Epidemiological register studies on pain - etiology, treatment, and mental health

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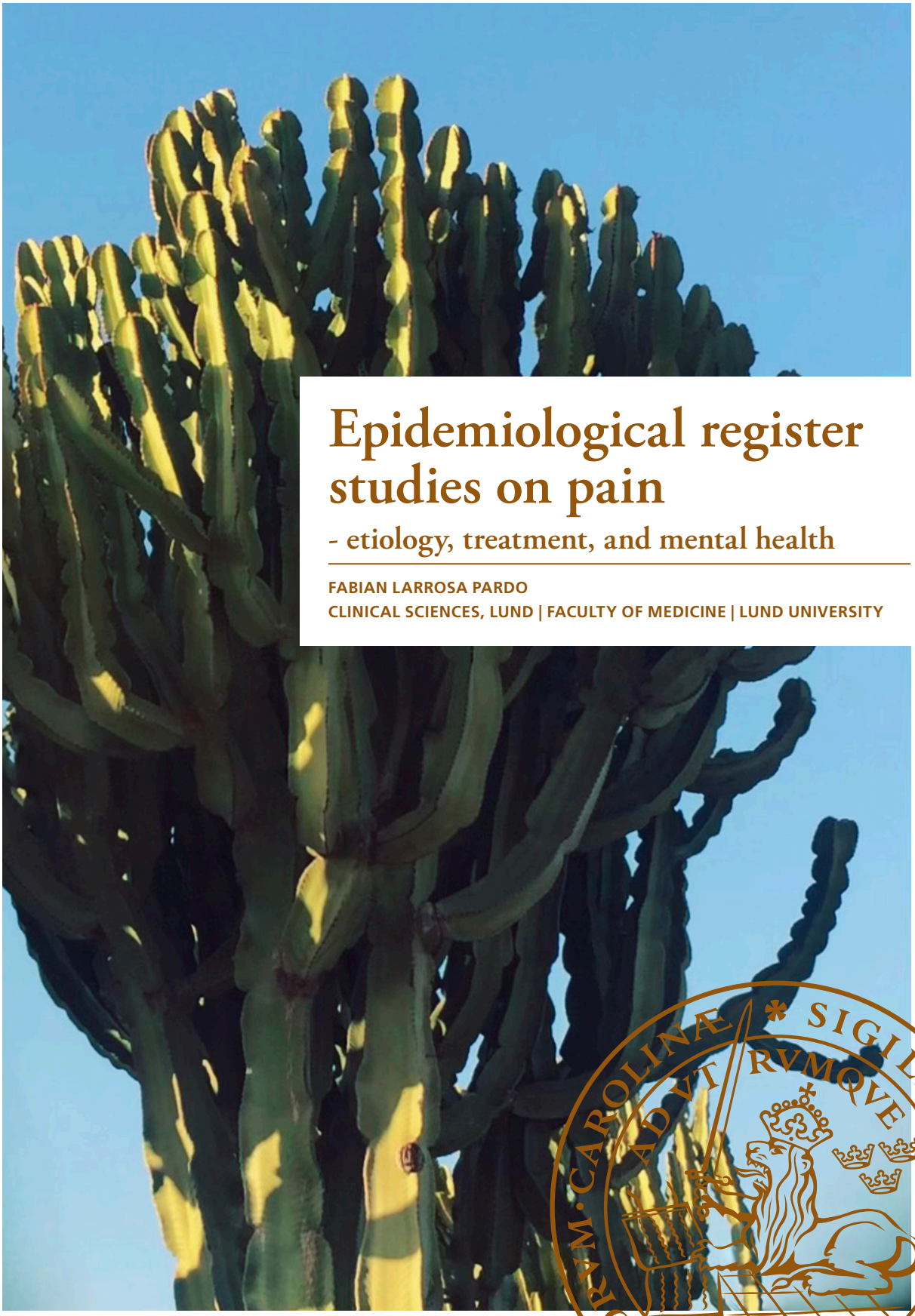

Epidemiological register studies on pain

- etiology, treatment, and mental health

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Epidemiological register studies on pain

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- etiology, treatment, and mental health

Fabian Larrosa Pardo

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on Friday September 1st at 09.00 in Belfragesalen, BMC, Lund

Faculty opponent
Associate prof. of epidemiology Kathryn Mansfield, London School of Hygiene and Tropical Medicine, Faculty of Epidemiology and Population Health, Department of Non-communicable Disease Epidemiology

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Abstract:

Pain is common in life and can be caused by trauma or underlying disease and is mostly temporary, but for some the pain can develop into a chronic pain condition. Pain leads to individual suffering as well as negative impact on the wider society. Especially since pain can start early in life and affect large parts of it.

The aim of this thesis was to identify potential risk factors for chronic and widespread pain, and to study associated comorbidities and prescription drug use. This was done by using the extensive electronic health records and registers available in Sweden to perform four population-based cohort studies.

Study I: We investigated the effect of rheumatoid arthritis, endometriosis, and inflammatory bowel disease, three diseases with recurrent pain as a common feature, on the risk of developing chronic pain. We showed that all three diseases were risk factors for widespread pain.
Study II: We investigated the temporal relationship between pain and mental illness and found a bidirectional relationship where the two conditions increase the risk for each other.
Study III: We investigated risk factors for prolonged opioid use after distal radius fracture. We found that previous opioid use, mental illness, and surgery acted as risk factors whereas occupational/physical therapy decreased the risk.
Study IV: We studied trends in yearly prevalence of diagnoses for pain and mental health conditions and associated prescription drug use in adolescents and young adults. We found decreasing prevalence of pain diagnoses but a steep increase in mental health conditions and associated prescription drugs.

Our results propose early identification and treatment for chronic diseases where recurrent pain is a common symptom to decrease the risk of chronic pain. Moreover, since pain and mental illness act as risk factors for each other monitoring both conditions among individuals affected by either could be beneficial to improve patient wellbeing. This is especially important since our studies also show that both pain and mental illness and associated prescription drugs are common in young people. Finally, screening for previous regular opioid use could be considered when initiating treatment for distal radius fracture.

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To my family and friends,
(cats included in both categories)

Table of Contents

Abstract

Pain is common in life and can be caused by trauma or underlying disease and is mostly temporary, but for some the pain can develop into a chronic pain condition. Pain leads to individual suffering as well as negative impact on the wider society. Especially since pain can start early in life and affect large parts of it.

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Populärvetenskaplig sammanfattning

Smärta är vanligt, och vi upplever alla den någon gång under vår livstid. Den kan komma akut efter en olycka, eller uppstå som del av annan sjukdom. Smärtan kan också bli en sjukdom i sig, utan pågående eller hotande skada i vävnaden. Smärta kan således uppstå av olika anledningar och på olika sätt. Man brukar därför klassificera smärta efter hur den mekanistiskt uppstår, hur utbred den är eller hur länge den funnits. En speciell typ av smärta är långvarig smärta, en smärta som pågått mer än 3–6 månader. En del utvecklar detta efter att först ha drabbats av akut smärta eller smärta från en annan underliggande sjukdom. Varför en del utvecklar detta och hur det påverkar individen är fortfarande till stor del oklart. En särskild typ av långvarig smärta är generaliserad smärta och fibromyalgi där smärtan är spridd i många delar av kroppen.

I denna avhandling studerar jag olika typer av smärta, riskfaktorer för att drabbas av smärta och smärtans effekter. Eftersom smärta kan uppstå i alla åldrar tittar jag också specifikt på smärta som debuterar i tidig ålder. Smärta är komplext, och likaså dess riskfaktorer och dess påverkan på individen och samhället. Därför är smärta ett stort forskningsområde där många pusselbitar ännu återstår att läggas. I min avhandling belyser jag ett par av dessa.

De specifika syftena i denna avhandlings fyra delar är: 1. Att kartlägga risken för att utveckla långvarig smärta efter annan sjukdom där smärta är ett av symptomen. 2. Studera hur samsjukligheten mellan smärta och psykisk ohälsa ser ut. 3. undersöka hur opiatanvändningen ser ut efter den mycket vanliga och smärtsamma handleds- (radius-) frakturen. 4. Att beskriva förekomsten av smärta, psykisk ohälsa och läkemedelsanvändning i unga åldrar.

Metoden som jag använder i denna avhandling är epidemiologiska observationella kohortstudier, där samtliga studier använder registerdata för att definiera både exponering och utfall. I Sverige finns det väldigt många olika typer av register som samlar information för alla individer som bor och söker vård i Sverige. Detta utgör en mycket bra grund för epidemiologisk forskning, där man vill följa individer och skeenden över en lång tid. Till exempel när man försöker finna orsakssamband eller tidssamband. Eftersom Sveriges hälso- och sjukvård är, till allra största del, skattefinansierad och offentligt styrd är den gratis för barn och erbjuds för låg kostnad till den vuxna befolkningen. Det finns därför relativt liten risk för selektion i användningen av hälso- och sjukvård i Sverige. Det innebär att de allra flesta i behov av vård erbjuds denna vilket i sin tur betyder att den data som samlas in om den vård som getts i Sverige har hög täckningsgrad. På nationell nivå samlas data för den specialiserade öppenvården och slutenvården in i nationella register, dessa register saknar dock primärvården. Smärta och också psykisk ohälsa som berörs mycket i denna avhandling behandlas till allra största del inom primärvården varför de nationella registren är mindre lämpade för dessa studier. På regional nivå däremot

samlas data i regionala register och där ingår också den vård som sker i primärvården. I Region Skåne samlas alla data i Region Skånes VårdDatabas (RSVD). I detta register återfinns bland annat diagnos, var och när man sökt vård samt eventuell åtgärd. Utifrån detta register utgår samtliga fyra delarbeten i denna avhandling. Eftersom alla medborgare i Sverige har ett unikt personnummer som registreras i alla register kan man även länka tex vårddata med annan information av vikt för frågeställningen om individen som finns i andra register, tex det nationella läkemedelsregistret över förskrivna läkemedel och administrativa register över olika socioekonomiska data så som yrke, inkomst och utbildningsnivå. Användning av registerdata i forskningssyfte sker efter etiskt tillstånd.

I delarbete ett studerade jag och medförfattarna risken att utveckla långvarig smärta efter föregående annan sjukdom där smärta är ett centralt symtom; reumatoid artrit (RA), endometrios och inflammatorisk tarmsjukdom (förkortat på engelska IBD). Detta är tre olika typer av sjukdomar men där alla har återkommande smärtsamma perioder som central del. Vår hypotes var att återkommande episoder av smärta under lång tid leder till sensitisering, det vill säga ökad känslighet för smärta, och senare långvarig smärta. Genom att följa individer över tid i register beräknade vi risken att utveckla långvarig smärta efter de tre olika sjukdomarna. Vi fann att alla tre sjukdomarna ökade risken för fibromyalgi markant och den största risken syntes efter RA men där risken var nästan lika hög efter endometrios. Vi såg även att det fanns en ökad risk för RA efter att först ha utvecklat fibromyalgi samt en ökad risk för långvarig smärta efter endometrios. Våra resultat är viktiga för att förstå vikten i att fokusera på smärta inom andra sjukdomar för att minska risken för efterföljande smärtsjukdom.

I delarbete 2 tittade vi specifikt på sambandet mellan smärta och psykisk ohälsa. Många som lever med smärta har också påverkan på sin psykiska hälsa. Detta är välkänt i kliniska sammanhang men det har varit metodologiskt svårt att studera vad som kommer först i detta samband. Genom att ta vara på data samlad under lång tid hade vi möjlighet att studera tidssambandet mellan de två; smärta och psykisk ohälsa genom att följa individer som drabbas först av smärta utan samtidig psykisk ohälsa och vice versa över tid. Vi fann att risken att utveckla psykisk ohälsa efter smärta var dubbelt så hög jämfört hos befolkningen utan smärta. Lika hög var risken att utveckla smärta efter att först ha drabbats av psykisk ohälsa. Således visar vår studie ett så kallat tvåvägssamband mellan smärta och psykisk ohälsa där båda utgör risk för den andra. Detta resultat innebär att man i det kliniska arbetet bör vara uppmärksam på båda sjukdomarna hos de patienter som diagnosticerats med den ena för att försöka minska risken för att utveckla den efterföljande sjukdomen eller bättre kunna behandla den om den uppstår. Resultatet väcker också frågan en om gemensam förklaringsmodell för smärta och psykisk ohälsa, där en hypotes är att (delvis) samma mekanismer leder till smärta hos vissa och psykisk ohälsa hos andra.

I det tredje arbetet studerade vi i stället läkemedelsbehandling för smärta efter handledsfraktur. För viss smärta förskrivs opiater till patienten och ett exempel kan

vara smärta efter fraktur. Då opiater är beroendeframkallande var syftet med denna studie att studera risken för långvarigt opiatbruk efter handledsfraktur. Vi identifierade alla radiusfrakturer I Skåne under 2015–2018, nästan 10 000 patienter, och studerade hur många som hade ett opiatanvändande längre än tre månader efter frakturen. Ungefär 7% av patienterna hade det och den tydligaste riskfaktorn för detta var tidigare opiatbruk, tidigare regelbundet bruk gav en tydligt ökad risk även om bruket låg upp till fem år bak i tiden. Även psykisk ohälsa ökade risken för långvarigt bruk av opiater. Däremot fann vi inget samband med smärta året innan frakturen. Våra resultat belyser betydelsen av tidigare bruk på risken att återfå ett långvarigt bruk och att detta bör tas i beaktande vid rutinanvändning av opiater efter fraktur.

I den sista delstudien fokuserar vi på barn och unga. Studien kartlägger både hur vanlig förekomsten av smärta och psykisk ohälsa är men också hur vanligt det är med läkemedelsanvändning för olika orsaker är i unga åldrar. Detta arbete växte fram under avhandlingens gång, då det blev allt tydligare att smärta debuterar i tidig ålder. Givet de stora negativa konsekvenserna av smärta, både som direkt effekt av smärta, samsjuklighet och läkemedelsbehandling som vi ser hos vuxna är det viktigt att förstå hur vanligt detta är redan i ung ålder så att hälso- och sjukvården och samhället vet och kan planera behovet därefter. Vi identifierade alla i åldern 13-24 år i Region Skåne per år under perioden 2011-2022 och beräknade hur vanligt smärta och psykisk ohälsa var samt hur det har förändrats över tid. Bland individerna med och utan smärta och psykisk ohälsa studerade vi dessutom hur läkemedelsanvändningen ser ut. Vi fann att både smärta och psykisk ohälsa är mycket vanligt i den unga populationen men att smärta generellt har minskat över åren samtidigt som psykisk ohälsa har ökat. Över lag har läkemedel som används för olika typer av psykiska tillstånd ökat under studieperioden. Den förskrivna opiatanvändningen är låg bland unga i Skåne och har också minskat under studieperioden.

Sammanfattningsvis visar denna avhandling att svenska populationsregister är en bra källa för epidemiologiska studier inom smärta kring samband som kräver detaljerade data på individnivå och över lång tid. De ingående studierna bidrar genom att visa på det temporala sambandet mellan återkommande smärta ifrån olika underliggande sjukdomar och senare långvarig smärta, samt sambandet mellan smärta och psykisk ohälsa. Båda dessa två delstudier är unika i sin design och kan ligga till grund för framtida studier där etiologin bakom långvarig smärta studeras liksom den eventuella liknande etiologin bakom smärta och psykisk ohälsa. En behandlingsstrategi för smärta är opiater, men då dessa är beroendeframkallande visar delstudie tre på vikten av att ta hänsyn till tidigare bruk inför insättning av ny opiatbehandling i samband med smärta till följd av radiusfraktur. Då smärta och psykiska sjukdomar är riskfaktorer för långvarig smärta bidrar delstudie fyra till att ytterligare belysa behovet av att fokusera på smärta och psykisk ohälsa redan i unga år då prevalensen av dessa tillstånd och diagnoser är hög i den unga populationen.

List of Papers

Paper I

Larrosa Pardo, F., Bondesson, E., Schelin, M. E. C., & Jöud, A. (2019). A diagnosis of rheumatoid arthritis, endometriosis or IBD is associated with later onset of fibromyalgia and chronic widespread pain. European Journal of Pain, 23(8), 1563–1573. https://doi.org/10.1002/ejp.1432

Paper II

Bondesson, E., Pardo, F. L., Stigmar, K., Ringqvist, Å., Petersson, I. F., Jöud, A., & Schelin, M. E. C. (2018). Comorbidity between pain and mental illness – Evidence of a bidirectional relationship. European Journal of Pain, 22(7), 1304–1311. https://doi.org/10.1002/ejp.1218

Paper III

Larrosa Pardo, F., Bondesson, E., Petersson, I. F., Schelin, M. E. C., & Jöud, A. (2023). Prolonged opioid use after distal radius fracture. European Journal of Pain, 27(7):848–59. https://doi.org/10.1002/ejp.2114

Paper IV

Larrosa Pardo, F., Bondesson, E., Petersson, I. F., Schelin, M. E. C., & Jöud, A. Occurrence of pain, mental health conditions and prescription drugs in adolescents and young adults – changes over time. *In manuscript*

Author's contribution to the papers

Paper I

Discussion on study design including methods used. Interpretation and discussion of results. Acquired the data, analysed, drafted and revised the manuscript.

Paper II

Participated in study design, analyses, and interpretation of results. Discussed the results and commented on the manuscript.

Paper III

Participated in study design, interpretation and discussion of results, Acquisition of data, analysed, drafted, and revised the manuscript.

Paper IV

Participated in study design, interpretation and discussion of results, Acquisition of data, analysed, drafted, and revised the manuscript.

Abbreviations

ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CWP	Chronic widespread pain
DAG	Directed Acyclic Graph
IASP	International Association for the Study of Pain
IBD	Inflammatory bowel disease
ICD 10	International Classification of Disease and related health problems 10th edition
IRR	Incidence rate ratio
LISA	Longitudinal integration database for health insurance and labour market studies
PIN	Personal Identification Number
PDR	Prescribed Drug Register
RA	Rheumatoid Arthritis
RR	Relative Risk
SHR	Skåne Healthcare Register
TPR	Total Population Register

Introduction

Epidemiology – a brief introduction

Epidemiology can be defined as *"The study of the occurrence and distribution of health-related states or events in specified populations, including the study of the determinants influencing such states, and the application of this knowledge to control the health problems"* (1).

To simplify, epidemiologists are focused on the health of a group rather than the specific individual and aim to understand how common diseases are, who gets affected and also why. Typically, epidemiology is divided into descriptive and analytical epidemiology. In descriptive epidemiology the condition of interest is described by different measures of occurrence such as prevalence or by calculating how many that fall ill, through incidences rates. In analytical epidemiology the aim is to understand important risk factors, which factors affects the condition, who is affected (or has a higher risk of being affected) and what causes the conditions. Epidemiology is also the core methodology within public health (2). In public health, epidemiology is used to not only identify the frequency of disease, but also causes, risk factors and populations at risk, and can help guide interventions, allocation of resources, organization of healthcare etcetera.

In Sweden we have many registers over different individual health factors and associated factors that are collected from birth to end of life. All data can be linked through the Swedish unique personal identification number. This makes Sweden a great country to pursue epidemiological register studies.

Pain– from skin to cerebral cortex and beyond

Pain is defined by the International Association for the Study of Pain (IASP) as:

"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

IASP further presents six keynotes to go with that definition:

''Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.

Pain and nociception are different phenomena.

Pain cannot be inferred solely from activity in sensory neurons. Through their life experiences, individuals learn the concept of pain. A person's report of an experience as pain should be respected.

Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.

Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain (3)*."*

As seen from the statement above, pain is a complex function in the body, and that the perception and interpretation of pain occurs at many levels and in many forms. However, pain is broadly classified into three different types based on the mechanism as classified by IASP.

Nociceptive pain:

Nociceptive pain is the type of pain that we all experience during our lifetime. It is *"pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors."* (3)

Nociceptors are peripheral nerve endings meant to signal about potentially harmful stimuli such as mechanical, thermal, and chemical stress. Nociceptors have a threshold for when a stimulus is strong enough to elicit a nerve signal. From the nociceptor the signal travels through nerves, to the spinal cord, through the brain stem, and then to several sites in the in the brain where it gives rise to both automatic responses but also the cognitive perception of pain in the cerebral cortex.

Neuropathic pain

In contrast from nociceptive pain where the nervous system transfers signals of nociception from other tissue, neuropathic pain arises from direct damage to the nervous system such as from a stroke, trauma to the nervous system or damage to nerves by other disease such as diabetes and can cause previous non-painful stimuli to be perceived as pain (4), and the definition of such pain is hence, *"Pain caused by a lesion or disease of the somatosensory nervous system."*(3)

Neuropathic pain is not the focus of this thesis apart from when it is part of another pain condition.

Nociplastic pain

A third type of pain is the nociplastic pain, *"Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain."*(3)

In this pain there is no evidence of tissue damage or damage to the nervous system, despite that nociception occurs (4). This type of pain is typical in chronic pain conditions such as fibromyalgia, where the signalling of pain becomes altered in a non-functional way leading to the perception of pain in the absence of ongoing or threatening injury. Here pain can become a disease in its own right, not just a symptom of another disease.

Apart from classifying pain based on the underlying mechanism pain can further be classified based on the duration of the pain.

Acute versus persistent or chronic pain

Acute pain is defined by IASP as: *"happening suddenly, starting out as sharp or intense, and serving as a warning sign of disease or threat to the body"*. Acute pain can be caused by injury, surgery, illness, trauma, or painful medical procedures and generally lasts from a few minutes to less than six months. Acute pain usually disappears whenever the underlying cause is treated or healed (5). The definition here is based on the duration not the mechanism, it can be nociceptive or neuropathic but the definition of nociplastic including no evidence of actual or threatened tissue damage would exclude it from the definition of acute pain as stated above.

Persistent or chronic pain is defined by IASP as pain that persist or recurs for more than three months (6), hence there is an overlap in time between the definitions of acute pain (lasting less than six months) and persistent pain. The definition is independent of the pain mechanism, and can be nociceptive, neuropathic or nociplastic.

Chronic widespread pain and fibromyalgia syndrome

Chronic pain can be localised regional or widespread in the body (7), two conditions with widespread pain, central in research, are Chronic Widespread Pain (CWP) and fibromyalgia syndrome ,where fibromyalgia is a form of CWP, but is associated with sleep disorders, cognitive dysfunction and somatic symptoms (8) in Sweden it

is still diagnosed according to the American College of Rheumatology (ACR) 1990 criteria which includes pain in 11/18 defined tender points (9) this definition has since been updated twice by the ACR (10,11) and in the latest version tender points have been replaced by widespread pain index giving points for pain in different sites and symptom severity score which includes points for cognitive symptoms and depression (11).

Sensitization

An acute nociceptive pain that persists or recurs long enough to become chronic can change the pain signalling and become a nociplastic pain. In contrast to other types of stimuli, such as for instance smell (where repeated stimulation leads to habituation and a dampening of the signal), repeated stimulation of the nociceptive system does not lead to a dampening of the sensation, instead it leads to sensitization. Sensitization is a process in which the threshold for a stimulus needed to evoke a painful signal in the nervous system is lowered, this can lead to a painful stimulus being perceived as more painful (called hyperalgesia), or a previously non-painful stimulus being perceived as painful (called allodynia). This process can occur in the peripheral and central nervous system and can be temporary, such as the sensitization that occurs in tissue damage such as after a sunburn, or become chronic and persist in the absence of tissue damage (12–14). Sensitization can also lead to the pain going from local to regional or generalized in the body (13). Of particular interest in this thesis (Study I) is the transition from repeated painful stimuli from different chronic diseases and the development of chronic and generalised pain or fibromyalgia.

Cognitive, emotional, and behavioural aspects of pain

When signals from nociception reaches the brain, they cause the cognitive experience of pain but also emotional and behavioural responses such as communication about pain or using different coping mechanisms such as avoiding painful stimuli or trying to find the cause of pain. Our interpretation of pain also affects the perception of it and for instance catastrophizing helplessness and anxiety and fear related to pain seems to be associated to poor adjustment to pain (15).

To only describe pain as a somatic process is not enough to fully understand it and the biopsychosocial model of disease proposed by George L Engel in 1977, in which biological, psychological and social factors must be taken in to account to understand disease (16) has gained wide recognition in pain medicine (13,17).

Pain prevalence in the population and pain in registers

Pain is an important public health issue. The prevalence of pain in the general population is high, in a survey covering 52 countries 27,5% had experienced at least moderate pain in the last 30 days (18), and in a study in 15 European countries and Israel, 19% of respondents had chronic pain (19). A systematic review on the prevalence of chronic widespread pain found a pooled prevalence of 10.6% (20). Moreover, pain is a very common cause for consultation in primary care (21,22). Since pain exists through all stages of life and even though prevalence increases with age (23), the one-year consultation prevalence for pain in ages 1-24 in Skåne, Sweden was 15.8% (24). The prevalence of pain as reported in surveys is typically higher compared to studies based on records from healthcare, this is since not all who experience pain need or chose to seek healthcare for it, or they do not access healthcare for their pain or are not diagnosed or treated for it specifically.

This thesis focuses on pain as presented in the health care system based on data from electronic health records based on registered diagnoses. Even though this does not constitute all true cases of pain in the society these are the ones accessible in the healthcare system and hence available for treatment and are also utilizing healthcare resources that must be appropriately dimensioned. With that said, the true occurrence of pain in the population under study is higher than what is recorded. The diagnoses used by healthcare in Sweden are the ones in the Swedish translation of international classification of diseases and related health problems (ICD) 10 system (25). Diagnoses of painful conditions are divided in several chapters depending where it appears such as M: diseases of the musculoskeletal system and connective tissue, G: diseases of the nervous system, or R: Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified, so it is important to properly identify all relevant diagnoses when designing studies. A special case in ICD-10 is the lack of a specific code for chronic widespread pain which poses problems since different codes are used locally for the same condition, this has luckily been amended in the eleventh revision of the international classification of disease (26) but has not yet been implemented clinically in Sweden.

Comorbidity and risk factors

As pain is complex, it affects the individual differently depending on many factors. Pain can be a symptom of many conditions, and chronic pain can lead to other types of medical conditions through negative effects on the body and mind such as increased levels of stress hormones, lower levels of physical activity or participation in society. Some known risk factors for chronic pain are for example, age, female sex and low socioeconomic status (27).

There is a clear association between pain and anxiety and depression (28–30), which are very common conditions in the population (31,32) and there are many potential

pathways for this relationship, either with pain causing anxiety or depression or the other way around (33). Pain and mental health conditions are common in adolescents and young adults (24,34) and the self-reported occurrence of both have been increasing (34,35). Previous pain problems increase the risk for chronic pain, and several inflammatory diseases have a comorbidity with chronic pain (36–38).

As mentioned before different types of non-functional coping mechanisms, such as catastrophic thinking, and behaviours like the use of medication, are observed in relation to pain and can affect the risk of chronic pain, some of these behaviours are learnt from parents (or caregivers) and can be manifest early in life (39–41). The way an individual is affected by pain as an adolescent or young adult may affect future management of pain (42). Additionally, a strong risk factor for pain and chronic pain later in life is pain during childhood and adolescence (43,44). Therefore, it is important to study pain present early in life.

Treatment of pain

The wider treatment of pain is not the main focus of this thesis, but it is of course a very central part of the study of pain in general.

As pain can arise from several mechanisms, the treatment of pain has many different targets and methods. The signal can be modulated by the body and exogenous agents such as analgesics on several levels of these pathways, but also by psychological intervention aiming for the cognitive aspects and other non-pharmaceutical therapies such as physiotherapy can change the bodies modulation and experience of pain.

Acute nociceptive pain can range from very brief self-limiting pain such as a stubbed toe to much more severe conditions leading to diverse forms of treatment. Acute pain can be treated with pharmacological analgesics, typically the first line treatment includes paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAID). In more severe cases of pain opioids are sometimes used. Opioids are addictive and the misuse of opioids has led to what has been called the opioid epidemic in the USA (45) and an increase in use has also been seen in Europe (45–48). Opioids are effective for various causes of acute pain, with exemptions (49), but have weak evidence for long term effect in non-cancer pain, instead they have risk for dependency and adverse effects (50–53).

Physical activity can lower pain (54) and in musculoskeletal pain (and also other types of chronic pain) physiotherapy/occupational therapy is used to both increase function and lower pain (55). For chronic pain, a multimodal approach including pharmacology, physiotherapy and psychological intervention is often used, in line with the biopsychosocial approach (56).

Aims

Overall aim

The overall aim of this thesis was to investigate risk factors for pain and chronic pain in the form of mental health conditions and chronic disease with painful episodes, and the effects of pain such as mental health conditions and prescription drug use. The overall aim was split into four specific aims.

Specific aims

- to investigate conditions with recurrent painful episodes as part of their symptoms, increases the risk of developing widespread pain (study I).
- to examine the temporal relationship between pain and mental illness (study II).
- to study risk factors for prolonged opioid use after acute pain from distal radius fracture (study III).
- to investigate the prevalence and temporal trends of pain and mental health conditions and the related use of prescribed drugs in adolescents and young adults (study IV).

Methods

Epidemiological methods

Study design

Epidemiological studies can be divided into two basic categories observational studies and experimental studies. In an observational study a researcher observes a process without intervening, for instance following smokers versus non-smokers over time to note differences in cancer occurrence, whereas in an experimental study there is an intervention on behalf of the researcher, such as giving a specific treatment to one group of people while comparing to an untreated group.

Examples of observational studies include cohort studies and case control studies while the most common experimental study design in epidemiology are clinical trials where the randomised controlled trial (RCT) is the most common. This thesis focuses on observational designs, and the most common observational study designs are presented in more detail below.

Observational study designs

Cohort studies

A cohort study begins with a cohort, a group of people, without the disease or outcome of study, classified by their exposure to one or several factors and then followed over time to determine if exposure status is associated to the risk of developing the outcome, giving the relative risk (RR) compared to the unexposed. Cohort studies are longitudinal, meaning that we see the exposure and outcome vary over time and see which comes first. Cohort studies provide valuable data on risk factors and the causes of disease but also have potential problems. Constructing a cohort and following over time can be costly and time consuming, particularly if the outcome is rare or takes a long time to develop. This can therefore be mitigated by using existing population-based registers to create and follow cohorts over time. Since there is no randomization to account for confounding it is of vital importance to take steps to avoid confounding and other systematic errors, explained later in this section. In a cohort study the most common measures of occurrence are

prevalence and incidence, while associations are measured via risk ratios or similar measures which can be calculated by various methods depending on type of data. The four studies in this thesis are cohort studies.

Cross-sectional studies

A specific type of the cohort study is the cross-sectional study design. Here, exposed and unexposed individuals are studied at one point of time. This is typically used to determine prevalence of conditions in a population. A cross-sectional study is like a snapshot of the occurrence of conditions in a population, simply measuring frequency of the conditions under study. Here it is possible to see the association of variables in that they occur more frequently together but not being longitudinal it is not possible to determine the direction of this association, meaning which occurred first, e.g., which factor that might have caused the other (unless one factor is a fixed condition like sex at birth that clearly predates the outcome). Cross-sectional studies are relatively inexpensive and easy to conduct and if repeated in the same population can give a good indication of trends. They are often used to assess health care needs of populations. If conducted by sampling the population this sampling must be done in a way to avoid bias and confounding and with enough responses to be representative. Using registers can make cross-sectional studies easier and cheaper especially if the aim is to repeat the measurements in several time periods. Paper IV is a cross-sectional study.

Case control studies

Another type of observational study design is the case control study, in which cases of the outcome of study are identified and compared to a control group without the outcome, then the exposure status between cases and controls is compared. E.g., the outcome could be laryngeal cancer, cases of this would be compared to a control group without laryngeal cancer and then compare the frequency of the exposure of interest, for example smoking. The benefits of a case control studies as compared to a cohort study are that it is cheaper and less time consuming to start with identified cases compared to following a large number of people over time to see if they develop the outcome, this is especially true for outcomes that are rare or takes a long time to develop. Some pitfalls of case control studies are for instance the risk of introducing bias when selecting the control group, as controls must be chosen from the same population from which the cases derived. A common bias in case control studies is the specific type of misclassification that occurs from so called recall bias. This can happen when asking about past exposure (if cases are more likely to recall and report an exposure asked about than those who did not develop the outcome even though no real difference exists) (57). Like cohort studies, case control studies are longitudinal meaning that it is possible to determine the direction of association, whether the exposure precedes the outcome in the cases. In the case control design the odds ratios are the most common measure of association, however risk ratios can and should be calculated via appropriate methods when possible, e.g., through

the modified Poisson calculation (58,59). A specific type of case control study is the nested case-control study. Here, a case control study is done within an existing cohort. This cohort can be a register that covers the total population.

Dealing with bias and confounding

In the broadest sense error occurs in two forms in epidemiological studies, random error and systematic error also called bias.

A random error is the type of error that would diminish with increasing study size. The typical example is when trying to find an average (weight, height, etc.) with measurements being done with an instrument that is a little unprecise but not in a particular direction. Some measurements are a little too large and some a little too small as compared to the true value in a random fashion. With a larger sample these differences would tend to cancel each other out and each faulty measurement would have less and less effect on the average which as the sample increases is closer to the real average in the population (60).

Systematic errors or bias instead occur in a non-random fashion and are not solved by increasing the sample size. In the example of measurements this would be like when for instance using an instrument that always exaggerates the measurement.

An important type of bias is selection bias, which occurs when the association between exposure and outcome differs between those that participate in the study compared to those who do not. This can be the result of the procedures used to select them or by factors in the subjects that affect participation. An example could be advertising a study on diet and obesity only in fast food restaurants.

Another type of bias relevant to cohort studies is immortal time bias, it occurs when the study design makes it so that for a period of follow-up no death or outcome can occur, typically when reaching the status exposed/treated requires time which is not necessary for the unexposed. A classic example is that generals live longer than lieutenants since they have to survive to an age when it is possible to become general, this time is “immortal” in a retrospective study since all who reached the rank has already survived it. In medicine this immortal time can instead be the time it takes to develop a condition or for a treatment to be completed that can lead to immortal time bias. It can be accounted for by example using a time-dependent analysis in which this time is counted as unexposed (61,62).

Information bias or misclassification is when information on or from study participants is incorrectly classified. This misclassification can be non-differential or differential.

Non-differential misclassification is when the misclassification is not differential on the exposure or the outcome under study, so that the risk of being misclassified is not greater among those with the outcome than without or vice versa. For instance,

a cohort study on future chronic pain that at the start registers physical activity as less or more than 150 min a week, in which some overestimate their activity and some underestimate so that some with less than 150 min are classified as having more and vice versa. This misclassification occurs before and is independent on later chronic pain, and what happens is that a true effect of physical activity on the risk of chronic pain is diluted by the misclassification. Those with less physical activity might in reality have an increased risk but in this study that group also includes those who actually have a higher level of physical activity lowering the risk for the group. This bias is referred to as bias toward the null.

Differential misclassification on the other hand is when the misclassification differs along with the value of another variable under study such as the exposure or the outcome (63). An example in case-control studies can be recall-bias previously mentioned under case-control studies where those with the outcome are more likely to report being exposed than an exposed without the outcome. In cohort study an example could be closer monitoring of exposed individual leading to a higher probability of being diagnosed with the outcome. Differential classification can exaggerate or underestimate an effect.

Confounding – confusion of effects

In epidemiological studies it is crucial to avoid confounding. in which the effect of the exposure on the outcome is confused or mixed with the effect of another (third) factor, a confounder. In the definition of a confounder, it must be associated to both the exposure and the outcome, (as a cause or proxy for a cause of the outcome) and cannot be caused by the outcome or by the exposure. Confounding can lead to both over- and underestimation of an effect(60). Take for instance a hypothetical study on workplace habits and sickness in which you find a correlation between taking many small breaks during the day and being sick more often, but that those who take many small breaks are more likely to be smokers which is the real cause for more sickness, the frequent small breaks are caused by the habit of smoking which in turn causes more sickness, smoking is a confounder for the effect of breaks on sickness. A factor that is caused by the exposure and then affects the risk of the outcome is not a confounder but a mediator. A mediator hence is a step on the causal pathway between the exposure and the outcome. A factor that is caused by both the exposure and outcome is instead called a collider, mediators and colliders must not be handled as confounders since that can instead introduce confounding (64).

The process of trying to avoid confounding is called controlling for confounding. Known and measured confounders can be taken care of both in the design phase of the study and in the analytical phase. So called un-measured confounders are instead confounders that you either are not aware of or do not have measure on and hence they are not directly handled in the study.

Controlling for confounding

Three different methods can be used to avoid confounding when it comes to study design: randomization, restriction, and matching. Randomization can be used in experimental study designs and the aim is to get an even distribution of confounding factors between groups so that the effect is minimized.

Restriction is when you select subjects for a study so that they have the same or almost the same value for a variable that could otherwise be a confounder, thus removing that effect, this can be done in both experimental and observational studies. For example, if sex is a confounder the study could be performed only among women. Matching in a cohort study can be done by matching exposed and unexposed on the confounding variable to remove that effect (63).

There are two ways to control for confounding in the analytical step of an epidemiological study stratification and the use of statistical models. Stratification is cross tabulating the data on exposure and outcome by categories of one or more potential confounding variables such as for example sex or age, so that the comparison so that the comparison between exposed and unexposed occur within the categories, thus removing the effect of that potential confounder (60).

Statistical modelling for example via regression models can be used as an alternative to stratification by adding several risk factors in the same model so that that the effect of each risk factor is unconfounded by the others (60). The challenge for handling confounders regardless of what method you use is to identify the confounders. Once you have done so, the use directed acyclic graphs (DAGs) is a tool or method for visualizing the causal pathways between exposure and outcome and helping to differentiate between colliders, mediators and confounders by drawing directed arrows symbolizing the causal pathway between the factors.

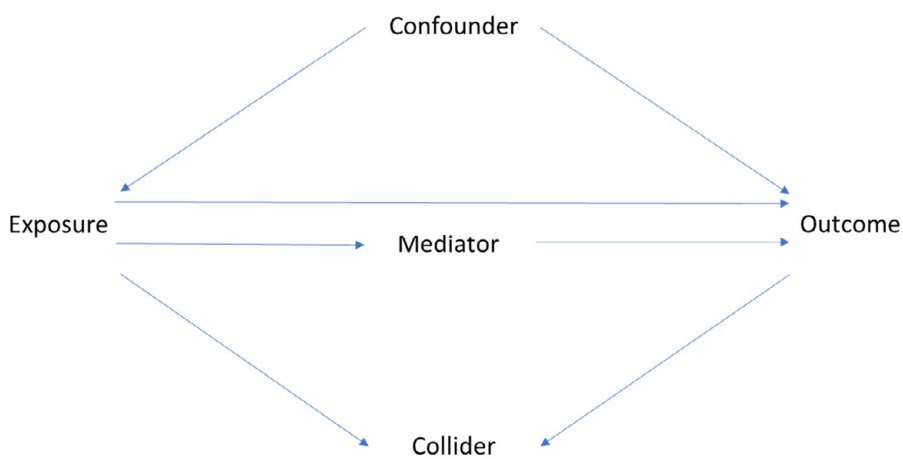


Figure 1 Example of a directed acyclic graph

In this thesis relevant confounders for each analysis have been visualized using DAGS and adjusted for.'

Analyses in this thesis

As previously mentioned in the section on controlling for confounding, regression analysis makes it possible to control for several variables at once when analysing the effect of an exposure on the outcome. Because of this, regression models are widely used in analytical epidemiology. In studies I-II I have used a method of regression analysis called Poisson regression and in study III a modified Poisson regression. Additionally, we used standard descriptive statistics to calculate proportions in all studies.

Poisson regression – Time to event, (Studies I & II)

In studies I-II we used time-to-event analysis, often called survival analysis, to calculate incidence rate ratios (IRR) for the combinations of exposures and outcomes. In these types of analysis, it is not the number of cases of the outcome per the number of persons at risk that is measured but rather the number of cases per person time at risk. The benefit of this model is that we can have a time-varying exposure, we chose this since the exposed did not start the study with the exposure present, their status changed to exposed so it is important that the time they contribute before that is correctly classified as unexposed and the time after exposure as exposed. Each individual contributes with person time from entering the study until they leave it by either getting the outcome, by moving away, by dying or reaching the end of the study, whichever comes first. If they get the exposure entering the study, they will contribute exposed time from that point onward until leaving the study. The incidence ratio is the number of cases/person years, The incidence rate ratio is the ratio between the incidence rate for the exposed person years divided by the incidence rate from unexposed person years.

Modified Poisson Regression (Study III)

Poisson regression tends to give conservative estimates and overestimate the error for the estimated risk when applied to binomial data (59). In study III a modified Poisson regression which addresses these issues was used.

Register epidemiology in Sweden

Sweden offers great opportunities for register based epidemiological research due to several factors. Primarily of course the extensive registers which exist in the country. Some registers exist at a national level striving to cover the entire population, such as registers on mortality and cause of death, registers on socioeconomic factors or retrieval of prescription drugs. Other registers are regional

such as the register of all health care consultations in Skåne, the Skåne HealthCare register. There are also many quality registers related to treatment of various conditions with the aim of comparing, improving, and maintaining the quality of treatment which are voluntary for patients to participate in, but which have overall good coverage (65). A second very important factor that facilitates register research is the personal identification number (PIN) given to each Swedish resident, allowing for easy linkage between all register, allowing for data from several registers to be combined for the population of interest, allowing for more variables of interest to be studied or used to control for confounding. In registers with good coverage, it is possible to study the entire population of interest instead of a sample giving more precise results.

In summary Swedish registers, being extensive and easily linkable trough PIN, offer great opportunities for epidemiological research.

Electronic health records

Electronic health records are registers in which patient data from health care visits is systematically stored digitally and these are extensive in Sweden.

On a national level all in-patient care and all doctor visits in specialized out-patient care are registered in the National Patient Register, which however lacks information from primary care.

In Sweden the health care is governed by 21 regions, and they keep their own electronic health records which differ in structure and content between regions.

In the region of Skåne, where the studies in this thesis were performed, all consultations to any health care provider, be it primary care, specialized outpatient care, in-patient care or private caregivers is to be registered in the same Region Skåne Healthcare Register. This provides a fantastic opportunity to follow patients over time across the entire healthcare system within a well-defined geographic area.

Data sources

Skåne Healthcare register (studies I-IV)

This register is held by Region Skåne the governing body for among other things health care in the region of Skåne. It contains data on all visits to health care, whether primary or specialist care, out- or inpatient care, public or privately organised. Data collected apart from the patient's personal identification number, includes date of consultation, which unit that provided the care, diagnostic codes, codes for procedures, and which type of health care professional that was consulted among other things. The validity of diagnostic codes in SHR has been shown to be

high with a high positive predictive value for diagnosis in specialized care and for repeated diagnosis in primary care (66–68).

Total population register (Studies I-III)

The total population register is governed by Statistics Sweden, and contains vital data on the population of Sweden including births, deaths, information on municipality, and relocation within Sweden or migration (69).

Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (Studies I-III)

This register held by Statistics Sweden and contains information on the Swedish population >16 years of age (>15 since 2010) and contains data on various social and economic factors related to health and disability such as education level, sick leave, disability pension, civil status, disposable income etc. (70). We used highest achieved education level as a proxy for socioeconomic status (28) in studies I, II and III, since it despite unclear mechanism is a risk factor for the diseases under study (71–74).

Swedish prescribed drug register (PDR) (studies III and IV)

This register, held by the Swedish National Board of Health and Welfare contains information on every dispensed drug prescription for the population of Sweden. This includes type of drug, dosage, pack size and time of prescription and when and where the purchase was made (75). Drugs are registered according to the international Anatomical Therapeutic Chemical (ATC) Classification, we used ATC-codes to identify the different drugs under study in this thesis.

Study populations and analyses

Table 1. Overview of study I-IV

	Study I	Study II	Study III	Study IV
Design	Population-based cohort study	Population-based cohort study	Population-based cohort study	Population-based cohort study Repeated Cross-sectional measures
Study population	Persons aged 21 or older living in Skåne with at least one healthcare visit between 2007-2016 n= 819 938	Adult patients in Skåne with at least one healthcare visit to a physician or physiotherapist year 2007-2016 n=504 365-761 180	All adults living in Skåne with distal radius fracture between 2015-2018 n= 9369	The total population 13-24 years old living in the Region of Skåne Sweden for each year 2011-2022 n=182,954- 196,692
Exposures	Diagnosis by physician at relevant clinic for RA, endometriosis, inflammatory bowel disease. (In reverse analysis also Chronic widespread pain (CWP) and fibromyalgia)	Healthcare visits for pain (back and abdominal pain and fibromyalgia) and mental illness (depression and anxiety)	Prior opioid use, prior pain, prior mental illness, prior addiction treatment with surgery, treatment with occupational or physical therapy.	
Outcome	Incidence rate ratios (IRR) for exposed vs unexposed for fibromyalgia or CWP. In the reverse analysis IRR for RA, endometriosis or IBD after Fibromyalgia or CWP	1. Incidence rates of consultations for pain and mental illness. 2. IRR for pain after mental illness and for mental illness after pain compared to the unexposed	1. Proportions of opioid use during treatment phase, and subsequent prolonged use in months 4-12. 2.Relative risk of different exposures for prolonged opioid use	Yearly prevalence of pain, mental health condition and associated prescription drug use
Data sources	TPR, SHR, LISA	TPR, SHR, LISA	TPR, SHR, LISA, PDR	SHR, PDR
Analysis	Poisson regression	Poisson regression	Cochrane Armitage test for trend Modified Poisson regression	Descriptive statistics

TPR= Total Population Register, SHR=Skåne Healthcare Register, LISA= Longitudinal integration database for health insurance and labour market studies, PDR= Prescribed Drug Register

A diagnosis of rheumatoid arthritis, endometriosis or IBD is associated with later onset of fibromyalgia and chronic widespread pain (Study I)

Study population

All individuals aged 21 or older on the 1st of January 2007, living in the region of Skåne, Sweden, that consulted health care at least once during the study period (2007–2016), were included. To ensure that we identified newly diagnosed cases and to avoid misclassification of exposure status or reverse causation, we used a 3-year washout period (2004–2006) prior to the start of the study and excluded individuals who already had either the exposure or the outcome. The washout was performed separately for each combination of exposure and outcome, leaving six

cohorts which largely overlapped the flow chart for this is seen in Figure 2. After washout all individuals who entered the study were free from both exposure and outcome at study start on January 1st, 2007, and were followed over time until outcome, death, moving from the region, or end of study period, whichever came first. They contributed unexposed time from start and if they were exposed, they instead contributed unexposed time from that point onwards, an illustration of this contribution of time is shown in Figure 3.

Definition of exposures and outcomes

RA: Diagnosis starting with M05 (Rheumatoid arthritis with rheumatoid factor) or M06 (Other rheumatoid arthritis) a primary diagnosis registered by a physician in rheumatology or internal medicine units.

Endometriosis: Diagnosis beginning with N80 (endometriosis) as a primary diagnosis registered by a physician in gynaecology/obstetrics units.

IBD: Diagnosis starting with K50 (K50 (Crohn's disease) or K51 (Ulcerative colitis) a primary diagnosis registered by a physician in gastroenterology, internal medicine, or surgery units.

CWP: A primary diagnosis of R52.2 (Other chronic pain or ache) registered by any physician or a diagnosis of M79.1 (myalgia) registered by a physician in a pain rehabilitation clinic.

Fibromyalgia: A primary diagnosis of M79.7 (Fibromyalgia) registered by a physician.

Washout: For the washout we excluded those with any diagnosis of the above conditions for the relevant cohort, not only primary diagnosis and from any clinic.

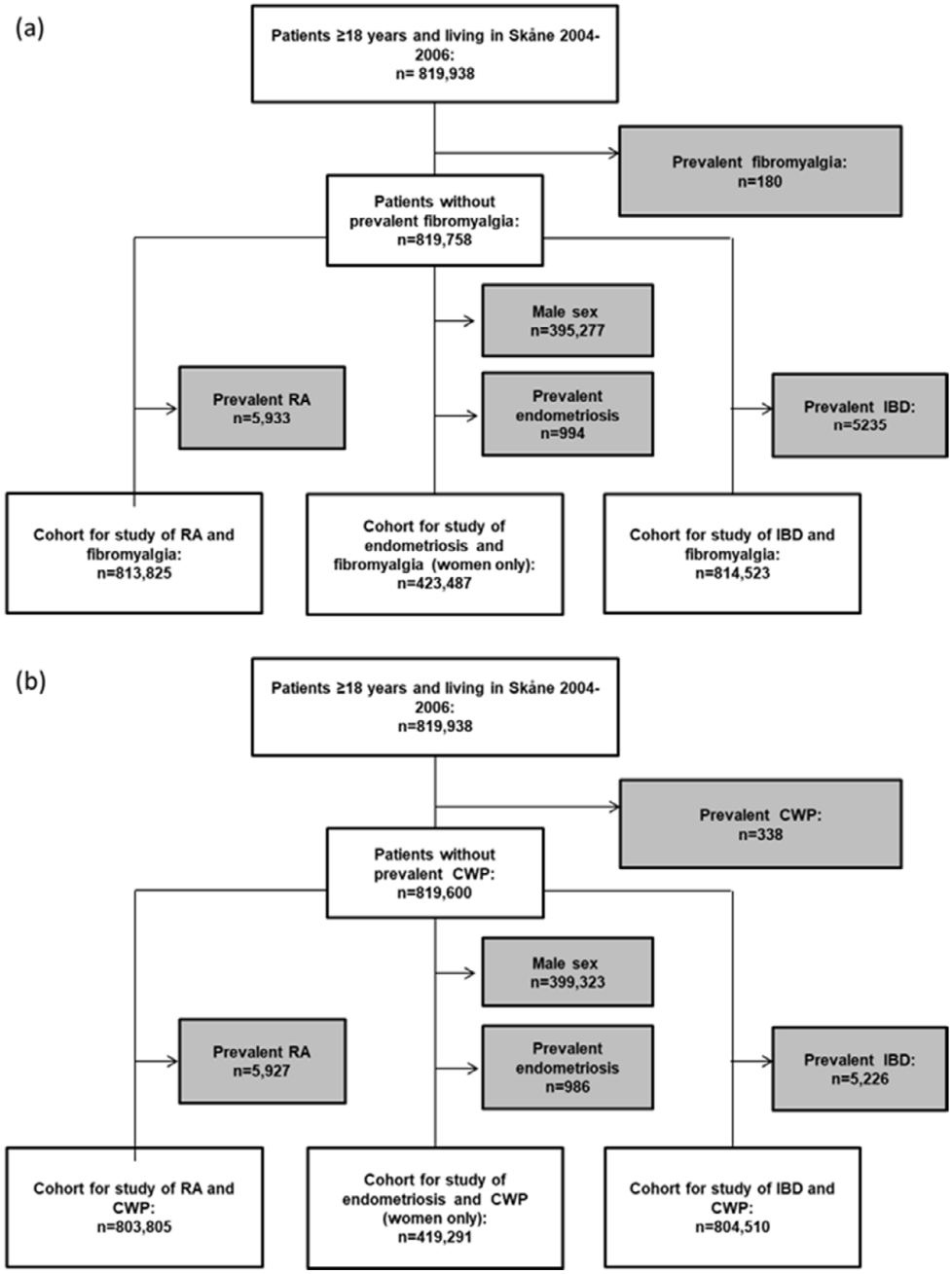


Figure 2 Panel (a) shows the flowchart for the analysis of risk of fibromyalgia. Panel (b) shows the corresponding flowchart for CWP

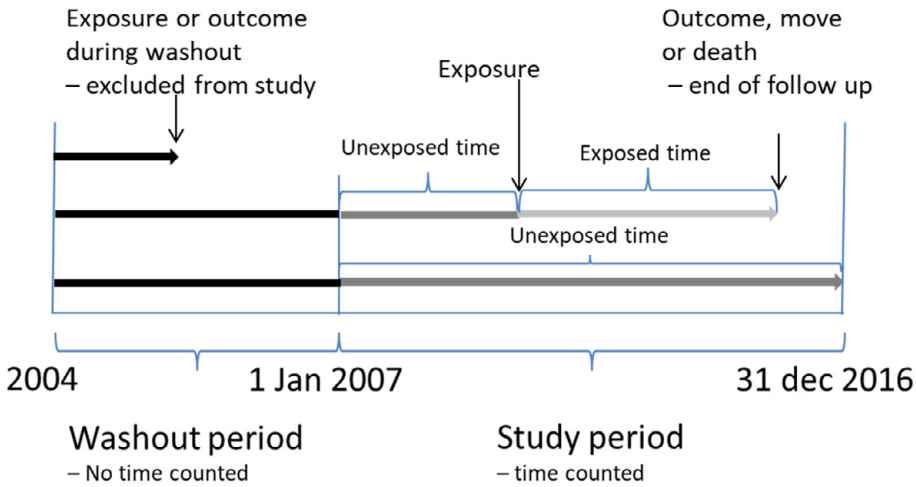


Figure 3 Illustrating how time with and without exposure is calculated for the time-varying exposure. Patients who are not excluded during the washout period contribute time to the study. The exposed patients contribute unexposed time before the exposure and exposed time after. Those who are never exposed contribute unexposed time. All patients were followed until they receive the outcome, move out of the region, or die, or until the end of the study on 31 December 2016, whichever comes first.

Analysis

Using Poisson regression and taking time under risk into account, we calculated incidence rate ratios (IRR) for the different exposures, both crude and adjusted for sex, age, education level and propensity to seek health care. In order to investigate the direction of the association, all analyses were also performed in reverse order, i.e. calculating the risk of the original exposures after fibromyalgia or CWP.

Comorbidity between pain and mental illness – Evidence of a bidirectional relationship (Study II)

Study population

In study II we included all individuals who had at least one consultation with a physician or a physiotherapist in the years 2007–2016. Patients had to be 18 years or older and living in the region of Skåne, Sweden. Patients with either a diagnosis of pain or mental illness in the three years preceding the study were excluded, this was used as a wash-out period to ensure incident cases and decrease the risk for reversed causality. Figure 4 is a flowchart illustrating this selection and washout. The exposure was time-varying with patients starting out as unexposed and contributing unexposed time, if exposed, there was a latency period of three months, where cases were not at risk, to reduce the risk of reversed causation which could

occur if symptoms for pain and mental illness appeared in the reverse order in which they were in fact diagnosed. In the latency period neither person time nor any outcomes were counted. This is visualised in Figure 5.

Definition of exposures and outcomes

To decrease the risk for reversed causality, we required the outcome to occur at least 90 days after the exposure date.

Pain: A physician or physiotherapist registered diagnosis starting with M54 (dorsalgia) or R10 (abdominal/pelvic pain)

Fibromyalgia: A registered physician diagnosis of M79.7 (Fibromyalgia)

Mental illness: A registered physician diagnosis starting with F32 (depression) or F41(anxiety).

Washout: We performed the analyses with two different restrictions in the washout period. In the first we excluded all diagnosed with the conditions under study as defined above, in the second we excluded those with any diagnosis in the chapters F (mental disorders) or M (musculoskeletal diagnoses)

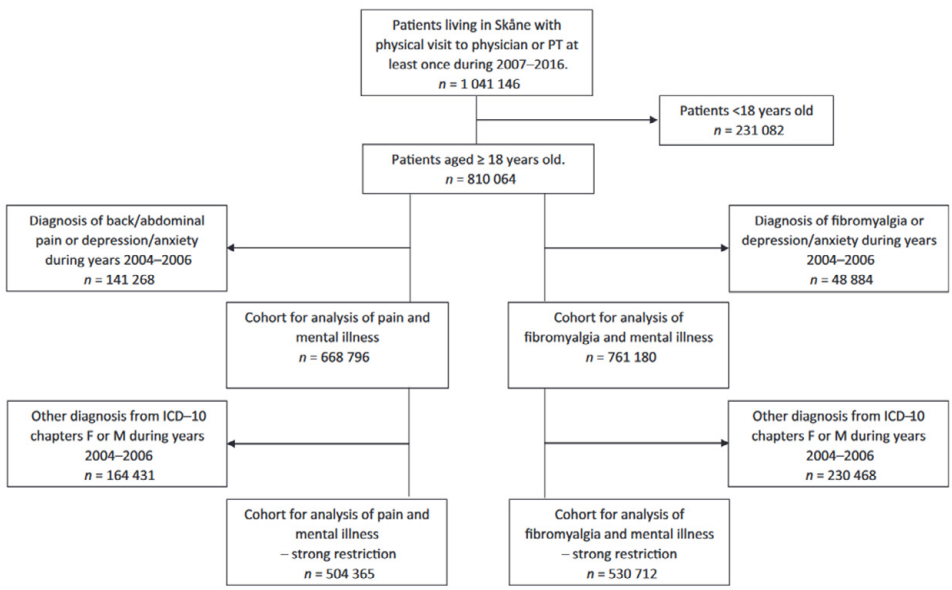


Figure 4 Flowchart for creating the cohorts in study II.

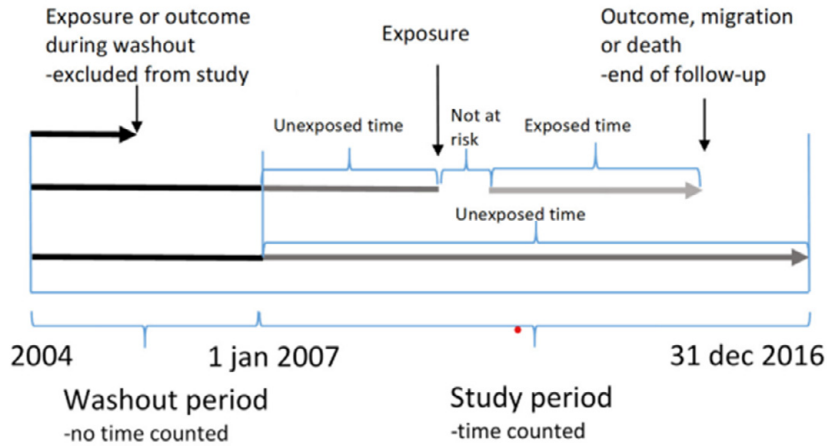


Figure 5 Illustrating how time with and without exposure is calculated for the time-varying exposure. Patients who are not excluded during the washout period contribute time to the study. The exposed patients contribute unexposed time before the exposure, no time during a three-month latency phase and exposed time after. Those who are never exposed contribute unexposed time. All patients were followed until they receive the outcome, move out of the region, or die, or until the end of the study on 31 December 2016, whichever comes first.

Analyses

We calculated incidence rates for pain (back/neck pain and fibromyalgia) and mental illness (depression/anxiety). Using Poisson regression, we calculated incidence rate ratios for pain and mental illness, both crude and adjusted for sex, age and education level. We used two separate restrictions in the washout period. In the main analysis we excluded all patients with any ICD-10 diagnosis in the F and/or M chapters, that is any mental or musculoskeletal disorders. In a second (sensitivity) analysis we excluded only patients with the investigated diseases (back/abdominal pain or fibromyalgia and depression/anxiety).

Prolonged opioid use after distal radius fracture (Study III)

Study population

All adults (18 years or older) diagnosed with distal radius fracture, in emergency medicine, orthopaedics, or hand surgery, in the region of Skåne, Sweden in the years 2015-2018, who were residents of Skåne at time of injury were included. Distal radius fracture was defined as having a registered diagnosis of ICD-10 code of S52.6 (fracture of lower end of radius) or S52.6 (fracture of lower end of both ulna and

radius). The first registered diagnosis of distal radius fracture in the study period was defined as the index fracture. To avoid misclassification all patients with a diagnosis of distal radius fracture in the year 2014, patients with a new fracture in the year from index fracture, and patients undergoing surgery for distal radius fracture more than three months from index fracture were excluded from analysis. We followed patients for 1 year from index fracture to determine opioid use. Those who died or moved from the region within the follow-up period (1 year from fracture) were excluded since they were unavailable to follow up in the registers.

Definition of exposures and outcomes

Prolonged opioid use: Data on prescribed and dispensed opioids were collected from the Swedish prescribed drug register. The time period 1–3 months after fracture was defined as the treatment period, month 4–6 after fracture was defined as follow-up period 1, month 7–9 as follow-up period 2 and month 10-12 as follow-up period 3. Having at least one purchase in both the treatment period and in follow-up period 1 was defined as having prolonged use. To be defined as having prolonged use in follow-up period 2 a patient would have to have a purchase in all the preceding three-month periods from fracture (see Figure 6).

Any prior opioid use was defined as any purchase of prescribed opioids in the period 365 days before the fracture up to 14 days before fracture, the last 14 days were excluded to avoid misclassification if the prescription related to distal radius fracture preceded the diagnosis being registered.

Regular opioid use was defined as purchase of opioids in three out of four quarters of a year. Years were counted as multiples of 365 days from the fracture, except for the year before fracture which was defined as 365 days to 14 days before fracture to avoid misclassification. Among those with no regular use in the last year, we studied presence or absence of regular use in years 2–5 years before fracture. This was done for patients who were adults (18+) and living in Skåne during that entire period (N = 8704, % of study population) the rest of the study population was excluded from this analysis. For those that had a regular use of opioids in this period, the latest year with regular use was registered.

Some opioids use was defined as any of opioids not reaching the criteria for regular use as stated above.

Mental Illness was defined as a registered diagnosis of any mental and/or behavioural disorder except substance addiction (ICD-10: F0 or F2–F9) 365 days before the day of fracture up until the day before fracture.

Addiction was defined as a registered ICD-10 diagnosis of any substance addiction (ICD-10: F1) anytime between 365 days before the day of fracture up until the day before fracture.

Pain was defined as any diagnosis in the Skåne Healthcare Register that had 'pain', '-algia' or 'ache' in the heading of the ICD-10 chapter, as well as migraine, in line with previous research in the Skåne Health Care Register (24). The Included diagnoses were: Abdominal and pelvic pain (R10), Dorsalgia (M54), Headache (R51), Migraine (G43), Other headache syndromes (G44), pain in joint (M25.5), myalgia (M79.1), pain in limb (M79.6), pain, unspecified (R52.9 and the Swedish ICD-10 version primary care specific code R52-), chronic intractable pain (R52.1), other chronic pain (R52.2), fibromyalgia (M79.7) and somatoform pain disorder (F45.4).

Surgery for distal radius fracture was defined using the Swedish Classification of Care Measures, as Surgical codes starting with NDJ, 'surgery for fracture on wrist hand or fingers', excluding code NDJ09 (closed reduction of fracture), registered in the Skåne Health Care Register, from date of fracture up until 90 days after fracture.

Occupational and physical therapy treatment was defined as a visit registered in the Skåne Health Care Register to an occupational therapist or physiotherapist in any clinic, but related to distal radius fracture, (ICD-10 S52.5 or distal radius and ulna ICD-10 S52.6) within 3 months of the initial fracture.

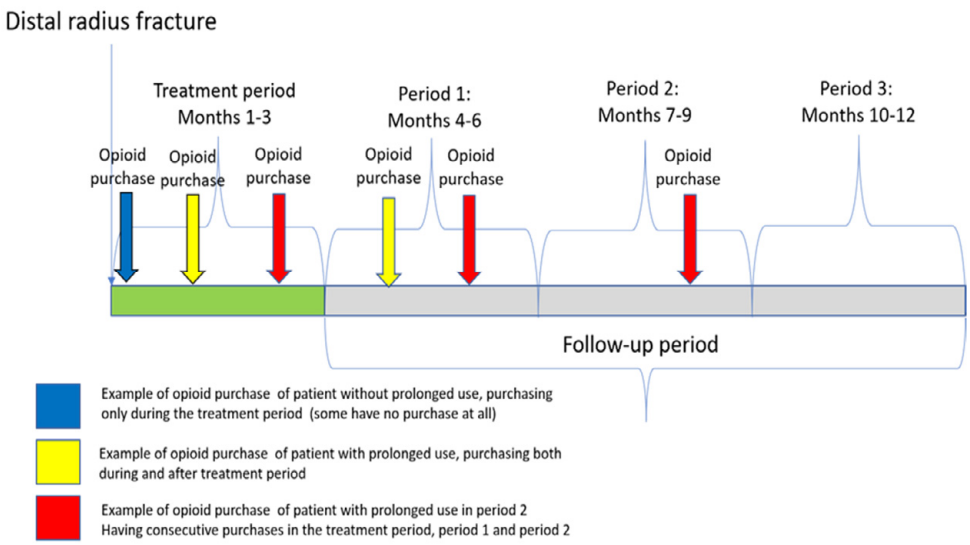


Figure 6 Illustration of defining prolonged opioid use.

Analyses

Descriptive statistics are presented as number and percent. The proportions of patients with prolonged opioid use during the different follow-up periods were calculated for all patients and separately by exposure status (any opioid use in the

last year, prior mental illness, prior pain, occupational/physical therapy treatment, surgery), the Cochrane Armitage trend test was used to test for trends between groups across the different follow-up periods. Relative risk for prolonged opioid use was calculated through modified Poisson regression (76), each exposure was tested separately.

In a separate sensitivity analysis, we estimated the effect of regular previous opioid use in the last year compared to some use or no opioid use. To examine the association between previous regular use of opioids in the past 5 years before fracture and prolonged opioid use after fracture, we included the exposure as latest year with regular use (i.e. 2,3, 4 or 5 years). No regular use during the last 5 years was used as the reference level.

Occurrence of pain, mental health conditions and prescription drugs in adolescents and young adults – changes over time (Study IV)

Study population

This study included the total population 13-24 years old living in the Region of Skåne Sweden for each year 2011-2022.

Identifying diagnoses and prescriptions:

We identified the following diagnoses and prescription for each individual year of the study.

Pain was**,** analogous to study III, defined as having any registered diagnosis of a pain condition according to ICD-10 as specified in was defined as any diagnosis in the Skåne Healthcare Register that had 'pain', '-algia' or 'ache' in the heading of the ICD-10 chapter, as well as migraine, in line with previous research in the Skåne Health Care Register (24).

A diagnosis of a mental health condition was defined as a diagnosis of a mental health conditions (any diagnosis in ICD10 category: Mental, behavioural, and neurodevelopmental disorders)

ADHD was defined as having an ICD-10 code starting with F900, corresponding to attention-deficit hyperactivity disorders. This group was analysed separately but is also part of the larger group with mental health conditions.

An individual could be included in none, one or more than one diagnostic group annually.

Analyses:

Descriptive data on the prevalence of pain and mental health condition was presented as percentages of the total population and were calculated for each year by sex and age group.

The prevalence of prescription drug use in young adults and adolescents with a diagnosis of pain and mental health conditions was calculated respectively. Here, the numerator for the percentage is the total number with the relevant diagnoses for each age group, sex, and year.

Ethics

This thesis and the studies included are in compliance with the World medical organization declaration of Helsinki – ethical principles for medical research involving human subjects, which includes research on identifiable data. The studies were approved by the Regional ethical review board, Studies I and II: DNR 2011/432, Study II: DNR 301/2007, Study IV DNR 2018/376 (amended in 2019/05509). All studies were performed using register data and permission was obtained from the authorities holding the respective registers.

According to the General Data Protection Regulation (GDPR)Data on health is considered a special category of personal data meriting higher protection (77) to further respect the privacy of individuals all data was pseudonymized during data management and analysis.

Results

A diagnosis of rheumatoid arthritis, endometriosis or IBD is associated with later onset of fibromyalgia and chronic widespread pain (Study I)

The characteristics of the study population are presented in Table 2.

The prevalence of fibromyalgia in the population at the end of the study was 0.5%.

All three exposures gave statistically significant increased risk of fibromyalgia. For patients with RA, we found about triple the risk for both fibromyalgia and CWP compared to those unexposed to RA. For those exposed to endometriosis we found almost triple the risk for fibromyalgia and five times the risk for CWP compared to unexposed. IBD patients had more than doble the risk of fibromyalgia, but we found no statistically significant higher risk for CWP, Table 3.

In the reverse analysis we found that fibromyalgia was associated with an increased risk of RA and that CWP increased the risk of endometriosis, Table 3.

Table 2. Characteristics of the study population in study I, n (%)

	No Fibromyalgia or CWP[a]	Fibromyalgia[b]	CWP[c]
Number of patients by pain status	804,003	4,016	1,739
Sex			
Women	415,156 (51.6)	3,811 (94.9)	1,335 (76.8)
Men	388,847 (48.4)	205 (5.1)	404 (23.2)
Education			
9 years	211,256 (26.3)	878 (21.9)	433 (24.9)
12 years	354,136 (44.0)	2,370 (59.0)	861 (49.5)
12+ years	225,066 (28.0)	725 (18.1)	402 (23.1)
Missing	13,545 (1.7)	43 (1.1)	43 (2.5)
Age Group			
18-30	137,802 (17.1)	619 (15.4)	332 (19.1)
30-39	144,354 (18.0)	1,296 (32.3)	426 (24.5)
40-49	140,196 (17.4)	1,284 (32.0)	401 (23.1)
50-59	146,008 (18.2)	607 (15.1)	245 (14.1)
60-69	115,177 (14.3)	168 (4.2)	180 (10.4)
70>	120,466 (15.0)	42 (1.0)	155 (8.9)
Health care seeking: Visits during washout 2004-2006[d]			
<2	132,829 (16.5)	128 (3.2)	90 (5.2)
2-5	169,216 (21.0)	339 (8.4)	192 (11.0)
6-12	165,250 (20.6)	515 (12.8)	243 (14.0)
13-28	174,343 (21.7)	984 (24.5)	442 (25.4)
29>	162,365 (20.2)	2,050 (51.0)	772 (44.4)
Incident Cases 2007-2016[e]			
Rheumatoid Arthritis	4,305 (0.5)	129 (3.2)	23 (1.3)
Endometriosis	1,602 (0.2)	56 (1.4)	27 (1.6)
Inflammatory bowel disease	3,413 (0.4)	63 (1.6)	0.7)

[a] No fibromyalgia or CWP during the study period i.e. the combined reference group.
[b] Incident cases of fibromyalgia during study period.
[c] Incident cases of CWP during study period.
[d] Number of visits to any type of healthcare provider for any type of diagnosis during the wash-out period.
[e] Number and percent.

Table 3. Results of statistical analysis in the separate cohorts for each combination of exposure and outcome (Study I)

Exposure	Outcome	Number of patients with exposure (% of population)[a]	Exposed (n) with subsequent outcome[b]	Incidence rate ratio (95% CI) Crude	Incidence rate ratio (95% CI) Adjusted[c]	Mean time between exposure/ outcome in days
RA	Fibromyalgia	4,421 (0.55)	50	**5.43 (4.11-7.19)**	**3.64 (2.75-4.81)**	996
RA	CWP	4,420 (0.55)	16	**3.81 (2.33-6.24)**	**2.96 (1.81-4.86)**	1163
Endo-metriosis	Fibromyalgia	1,676 (0.40[d])	29	**4.46 (3.09-6.43)**	**2.83 (1.96-4.08)**	1130
Endo-metriosis	CWP	1,673 (0.40[d])	17	**7.08 (4.38-11.44)**	**5.02 (3.10-8.13)**	998
IBD	Fibromyalgia	3,465 (0.43)	26	**3.16 (2.15-4.65)**	**2.32 (1.58-3.42)**	1276
IBD	CWP	3,463 (0.43)	11	**3.04 (1.68-5.51)**	1.42 (0.93-2.17)	1111
Reverse						
Fibro-myalgia	RA	3,892 (0.48)	47	**4.86 (3.65-6.49)**	**3.41 (2.54-4.57)**	1046
CWP	RA	1,706 (0.21)	7	1.66 (0.79-3.48)	1.38 (0.66-2.90)	280
Fibro-myalgia	Endometriosis	3,710 (0.88 d)	15	**2.32 (1.39-3.85)**	**1.59 (0.95-2.66)**	934
CWP	Endometriosis	1,315 (0.31d)	10	**4.38 (2.35-8.16)**	**2.32 (1.16-4.65)**	1056
Fibro-myalgia	IBD	3,924 (0.49)	10	1.19 (0.64-2.21)	0.94 (0.50-1.74)	504
CWP	IBD	1,707 (0,21)	2	0.56 (0.14-2.25)	0.47 (0.12-1.88)	556

[a]The percentage is compared to the corresponding cohort for the combination of exposure/outcome, see Figure
[b]Individuals with the same date for exposure and outcome are counted as unexposed who developed the outcome.
[c]Adjusted for sex, age group, education level and visits to health care during the washout period 2004-2006.
[d]% of women

Comorbidity between pain and mental illness – Evidence of a bidirectional relationship (Study II)

The characteristics of the study cohorts are presented in Table 4.

We found pain to be a risk factor for mental illness giving about twice the risk compared to those unexposed to pain. In the same way mental illness also gave around twice the risk of pain compared to those unexposed to mental illness.

The risk for mental illness after fibromyalgia was more than three times as high compared to those unexposed to fibromyalgia and even higher with the stronger restriction in the washout. The risk for fibromyalgia after mental illness was four times as high compared to those without mental illness and even higher with the stronger restriction, Table 5.

Table 4. Characteristics of the study cohorts, Study II

Characteristics	Analysis of pain and mental illness[a] N = 668,796	Analysis of pain and mental illness – strong restriction[b] N = 504,365	Analysis of fibromyalgia and mental illness[c] N = 761,180	Analysis of fibromyalgia and mental illness – strong restriction[d] N = 530,712
Female sex, n (%)	332,712 (50)	241,793 (48)	388,048 (51)	258,358 (49)
Age year 2004, mean (SD)	49 (18)	47 (18)	49 (18)	47 (18)
Education level, n (%)[e]				
Low	144,144 (23)	100,908 (21)	168,262 (23)	106,698 (21)
Medium	276,030 (44)	207,302 (43)	316,450 (44)	218,349 (43)
High	211,425 (33)	170,751 (36)	233,486 (33)	178,810 (35)
Missing	37,197	25,404	42,982	26,855
Diagnosis, n (%)				
Mental illness	102,198 (15)	68,677 (14)	125,058 (16)	74,514 (14)
Depression	60,094	39,940		
Anxiety	47,158	32,346		
Pain	235,317 (35)	161,750 (32)		
Back pain	125,799	84,860		
Abdominal pain	110,304	77,443		
Fibromyalgia			4951 (0.7)	1876 (0.4)
Diagnosis in primary care, n (%)[f]				
Mental illness	84,524 (83)	57,471 (84)		
Pain	161,625 (69)	110,731 (68)		
Fibromyalgia			1128 (23)	478 (25)

[a]Patients with an ICD-10 diagnosis of M54, R10, F32 or F41 during the washout period were excluded.
[b]Patients with any ICD-10 diagnosis in M and/or F chapters or of R10 during the washout period were excluded.
[c]Patients with an ICD-10 diagnosis of M797, F32 or F41 during the washout period were excluded. [d]Patients with any ICD-10 diagnosis in M and/or F chapters during the washout period were excluded.
[e]Education level: low (up to 9 years), medium (10–12 years), high (more than 12 years).
[f]Diagnosis in primary care, outpatient specialized care or inpatient care.

Table 5. IRR for mental illness after pain/fibromyalgia and for pain/fibromyalgia after mental illness, Study II

	Crude IRR (95% CI)	Adjusted IRR[a] (95% CI)	Adjusted IRR[b] (95% CI)
Mental illness after pain	2.10 (2.07–2.13)	2.03 (2.00–2.06)	2.18 (2.14–2.22)
Mental illness, no prior pain	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Pain after mental illness	1.93 (1.90–1.96)	1.89 (1.87–1.92)	2.02 (1.98–2.06)
Pain, no prior mental illness	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Mental illness after fibromyalgia	3.88 (3.62–4.17)	3.25 (3.02–3.49)	4.05 (3.58–4.59)
Mental illness, no prior fibromyalgia	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Fibromyalgia after mental illness	5.38 (5.05–5.74)	4.05 (3.80–4.32)	5.54 (4.99–6.16)
Fibromyalgia, no prior mental illness	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)

[a]Adjusted for age, sex and level of education.
[b]Adjusted for age, sex and level of education and restricted to patients with no ICD-10 diagnosis in M and/or F chapters during the washout.

Prolonged opioid use after distal radius fracture (Study III)

The descriptive data on the study cohort is presented in Table 6.

We found that the proportions of prolonged opioid use across all follow-up periods to be higher for those exposed to any opioid use in the last year, prior mental illness, and prior pain, compared to the unexposed for the respective exposure. While those exposed to surgery and occupational/physical therapy had higher proportions of prolonged opioid use for follow-up periods 4-6 month and 7-9 month after fracture the proportions of prolonged use in months 10-12 was lowered compared to the unexposed, Table 7.

We found that exposure to any opioids in the year before fracture increased the risk tenfold, and that prior mental illness and surgery were risk factors for prolonged use. Occupational/physical therapy lowered the risk of prolonged use but not significantly in the opioid naïve subgroup. Prior pain was not significantly associated with prolonged use when adjusted for confounding, Table 8.

In the analysis of regular vs some opioid use in the last year we found that regular use increased the risk 24 times compared to those with no opioid use in the last year but also that some, but not regular, use increased the risk almost fivefold compared to those without opioid use, Table 9.

We found previous but since discontinued regular use of opioids in the years 2-5 before fracture to give a large increase in risk for prolonged use, with use in year five before fracture giving a threefold increase in risk compared to those without regular use in the five years before fracture and the relative risk of prolonged use increased the closer the regular use was to fracture, Table 10.

Table 6. Descriptive data of cohort, stratified by surgery or non-surgical treatment, Study III.

	Surgery N (%)	No surgery N (%)	Total N (%)
All patients	2084 (22.2)	7285 (77.8)	9369 (100)
Female	1661 (79.7)	5455 (74.9)	7116 (76.0)
Male	423 (20.3)	1830 (25.1)	2253 (24.0)
Age			
19-49 years	372 (17.9)	1596 (21.9)	1968 (21.0)
50-59 year	395 (19.0)	1118 (15.3)	1513 (16.2)
60-69	623 (29.9)	1535 (21.1)	2158 (23.0)
70-79	540 (25.9)	1471 (20.2)	2011 (21.5)
80+	154 (7.4)	1565 (21.5)	1719 (18.4)
Formal education[a]			
9 years or less	411 (19.7)	1874 (25.7)	2285 (24.4)
10-12 years	609 (29.2)	1872 (25.7)	2481 (26.5)
More than 12 years	935 (44.9)	2872 (39.4)	3807 (40.6)
Prior drug use[b]			
Any opioids last year	289 (13.8)	1095 (15.0)	1379 (14.7)
Regular use last year[c]	92 (4.4)	358 (4.9)	450 (4.8)
Some opioids last year	197 (9.5)	737 (10.1)	929 (9.9)
No opioids last year	1506 (72.3)	5095 (69.9)	7990 (85.3)
Prior mental illness[d]	404 (19.4)	1588 (21.8)	1992 (21.3)
Prior addiction	68 (3.3)	264 (3.6)	332 (3.5)
Prior pain	257 (12.3)	957 (13.1)	1214 (13.0)
Occupational/physical therapy	1466 (70.4)	3284 (45.1)	4750 (50.7)
Prescribed opioids	1605 (77.0)	1690 (23.2)	3295 (35.2)

[a]Highest level registered in 2010. Missing data n= 789 (surgery group n= 131, no surgery group n=667).
[b]During the one-year period before date of fracture.
[c]Purchase of opioids in 3 out of 4 quarters in the year before fracture.
[d]Excluding diagnosis of addiction.
[e]The period between date of fracture and the following three months.

Table 7. Number and percentage of the total study population with prolonged use in each follow-up period by exposure. Study III

	Treatment period	Prolonged opioid use months 4–6	Prolonged opioid use months 7–9	Prolonged opioid use months 10–12	p-value
All patients	3295 (35.17%)	664 (7.09%)	456 (4.87%)	389 (4.15%)	
Any opioids last year	811 (58.81%)	465 (33.72%)	374 (27.12%)	334 (24.22%)	P<0.01[a]
No opioids last year	2484 (31.09%)	199 (2.49%)	82 (1.03%)	55 (0.69%)	
Prior mental illness	816 (40.96%)	264 (13.25%)	194 (9.74%)	170 (8.53%)	P<0.01[a]
No prior mental illness	2479 (33.6%)	400 (5.42%)	262 (3.55%)	219 (2.97%)	
Prior pain	411 (46.08%)	188 (15.48%)	145 (11.94%)	127 (10.46%)	P<0.01[a]
No prior pain	2884 (34.02%)	476 (5.83%)	311 (3.81%)	262 (3.2%)	
Occupational/ Physical therapy	1845 (38.84%)	305 (6.42%)	195 (4.11%)	162 (3.41%)	P<0.01[a]
No occupational/ Physical therapy	1450 (31.39%)	359 (7.77%)	261 (5.65%)	227 (4.91%)	
Surgery	1605 (77.02%)	173 (8.3%)	103 (4.94%)	80 (3.84%)	P<0.01[a]
No surgery	1690 (23.2%)	491 (6.74%)	353 (4.85%)	309 (4.24%)	

Table 8. Effect of the exposures on prolonged opioid use (having purchased opioid during month 4-6 post fracture). RR (95% CI), Study III

	Risk Ratios			
Exposure	**Model 1**	**Model 2**	**Model 3**	**Opioid Naïve**
Any opioids last year	12.5 (10.7-14.7)	12.1 (10.3-14.2)	10.8 (9.12-12.8)[a]	N/A
No opioids last year	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	N/A
Prior mental illness	2.21 (1.90-2.56)	2.16 (1.86-2.51)	1.30 (1.15-1.48)[b]	1.38 (1.02-1.87)[b]
No prior mental illness	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Prior pain	2.47 (2.11-2.90)	2.40 (2.05-2.81)	1.12 (0.98-1.28)[c]	1.29 (0.81-2.06)[c]
No prior pain	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Occupational/ Physical therapy	0.84 (0.72-0.97)	0.83 (0.71-0.96)	0.77 (0.66-0.89)[d]	0.83 (0.63-1.10)[d]
No occupational/ Physical therapy	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Surgery	1.38 (1.16-1.63)	N/A	N/A	2.20 (1.63-2.97)
No surgery	1.00 (Ref)			1.00 (ref)

Model 1: Adjusted for sex. age group,

Model 2: adjusted for sex age group and education level 2010

Model 3 and opioid naïve. a) additionally adjusted for psychiatric diagnosis. addiction and consultation for pain in the year before distal radius fracture b) additionally adjusted for diagnosis of addiction, consultation for pain in the year before distal radius fracture and latest regular use c) additionally adjusted for psychiatric diagnosis, diagnosis of addiction in the year before distal radius fracture and latest regular use d) additionally adjusted for surgery for distal radius fracture and consultation for pain in the year before distal radius fracture

Table 9. Effect of opioid use last year on prolonged opioid use categorized as regular use and some but not regular use in the last year. Study III

Opioid use in the last year	**Risk ratio[d] (95% CI)**
Regularly[a]	24.1 (20.4-28.6)
Some[b]	4.93 (3.97-6.13)
None[c]	(ref)

[a]Regularly: defined as a purchase of opioids in at least 3 out of 4 quarters in the year before purchase n= 450

[b]Some: any use other than the definition of regularly n=934

[c]None: n=7985

[d]Adjusted for psychiatric diagnosis consultation for pain in the year before distal radius fracture.

Table 10. Effect of the exposure to previous regular use on prolonged opioid use. Study III

Last regular use[a]	**N (%)**	**Risk ratio[b] (95% CI)**
2 years before fracture	103 (1.18 %)	9.88 (7.33-13.3)
3 years before fracture	63 (0.72 %)	5.89 (3.56-9.74)
4 years before fracture	60 (0.69%)	3.31 (1.61-6.80)
5 years before fracture	46 (0.53%)	3.09 (1.33-7.18)
No regular use in last five years	7999 (91.9%)	1.0 (ref)

[a]Purchase of opioids in at least 3 out of 4 quarters in a single year, only patients who were >=18 years old 5 years before fracture were included in the analysis n=8704

[b]Adjusted for sex, age group and education

Occurrence of pain, mental health conditions and prescription drugs in adolescents and young adults – changes over time (Study IV)

The yearly prevalence of a pain diagnosis has slightly decreased over the study period, after a peak in 2012 for all groups except for young adult females where it instead peaked in 2013. For mental health conditions, the prevalence of a diagnosis has increased over the study period. However, the increase for the males slowed after 2017 with some years having a slightly lower prevalence than the year before. Specifically, the prevalence of ADHD has increased steadily from 2011 to 2022. The prevalence was higher among adolescent males than females throughout, but this difference was not seen in the young adult group, where the prevalence were more similar between the sexes. The prevalence of being diagnosed with both pain and a mental health condition in the same year increased across the study period, in the last year the increase was seen in females of both age groups but remained stable in males, Figure 7.

The yearly prevalence of a filled prescription for analgesics decreased during the years of the study for both age groups and has also decreased among those diagnosed with pain, mental health conditions or both, Figure 8. Likewise, the use of prescription opioids has decreased since 2013 for all groups, Figure 9.

In the general population the prevalence of anxiolytics, antidepressants hypnotics and central stimulants increased during the study, whereas in the growing subgroup of young adults with mental health conditions the prevalence remained stable during the study. Patients with pain and patients with mental health conditions had a higher prevalence of prescription drug use compared to the general population. This was especially true for those patients with a combination of both pain and mental health conditions which had the highest prevalence for all drugs except antidepressants, exemplified by anxiolytics in figure 10.

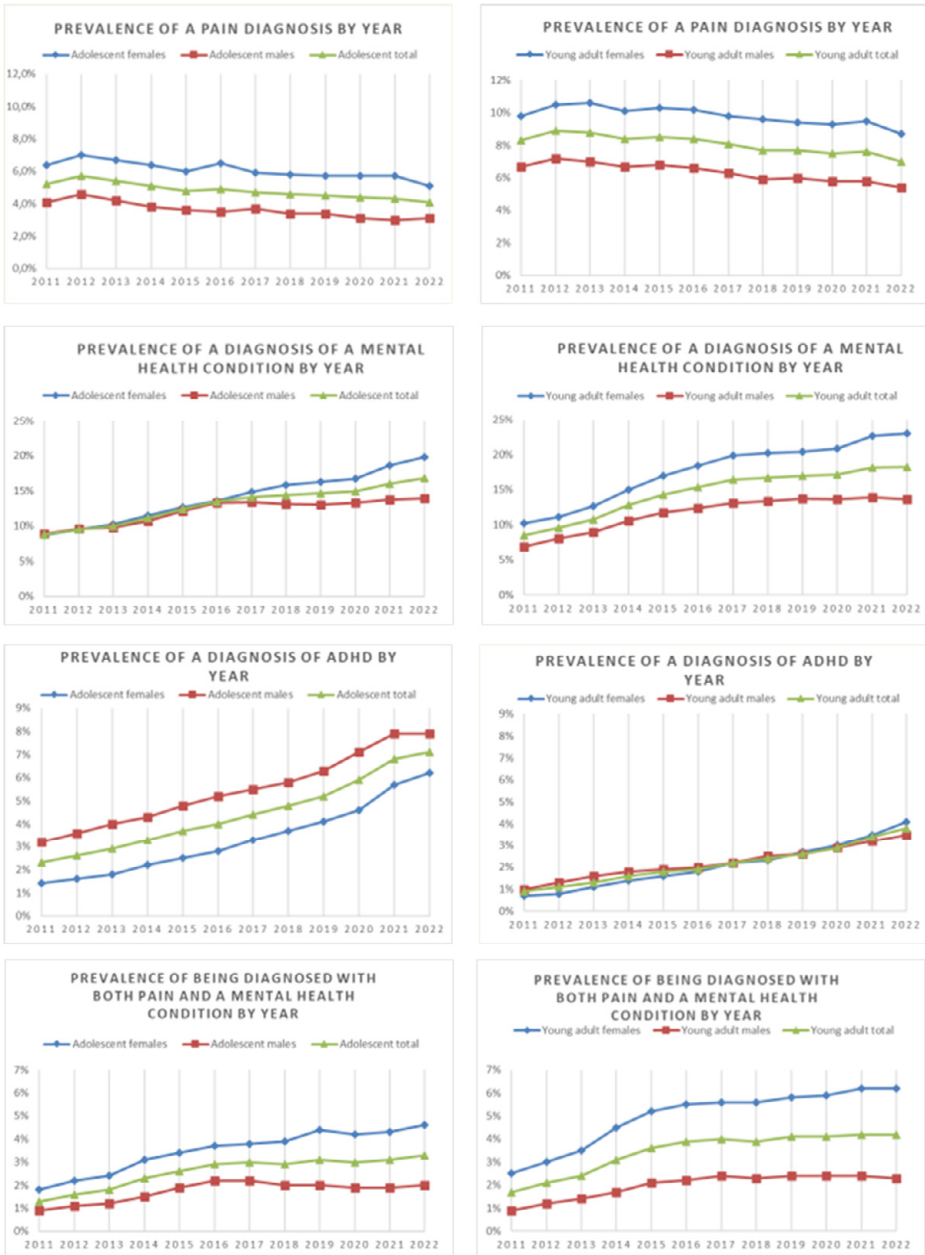


Figure 7 Yearly prevalence of diagnosis of pain, mental health conditions and ADHD for adolescents 13-18 years of age and young adults 19-24 years of age in the Region of Skåne Sweden, years 2011-2022, note the different scales between conditions

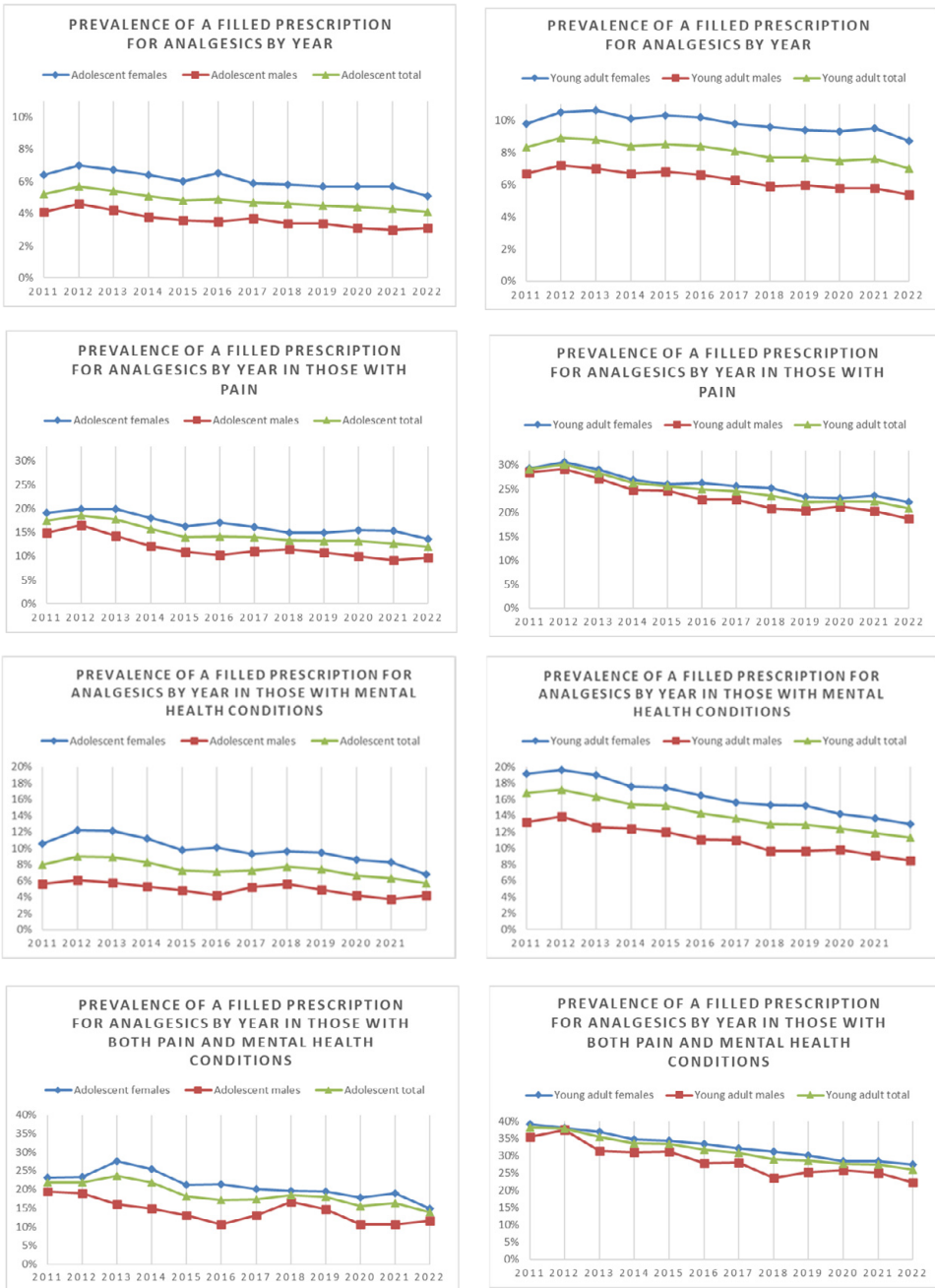


Figure 8 Prevalence of a filled prescription of analgesics in adolescents 13-18 years of age, young adults 19-24 years of age, in the region of Skåne Sweden, years 2011-2022, presented as total, in those diagnosed with pain, in those with mental health conditions and in those diagnosed with both pain and a mental health condition. Note the different scales between the three different populations.

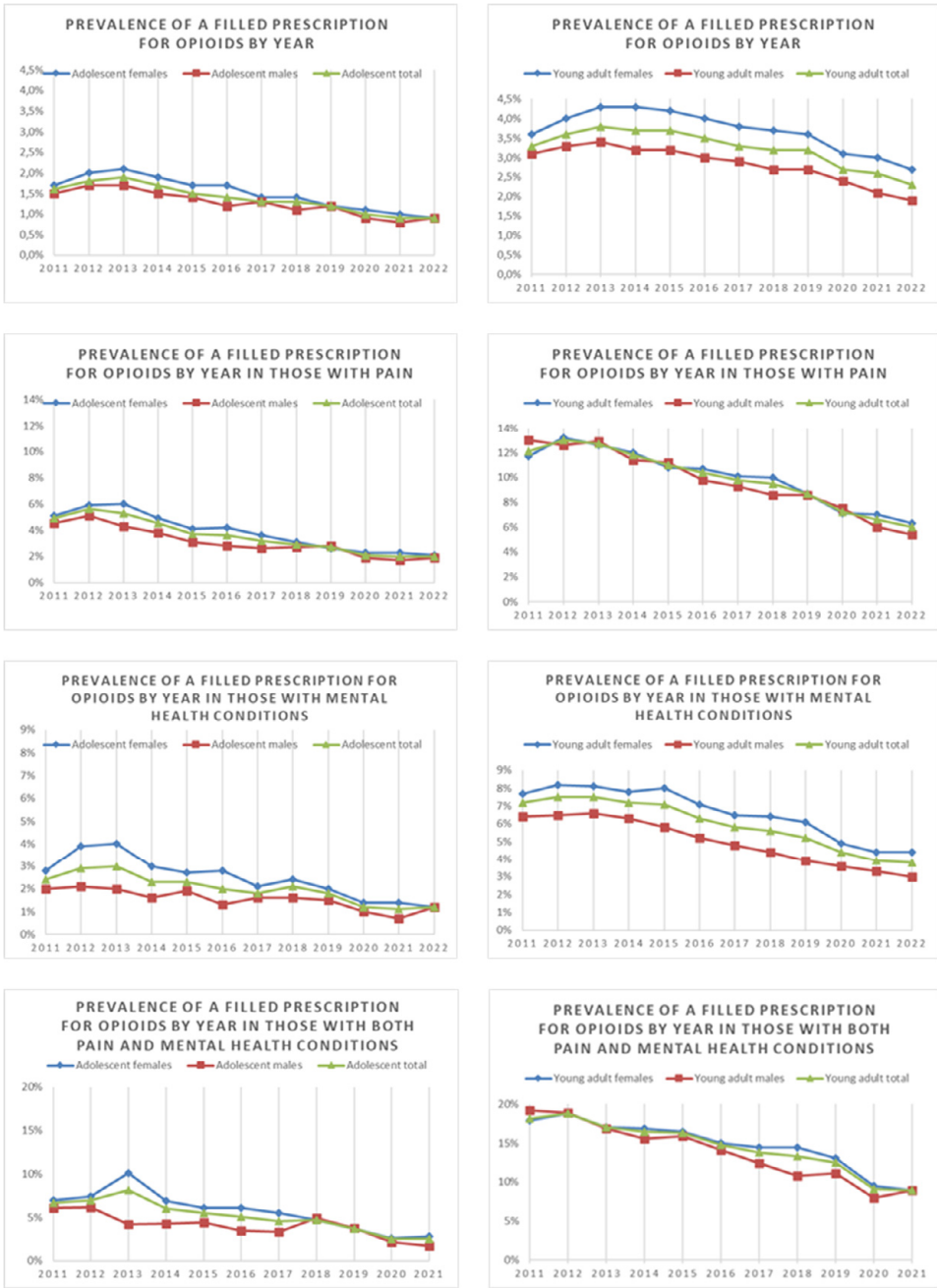
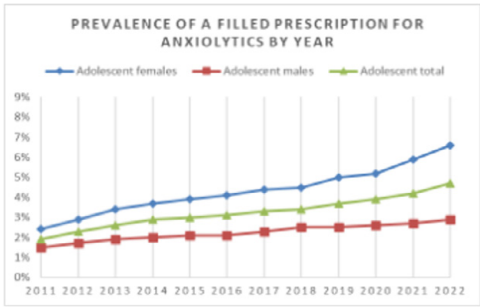
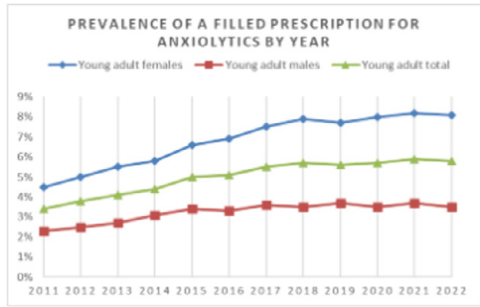
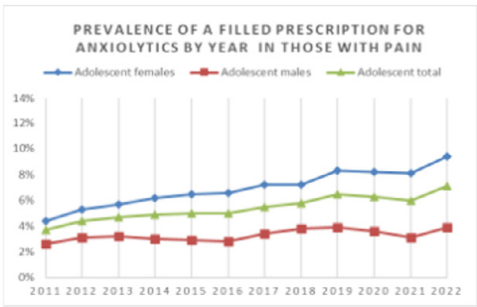
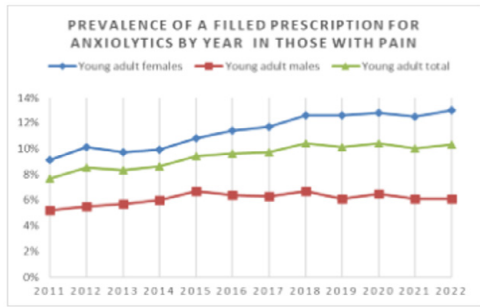


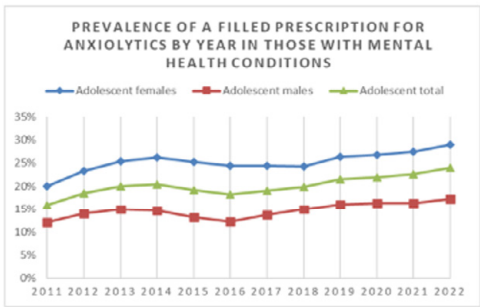
Figure 9 Prevalence of a filled prescription of opioids in adolescents 13-18 years of age, young adults 19-24 years of age, in the region of Skåne Sweden, years 2011-2022, presented as total, in those diagnosed with pain, in those with mental health conditions and in those diagnosed with both pain and a mental health condition. Note the different scales between the three different populations.

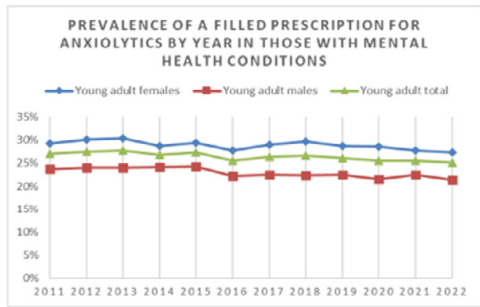


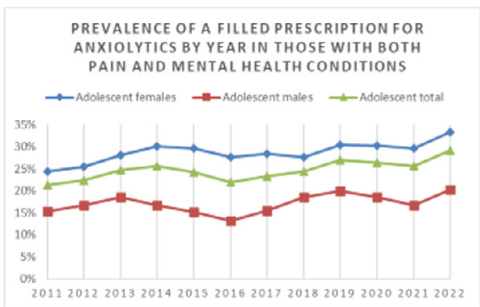












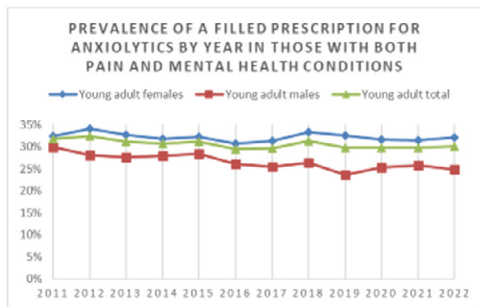


Figure 10 Prevalence of a filled prescription of anxiolytics in adolescents 13-18 years of age, young adults 19-24 years of age, in the region of Skåne Sweden, years 2011-2022, presented as total, in those diagnosed with pain, in those with mental health conditions and in those diagnosed with both pain and a mental health condition. Note the different scales between the three different populations.

Discussion

Risk factors for pain

The reasoning between the design of study I was the chance to study the effect of recurrent painful stimuli over time on the risk of developing chronic and widespread pain conditions in the form of fibromyalgia and CWP. It is believed that central sensitization is key in these conditions and that recurrent painful stimuli can trigger sensitization (12,78). To study this we choose conditions with diverse pathophysiology in the form of rheumatoid arthritis (RA), endometriosis and inflammatory bowel disease (IBD) but with recurrent painful episodes as part of their symptomatology as exposures (79–81). RA served as an important positive control, having previously been shown to be a risk factor for fibromyalgia (38) whereas endometriosis had been shown in cross-sectional studies to be associated with fibromyalgia (37,82). In regards to IBD as a risk factor for fibromyalgia and CWP, previous studies had shown conflicting results (36,83). We found that RA, endometriosis and IBD all increased the risk for widespread pain. Hence, we confirmed the previously found association between RA and fibromyalgia. The risk for fibromyalgia in those exposed for RA was more than triple that of the general population. That endometriosis was almost as high as risk factor as RA was an important finding. Endometriosis is a common but understudied disease therefore it is important to highlight additional negative effects of the disease. Finally, we also found a clear link between IBD and fibromyalgia with a doubled risk compared to the general population. The previous study that had found no increased risk for fibromyalgia after IBD had compared the prevalence of fibromyalgia in IBD after five years to the prevalence estimate from another study in the general population and found no significant difference, here we had the advantage of comparing the risk directly with the unexposed in the same population.

That all exposures increased the risk for fibromyalgia or CWP (the latter not significant for IBD) is consistent with the original hypothesis behind the study that recurrent pain regardless of origin would increase the risk for widespread pain, and this has implications beyond the studied exposures since many different conditions can cause recurrent pain and these are treated in diverse parts of the healthcare system. One could wonder if inflammation, a hallmark of RA (80) and IBD (84) and

also present in endometriosis could be a confounder, but the level of inflammation has been found to not be correlated to widespread pain for both RA (38,85) and IBD (36,83). To identify patients with recurrent pain early and dedicate time to pain management could potentially hinder the progression to widespread pain helping both the patient and the health care system.

In study II we explored, with similar design as in study I, the risk of pain in the form of dorsalgia (back pain)/abdominal pain/pelvic pain, or fibromyalgia after mental illness in the form of depression and anxiety and the other way around and found an increase in risk of similar magnitude of about double the risk of the rest of the general population for the two correlations, pain to mental illness and mental illness to pain. We found an even higher risk for fibromyalgia after mental illness and vice versa. Pain and depression/anxiety share biological pathways and neurotransmitters (86–88) and their comorbidity is known, also that treatment of pain in a depressed patient is harder as well as treatment of depression in a patient with pain (30), a study found that many patients with anxiety/depression did not seek healthcare for it but two thirds sought for associated somatic symptoms (89), can pain and mental health conditions sometimes be two sides of the same coin?

In study IV we found a decreasing prevalence of pain in adolescents and young adults but increasing prevalence of mental health conditions, the same trend can also be seen in the most common causes of sick leave in Sweden with mental health conditions replacing pain as the most common cause (90). A patient with ill health from both pain and mental illness might present in healthcare with one of these conditions and be diagnosed depending on several factors such as what is socially most acceptable, sex or gender (91), which condition is given priority in the healthcare setting or what is perceived as the most acute problem since time in a health care visit is limited. To identify comorbid pain and mental illness is important for adequate treatment, we observed that the bidirectional relationship exist before progression to fibromyalgia, and potentially earlier treatment could prevent cases of progression from more acute to chronic pain.

Effects of pain

In study I and II pain was not only an outcome but also a risk factor in the “reverse” analyses. In study I we did not anticipate a pathway in the opposite direction. Possible pathways were found in the literature given that studies had found RA being triggered by psychological distress (92,93), this distress also exists in fibromyalgia (94). Consistent with our own findings in study II on the risk of mental illness after fibromyalgia, this could be a potential etiological pathway. A similar effect could be behind the increased risk of endometriosis but given that endometriosis is suspected to be underdiagnosed with a long time from start of

symptoms to diagnosis (95), there is a risk of patients suffering from undiagnosed endometriosis progressing to and being diagnosed with CWP before the underlying endometriosis, giving rise to reverse causation in the material but not in vivo. For the relationship between fibromyalgia and RA, with fibromyalgia being more stigmatized than RA with fewer clinics available for diagnostics compared to RA, which has typical symptoms with arthritis and sometimes affected lab tests I find it implausible that this correlation would be driven mainly by patients being diagnosed first with fibromyalgia with a missed diagnosis of RA present even though such cases could of course exist.

In study III distal radius fracture served as an example of acute pain leading sometimes to opioid use and in some cases progressing to prolonged use, putting the patient at risk for dependency, non-medical use and other adverse effect with unclear effect on pain (50,52,53,96,97). This is a complex outcome since it heavily depends on the health care system's management of pain since a physician needs to prescribe the opioids in the first place and the prescription must either last for repeated purchases during more than three months or be renewed by a physician. Prescription of medication in this health care setting is fast and easy whereas talking to patients about their pain and motivating them to other pain management strategies can be time consuming. The Swedish treatment guidelines for distal radius fracture do not mention pharmacological treatment (98) and in an inquiry 10/15 Swedish centres treating distal radius fracture prescribed opioids (99). Discontinuing prescription has been described as difficult by physicians (100) and these mechanisms might drive prolonged opioid use. What makes this outcome important in a clinical setting is that it is an undesirable outcome that requires the healthcare setting to enable it, and while the intention to treat pain is positive, relying on opioids with insufficient follow-up can lead to harm for the patient. Since iatrogenic prolonged opioid use is caused by the healthcare system it is theoretically possible to avoid it by changing the management of these cases. The most important risk factor for prolonged opioid use was previous opioid use, especially in the year preceding fracture, in line with previous studies in other conditions (101–103), however some of these patients might simply be continuing a prolonged opioid use from before the fracture, so we also studied those with previous regular use in the last year (purchase of opioids in ¾ quarters of the year) and some but not regular use, and while considerably lower compared to those with regular use, the latter group had almost five times the risk of prolonged use compared to those unexposed. A main finding was that having a previous regular use, that had since been discontinued two to five years before fracture, gave an important increase in risk ratio compared to unexposed. Those with regular use five years previous having three times the risk of prolonged use compared to those with no use in the previous five years and the risk increased the closer the regular use was to the fracture. Another important risk factor and in line with previous studies (104,105) was mental illness. Mental illness is common in patients with non-medical use of opioids and

opioid use disorder (97,106). Giving our findings of a bidirectional relationship between pain and mental illness in study II it is probable that these patients experience more pain after fracture which might lead to a higher level of prescription of opioids.

We found that physical or occupational therapy lowered the risk of prolonged opioid use, and this should be encouraged. Interestingly while surgery increased the risk of prolonged use the proportion continuing the prolonged use in months 10-12 after fracture was lower in the surgery group compared to those who did not have surgery. We cannot be sure of the mechanism, but a potential hypothesis is the more stringent and standardized follow up received by patients undergoing surgery. Those undergoing surgery where also had a higher proportion actually attending physical or occupational therapy, which is recommended for all patients with distal radius fracture. To better identify patients at risk, encouraging physical or occupational therapy, avoiding unnecessary opioid prescription or following up more closely with a plan for discontinuation could help avoid causing harm in the form of prolonged opioid use.

In study IV we studied the changes in yearly prevalence of diagnosed pain and mental health conditions and associated prescription drug use in adolescents and young adults. Both pain and mental illness are common in adolescents and young adults and the self-reported prevalence has been increasing in the last years (34,35,107). In our study the prevalence of consultations for pain in adolescents and young adults decreased from 2012 while the consultations for mental health conditions increase across the entire period showing a difference between self-reported pain and what leads to consultation. The pattern found here with less consultations for pain and more for mental health conditions is mirrored in the sick leave of the adult population with mental health conditions surpassing musculoskeletal disorders as the most common cause of sick leave in 2014 (90).

The use of prescription drugs for mental health conditions has increased with the number of consultations for these conditions, however many of these conditions can also be treated by other means such as therapy. In our study the association between pain and mental health condition from study II is seen in several ways. Interestingly even though the total prevalence of pain decreased the prevalence of being diagnosed with both pain and mental illness in the same year increased across the period, and adolescents with pain have a higher prevalence of mental health conditions than the general population. In those diagnosed with pain the use of all prescription drugs is higher than in the general population regardless of if the drugs are primarily used for pain or mental health conditions, and the same is seen in those with mental health conditions compared to the general population. What is clear from the results is that in those diagnosed with both pain and mental health conditions the prevalence for all prescription drugs is even higher than when looking at pain and mental health conditions separately, consistent with the proposed complicating effect of pain and mental illness on each other (108). The findings in

study IV points to increasing healthcare consultations for mental health conditions in the young population, which will require appropriate resources and further investigation as to the underlying causes. Prescribing medication is fast and simple compared to psychotherapy or other non-pharmacological intervention which could be preferable, this is a potential risk factor for suboptimal treatment.

Methodological discussion

A strength of this thesis is the population-based cohort approach of all four studies. Including the entire population under study lowers the risk of selection bias and increases both the internal and external validity, the extent to which the association is true in both the population of study and in the general population. Using the extensive electronic healthcare data available in the region of Skåne Sweden in combination with other Swedish registers gave us a unique opportunity to follow individuals across time and healthcare providers, which is still rare in an international setting.

Study I was designed to test the effect of recurrent pain on the risk of fibromyalgia and CWP in a register setting by choosing different exposures with recurrent pain as a common symptom. We could of course not tell exactly how much or how little pain the exposed patients suffered from, but despite this, the results were consistent with the hypothesis of recurrent pain increasing the risk of widespread pain. An alternative approach would be to conduct surveys of patients with the exposures but since not all answer surveys are answered it would lead to only a subset of the population being studied, potentially introducing selection bias and possibly recall bias. The lower prevalence of fibromyalgia of 0,5% in the population found in study I compared to 1.3%–5.4% proposed in previous studies (109–111), probably illustrates the difference between reporting an experience of widespread pain when questioned and the additional steps required for an individual to actively seek medical attention and obtain a diagnosis. The path from symptoms to a diagnosis of fibromyalgia is often long due to insufficient medical attention with few specialist clinics, there is also a stigma inside and outside the health care organization regarding the diagnosis (112–115) although this has changed over the years.

CWP has a lower incidence in our study compared to fibromyalgia, this is the opposite of what is expected of the true prevalence in the population where fibromyalgia represents a smaller subset of CWP(116). This reflects a limitation imposed by the register data due to the fact that CWP does not have its own ICD-10 code. Therefore, several different codes are used throughout the region, and sometimes also used for cases of non-chronic or widespread pain: We preferred to use a strict definition of CWP and to rather miss true cases than to include false cases.

Individuals in our study populations that did not have a diagnosis with pain or mental health conditions, or other exposures are not necessarily free of these conditions. They are free of such diagnosis. They might have the conditions but may simply not have sought healthcare or been diagnosed with it. This means that in our reference population there are some misclassified individuals having the exposure while being classified as unexposed, this would decrease the difference between the unexposed and exposed group and therefore the strength of the association in what is called bias towards the null, despite this we still found clear associations between the studied exposures and outcome.

Our data from the registers is dependent on diagnoses from healthcare registered in SHR, while these have shown high validity in other studies (66–68) still not all who experience symptoms seek healthcare and are therefore not in the register. From a healthcare perspective however the ones seeking health care could be seen as the most relevant cases since they are the ones the system manages and treats. In the setting of the studies in this thesis, the propensity to consult healthcare increases the risk/chance of being diagnosed with pain (or anything else), since a consultation is a prerequisite for being diagnosed. This is however not the same as a true risk factor for pain or other disease but rather the chance of it being discovered by the healthcare system. It could also therefore be that propensity to consult healthcare is a confounder in the association you want to study. In study I this potential confounder is handled by adjusting for number of visits to healthcare in the washout period. In the otherwise similar in design, study II, this was not done and may therefore have affected the results. Regardless, all patients in all our studies have demonstrated that they at least seek healthcare once during the study period to be included.

In the analysis for studies I-III we have chosen a time-varying approach with Poisson regression to study person time at risk, meaning that patients who develop the exposure first contribute unexposed time before getting the exposure and contributing exposed time. This brings us closer to the actual effect of the exposure on the outcome since if they would be categorized as exposed from the start of the study a lot of that time would be misclassified as exposed.

The extensive registers in Sweden and Skåne have given us a unique opportunity to study various associations and provide plausible data on etiological causes. It is important to keep in mind that associations do not equal to causation, but I believe that we have taken the appropriate steps to try to minimize confounding when possible and to get as close to the true temporal associations as possible with the data available. The nature of the data does not allow us to test more profound mechanistical causes between the associations, such as biological or psychological processes. To study those processes will require other types of studies including laboratory studies and interventions.

Conclusions Summary

This thesis has shown that Swedish population-based registers are a good source for epidemiological studies in pain to study associations requiring detailed data on individuals over long periods of time to be studied. The unique designs of studies I and II allowed us to test two common hypotheses on the underlying causes of pain in the general population in a way that had been impossible in other settings. A problematic consequence of pain can be inappropriate opioid use and Study III focused on risk factors for prolonged opioid use after the common distal radius fracture. Since pain and mental illness are risk factors for later chronic pain Study IV serves to study the trends in prevalence of these conditions in the young population as well as associated prescription drug use. The studies included herein have shown:

- That RA, endometriosis and IBD strongly predispose for later widespread pain, indicating that recurring pain from diverse causes increases the risk of widespread pain. To better identify and treat pain from chronic conditions early could potentially decrease the risk of generalized pain.
- Evidence of a bidirectional influence of similar magnitude of pain and mental illness on one another, independent of sex, age, and socioeconomic status. This means that in managing patients with one of the conditions it could be beneficial to screen for and treat the other to improve patient wellbeing.
- That acute injury such in the form of distal radius fracture can be a gateway to prolonged use of opioids, especially among patients with previous history of opioid use or mental illness. That previous regular, but since discontinued, opioid use increases the risk several years after it ended and should be considered when initiating treatment and that rehabilitation seems to have a protective effect and should be encouraged.
- That while consultations for pain have decreased among adolescents and young there is a high and increasing prevalence of mental health conditions especially in females. Those with concurrent pain and mental health conditions had a higher prevalence of all prescription drugs Our result underscore the need to put extra focus on mental health conditions, with or without concurrent pain to prevent further negative impact on the individuals, the health-care organization, and the society.

Clinical implications

Many chronic conditions such as the studied RA, endometriosis and IBD lead to recurrent painful episodes which could potentially lead to sensitization and chronic or widespread pain. These patients are followed and managed in many different clinics in the healthcare system, but it is important to ask about and manage the pain early and identify patients at risk for developing chronic pain conditions and offer interventions were appropriate to try to stop this progression.

In dealing with patients consulting for either pain or mental illness it is important to keep in mind the bidirectional effect that these conditions might have on each other. This can make treatment more difficult, and by simply asking about if they are experiencing concurrent symptoms of the other condition can give the healthcare professional the chance to better understand and treat the patient.

Opioids are used for a variety of painful conditions, but they also put the patient at risk for dependency, non-medical use, and other adverse effects. When initiating treatment for opioids it could be beneficial to take into consideration risk factors for prolonged use in the patients such as earlier use and mental illness and make a plan for follow up and discontinuation as well as encourage rehabilitation in the form of occupational or physical therapy.

There is an alarming increase in consultation prevalence for mental health conditions in the young population with increased prescription drug use. This will require resources in the health care setting but also more investigation to identify and address the causes of this mental ill-being among the young. While consultation for pain have decreased slightly there is an increased prevalence for being diagnosed with both pain and mental illness in the same year, showing the continued need to monitor for pain in those with mental illness.

Future research

The next step regarding recurrent pain from underlying disease could be to do an intervention with tighter monitoring and follow up to try to manage pain earlier and decrease the risk of chronic pain, this has actually been done successfully in a cohort study on RA patients by Aronsson et al. (114). This approach could also be analyzed in the other exposures from study I as well as in other conditions with recurrent painful episodes.

There is an ongoing follow-up of study II within the research group studying the relationship between pain and mental illness in adolescents and young adults the population under study in study IV.

As a follow-up to study III it would be interesting to further study patients after acute pain from trauma such as surgery both regarding persistent postoperative pain and prolonged opioid use, to try to identify further risk factors and then design an intervention study based around these to see if can lower the risk by changing the perioperative management of these patients.

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