However, there is no universal definition of long-term morbidity making comparisons between studies and countries difficult. Several injury-related predictors for worse outcomes have been suggested including ISS and traumatic brain injury, but long-term outcomes are most likely influenced by numerous factors of which non-trauma related factors such as being older and socioeconomic factors might be even more important[36, 120-123].

Using sick leave as a proxy for long-term morbidity in study I and II originated from the idea that sociodemographic factors are important when addressing long-term outcomes. In addition, sick leave carries high costs both for employers and society, but also for the individual and seems to be a feasible surrogate for morbidity. In study I, injured individuals had significantly more sick leave before and after trauma compared to matched controls. This could partly be explained by the fact that trauma patients more often have comorbid psychiatric illness compared with the general population. In Sweden, mental health disorders are the most common causes of sick leave and disability pension[31]. Sick leave rates did not return to pre-traumatic rates during follow-up of one year and more than 50 % reported full time sick leave three years after trauma indicating a significant long-term effect[36]. Furthermore, low educational level was associated with increased risk of sick leave after trauma. Previous studies have shown that low socioeconomic status is a predictor of sick leave[124], but is also associated with risk of being a trauma victim[125, 126].

Being older was not surprisingly associated with prolonged sick leave given that age is regularly included and associated with sickness absence in previous reports[127]. Females had more sick leave before trauma, but in contrast to previous studies this difference was omitted after trauma[36] and sex did not influence the post-traumatic risk of sick leave. This might reflect the fact that despite women in Sweden having more sick leave, this is restricted to shorter periods of sickness absence rather than long-term which is common after severe traumatic injury[128].

More seriously injured patients had significantly more sick leave except for individuals with ISS > 40. Severe spinal injury and low GCS on arrival was associated with sick leave after trauma, whereas severe head injury did not reach statistical significance. Patients with long hospital stay also showed an association with long-term sick leave. Our cohort had a rather low median ISS of 5, but when restricting to individuals with ISS > 15 the results were unchanged. Thus, comparisons with other studies exploring associations between trauma and return to work are possible[36, 44, 129]. The most noteworthy finding was the strong association between sick leave before and after trauma. This might reflect the fact that post-injury sick leave not only is connected to the specific traumatic event, but rather is associated with several factors such as working conditions, socioeconomic factors and residency that in different ways influence the risk of long-term sick leave[33].

In study II, we propose two prognostic models for predicting long-term morbidity defined as full-time sick leave one year after trauma among trauma survivors. Prediction models cannot determine whether an individual will develop a particular state or disease but can be useful in identifying groups of individuals at increased risk of a particular outcome, for example future sick leave. This gives the clinician a chance to implement prophylactic measures. Variables were entered into the model if they were potentially causative or known to be associated with risk of sick leave[130]. Trauma-related parameters as well as non-trauma related factors including socioeconomic factors were assessed in the model building.

The initial comprehensive predictive model included nine predictors and demonstrated an AUC of 81 % and showed excellent discrimination and very good calibration. The inclusion of the injury-related parameter ISS was expected given the known association with conditions that demonstrate significant long-term morbidity, whereas the prognostic value of initial GCS appears inconsistent in previous studies[47, 131]. ICU admittance, hospital length of stay and discharge destination reflect the overall response to the injury. As in study I, non-trauma related parameters were even more important and age, psychiatric comorbidity, level of education and pre-injury sick leave were included as predictors. Low socioeconomical status and psychiatric disease have been discussed previously and are associated both with increased risk of becoming a trauma victim as well as increased risk of sick leave[125, 130]. Pre-injury sick leave was strongly associated with prolonged sick leave in study I and was included as a predictor also in the comprehensive model in study II.

Furthermore, a less complex, simplified model was developed with the ambition to be useful bedside including only parameters easily accessible already at discharge. The simple model included seven parameters and performed less well, but surprisingly good. The two different prediction models might be useful in clinical treatment decisions and may aid physicians when allocating scarce medical resources for future follow up, intensified rehabilitation or establishing contact with the social security agency already at discharge. Future external validation in other datasets of these models is necessary before clinical use.

6.2.3 Opioid use after trauma and intensive care

Opioids are derived from, or a synthetic version of, opium. Evidence of any long-term use is limited and instead there is evidence of adverse effects for anything but short-term treatment. No randomized controlled trials have been performed exploring the effectiveness of opioids, and even though they are commonly used when treating moderate to severe pain, the misuse of prescription opioids is frequent. In the U.S. and Canada, opioid misuse has turned into a serious crisis over the last years, but also countries outside North America are facing increased problems with opioids[132]. Most trauma victims and intensive care survivors report pain both at discharge and for many years after discharge[29, 133] and a majority of ICU and trauma patients receive opioids for pain management or as part of a sedation regimen[134]. The fact that pain should be treated is self-evident. The question is how to prescribe responsibly and for how long? The magnitude of long-term use of opioids after trauma and ICU care is not fully investigated, neither is the possibility of trauma and ICU care being gateways to future opioid misuse.

In study III, trauma patients used more opioids before and after trauma compared with matched controls, possibly explained by differences in prevalence of comorbid psychiatric illness[125, 135], substance abuse[61], lower socioeconomic status and somatic comorbidities. Opioid use increased after trauma despite the high baseline use, but this finding was somewhat expected given tolerance development and subsequent dose-escalation. However, the additional increase in their opioid use for three calendar quarters following trauma is beyond the point where opioids should have been tapered and discontinued at least back to their own pre-injury baseline.

In study IV, no matched controls existed, but ICU patients used more opioids both before and after ICU admission when compared with data from the general population[136, 137]. Intensive care is complex given the heterogenous group of patients admitted, and the high baseline consumption might be explained by medical conditions known to be associated with increased opioid use[138]. Furthermore, similar to trauma patients, ICU patients also have a high prevalence of comorbid psychiatric illness and substance abuse[139]. The mean opioid consumption was increased for more than 24 months after ICU admission compared with baseline levels 9-12 months before admission indicating an even greater concern that opioids are being used in a way not supported by evidence. One possible explanation is the fact that most ICU patients report pain for several years after discharge, a well-known risk factor for chronic opioid treatment[73].

Interestingly, in the subset of patients without opioid exposure six months prior to trauma in study III, findings were similar indicating that the study not only describes individual with an ongoing misuse of opioids already before the trauma. The same findings were evident in Study IV where mean opioid use was substantial during the follow-up period of two years also for individuals without previous opioid use.

Risk factors for chronic opioid use in both study III and IV included being older and female sex where other reports demonstrate similar associations for age but contrasting results for sex[140-142]. Comorbid psychiatric illness was associated with long-term use of opioids in both studies, a patient group with a known increased likelihood of heavy opioid utilization even without injury or hospitalization[135]. Surprisingly, and as opposed to previous studies, having a substance use disorder was only associated with chronic opioid use in the univariate, but not in the multivariable analyses. Pre-injury opioid usage was strongly associated with chronic post-injury use of opioids in study III and IV, a recognized risk factor for chronic opioid usage[60, 137]. This has been demonstrated in other trauma populations[60], and especially in orthopedic settings[59] supported by the fact that severe injury to the legs had the strongest association with chronic opioid use in study III. In addition, chronic opioid users after both trauma and ICU care had lower socioeconomic status[143]. In study III admittance to ICU was associated with chronic use and in study IV increasing ICU length of stay had the same effect.

Both in study III and IV, long-term opioid use was associated with increased risk of death 6 – 18 months after trauma and ICU admission respectively. Previous studies show that trauma survivors have an increased mortality for several years following trauma, partly because of substance abuse and opioid use might be part of that finding[17]. Several plausible mechanisms for an increased mortality for opioid users have been presented in previous studies such as increased risk of stroke[144], cardiac events[69] and overdose[67], but also delirium, constipation and respiratory depression[145, 146]. Interestingly, HR was even greater in the subset of patients without exposure to opioids preceding ICU admission in study III and IV. A finding in contrast with previous studies where the risk of death was higher among chronic users compared to opioid naïve patients[147, 148].

7 CONCLUSIONS

Trauma patients have more sick leave compared to matched controls both before and after injury. The difference is maximal early after trauma and sustained during follow up. Being older, low level of education, psychiatric comorbidity, pre-injury sick leave, injury severity, spinal injury, low GCS at admission, hospital length of stay and discharge to other destination than home are all associated with full-time sick leave one year after trauma.

Predicting long-term morbidity using sick leave as a proxy for morbidity is feasible and has a good predictive accuracy. Predictors for sick leave following trauma include both factors related to the trauma and host factors. Prediction models might help identifying individuals with high risk of sick leave and may be used when allocating resources for future follow-up. External validation is necessary in order to evaluate generalizability.

Exposure to trauma is associated with chronic opioid use and injured patients use more opioids both before and after injury compared to matched controls. Trauma as well as non-trauma-related factors are associated with chronic opioid use. Individuals with chronic post-traumatic use of opioids have an increased risk of death. The same findings are noted for individuals not using opioids before trauma. For chronic opioid users dying, cardiovascular events were the most common causes of death.

Mean opioid consumption is increased two years after ICU admission despite lack of evidence for long-term use of opioids. Being older, female sex, prior opioid use, surgery and ICU length of stay were among risk factors for chronic opioid use. The same applied for individuals not using opioids before admission to critical care. Chronic opioid users had an increased risk of death.

8 POINTS OF PERSPECTIVE

With improved survival after trauma and critical care, long-term sequelae and morbidity become more important. The question remains how to best describe and quantify long-term morbidity and needs to be studied further. As of today, there is no method for selecting patients for follow-up after traumatic injury. By implementing the use of sick leave as a proxy for long-term morbidity and utilizing the prediction models developed in this thesis, high-risk cohorts of patients can be identified. Hopefully, this can lead to a better selection of patients that may benefit from follow-up and enabling resources to be concentrated on these individuals. The prediction instruments need external validation before use.

Many authors agree on the fact that more effort must be put in preventing opioid misuse and several suggestions have been presented on how to decrease opioid use, but so far these efforts do not seem to have slowed the negative effects and adverse outcomes. Awareness of prolonged use of opioids should be part of follow-up after traumatic injury and intensive care but is not regularly performed in current systems. With the identification of high-risk patients, interventional studies can be performed with the potential to improve patient outcomes by implementing early interventions.

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10 REFERENCES

1. The American Association for the Surgery of Trauma. Trauma facts. 2021. https://www.aast.org/resources/trauma-facts. Accessed August 11, 2021.
2. Sleat GK, Ardolino AM, Willett KM. Outcome measures in major trauma care: a review of current international trauma registry practice. *Emerg Med J*. Dec 2011;28(12):1008-12. doi:10.1136/emermed-2011-200326
3. Swedish Board of Health and Welfare. Causes of Death 2019. https://sdb.socialstyrelsen.se/if_dor/val.aspx. Accessed September 7, 2021.
4. Centre For Trauma Sciences University of London. Trauma facts. 2021. http://www.c4ts.qmul.ac.uk. Accessed August 11, 2021.
5. Global Burden of Diseases and Injuries, Collaborators. 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. Oct 17 396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9
6. World Health Organization. Global Status Report on Road Safety 2018. https://apps.who.int/iris/bitstream/handle/10665/277370/WHO-NMH-NVI-18.20-eng.pdf?ua=1. Accessed September 7, 2021.
7. Tisherman SA, Stein DM. ICU Management of Trauma Patients. *Crit Care Med*. Dec 2018;46(12):1991-1997. doi:10.1097/CCM.0000000000003407
8. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. *Crit Care Med*. Dec 2010;38(12):2386-400. doi:10.1097/CCM.0b013e3181f3dec5
9. The Swedish Intensive Care Registry (SIR). 2021. https://www.icuregswe.org/en/. Accessed September 11, 2021.
10. Rating the severity of tissue damage. I. The abbreviated scale. *JAMA*. Jan 11 1971;215(2):277-80.
11. Baker SP, O'Neill B, Haddon W, Jr., Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. Mar 1974;14(3):187-96.
12. Soreide K. Epidemiology of major trauma. *Br J Surg*. Jul 2009;96(7):697-8. doi:10.1002/bjs.6643
13. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008. *J Trauma*. Sep 2010;69(3):620-6. doi:10.1097/TA.0b013e3181bbfe2a
14. MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med*. Jan 26 2006;354(4):366-78. doi:10.1056/NEJMsa052049

15. Baker CC, Oppenheimer L, Stephens B, Lewis FR, Trunkey DD. Epidemiology of trauma deaths. *Am J Surg*. Jul 1980;140(1):144-50.

16. Santry HP, Psoinos CM, Wilbert CJ, et al. Quadrimodal distribution of death after trauma suggests that critical injury is a potentially terminal disease. *J Crit Care*. Jun 2015;30(3):656 e1-7. doi:10.1016/j.jcrc.2015.01.003

17. Eriksson M, Brattstrom O, Larsson E, Oldner A. Causes of excessive late death after trauma compared with a matched control cohort. *Br J Surg*. Sep 2016;103(10):1282-9. doi:10.1002/bjs.10197

18. Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. *Crit Care*. Apr 27 2013;17(2):R81. doi:10.1186/cc12695

19. van Breugel JMM, Niemeyer MJS, Houwert RM, Groenwold RHH, Leenen LPH, van Wessem KJP. Global changes in mortality rates in polytrauma patients admitted to the ICU-a systematic review. *World J Emerg Surg*. Sep 30 2020;15(1):55. doi:10.1186/s13017-020-00330-3

20. Strandberg G, Walther S, Agvald Ohman C, Lipcsey M. Mortality after Severe Sepsis and Septic Shock in Swedish Intensive Care Units 2008-2016-A nationwide observational study. *Acta Anaesthesiol Scand*. Aug 2020;64(7):967-975. doi:10.1111/aas.13587

21. Rydenfelt K, Engerstrom L, Walther S, Sjoberg F, Stromberg U, Samuelsson C. In-hospital vs. 30-day mortality in the critically ill - a 2-year Swedish intensive care cohort analysis. *Acta Anaesthesiol Scand*. Aug 2015;59(7):846-58. doi:10.1111/aas.12554

22. Vasilevskis EE, Kuzniewicz MW, Dean ML, et al. Relationship between discharge practices and intensive care unit in-hospital mortality performance: evidence of a discharge bias. *Med Care*. Jul 2009;47(7):803-12. doi:10.1097/MLR.0b013e3181a39454

23. Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *JAMA*. Jun 1 2011;305(21):2175-83. doi:10.1001/jama.2011.697

24. Ringdal KG, Coats TJ, Lefering R, et al. The Utstein template for uniform reporting of data following major trauma: a joint revision by SCANTEM, TARN, DGU-TR and RITG. *Scand J Trauma Resusc Emerg Med*. Aug 28 2008;16:7. doi:10.1186/1757-7241-16-7

25. Ulvik A, Wentzel-Larsen T, Flaatten H. Trauma patients in the intensive care unit: short- and long-term survival and predictors of 30-day mortality. *Acta Anaesthesiol Scand*. Feb 2007;51(2):171-7. doi:10.1111/j.1399-6576.2006.01207.x

26. Davidson GH, Hamlat CA, Rivara FP, Koepsell TD, Jurkovich GJ, Arbabi S. Long-term survival of adult trauma patients. *JAMA*. Mar 9 2011;305(10):1001-7. doi:10.1001/jama.2011.259

27. Probst C, Zelle BA, Sittaro NA, Lohse R, Krettek C, Pape HC. Late death after multiple severe trauma: when does it occur and what are the causes? *J Trauma*. Apr 2009;66(4):1212-7. doi:10.1097/TA.0b013e318197b97c

28. Brinkman S, de Jonge E, Abu-Hanna A, Arbous MS, de Lange DW, de Keizer NF. Mortality after hospital discharge in ICU patients. *Crit Care Med*. May 2013;41(5):1229-36. doi:10.1097/CCM.0b013e31827ca4e1

29. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. Apr 7 2011;364(14):1293-304. doi:10.1056/NEJMoa1011802

30. Parry SM, Denehy L, Beach LJ, Berney S, Williamson HC, Granger CL. Functional outcomes in ICU - what should we be using? - an observational study. *Crit Care*. Mar 29 2015;19:127. doi:10.1186/s13054-015-0829-5

31. Swedish Social Insurance Agency. 2021. https://www.forsakringskassan.se. Accessed August 15, 2021.

32. Hashemi L, Webster BS, Clancy EA. Trends in disability duration and cost of workers' compensation low back pain claims (1988-1996). *Journal of occupational and environmental medicine*. Dec 1998;40(12):1110-9.

33. Swedish Social Insurance Agency. Social Insurance Report 2016. https://www.forsakringskassan.se/wps/wcm/connect/a2001891-5c47-4b8a-b47b-64dfbbd48555/sjukfranvarons-utveckling-2016-socialforsakringsrapport-2016-7.pdf?MOD=AJPERES&CVID=. Accessed August 14, 2021.

34. Wallman T, Wedel H, Johansson S, et al. The prognosis for individuals on disability retirement. An 18-year mortality follow-up study of 6887 men and women sampled from the general population. *BMC Public Health*. Apr 22 2006;6:103. doi:10.1186/1471-2458-6-103

35. Parks JK, Diaz-Arrastia R, Gentilello LM, Shafi S. Postinjury employment as a surrogate for functional outcomes: a quality indicator for trauma systems. *Proc (Bayl Univ Med Cent)*. Oct 2010;23(4):355-8.

36. Gabbe BJ, Simpson PM, Harrison JE, et al. Return to Work and Functional Outcomes After Major Trauma. *Annals of surgery*. Jan 15 2016;263(4):623-632. doi:10.1097/sla.0000000000001564

37. Livingston DH, Tripp T, Biggs C, Lavery RF. A fate worse than death? Long-term outcome of trauma patients admitted to the surgical intensive care unit. *J Trauma*. Aug 2009;67(2):341-8; discussion 348-9. doi:10.1097/TA.0b013e3181a5cc34

38. McMillan T, Wilson L, Ponsford J, Levin H, Teasdale G, Bond M. The Glasgow Outcome Scale - 40 years of application and refinement. *Nat Rev Neurol*. Aug 2016;12(8):477-85. doi:10.1038/nrneurol.2016.89

39. Ardolino A, Sleat G, Willett K. Outcome measurements in major trauma--results of a consensus meeting. *Injury*. Oct 2012;43(10):1662-6. doi:10.1016/j.injury.2012.05.008

40. Gabbe BJ, Simpson PM, Sutherland AM, et al. Functional measures at discharge: are they useful predictors of longer term outcomes for trauma registries? *Ann Surg*. May 2008;247(5):854-9. doi:10.1097/SLA.0b013e3181656d1e

41. Beach J, Benoit M, Rowe BH, Cherry N. Can emergency physicians predict severity and time away from work? *Occupational medicine (Oxford, England)*. Dec 2012;62(8):648-50. doi:10.1093/occmed/kqs174

42. *Sjukskrivningarnas anatomi – en ESO-rapport om drivkrafterna i sjukförsäkringssystemet.* 2016. Finansdepartementet.

43. MacKenzie EJ, Shapiro S, Smith RT, Siegel JH, Moody M, Pitt A. Factors influencing return to work following hospitalization for traumatic injury. *Am J Public Health*. Mar 1987;77(3):329-34.

44. Soberg HL, Finset A, Bautz-Holter E, Sandvik L, Roise O. Return to work after severe multiple injuries: a multidimensional approach on status 1 and 2 years postinjury. *J Trauma*. Feb 2007;62(2):471-81. doi:10.1097/TA.0b013e31802e95f4

45. Toien K, Skogstad L, Ekeberg O, Myhren H, Bredal IS. Prevalence and predictors of return to work in hospitalised trauma patients during the first year after discharge: A prospective cohort study. Article. *Injury-Int J Care Inj*. Sep 2012;43(9):1606-1613. doi:10.1016/j.injury.2011.03.038

46. Clay FJ, Newstead SV, McClure RJ. A systematic review of early prognostic factors for return to work following acute orthopaedic trauma. *Injury*. Aug 2010;41(8):787-803. doi:10.1016/j.injury.2010.04.005

47. Jourdan C, Bosserelle V, Azerad S, et al. Predictive factors for 1-year outcome of a cohort of patients with severe traumatic brain injury (TBI): results from the PariS-TBI study. *Brain Inj*. 2013;27(9):1000-7. doi:10.3109/02699052.2013.794971

48. Nehra D, Nixon ZA, Lengenfelder C, et al. Acute Rehabilitation after Trauma: Does it Really Matter? *J Am Coll Surg*. Dec 2016;223(6):755-763. doi:10.1016/j.jamcollsurg.2016.09.001

49. World Health Organization. *Cancer pain relief. With a guide to opioid availability. 2nd edn, Geneva.* 1996.

50. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med*. Jan 15 2015;372(3):241-8. doi:10.1056/NEJMsa1406143

51. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. Nov 13 2003;349(20):1943-53. doi:10.1056/NEJMra025411

52. Degenhardt L, Charlson F, Mathers B, et al. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addiction*. Aug 2014;109(8):1320-33. doi:10.1111/add.12551

53. Stein C. New concepts in opioid analgesia. *Expert Opin Investig Drugs*. 2018;27(10):765-775. doi:10.1080/13543784.2018.1516204

54. Davis MP, Mehta Z. Opioids and Chronic Pain: Where Is the Balance? Review. *Curr Oncol Rep*. Dec 2016;18(12):14. 71. doi:10.1007/s11912-016-0558-1

55. Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. *Clin J Pain*. Jul-Aug 2008;24(6):521-7. doi:10.1097/AJP.0b013e318169d03b

56. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. *Pain*. Dec 2013;154 Suppl 1:S94-100. doi:10.1016/j.pain.2013.09.009

57. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid Use for Chronic Low Back Pain A Prospective, Population-based Study Among Injured Workers in Washington State, 2002-2005. Article. *Clin J Pain*. Nov-Dec 2009;25(9):743-751. doi:10.1097/AJP.0b013e3181b01710

58. Flanagan CD, Wysong EF, Ramey JS, Vallier HA. Understanding the Opioid Epidemic: Factors Predictive of Inpatient and Postdischarge Prescription Opioid Use After Orthopaedic Trauma. *J Orthop Trauma*. Oct 2018;32(10):e408-e414. doi:10.1097/BOT.0000000000001256

59. Holman JE, Stoddard GJ, Higgins TF. Rates of prescription opiate use before and after injury in patients with orthopaedic trauma and the risk factors for prolonged opiate use. *J Bone Joint Surg Am*. Jun 19 2013;95(12):1075-80. doi:10.2106/JBJS.L.00619

60. Mohamadi A, Chan JJ, Lian J, et al. Risk Factors and Pooled Rate of Prolonged Opioid Use Following Trauma or Surgery: A Systematic Review and Meta-(Regression) Analysis. *J Bone Joint Surg Am*. Aug 1 2018;100(15):1332-1340. doi:10.2106/JBJS.17.01239

61. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain*. Jul-Aug 2008;24(6):497-508. doi:10.1097/AJP.0b013e31816b1070

62. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA*. Mar 7 2012;307(9):940-7. doi:10.1001/jama.2012.234

63. Quinn PD, Hur K, Chang Z, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: a national study of commercial health care claims. Article. *Pain*. Jan 2017;158(1):140-148. doi:10.1097/j.pain.0000000000000730

64. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. Feb 17 2015;162(4):276-86. doi:10.7326/M14-2559

65. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain*. Jul-Aug 2008;24(6):469-78. doi:10.1097/AJP.0b013e31816b2f26

66. Trevino CM, deRoon-Cassini T, Brasel K. Does opiate use in traumatically injured individuals worsen pain and psychological outcomes? *J Pain*. Apr 2013;14(4):424-30. doi:10.1016/j.jpain.2012.12.016

67. Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med*. Apr 2015;175(4):608-15. doi:10.1001/jamainternmed.2014.8071

68. Monarrez-Espino J, Laflamme L, Rausch C, Elling B, Moller J. New opioid analgesic use and the risk of injurious single-vehicle crashes in drivers aged 50-80 years: A population-based matched case-control study. Article. *Age Ageing*. Sep 2016;45(5):628-634. doi:10.1093/ageing/afw115

69. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. *Pharmacoepidemiol Drug Saf*. Jul 2011;20(7):754-62. doi:10.1002/pds.2131

70. Mosher HJ, Jiang L, Sarrazin MSV, Cram P, Kaboli PJ, Vander Weg MW. Prevalence and Characteristics of Hospitalized Adults on Chronic Opioid Therapy. Article. *J Hosp Med*. Feb 2014;9(2):82-87. doi:10.1002/jhm.2113

71. Muhuri PK GJ, Davies C. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. CBHSQ Data Review, 2013. https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm. Accessed December 23, 2018.

72. Trang T, Al-Hasani R, Salvemini D, Salter MW, Gutstein H, Cahill CM. Pain and Poppies: The Good, the Bad, and the Ugly of Opioid Analgesics. Article. *J Neurosci*. Oct 2015;35(41):13879-13888. doi:10.1523/jneurosci.2711-15.2015

73. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. Apr 2015;156(4):569-76. doi:10.1097/01.j.pain.0000460357.01998.f1

74. Quinones MA. Drug abuse during the Civil War (1861-1865). *Int J Addict*. 1975;10(6):1007-20.

75. JN. C. The American Pain Society 1995 Presidential address. 1996;5:85–8.;

76. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*. Sep 5 2017;167(5):293-301. doi:10.7326/M17-0865

77. Centers for Disease Control and Prevention. Drug Overdose Deaths. 2021. https://www.cdc.gov/drugoverdose/deaths/index.html. Accessed August 15, 2021.

78. Adams ET, Cohen EL, Bernard A, Darnell W, Helme DW. Trauma Trainees' Multiple Competing Goals in Opioid Prescription Communication. *Qualitative health research*. Nov 2018;28(13):1983-1996. doi:10.1177/1049732318784896

79. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I--evidence assessment. *Pain Physician*. Jul 2012;15(3 Suppl):S1-65.

80. Ulvik A, Kvale R, Wentzel-Larsen T, Flaatten H. Quality of life 2-7 years after major trauma. *Acta Anaesthesiol Scand*. Feb 2008;52(2):195-201. doi:10.1111/j.1399-6576.2007.01533.x

81. Williamson OD, Epi GD, Gabbe BJ, et al. Predictors of moderate or severe pain 6 months after orthopaedic injury: a prospective cohort study. *J Orthop Trauma*. Feb 2009;23(2):139-44. doi:10.1097/BOT.0b013e3181962e29

82. Castillo RC, MacKenzie EJ, Wegener ST, Bosse MJ, Group LS. Prevalence of chronic pain seven years following limb threatening lower extremity trauma. *Pain*. Oct 2006;124(3):321-9. doi:10.1016/j.pain.2006.04.020

83. Rivara FP, Mackenzie EJ, Jurkovich GJ, Nathens AB, Wang J, Scharfstein DO. Prevalence of pain in patients 1 year after major trauma. *Arch Surg*. Mar 2008;143(3):282-7; discussion 288. doi:10.1001/archsurg.2007.61

84. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2016 National Summary Tables. https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2016_namcs_web_tables.pdf. Accessed August 15, 2021.

85. Rosenbloom BN, McCartney CJL, Canzian S, Kreder HJ, Katz J. Predictors of Prescription Opioid Use 4 Months After Traumatic Musculoskeletal Injury and Corrective Surgery: A Prospective Study. *J Pain*. Aug 2017;18(8):956-963. doi:10.1016/j.jpain.2017.03.006

86. Alghnam S, Castillo R. Traumatic injuries and persistent opioid use in the USA: findings from a nationally representative survey. *Inj Prev*. Apr 2017;23(2):87-92. doi:10.1136/injuryprev-2016-042059

87. Al Dabbagh Z, Jansson KA, Stiller CO, Montgomery S, Weiss RJ. Long-term pattern of opioid prescriptions after femoral shaft fractures. *Acta Anaesthesiol Scand*. May 2016;60(5):634-41. doi:10.1111/aas.12666

88. Zwisler ST, Hallas J, Larsen MS, Handberg G, Mikkelsen S, Enggaard TP. Opioid prescriptions before and after high-energy trauma. *J Opioid Manag*. Jul-Aug 2015;11(4):313-8. doi:10.5055/jom.2015.0280

89. Cannon R, Bozeman M, Miller KR, et al. The prevalence and impact of prescription controlled substance use among injured patients at a Level I trauma center. *J Trauma Acute Care Surg*. Jan 2014;76(1):172-5. doi:10.1097/TA.0b013e3182ab10de

90. Ruder J, Wally MK, Oliverio M, Seymour RB, Hsu JR. Patterns of Opioid Prescribing for an Orthopaedic Trauma Population. *J Orthop Trauma*. Jun 2017;31(6):e179-e185. doi:10.1097/bot.0000000000000834

91. Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. *J Am Acad Orthop Surg*. May 2015;23(5):267-71. doi:10.5435/JAAOS-D-14-00163

92. A. Chen BP, A. Chowdhury, A. Duggal. Use of Opioids in the Medical Intensive Care Unit Is Not Associated with Outpatient Opiate Use. *ICU Management & Practice*. 2019;19(2):73.

93. Jenna Clark JE, Prema Menon, Wesley McMillian. Incidence of prescribing opioids at hospital discharge after admission to a medical ICU. *Crit Care Med*. 2018;46(1):443.

94. Yaffe PB, Green RS, Butler MB, Witter T. Is Admission to the Intensive Care Unit Associated With Chronic Opioid Use? A 4-Year Follow-Up of Intensive Care Unit Survivors. *J Intensive Care Med*. Aug 2017;32(7):429-435. doi:10.1177/0885066615618189

95. Wunsch H, Hill AD, Fu L, et al. New Opioid Use After Invasive Mechanical Ventilation and Hospital Discharge. *Am J Respir Crit Care Med*. Apr 29 2020;doi:10.1164/rccm.201912-2503OC

96. Skrobik Y. Insights into Critical Care and Post-ICU Opiate Administration. *Am J Respir Crit Care Med*. Aug 15 2020;202(4):484-486. doi:10.1164/rccm.202005-1815ED

97. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24(11):659-67. doi:10.1007/s10654-009-9350-y

98. Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol*. Apr 2019;34(4):423-437. doi:10.1007/s10654-019-00511-8

99. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450. doi:10.1186/1471-2458-11-450

100. Swedish Board of Health and Welfare. The National Patient Register. 2020. https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/patientregistret/bortfall-och-kvalitet/. Accessed August 16, 2021.

101. Swedish Board of Health and Welfare. Causes of Death Register. 2020. https://www.socialstyrelsen.se/en/statistics-and-data/statistics/. Accessed August 11, 2021.

102. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. Sep 2017;32(9):765-773. doi:10.1007/s10654-017-0316-1

103. Swedish Board of Health and Welfare. *Dödsorsaksstatistik. Historik, produktionsmetoder och tillförlitlighet.* 2010.

104. The Swedish Intensive Care Registry (SIR). Annual report 2019. https://www.icuregswe.org/globalassets/arsrapporter/arsrapport_2019_final.pdf. Accessed September 14, 2021.

105. The Swedish Intensive Care Registry (SIR). National Quality Registry for Intensive Care. 2021. https://www.kvalitetsregister.se/en/kvalitetsregister/hittaregister/registerarkiv/intensivvard.44215.html. Accessed September 7, 2021.

106. The Swedish Prescribed Drug Register. http://www.socialstyrelsen.se/register/halsodataregister/lakemedelsregistret. Accessed September 13, 2021.

107. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. Jul 2007;16(7):726-35. doi:10.1002/pds.1294

108. Statistics Sweden (SCB). The Register of Total Population. 2021. https://www.scb.se/vara-tjanster/bestall-data-och-statistik/bestalla-mikrodata/vilka-mikrodata-finns/individregister/registret-over-totalbefolkningen-rtb/. Accessed August 16, 2021.

109. Gabbe BJ, Magtengaard K, Hannaford AP, Cameron PA. Is the Charlson Comorbidity Index useful for predicting trauma outcomes? *Acad Emerg Med*. Apr 2005;12(4):318-21. doi:10.1197/j.aem.2004.12.002

110. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. Nov 2005;43(11):1130-9.

111. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. Jun 22 2000;342(25):1887-92. doi:10.1056/NEJM200006223422507

112. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med*. Jun 22 2000;342(25):1878-86. doi:10.1056/NEJM200006223422506

113. Gedeborg R, Warner M, Chen LH, et al. Internationally comparable diagnosis-specific survival probabilities for calculation of the ICD-10-based Injury Severity Score. *J Trauma Acute Care Surg*. Feb 2014;76(2):358-65. doi:10.1097/TA.0b013e3182a9cd31

114. Gagne M, Moore L, Beaudoin C, Batomen Kuimi BL, Sirois MJ. Performance of International Classification of Diseases-based injury severity measures used to predict in-hospital mortality: A systematic review and meta-analysis. *J Trauma Acute Care Surg*. Mar 2016;80(3):419-26. doi:10.1097/TA.0000000000000944

115. Wutzler S, Maegele M, Marzi I, et al. Association of preexisting medical conditions with in-hospital mortality in multiple-trauma patients. *J Am Coll Surg*. Jul 2009;209(1):75-81. doi:10.1016/j.jamcollsurg.2009.03.015

116. Shoko T, Shiraishi A, Kaji M, Otomo Y. Effect of pre-existing medical conditions on in-hospital mortality: analysis of 20,257 trauma patients in Japan. *J Am Coll Surg*. Sep 2010;211(3):338-46. doi:10.1016/j.jamcollsurg.2010.04.010

117. Skaga NO, Eken T, Sovik S, Jones JM, Steen PA. Pre-injury ASA physical status classification is an independent predictor of mortality after trauma. *J Trauma*. Nov 2007;63(5):972-8. doi:10.1097/TA.0b013e31804a571c

118. Nielsen MW, Sondergaard B, Kjoller M, Hansen EH. Agreement between self-reported data on medicine use and prescription records vary according to method of analysis and therapeutic group. *J Clin Epidemiol*. Sep 2008;61(9):919-24. doi:10.1016/j.jclinepi.2007.10.021

119. van Diepen M, Ramspek CL, Jager KJ, Zoccali C, Dekker FW. Prediction versus aetiology: common pitfalls and how to avoid them. *Nephrol Dial Transplant*. Apr 1 2017;32(suppl_2):ii1-ii5. doi:10.1093/ndt/gfw459

120. Haider AH, Herrera-Escobar JP, Al Rafai SS, et al. Factors Associated With Long-term Outcomes After Injury: Results of the Functional Outcomes and Recovery After Trauma Emergencies (FORTE) Multicenter Cohort Study. *Ann Surg*. Jun 2020;271(6):1165-1173. doi:10.1097/SLA.0000000000003101

121. Martino C, Russo E, Santonastaso DP, et al. Long-term outcomes in major trauma patients and correlations with the acute phase. *World J Emerg Surg*. 2020;15:6. doi:10.1186/s13017-020-0289-3

122. Collie A, Simpson PM, Cameron PA, et al. Patterns and Predictors of Return to Work After Major Trauma: A Prospective, Population-based Registry Study. *Ann Surg*. May 2019;269(5):972-978. doi:10.1097/SLA.0000000000002666

123. Gabbe BJ, Simpson PM, Cameron PA, et al. Long-term health status and trajectories of seriously injured patients: A population-based longitudinal study. *PLoS Med*. Jul 2017;14(7):e1002322. doi:10.1371/journal.pmed.1002322

124. Lund T, Labriola M, Villadsen E. Who is at risk for long-term sickness absence? A prospective cohort study of Danish employees. *Work*. 2007;28(3):225-30.

125. Brattstrom O, Eriksson M, Larsson E, Oldner A. Socio-economic status and co-morbidity as risk factors for trauma. *Eur J Epidemiol*. Feb 2015;30(2):151-7. doi:10.1007/s10654-014-9969-1

126. Hanna CL, Hasselberg M, Laflamme L, Moller J. Road traffic crash circumstances and consequences among young unlicensed drivers: a Swedish cohort study on socioeconomic disparities. *BMC Public Health*. Jan 14 2010;10:14. doi:10.1186/1471-2458-10-14

127. Allebeck P, Mastekaasa A. Swedish Council on Technology Assessment in Health Care (SBU). Chapter 5. Risk factors for sick leave - general studies. *Scand J Public Health Suppl*. 2004;63:49-108. doi:10.1080/14034950410021853

128. Lidwall U. Sick leave diagnoses and return to work: a Swedish register study. *Disabil Rehabil*. 2015;37(5):396-410. doi:10.3109/09638288.2014.923521

129. Vles WJ, Steyerberg EW, Essink-Bot ML, van Beeck EF, Meeuwis JD, Leenen LP. Prevalence and determinants of disabilities and return to work after major trauma. *J Trauma*. Jan 2005;58(1):126-35.

130. von Oelreich E, Eriksson M, Brattstrom O, et al. Post-trauma morbidity, measured as sick leave, is substantial and influenced by factors unrelated to injury: a retrospective matched observational cohort study. *Scand J Trauma Resusc Emerg Med*. Oct 13 2017;25(1):100. doi:10.1186/s13049-017-0444-3

131. Willemse-van Son AH, Ribbers GM, Verhagen AP, Stam HJ. Prognostic factors of long-term functioning and productivity after traumatic brain injury: a systematic review of prospective cohort studies. *Clin Rehabil*. Nov 2007;21(11):1024-37. doi:10.1177/0269215507077603

132. OECD. Health policies and data. Opioids. 2019. https://www.oecd.org/els/health-systems/opioids.htm. Accessed August 29, 2021.

133. Chaudhary MA, Schoenfeld AJ, Harlow AF, et al. Incidence and Predictors of Opioid Prescription at Discharge After Traumatic Injury. *JAMA Surg*. Oct 1 2017;152(10):930-936. doi:10.1001/jamasurg.2017.1685

134. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. Jan 2013;41(1):263-306. doi:10.1097/CCM.0b013e3182783b72

135. Edlund MJ, Martin BC, Fan MY, Braden JB, Devries A, Sullivan MD. An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. *J Pain Symptom Manage*. Aug 2010;40(2):279-89. doi:10.1016/j.jpainsymman.2010.01.012

136. Bäckryd E, Heilig M, Hoffmann M. [Opioid prescription changes in Sweden 2000–2015]. *Lakartidningen*. May 2 2017;114Dynamiken i förskrivningen av opioider i Sverige 2000–2015 - Markanta omfördelningar inom opioidgruppen, men ingen »epidemi«.

137. von Oelreich E, Eriksson M, Brattström O, et al. Risk factors and outcomes of chronic opioid use following trauma. *Br J Surg*. Mar 2020;107(4):413-421. doi:10.1002/bjs.11507

138. Bedene A, Lijfering WM, Niesters M, et al. Opioid Prescription Patterns and Risk Factors Associated With Opioid Use in the Netherlands. *JAMA Netw Open*. Aug 2 2019;2(8):e1910223. doi:10.1001/jamanetworkopen.2019.10223

139. Abrams TE, Vaughan-Sarrazin M, Rosenthal GE. Preexisting comorbid psychiatric conditions and mortality in nonsurgical intensive care patients. *Am J Crit Care*. May 2010;19(3):241-9. doi:10.4037/ajcc2010967

140. Darnall BD, Stacey BR. Sex differences in long-term opioid use: cautionary notes for prescribing in women. *Arch Intern Med*. Mar 12 2012;172(5):431-2. doi:10.1001/archinternmed.2011.1741

141. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med*. Sep 1 2016;176(9):1286-93. doi:10.1001/jamainternmed.2016.3298

142. Cicero TJ, Wong G, Tian Y, Lynskey M, Todorov A, Isenberg K. Co-morbidity and utilization of medical services by pain patients receiving opioid medications: data from an insurance claims database. *Pain*. Jul 2009;144(1-2):20-7. doi:10.1016/j.pain.2009.01.026

143. Svendsen K, Fredheim OM, Romundstad P, Borchgrevink PC, Skurtveit S. Persistent opioid use and socio-economic factors: a population-based study in Norway. *Acta Anaesthesiol Scand*. Apr 2014;58(4):437-45. doi:10.1111/aas.12281

144. Fonseca AC, Ferro JM. Drug abuse and stroke. *Curr Neurol Neurosci Rep*. Feb 2013;13(2):325. doi:10.1007/s11910-012-0325-0

145. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. Apr 14 2004;291(14):1753-62. doi:10.1001/jama.291.14.1753

146. Gacouin A, Camus C, Gros A, et al. Constipation in long-term ventilated patients: associated factors and impact on intensive care unit outcomes. *Crit Care Med*. Oct 2010;38(10):1933-8. doi:10.1097/CCM.0b013e3181eb9236

147. Munch T, Christiansen CF, Pedersen L, Sorensen HT. Impact of Preadmission Opioid Treatment on 1-Year Mortality Following Nonsurgical Intensive Care. *Crit Care Med*. Jun 2018;46(6):860-868. doi:10.1097/CCM.0000000000003080

148. Oh TK, Song IA, Lee JH, et al. Preadmission chronic opioid usage and its association with 90-day mortality in critically ill patients: a retrospective cohort study. *Br J Anaesth*. Jun 2019;122(6):e189-e197. doi:10.1016/j.bja.2019.03.032