Register studies on pain throughout the course of life - its occurrence and relation to mental illness

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Register studies on pain throughout the course of life
its occurrence and relation to mental illness

Pain and mental illness are both common public health concerns in Sweden and therefore important to study from an epidemiological perspective. Pain can affect an individual at different points in life, from childhood until the end of life but the occurrence of pain at different ages is not fully clarified. Pain and mental illness constitute suffering for the individual but are also a great burden for society when leading to healthcare consultations and drug consumption. There is a well-established comorbidity between pain and mental illness but knowledge gaps on temporal and causal relationship still remains.

The overarching aim of this thesis was to increase the knowledge about pain throughout the course of life based on epidemiological studies, investigating its occurrence and relation to mental illness in the general population. We used several Swedish registers to deepen the understanding about pain and mental illness.

Paper I is a descriptive study investigating the one-year consultation prevalence of different pain conditions in the general population of children, adolescents and young adults. In total 16% of children and young people 1-24 years old, in Skåne consulted for pain. We could also show that children and young people with pain had around 1,5 to 2 times as many consultations as those without pain and the majority of those consultations were for other reasons than their pain.

Paper II is a prospective cohort study where we studied the risk for mental illness (anxiety/depression) after pain (back/abdominal pain) and the reverse; the risk for pain after mental illness. In this study we could show that there was a doubled risk for mental illness after pain but also that there was doubled risk for pain after mental illness.

Paper III is a register-based 3-year follow-up of a randomised controlled trial (REGASSA). In this study we investigated the long-term effectiveness of two different interventions, physical exercise and internet-based cognitive behavioural therapy compared to usual care for patients with mild to moderate depression in primary care. Outcomes were utilisation of healthcare and medicines. We found no difference between the three groups during follow-up with two exceptions year 2-3 after inclusion. The number of outpatient visits for pain was 36% lower for the physical activity group and 39 % lower for internet-based cognitive behavioural therapy group compared to the usual care group and there was also a 28% lower risk of being dispensed hypnotics and sedatives in both treatment arms compared to the usual care group.

Paper IV is a cohort study where we investigated occurrence of pain at the end of life and quantified the risk and risk factors for dying with unrelieved pain. Pain during the last week of life was reported for 68% of patients and of those, one fourth died with some degree of unrelieved pain, despite opioids PRN (as needed) prescribed to the vast majority (97%). Dying in hospital was associated with an 82% increased risk of unrelieved pain as compared to specialist palliative care and not having an end of life conversation was associated with a 42% increased risk of unrelieved pain.

In summary, my thesis contributes to new knowledge about pain and the relation to mental illness. In-depth clinical epidemiological knowledge about pain and mental illness in different phases of life can facilitate planning of care and provide a basis for research, to eventually guide clinicians to better assess patients and tailor interventions based on the individual patient's needs.

Key words: pain, persistent pain, mental illness, depression, register, epidemiology, healthcare consultation, internet cognitive behavioural therapy, physical exercise, palliative care

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To my family

"För att hitta den vackraste gläntan i skogen
måste man våga vara vilsen en liten stund"

Tomas Tranströmer

Table of Contents

Abstract 8
Svensk populärvetenskaplig sammanfattning 10
List of papers 12
Description of contributions 13
Thesis at a glance 15
Abbreviations 16
Preface 17

Background 19
Epidemiology – a brief introduction 19
Epidemiological opportunities in Swedish registers 19
Pain 20
Introduction 20
Classification of pain 21
Prevalence of pain 21
Risk factors for pain 23
Treatment of pain 23
Comorbidity 24
Biopsychosocial model 26

Aims 29
Overall aim 29
Specific aims 29

Methods 31
Study design 31
Experimental study designs 32
Observational study designs 33
Systematic errors 34
Approach and analyses 36
Data sources used in this thesis 37
Total Population Register 37
Skåne Healthcare Register 37

Longitudinal integration database for health insurance and labour market studies....38
Swedish National Patient Register....38
Swedish Prescribed Drug Register....39
Swedish Register of Palliative Care....39
Swedish Cause of Death Register....39
Diagnostic codes and diagnostic groups....40
Study populations and analyses, study I-IV....41
Consultation prevalence of pain conditions in a young population (Study I)....41
Comorbidity between pain and mental illness (Study II)....42
Utilisation of healthcare and prescription medicines after interventions for depression (Study III)....44
Dying with unrelieved pain – risk and risk factors (Study IV)....47
Ethics....49
Results....51
Consultation prevalence of pain conditions in a young population (Study I)....51
Comorbidity between pain and mental illness (Study II)....55
Utilisation of healthcare and prescription medicines after interventions for depression (Study III)....57
Dying with unrelieved pain – risk and risk factors (Study IV)....60
Discussion....65
Occurrence of pain in the young population and at the end of life....65
Relations between pain and mental illness....69
Methodological discussion....70
Summary and conclusions....73
Clinical implications....75
Future research....77
Acknowledgements....79
References....81

Abstract

Epidemiology is the study of distribution of disease and health in the population and in epidemiological research, frequencies, patterns and causes of diseases are among the investigated measures. Pain and mental illness are common public health concerns in Sweden and therefore important to study from an epidemiological perspective. Pain can affect an individual at different points in life, from childhood until the end of life, but the occurrence of pain at different ages is not fully clarified. Pain and mental illness constitute suffering for the individual and are also a great burden for society when leading to healthcare consultations and drug consumption.

There is a well-established comorbidity between pain and mental illness but knowledge gaps on temporal and causal relationships still remains. In epidemiological register studies using administrative healthcare databases, we have opportunities to fill some of these gaps.

The overarching aim of this thesis was to increase the knowledge about pain throughout the course of life based on epidemiological studies, investigating its occurrence and relation to mental illness in the general population. We used Swedish registers to deepen the understanding about pain and mental illness.

Paper I is a descriptive study where we investigated the one-year consultation prevalence of different pain conditions in the general population of children, adolescents and young people. We used the Skåne Healthcare Register containing information on all healthcare in Region Skåne. In total, 16% of children and young people 1-24 years old, in Skåne consulted for pain. We compared the total amount of healthcare that children and young people with pain sought in one year, to the same age group without pain. We could show that children and young people with pain had around 1.5 to 2 times as many consultations as those without pain and that the majority of those consultations were for other reasons than pain. Increased awareness in both research and planning of future healthcare are warranted.

Paper II is a prospective cohort study where we used the Skåne Healthcare Register and the LISA database from Statistics Sweden containing information on education and socioeconomics. We studied the risk for mental illness (anxiety/depression) after pain (back/abdominal pain) and the reverse, the risk for pain after mental illness. In this study we could show that there was a doubled risk for mental illness after pain but also a doubled risk for pain after mental illness. When clinicians meet patients with pain or mental illness, they need to be aware that comorbidity between the two conditions can occur early on as well as later.

Paper III is a register-based 3-year follow-up of a randomised controlled trial (REGASSA). In this study we investigated the long-term effectiveness of two different interventions; physical exercise and internet-based cognitive behavioural therapy, which were compared to usual care, for patients with mild to moderate

depression in primary care. Outcomes were utilisation of healthcare and dispensed prescription medicines. We found no difference between the three groups regarding proportion of participants consulting healthcare due to mental illness or pain during follow-up. However, the number of outpatient visits for pain was 36% lower for the physical activity group and 39% lower for internet-based cognitive behavioural therapy group compared with the usual care group, year 2-3 after inclusion in the study. Regarding dispensed prescription medicines (antidepressants, anxiolytics, hypnotics and sedatives and opioids) we found a 28% lower risk of being dispensed hypnotics and sedatives in both treatment arms year 2-3 after inclusion, compared to the usual care group. No other differences between the groups were found. Both internet-based cognitive behavioural therapy and physical exercise, being resource-efficient treatments, could be considered as relevant additions for patients with mild to moderate depression in primary care settings.

Paper IV is a cohort study where we used the Swedish Register of Palliative Care and the Cause of Death Register to investigate occurrence of pain at the end of life and to quantify the risk and risk factors for dying with unrelieved pain.
Pain during the last week of life was reported for 68% of patients and of those, 25% died with some degree of unrelieved pain, despite opioids PRN (as needed) prescribed to the vast majority (97%). Dying in hospital was associated with 84% increased risk of unrelieved pain as compared to specialist palliative care and not having an end of life conversation was associated with 42% increased risk. In pain management at the end of life, opioids are important interventions but could possibly be improved, especially in hospitals, concerning assessment, administration and evaluation of effect. A combination of pharmacological and non-pharmacological interventions, such as an end of life conversation, can possibly yield even better pain relief.

In summary, my thesis contributes to new knowledge about pain and the relation to mental illness. In-depth clinical epidemiological knowledge about pain and mental illness in different phases of life can facilitate planning of care and provide a basis for research, to eventually guide clinicians to better assess patients and tailor interventions based on the individual patient's needs.

Svensk populärvetenskaplig sammanfattning

Epidemiologi är läran om sjukdomars utbredning i befolkningen och inom epidemiologisk forskning studeras sjukdomars förekomst, orsaker och förlopp. Att ha smärta och psykisk ohälsa, är så vanligt att de närmast kan betraktas som folksjukdomar i Sverige. De är därför viktiga att studera ur ett epidemiologiskt perspektiv. Smärta kan drabba en människa närsomhelst i livet: från barndomen till livets slut, men hur vanligt det är med smärta i olika åldrar är inte helt klarlagt. Smärta och psykisk ohälsa utgör ett stort lidande för individen, och skapar också en belastning på samhället eftersom de leder till kontakter med hälso- och sjukvården och användning av läkemedel.

Det finns en väl studerad samsjuklighet mellan smärta och psykisk ohälsa, men det kvarstår kunskapsluckor vad gäller tids- och orsakssambandet mellan dessa båda. Genom epidemiologiska registerstudier av bland annat administrativa vårddatabaser har vi möjligheter att fylla några av dessa luckor.

Det övergripande syftet med denna avhandling var att få ökad kunskap om smärta i olika faser av livet samt om smärtans relation med psykisk ohälsa i den allmänna befolkningen. Vi använde svenska register för att fördjupa den epidemiologiska kunskapen om smärta och psykisk ohälsa.

Delarbete I är en deskriptiv studie där vi beskriver hur stor andel av barn och unga vuxna som behövde söka vård för olika smärttillstånd. Vi använde Region Skånes Vårddatabas som innehåller information om all den vård som genomförts i Skåne. Vi fann att under ett år sökte 16% av alla skåningar i åldern 1–24 år vård på grund av smärta. Vi jämförde också hur mycket vård dessa barn och unga vuxna med smärta totalt sökte under ett år jämfört med andra i samma ålder. Det visade sig att barn och unga vuxna med smärta hade ungefär 1.5 till 2 gånger fler vårdkontakter generellt jämfört med dem utan smärta och att majoriteten av dessa kontakter handlade om annat än smärtan. Det behövs ökad medvetenhet om smärta hos barn och unga vuxna både i forskning och i planering av framtida vård.

Delarbete II är en prospektiv kohortstudie där vi använde Region Skånes Vårddatabas och LISA-databasen från Statistiska centralbyrån som innehåller information om utbildning och socioekonomi. Vi studerade risken för psykisk ohälsa (ångest/depression) efter smärta (rygg/buksmärta) liksom det omvända, risken för smärta efter psykisk ohälsa. Vi visade att både risken för psykisk ohälsa efter smärta och risken för smärta efter psykisk ohälsa var dubblerad jämfört med dem som inte hade smärta respektive psykisk ohälsa. Kliniker som möter patienter med smärta eller psykisk ohälsa behöver vara uppmärksamma på denna samsjuklighet och att den kan förekomma både tidigt och senare i ett vårdförlopp.

Delarbete III är en registerbaserad 3-årsuppföljning av en randomiserad kontrollerad studie (REGASSA) där vi undersökte långtidseffekten av två olika interventioner,

fysisk träning och internet-baserad kognitiv beteendeterapi jämfört med sedvanlig behandling för mild till måttlig depression i primärvården. Utfallen var nyttjande av vård och läkemedel. Vi fann ingen skillnad mellan behandlingsarmarna avseende andel av patienter med öppenvårdsbesök för psykisk ohälsa eller smärta. Däremot var antalet öppenvårdsbesök för smärta för båda interventionerna mindre jämfört med gruppen som fick sedvanlig behandling 2–3 år efter studiens start. När det gäller förskrivning av läkemedel (antidepressiva, lugnande, sömnmedel och opioder) fann vi inga skillnader mellan behandlingsgrupperna avseende andel patienter som nyttjade läkemedel eller av antal dagliga doser av olika läkemedel med ett undantag; andelen patienter som använde sömnmedel var mindre för båda interventionerna jämfört med gruppen som fick sedvanlig behandling. Både internet-baserad kognitiv beteendeterapi och fysisk träning kan ses som resurseffektiva behandlingstillägg för patienter med mild till måttlig depression i primärvården.

Delarbete IV är en kohortstudie där Svenska Palliativregistret och Socialstyrelsens dödsorsaksregister användes för att undersöka förekomst av smärta i livets slutskede samt riskfaktorer för att ha delvis/inte alls lindrad smärta i livets slutskede. Totalt rapporterades smärta för 68% av individerna under sista veckan i livet och för 25% av dem förblev smärtan bara delvis/inte alls lindrad trots att 97% hade ”vid behov förskrivning” av opioder. De största riskfaktorerna för att inte ha fullt lindrad smärta i livets slutskede var att dödsfallet skedde på sjukhus samt avsaknad av brytpunktssamtal. Den palliativa vården på sjukhus behöver stärkas och brytpunktssamtal kan vara en möjlig intervention för att minska andelen patienter som dör med delvis/inte alls lindrad smärta.

Sammanfattningsvis bidrar min avhandling med nya kunskaper om smärta och psykisk ohälsa. En fördjupad klinisk epidemiologisk kunskap om smärta och psykisk ohälsa i olika faser av livet kan underlätta planering av vård samt ge underlag för forskning, för att på sikt även vägleda kliniker att bättre utreda patienter och skräddarsy insatser utifrån den enskilde patientens behov.

List of papers

I. **Bondesson E**, Olofsson T, Caverius U, Schelin MEC, Jöud A. Consultation prevalence among children, adolescents and young adults with pain conditions: A description of age- and gender differences. *Eur J Pain. 2020 Mar;24(3):649-658.*

II. **Bondesson E**, Larrosa Pardo F, Stigmar K, Ringqvist Å, Petersson IF, Jöud A, Schelin MEC. Comorbidity between pain and mental illness - Evidence of a bidirectional relationship. *Eur J Pain. 2018 Aug;22(7):1304-1311.*

III. **Bondesson E**, Jöud A, Stigmar K, Ringqvist Å, Kraepelien M, Kaldo V, Wettermark B, Forsell Y, Petersson IF, Schelin MEC. Utilization of healthcare and prescription medicines after non-pharmacological interventions for depression - a 3-year register follow-up of an RCT in primary care. *In manuscript.*

IV. Klint Å, **Bondesson E**, Rasmussen BH, Fürst CJ, Schelin MEC. Dying with unrelieved pain - Prescription of opioids is not enough. *J Pain Symptom Manage. 2019 Nov;58(5):784-791.*

Description of contributions

Paper I

Study design	Elisabeth Bondesson, Maria EC Schelin, Anna Jöud
Data collection	Anna Jöud
Data analyses	Elisabeth Bondesson, Tor Olofsson, Ulla Caverius, Maria EC Schelin, Anna Jöud
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Paper III

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Manuscript revision	Åsa Klint, Elisabeth Bondesson, Birgit Rasmussen, Carl Johan Fürst, Maria EC Schelin

Thesis at a glance

	Study purpose	Study population	Main results	Conclusions
I	Describe the annual consultation prevalence of a wide range of pain conditions in the general population of young people.	General population of Skåne aged 1-24 years n=373 178	The one year consultation prevalence was 15.8% (95% CI 15.7%–15.9%). Estimates were generally higher in females and this difference increased with age. 80% of consultations took place in primary care. Young people with pain sought more care (1.5 to 2.2 times more) for conditions other than pain as compared to young people with other health conditions.	A significant proportion consult for pain already in early ages. The even higher consultation rates among young females need additional attention, both in the clinic and in research.
II	Study risk for mental illness after pain and the reverse, risk for pain after mental illness.	Adult patients in Skåne with at least one healthcare visit to physician or physiotherapist year 2007-2016 n=504 365-761 180	There was a bidirectional relationship between pain and mental illness. The incidence rate ratio (IRR) for developing mental illness after pain was 2.18 (95% CI 2.14–2.22) compared to without pain. IRR for pain after mental illness was 2.02 (95% CI 1.98– 2.06) compared to without mental illness.	When meeting patients with pain or mental illness in the clinic, a focus on both conditions is important for developing appropriate, targeted interventions that may increase the likelihood of improved outcomes.
III	Investigate the long-term effect on healthcare utilisation and dispensed medicines of two different interventions for mild to moderate depression: physical exercise and internet-based cognitive behavioural therapy, as compared to usual care.	Adult patients with mild to moderate depression in primary care. Clinical cohort from the REGASSA-study n=940	Overall, no differences between the groups was found with 2 exceptions: Year 2-3 after inclusion: 1. the *number* of consultations for pain were 36% and 39% lower in the physical exercise group and in the internet-CBT group 2. both the physical exercise group and the internet-CBT group had 28% lower risk of being dispensed hypnotics/sedatives compared to usual care.	Both interventions, being resource-efficient treatments, could be considered as relevant additions for patients with mild to moderate depression in primary care settings when considering long-term effects.
IV	Quantify the risk and investigate risk factors for dying with unrelieved pain, with the overarching goal to identify areas of improvement.	Patients in the final week of life (expected deaths) identified in the Swedish Register of Palliative Care year 2011-2015 n=236 527	In total, 68% were reported to have pain and for 25% of them, the pain was partly unrelieved, despite prescription of opioids as needed (PRN) in 97% of cases. Risk factors for unrelieved pain included hospital death (RR=1.84, 95% CI 1.79-1.88) and absence of an end of life conversation (RR= 1.42, 95% CI 1.38-1.45).	Healthcare providers, hospitals in particular, need to improve care structure for pain relief in dying patients. An end of life conversation is one achievable intervention.

Abbreviations

ATC	Anatomical Therapeutic Chemical
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
DAG	Directed acyclic graph
EoL	End of Life
IASP	The International Association for the Study of Pain
ICD	International Classification of Diseases and Related Health Problems
IRR	Incidence rate ratio
ITT	Intention to treat
LISA	Longitudinal integration database for health insurance and labour market studies
NPR	Swedish National Patient Register
PDR	Swedish Prescribed Drug Register
PIN	Personal Identity Number
PRN	pro re nata, which means the medicine is taken as needed
RCT	Randomised Controlled Trial
RR	Relative risk/Risk Ratio
SDR	Swedish Cause of Death Register
SHR	Skåne Healthcare Register
SMR	Standardised morbidity ratio
SRPC	Swedish Register of Palliative Care
TPR	Total Population Register
VAL	Stockholm Regional Healthcare Data Warehouse
VEGA	Healthcare database held by Region Västra Götaland
UC	Usual care

Preface

Pain and mental illness are public health concerns that affect the individual and the near family as well as society to a great extent. Nearly all of us will experience pain and mental ill health at some stage of our life. Most of the patients I have met in my profession as a physiotherapist have had a pain problem and many of them were depressed or, at the very least, worried about their pain and how it affected their life. I have always been interested in the psychological aspects of pain and when I in 2015 was given the opportunity to become a PhD student, the first question I tried to answer was: *Does pain lead to mental illness or is it the opposite, that mental illness leads to pain?*

In this first study, I was introduced to two valuable tools that I have since used throughout my PhD period; Swedish registers and a comprehensive statistical and data management program. Not knowing much about these tools, they appeared like a mountain for me to climb. However, gradually they became my best companions and, in this thesis, they have helped me answer research questions about pain and mental illness.

I believe that a more in-depth epidemiological knowledge about pain and mental illness can facilitate the planning of care, provide a basis for future research and ultimately contribute to better care for patients with these conditions.

Background

Epidemiology – a brief introduction

Epidemiology is often described as the basic science of public health because it is the science that describes the relationship of health or disease with other health-related factors in human populations. Epidemiology has several definitions which have changed over time but can be summarized as *the study of the distribution of disease and health in the population* (1). In epidemiology, frequencies or patterns of disease or other events are often studied. Knowledge of the distribution of diseases in the population is necessary to optimally plan resources needed at different levels of care. How many that are affected in different age groups will for example have impact on resource planning. So, occurrence is one aspect, but equally important is to know *who* is at risk for a worse prognosis or development of disease and what type of care or intervention is optimal for that specific individual. By studying cause and effect, risk factors and comorbidities, that in different ways can affect prognosis and development of disease, care and interventions can be developed and more successfully tailored to the individual needs. The gained knowledge from research should be applied both clinically and in the organisation of care, with the purpose of improving public health or healthcare.

Pain and mental illness are examples of diseases that are large public health concerns affecting individuals through the entire course of life. Both conditions lead to suffering for the individual, and they also constitute a burden for society in utilisation of healthcare and medicines. In this thesis, epidemiological methods have been used to study pain through the life course, investigate occurrence, comorbidity and risk factors and explore the relation between pain and mental illness.

Epidemiological opportunities in Swedish registers

Sweden has exceptional possibilities to perform epidemiological register-based research due to several available registers and the unique personal identity number (PIN) given to each Swedish resident (2). This enables researchers to combine register data on an individual level. Among the available registers are national public administrative registers including population and health registers, which are mandatory. Additionally, Sweden has over one hundred quality registers established

in specific disease (or treatment) areas to systematically and continuously develop and ensure the quality of healthcare. These registers are not mandatory to participate in, but the majority of patients agrees to be registered (3).

Through the national administrative registers e.g. sociodemographic data is accessible and through the national health registers, data such as healthcare consultations from secondary care and hospitalisations as well as drugs prescribed and dispensed are available for the entire adult population (4, 5). Furthermore, regional healthcare registers that hold data from primary care are available and are growing prospectively by automatic transfer. However, these regional registers are developed to a very different extent, hence usability for research purposes varies.

Overall, there is ample opportunity to combine data from different registers for epidemiological research. Common bias, such as recall bias and response bias, could thus be kept at a minimum. An additional strength is the access to a large sample size and the ability to track patients with different diseases over time which enables time-to-event analysis (6). As with all research on personal data, ethical approval as well as approval from the authorities holding the different registers is required (7).

In summary, linkage opportunities that are quite unique for Sweden enable us to study consultation prevalence of different conditions in all age groups on a population-based level. Registers also allow us to track patients over time in all levels of care and study risk estimates, time-varying exposures and risk factors for developing disease or symptoms. Finally, register data can also be used as outcome measurements, for instance utilisation of healthcare and prescribed medicines.

Pain

Introduction

Pain is a fundamental human experience. All of us will at some point during the life course experience pain. The International Association for the Study of Pain (IASP) defines pain as “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (8). To be able to feel pain is an essential part of our life. As children, the pain sensation teaches us what could be potentially harmful, and this has survival value. Some individuals will however develop a problematic recurrent or persistent pain. Persistent or chronic pain is pain that persists or recurs for more than three months (9), and as such no longer has survival value. Instead of being a signal for harm, the pain itself becomes the problem. To prevent acute pain from developing into persistent pain, interventions should optimally be both early in time and tailored to the specific individual (10-12).

Classification of pain

The specific diagnosis has impact on prognosis and the choice of treatment for patients with pain and is hence an important component of clinical practice (13). Pain conditions, as other diseases, are diagnosed using the ICD (International Classification of Diseases and related health problems) system (14). To establish a diagnosis, clinicians need to define what kind of pain the patient is suffering from. The diagnosis and the definition facilitate communication about pain between clinicians and patients, but also between researchers. As previously mentioned, pain can be defined according to temporality and divided into acute and persistent pain. Another way of classifying pain is by mechanisms, where pain can be nociceptive, i.e. generating from tissue, such as from a wound, fracture or muscle. Pain can also be neuropathic, which is pain from the nervous system or a nerve, such as diabetes neuropathy or radiating pain from a prolapsed disc (15). Finally, pain can be nociplastic, which was recently defined by IASP as "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" (8, 16). The term nociplastic and its characteristics is under debate but nociplastic pain has generally been considered as being maintained by altered central processing including central sensitization (16) and this type of pain is often preceded by a specific pain condition, for example back pain. Fibromyalgia is one example of pain that is classified as nociplastic. Fibromyalgia is characterized by widespread musculoskeletal pain and often comes later, after a progression from acute to persistent pain (9, 17, 18). Pain distribution can also be used to define pain into local, regional or widespread pain. Regional pain is most common in the adult population (19) and both local and regional pain is known to increase the risk of later widespread and persistent pain (20-22).

Prevalence of pain

The proportion of a population with a certain disease or health event at a specific time point is called *prevalence*. It can be measured at a single point in time (point prevalence) or for a time period (period prevalence). How prevalence is reported depends on differences between studies and type of pain that are studied (23). The stricter the definition, and the shorter the time period, the lower prevalence. In survey studies people are asked questions about where, how often and how severe pain they have. This can give a lot of detailed information. A prevalence from a survey depends on who chooses to participate, and this can lead to problems with selection and thus the representativeness/generalisability.

In this thesis, the focus is on pain as defined and seen within healthcare. As a healthcare professional and as a healthcare organisation, those with pain that also consult healthcare are the ones we can reach with advice, care and interventions.

Therefore, another way to assess pain prevalence is to study the healthcare consultation prevalence. This is a largely unexplored way of studying prevalence and one that has a much higher probability of representativeness. These types of studies require large population-based data sources. One great advantage is that, depending on healthcare regulations, the total care-seeking population is included and it is possible to study several pain conditions simultaneously and data sources can be linked together to gain more information on the individual level.

Pain is common throughout the entire course of life. High prevalence of recurrent and persistent self-reported pain is reported both in adolescents, adults and the elderly in survey studies (24-27). Looking at the global burden of disease study, low back pain (fourth) and headache disorders (fifth) were both in the top ten most important causes for the 10-49 year age-group. Moreover, low back pain and other musculoskeletal disorders were also found to be common from teenage years into old age (28). In the adult general population, an overall prevalence of moderate to severe chronic pain of 19% (18% in Sweden) has been reported in a large international survey. Of the 19%, about half have back pain, 40% have joint pain and one in 5 has headache (24).

From a mainly European survey, among schoolchildren 11 to 15 years old, it was reported that 12.5% have headache, 7.7% have backache, 4.6% have abdominal pain and 24.3% have multisite pain when asked about at least weekly pain during the last six months (25). However, we lack knowledge about how much care the young population seek for their pain. Both in children and adults, musculoskeletal disorders such as back pain, but also headache and nonspecific abdominal pain, are common pain locations (29-33) and prevalence rates are generally higher in females (24, 26).

The prevalence of persistent pain in older people range from 25% to 93% (34). In a Swedish survey in the age group over 65 years old, 38% reported persistent pain and the most common locations were pain in the back/pelvis and in the lower extremities (35). Pain is common in the advanced stages of many chronic diseases (36) and clinically, unrelieved pain is a common problem in dying patients but prevalence of pain at the very end of life is not well studied.

Since not everyone with pain consult healthcare, the consultation prevalence of pain is of course lower compared to survey studies. Consultation prevalence is mostly studied for musculoskeletal disorders. In a study from Canada it was reported that 12.2% of children and youth (0-19 years old) annually had visits for a musculoskeletal disorder. The majority of children present to primary care physicians (74.4%), surgeons (22.3%), and paediatricians (10.1%) (37). A UK study, investigating only primary care, found that 8.3% of children (aged 3-17) consulted annually for a musculoskeletal problem and the most common body regions consulted for were the foot, knee and back (38). In general, prevalence

increased with age and in this particular study prevalence was higher in males than females, but this varied between different pain conditions (38).

In the adult Swedish population, the 1-year consultation prevalence of back pain in the population varies between 3.8% and 6.0% depending on the definition of back pain and care setting (32, 39). As in the young population, the prevalence increases with age and are higher among females. Looking at Swedish primary care only, consultation prevalence for back pain has been shown to increase during a five-year period (2014-2018) from 4.8% to 6.0% (39).

Risk factors for pain

For recurrent or persistent pain in general, risk and maintenance factors interact in complicated ways. Identified risk factors are found in several different domains such as medical, work-related and psychosocial (40, 41) Among the more well-proven risk factors is first and foremost previous pain problems (42, 43) but also severe disability, anxiety, depression, catastrophic thoughts, female sex and low sociodemographic status (41, 42, 44). However, temporality is often lacking in studies of risk factors and consequently it is difficult to determine causality (41).

Treatment of pain

Treatment of pain is not the main focus in this thesis. However, treatment has bearing on the prognosis and may slow down or stop transition from acute to persistent pain. Acute pain can subside without any specific treatment and individuals often adapt during healing and regain function. Nevertheless, it is not uncommon for pain conditions such as back pain to be recurrent (45-47). Patients with acute or subacute musculoskeletal pain problems can often be successfully treated by physiotherapists, where a thorough individual assessment guides the intervention. In general, recommended interventions include patient-centred care and providing patients with education about their condition and management options. Physical exercise or activity should always be a part of the treatment and it is important to facilitate continuation or resumption of work (48). For some individuals, medication, surgical or orthopaedic interventions are needed to treat the pain. During surgical or orthopaedic procedures, strategies for pain treatment is very important to prevent persistent pain (15). Patients with persistent pain and tangible consequences in life, such as fear of movement and physical and social inactivity, demand different treatment strategies, e.g. multimodal rehabilitation. In this type of intervention, several professions work together with the patient in a team (49). The specific rehabilitation interventions often depend, not on the pain condition itself, but on the consequences of pain for the individual. Interventions such as physical and activity-based exercises, education, cognitive- and behavioural interventions,

are common (50-52) and the length and intensity of the programs varies (53). The goal with rehabilitation of recurrent or persistent pain is for the patient to develop better strategies to cope with pain, in order to enable participation in activities deemed valuable by the patient. Wherever patients with pain are assessed or treated, an approach where the biopsychosocial model is adopted is always an advantage (54, 55).

In the very last phase of life, fear of pain is often expressed by patients and their nearest family and relief of pain and other distressing symptoms become more in focus (56, 57). Opioids are often prescribed, but also non-pharmacological interventions can contribute to a "good death" (58). Despite efficient methods for the assessment and treatment of pain, unrelieved pain is a common problem in dying patients and what factors that affect relief of pain at the end of life is uncertain. More knowledge about these risk factors would be helpful to identify areas of improvement for dying patients.

Comorbidity

Patients with pain often have concomitant health problems, such as heart disease, obesity or depression and they consult healthcare more than the general population (59). Especially mental illness is common in patients with pain. Depression, anxiety and pain often occur simultaneously (60-63) and relapse into all these conditions is common (46, 64, 65). Mean prevalence of pain symptoms in patients with depression is estimated to 57% (43%-69%) while the prevalence for depressive and anxiety disorders in patients with pain range between 2-83% and 1-65% respectively (63). This comorbidity has impact on disease development. Depression is less successfully treated if the patients have concomitant pain, and correspondingly, patients with pain are less responsive to treatment if they simultaneously have depression (60, 63). It can be assumed that there are similar biological and psychosocial factors that contribute to both pain and mental illness such as depression. Restrictions of daily activities have been shown to be a strong predictor of onset for both persistent pain and mental disorders, suggesting that disability, or withdrawal from rewarding daily activities, is an important link between the two (66). Biological links have also been proposed; pain and depression are closely correlated from the perspectives of brain regions and the neurological function system (67, 68). Finally, a common genetic background between depression and low back pain as well as depression and chronic widespread pain has been shown in twin studies (69, 70). There is no doubt that there is a strong association between pain and mental illness in cross-sectional studies, but we still lack knowledge about the temporal and causal relationship between the conditions.

Prevalence and characteristics of depression and anxiety

Mental illness in the form of depression or anxiety is today, as pain, a public health issue (71). Depression is characterized by persistent sadness and a lack of interest or pleasure in previously rewarding or enjoyable activities. It can also disturb sleep and appetite; tiredness and poor concentration are common (72). People with anxiety disorders usually have recurring intrusive thoughts or concerns. It is a condition characterized by an excessive and persistent sense of apprehension, with physical symptoms such as sweating, palpitations, and feelings of stress. Prevalence estimates of mental illness are high. Major depression is the second most common cause of the global burden of disease (73), anxiety is the seventh (74). The point prevalence of major depression and anxiety disorders worldwide is 3.6% and 3.7%, respectively (75). In Sweden, an epidemiological study estimated the point-prevalence of clinically significant depression and anxiety to 10.8% and 14.7% respectively and nearly 50% had comorbid disorders (76).

Treatment of depression and anxiety

For mild to moderate depression and anxiety psychological interventions, such as cognitive behavioural therapy (CBT), is the first choice of treatment (77, 78). For more severe cases a combination of medication and psychological interventions are recommended. Antidepressants are most frequently used but not all patients can use them, for a variety of different reasons (79, 80) and the risk of relapse after antidepressants seems to be larger compared to psychological treatment (81). Given the burden of these diseases for society and the limitations with current interventions, treatments that are effective, have few negative side effects and demands few resources are desirable. Internet-based CBT could be one such alternative, since it allows the therapist to treat four times as many patients in the same amount of time as face-to-face CBT (82) and also has comparable treatment effects both for depression and anxiety (82-84). The shown effects have so far mainly been short-term and there is a lack of studies investigating the long-term effectiveness (85). Physical exercise is another promising treatment option that also has been reported to have effects on both depression (86) and anxiety (87, 88). An additional benefit is that physical exercise has positive effects on common comorbidities with mental illness such as pain (89) and cardiovascular disease (90, 91). Both internet-CBT and physical exercise are aimed at giving the patients tools to cope with their problems on their own, in the event of a flare or recurrence, which is a further advantage.

Consequences of pain and mental illness

Recurrent or persistent pain and mental illnesses such as depression or anxiety have much in common with regard to consequences. These disorders often lead to avoidance behaviour and subsequently withdrawal from engaging in work and from social and physical activities. These behaviours, in turn, worsen problems and

symptoms. The experience of recurrent or persistent pain has long-term effects for both children and adults and contribute to a poorer quality of life, functional limitations, difficulties in developing social relationships, sleep disturbance, problems with school attendance, workability and sick leave (24, 92-96). Both back pain, depression and anxiety increase the risk of disability pension and comorbidity between them increases the risk further (97, 98). There are also indications that pain in the younger years predisposes for both pain (99-101), mental illness (102) and difficulties in working life as adults (103). But knowing who will develop persistent problems remains a challenge (104).

Pain and mental illness are common causes of seeking healthcare (105). Together they constitute a large burden, especially for primary care (106-109). About three-fourths of depression cases are handled exclusively in primary care and pain-related conditions are very common reasons for visits to a physician (110). Patients with pain and depressive or anxiety symptoms combined, have more visits to both emergency departments and physicians than those with pain alone (111, 112). Patients with pain and mental illness are additionally large consumers of different kind of medicines. (113-115). From a public health perspective, individuals that are affected to an extent that renders high healthcare utilisation, reduced work productivity and drug consumption are important to study.

Biopsychosocial model

Considering the comorbidity and the consequences of pain and mental illness, a biopsychosocial perspective is crucial when planning healthcare for these conditions (116). According to the biopsychosocial model, every state of illness or health depends on biological, psychological and social conditions and there is a constant interaction between them in an individual's life (55, 117, 118) (Figure 1). However, biomedical reductionism, that body and mind function separately and independently, has since the renaissance been the dominating view, and researchers and clinicians that advocate the biopsychosocial model have struggled to establish the model. Looking at the pain domain, despite many years of research showing the importance of psychology and processes in the brain for pain perception, the norm in Western medicine is still in many ways this dualist approach (116). A medical explanation is still first and foremost the focus although pain does not evolve in a vacuum. Rather, it affects an individual with a certain status of health, both mentally and physically, and in a social context. All these aspects can influence onset and development of disease. The biopsychosocial model underlies person-centred care and should therefore be used in clinical care, when assessing and treating patients (54, 119). In some areas of medical practice, such as rehabilitation, chronic pain management services, palliative care and psychiatry the model is at least partly used, while in other areas, such as acute medical and surgical services, it is almost unknown (55). The healthcare would probably improve if all healthcare teams were

more aware of and used the biopsychosocial model of illness. Though, this would demand organising and funding of healthcare in a way that supported this approach (55). The model is also used in research of many disabling conditions, one example being chronic low-back pain where the evidence supports the model (51).

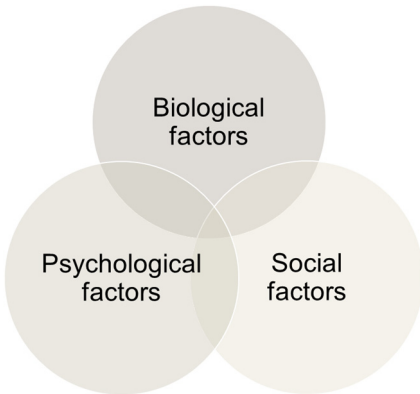

Figure 1.
Illustration of the biopsychosocial model.

Aims

Overall aim

The overarching aim of this thesis was to increase epidemiological knowledge about pain throughout the course of life, investigating its occurrence and relation to mental illness in the general population.

Specific aims

- Describe the annual consultation prevalence of pain conditions in the general population of children, adolescents and young adults, in order to show the burden of disease.
- Study if patients with pain have an increased risk of developing mental illness and the reverse, study if patients with mental illness have an increased risk of developing pain, compared to the rest of the general population, in order to shed light on the causal relationship.
- Investigate the long-term effectiveness measured as healthcare utilisation and dispensed medicines of two different interventions, physical exercise and internet-based cognitive behavioural therapy (internet-CBT), compared to usual care in adult patients with mild to moderate depression in a Swedish primary care setting, in order to complement the RCT with information on long-term effect.
- Quantify the risk and investigate risk factors for dying with unrelieved pain, in order to identify areas of improvement.

Methods

This section starts with a brief general introduction to epidemiological study designs and systematic errors. This is followed by a presentation of the data sources and diagnostic codes used in this thesis. The last part of this section describes the methods and statistical analyses used in study I-IV, respectively.

Study design

Epidemiological studies are typically divided into two main types: observational studies and experimental studies. In observational studies, researchers observe the natural process without intervening, while in experimental studies researchers introduce an intervention and study the effects. Cohort design, including also cross-sectional studies and case-control studies, are common designs among observational studies, while randomised controlled trials (RCTs) are the most common experimental type.

In this thesis study I is a cross-sectional study, study II and IV are cohort studies and study III is an RCT. An overview of the study designs used is presented in Table 1.

Table 1.
Overview of design.

	Study I	Study II	Study III	Study IV
Design	Population-based cross-sectional study	Population-based prospective cohort study	Randomised controlled trial – long-term follow-up	Population-based cohort study
Study population,	General population of Skåne aged 1-24 years n=373 178	Adult patients in Skåne with at least one healthcare visit to a physician or physiotherapist year 2007-2016 n=504 365-761 180	Adult patients with mild to moderate depression in primary care. Clinical cohort from the REGASSA-study n=940	Patients in the final week of life (expected deaths) identified in the Swedish Register of Palliative Care year 2011-2015 n=236 527
Exposure	Healthcare consultations for different pain conditions	Healthcare visits for pain (back and abdominal pain and fibromyalgia) and mental illness (depression and anxiety)	Internet-CBT and physical exercise compared to usual care	Risk factors: cause of death, place of death, end of life conversation, lack of contact with pain management expertise
Outcomes	1. Consultation prevalence of pain conditions 2. Proportion of frequent consulters 3.Standardised morbidity Ratio (SMR)	1. Incidence rates of consultations for pain and mental illness. 2. Incidence Rate Ratios (IRR) for pain after mental illness and for mental illness after pain compared to the unexposed	1. Proportion of and number of healthcare consultations for mental illness and pain 2. Proportion of and number of dispensed medicines for mental illness and pain	1.Occurence of pain (relieved and unrelieved) 2. Dying with or without unrelieved pain
Analysis method	Descriptive statistics	Descriptive statistics Poisson regression	Descriptive statistics Modified Poisson regression Negative binomial regression	Descriptive statistics Modified Poisson regression
Data sources	TPR, SHR	TPR, SHR, LISA	TPR, NPR, SHR, VAL, VEGA, LISA, PDR	SRPC, SDR

TPR= Total Population Register, SHR=Skåne Healthcare Register, LISA= Longitudinal integration database for health insurance and labour market studies, NPR=National Patient Register, VAL= Stockholm Regional Healthcare Data Warehouse, VEGA=Healthcare database held by Region Västra Götaland, PDR= Prescribed Drug Register, SRPC= Swedish Register of Palliative Care, SDR= Cause of Death Registered controlled design.

Experimental study designs

Randomised controlled design

A randomised controlled trial (RCT) design is often preferred for studying causality. However, a recent Cochrane report concluded that there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design (120). A primary role of RCTs is to assess the efficacy of different forms of therapy. If the study design is optimal

e.g. randomisation is performed correctly and sample size adequate, the advantage is that both measured and unmeasured confounding factors are distributed randomly, and thus cannot cause imbalance between the groups. In a well performed unbiased RCT the only thing that differs between the groups (or arms) is the intervention and any effect can be ascribed to it. A well performed RCT is therefore described as having high internal validity. Internal validity refers to that the studied effect or association estimate is correct within the studied population. However, RCTs are often not feasible due to high economic cost and/or ethical concerns. It can also be difficult to encourage patients and clinicians to participate actively throughout the whole study period. Loss-to-follow-up can lead to selection bias and this can affect the generalisability of the results. Generalisability or external validity is whether the results from a study are valid for the population that the researcher intended to target. Another limitation with RCT design is that inclusion criteria are sometimes very strict, resulting in the sample not reflecting the general population with the disease under study, this also affects the generalisability. Study III is a randomised controlled trial.

Observational study designs

Cohort design

A cohort study is where a group of individuals (called a cohort) are prospectively followed over a period of time. The individuals in the cohort should be free from the studied outcome at study start. It involves measuring the incidence (rate of new cases) of disease in a population or comparing the rate of disease or outcome in exposed and unexposed individuals in the cohort. The exposure is the factor whose effect the researcher wants to investigate. It can e.g. be environmental factors, genetic factors or a disease, such as pain or mental illness in study II or different clinical risk factors, as in study IV. The group of people who we eventually wish to be able to apply our results to, is called the *target population*. Often it is not possible to conduct studies on the entire target population, instead a sample (a cohort) from the target population is drawn and the study is performed with the individuals in the sample.

Registers, such as healthcare databases, contain routinely prospectively collected data and as such could be regarded as large cohorts. When studying the care-seeking population, these cohorts make it possible to include large populations and allow for real-life studies including follow-up at a low cost. A register-based cohort study has a further advantage in often low loss-to-follow-up, hence less selection bias. In study II we used a cohort design with a 10-year follow-up period which made it possible to determine both the underlying risk and calculate the incidence rate ratio, i.e. the effect of the exposure.

Cross-sectional design

A cross-sectional study is a type of cohort study that involves data derived from a defined time point or time period. Cross-sectional design is often used to assess the prevalence of medical conditions but can only rarely be used to answer questions about the causes of disease or the results of interventions since participants are not followed over time. Study I has a cross-sectional design and here the prevalence of pain conditions during one year among young people is studied.

Systematic errors

In experimental studies, the idea is that the only thing that differs between the intervention arms is the intervention and therefore, in a well-designed study, the causal effect or causal relation can be defined. In observational studies, this is typically more difficult to establish and define, because there is a higher risk of systematic differences between those exposed and unexposed (except the actual exposure) and this can distort the association under study and bias the result. There are three main areas of systematic errors: misclassification, confounding and selection bias.

Misclassification

Misclassification (or information bias) is when information on exposure or outcome for study subjects is inaccurate, leading to participants being assigned to an incorrect category of exposure or outcome. It can occur when a patient is classified as having a disease when in fact there is no disease present. Another example is when a patient is being classified as being treated with a prescribed medication, e.g. opioids when he or she is not. Misclassification of exposure that are dependent on outcome status (or the other way around) is called *differential misclassification* while misclassification that does not depend on the other variable is called *nondifferential misclassification* (121). Differential misclassification is the most problematic and can lead to effects either being exaggerated or underestimated. Bias introduced by nondifferential misclassification of a binary exposure or outcome is predictable in only one direction, towards the null i.e. towards no effect of the exposure on the outcome, as it can be seen as dilution of the effect (121).

Confounding

Another example of systematic error is confounding, which is a situation when the association between exposure and outcome is distorted by a third variable (122). To be defined as a confounding factor the third variable must independently affect both exposure and outcome. An example of confounding is the association between birth order and Down syndrome shown in a classic study. Data from this study show an increased prevalence of Down syndrome with increasing birth order (123).

However, this association is confounded by the age of the mother which is closely correlated to birth order (122, 123).

Confounding leads to study groups lacking comparability and is therefore a threat to the internal validity of the study. Confounding can be divided into measured and unmeasured confounding. Measured confounding is such that we have knowledge and information about, while unmeasured confounding is caused by unknown/unobserved characteristics and therefore more difficult to handle (122).

Confounding can be handled in the study design or in the analysis phase. In the study design randomisation (discussed previously), restriction and matching can be used. Restriction means that you limit your study to only one category of the confounder, for example to only include females in a study if sex is a confounding factor. In matching, which is often used in case-control studies, you match on the confounding factor, for example age, so that the distribution is the same between cases and controls in the study. However, confounding is more commonly addressed in the data analyses, primarily by adjustment in the modelling but also by stratification. In stratification you control for confounding by creating two or more categories in which the confounding variable either does not vary or does not vary very much. In regression modelling you can simultaneously control several confounders by including them as independent variables in the model.

Causal diagrams, also known as directed acyclic graphs (DAGs), is a tool used to visualize the causal relationships between exposure and outcome. DAGs thereby help to identify and select what confounders to adjust for in a statistical model (124). The presence of an arrow in a DAG indicates a (potential) association as well as the assumed direction of association between two variables. The absence of an arrow symbolises an absence of association. DAGs are also helpful to differentiate between factors that are confounders and those that are mediators or colliders. Variables on the causal pathway are mediators, not potential confounders and a collider is a factor that is caused by both exposure and outcome. Adjusting for a collider opens that path, causing a spurious association (Figure 2).

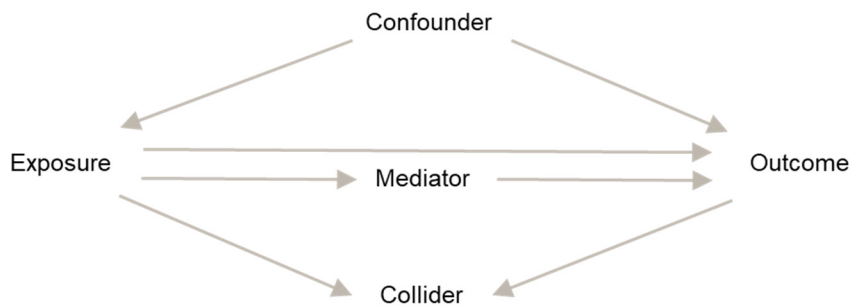

Figure 2.
DAG illustrating directions of associations with a confounder, mediator and collider.

Selection bias

Selection bias result from procedures used to select subjects and from factors that influence study participation. The common component of such biases is that the association between exposure and outcome (e.g. disease) differs for those who participate and for all those who should have been eligible in theory, including those who do not participate (121), also known as lack of generalisability. The sample selection might not accurately reflect the target population or there can be a selective loss-to-follow-up of participants or data. A common source of selection bias is *self-selection* (122). For example, those who volunteer for a new screening test for a specific disease may be more worried about their own disease risk due to a family history of this disease and thus be at higher risk than non-volunteers. This type of selection bias affects the external validity of the study. When selection into the population under study or into a study sample itself is affected by *both* exposure and outcome, this is called *collider bias* (see Figure 2), or *Berksonian bias* (121). Collider bias can affect both internal and external validity and can arise during the design of the study or during the analysis phase, if adjusting for a collider.

Approach and analyses

In regression analysis it is possible to control for several variables at once when analysing an exposure on the outcome. Therefore, regression models are some of the most used tools in analytical epidemiology. For our study questions, we have both binary, discrete and continuous outcome data, and hence different regression models have been used.

Poisson regression – time to event (Study II)

Time-to-event analysis, often called survival analysis, was performed in study II. In these analyses, the focus is not on the number of persons at risk for the outcome but on the *person time* at risk. The outcome, thus, has two dimensions, the event and the time before it happened. The study participants contribute with person time from the time they enter the study until they either have the outcome, are lost to follow-up (e.g. die), or the study ends whichever comes first. This analysis method allows for analyses of time-varying exposures. Survival analyses can be performed by Cox regression or Poisson regression.

Negative binomial regression (III)

Poisson regression assumes equal mean and variance and in cases of greater variance than mean, called *overdispersion*, negative binomial regression can instead be used. In study III we compared the risk ratio (RR) between the three treatment groups for number of healthcare visits and dispensed medicines and had overdispersion for both these count variable outcomes. To overcome the problem, we thus used negative binomial regression, which also yields RR.

Modified Poisson regression (Study III, study IV)

In study III and IV we performed modified Poisson regression for categorical variables and estimated crude and adjusted risk ratios (RR). In study III we compared the RRs between the three treatment groups for the dichotomous outcomes to have or not to have *any* healthcare consultation and *any* dispensed medicines. In study IV we estimated the RR for different dichotomous or categorical risk factors on the outcome dying with unrelieved pain or not. Logistic regression could also have been used but RR is preferable to odds ratio (OR) since OR is an estimation of the true RR and may overestimate the risk when the prevalence of the outcome increases (125).

Data sources used in this thesis

Total Population Register

We used the Swedish Total Population Register to identify the study population in study I and to exclude residents who died or relocated in study II and III. This register contains the civil registration of vital events (births, deaths, change of residential address) of the entire Swedish population and is administered by the Swedish Tax Agency.

Skåne Healthcare Register

Essential for the function of the Swedish healthcare registers is the organisation of healthcare. Sweden has a universal publicly funded healthcare system with all residents having access to healthcare and it is virtually free of charge for the patient (126). Hospitals are generally publicly run, but primary care is available at both private and public units, still tax financed. The healthcare is decentralised and administered by 21 regions who are responsible for organising health and medical care. The municipalities (n=290) are responsible for care for the elderly and individuals with chronic disabilities at home or in special accommodation. The first contact in primary care is normally a nurse who, based on a standard triage model, makes an assessment of whether advice is sufficient, or the patient needs to see a physician or another healthcare professional. Most often, for musculoskeletal pain conditions, there is direct access to physiotherapy in primary care, no referral from a physician is necessary.

In study I and II healthcare consultations from the Skåne Healthcare Register was used to define the study populations. Region Skåne is located in the southernmost part of Sweden and has a population of 1 377 827 (2019). Each healthcare

consultation in the region generates data entries to the regional database Skåne Healthcare Register. The Skåne Healthcare Register covers practically all delivered care in the area and contains data from visits to all primary care as well as secondary care (outpatient specialised care and hospital admissions, including day-care procedures). The Skåne Healthcare Register includes, for example, date of consultation, type of healthcare professional (physician, physiotherapist, psychologist etc.), type of consultation (physical visit, telephone etc.), level of care (primary or secondary care, public/private, outpatient care or hospitalisation) and diagnostic code. Diagnoses are classified according to the Swedish translation of the International Classification of Diseases and Related Health Problems system, version 10 (ICD-10-SE). The majority of all consultations recorded in the Skåne Healthcare Register have an assigned diagnosis. However, this differs between the levels of care and between types of consultations. The Skåne Healthcare Register has previously been used to perform both cohort and case-control studies (127).

Regional healthcare databases in Sweden, apart from the Skåne Healthcare Register, are for example the Stockholm Regional Healthcare Data Warehouse and the VEGA database held by Region Västra Götaland. These, as the Skåne Healthcare Register, include routinely collected healthcare data from all levels of care for a whole population in a well-defined geographic area. In study III healthcare consultations from the Skåne Healthcare Register, the Stockholm Regional Healthcare Data Warehouse and the VEGA database are used as outcomes.

Longitudinal integration database for health insurance and labour market studies

In study II data from the Longitudinal integration database for health insurance and labour market studies (LISA) was used to control for confounding and in study III to characterise the study population. The LISA database is held by Statistics Sweden and covers the adult Swedish population aged ≥ 16 years registered on December 31 each year since 1990 (since 2010 individuals aged ≥ 15 years). The LISA database contains annual sociodemographic information on for example country of birth, educational level, civil status, type of work, work status and income. This information is useful for medical researchers that want to adjust for such factors, in order to improve their studies (128).

Swedish National Patient Register

We used healthcare consultations from the National Patient Register as outcome measurement in study III. The National Patient Register is administered by The National Board of Health and Welfare. This register includes information about healthcare visits, including main and all side diagnoses coded according to the

Swedish version of the ICD at time of visit. The National Patient Register has had nationwide coverage since 1987 of in-patient admissions and of out-patient specialist visits since 2001 (129), but not primary care consultations.

Swedish Prescribed Drug Register

In study III prescribed and dispensed medicines from the Prescribed Drug Register were used as outcome measurement. The Prescribed Drug Register is administered by The National Board of Health and Welfare and includes information on all dispensed prescription medicines from all pharmacies in Sweden, from July 2005 and onwards (5, 114). Medicines in this register are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. This register includes information on ATC codes of prescribed drugs, amount dispensed, dosage, and date of dispensing.

Swedish Register of Palliative Care

In study IV data from the Swedish Register of Palliative Care was used. The Swedish Register of Palliative Care is a quality register founded in 2005 with an aim to evaluate and improve end of life care for dying patients in Sweden, regardless of diagnosis, place of residence and level of care (130). Data are mainly collected with an end of life questionnaire, which is completed after death by one or more members of the professional team (physician or nurse) engaged in the care of the dying patient. The questionnaire focuses on the last week of life and includes questions on whether the patient, as perceived by the team, experienced any symptoms, to what extent these were relieved, and whether external consultants were engaged to achieve symptom relief. The register has nationwide coverage, which has increased with time, and in 2015, 66% of all deaths in Sweden were covered (131). Validity of the register has been assessed and shown improvement over time (131, 132).

Swedish Cause of Death Register

The Swedish Cause of Death Register was used in study IV to obtain cause of death information. This register, held by the National Board of Health and Welfare, is a high quality, virtually complete register of all deaths in Sweden since 1952. Registration of cause of death is mandatory and is based on the International Classification of Diseases, 10th revision (133).

Diagnostic codes and diagnostic groups

The diagnostic codes registered in the healthcare registers were an essential part in three of the studies. In study I and II the subjects are identified by ICD-10-SE diagnostic codes and in study III diagnostic codes define the outcome (Table 2). Consensus on which codes to use in the different studies have been made through searches in the scientific literature and discussions within the author groups, which included physicians in relevant fields. In this thesis mental illness refers to a diagnosis of depression (F32) or anxiety (F41) in study II. In study III the outcome of healthcare visits related to mental illness refers to all diagnostic codes in the F chapter.

Table 2.
Diagnostic codes (ICD-10-SE codes) and diagnostic groups in study I-III.

Diagnostic groups	ICD-10 SE code	Description	Study
Abdominal pain	R10[a]	Abdominal and pelvic pain	I, II, III
Headache	G43[a]	Migraine	I, III
	G44[a]	Other headache syndromes	I, III
	R51[a]	Headache	I, III
Back/neck pain	M54[a]	Dorsalgia	I, II, III
Joint pain/myalgia	M25.5[a]	Pain in joint	I, III
	M79.1[a]	Myalgia	I, III
	M79.6[a]	Pain in limb	I, III
Pain – not specified (PC)	R52-	Diagnostic code used in primary care; Pain, not elsewhere classified	I, III
	R52.9	Pain, unspecified; Generalised pain NOS (not otherwise specified)	I, III
Persistent pain	M79.7	Fibromyalgia	I, II, III
	R52.1	Chronic intractable pain	I, III
	R52.2	Other chronic pain	I, III
	F45.4	Persistent somatoform pain disorder	I, III
Depression	F32[a]	Major depressive disorder, single episode	II
Anxiety	F41[a]	Other anxiety disorders	II
Mental disorders	F00-F99	Mental, Behavioural and Neurodevelopmental disorders	III

[a]Diagnostic code including all subcategories.

Study populations and analyses, study I-IV

Consultation prevalence of pain conditions in a young population (Study I)

Study population

In study I we identified all individuals aged 0-23, who resided in Region Skåne in 2016 (1-24 years old in 2017) from the total population register. They constituted the *general population cohort*. Among those, all individuals who had at least one consultation at any healthcare unit, in primary care or secondary care, during 2017 constituted the *healthcare cohort*. Patients from the healthcare cohort who had at least one registered diagnosis of any of the pain conditions investigated were defined as *pain cases* (Figure 3). In this study we wanted to be certain that pain was the primary reason for consulting. Therefore, we selected the diagnostic codes from the ICD-10 classification system that had 'pain', 'ache' or '-algia' in the heading (migraine was also included in headache). Selected diagnoses for pain were grouped as abdominal pain, headache, back/neck pain, joint pain/myalgia, pain not specified in primary care, and persistent pain (Table 2).

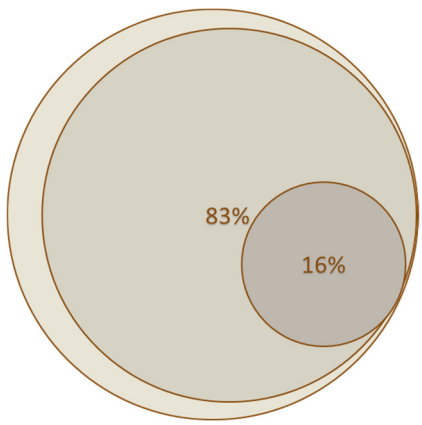

Figure 3.
The general population cohort in 2017 n=373,178 (100%).The healthcare cohort n=309,026 (83%). Pain cases n=59,376 (16%).

Analyses

The annual consultation prevalence and the 95% confidence interval was calculated by dividing the pain cases by the number of people in the general population. This was done for any pain condition as well as each separate pain condition. An individual with e.g. both abdominal pain and back/neck pain was included in both

groups, but each individual was only counted once per pain condition, and only once in the calculation of any pain condition.

Further, the proportion of frequent consulters among the pain cases was estimated, by calculating the ratio between patients who had four or more healthcare consultations and the total number of individuals among the pain cases.

Finally, we wanted to compare the overall healthcare burden between young people with and without pain conditions. In the healthcare cohort, we therefore calculated the number of healthcare consultations (regardless of diagnosis) per patient among the pain cases (i.e. number of consultations/number of patients) and this was then divided by the corresponding figure for the individuals without any pain condition, which gave us the standardised morbidity ratios (SMR) and the 95% confidence interval. An SMR of one means that the pain cases and the rest of the healthcare cohort consult healthcare to the same extent. A SMR above one means that pain cases consult more, compared to the rest of the healthcare cohort. Hence, the SMR describes the excess healthcare consultation for the pain cases. All analyses were estimated per specific pain condition and for any pain condition and stratified by sex and age. Sex differences were analysed using Fisher's exact test.

Comorbidity between pain and mental illness (Study II)

Study population and design

In study II all individuals who had consulted a physician or a physiotherapist at least once during 2007–2016 were included. Inclusion criteria further required patients to be 18 years or older and living in Region Skåne. Patients with a pain or mental illness diagnosis during the 3 years preceding the study were excluded (i.e. the years 2004–2006 was defined as a washout period).

This way a “healthy cohort” was created and cases that occurred were thus incident cases and the risk for reversed causality was decreased. Everyone was unexposed at study start and cases moved from unexposed to exposed at different time points during the study (a time-varying exposure). After exposure there was a latency period, of three months, where cases were not at risk, again to reduce the risk of reversed causation. During these three months neither person time nor any outcomes were counted. Person time was counted from study start (1 January 2007), and if a patient went through the whole 10-year period without neither exposure nor outcome he or she contributed with unexposed time. Otherwise the patient contributed with unexposed time until exposed and then, after three months, with exposed time until outcome, migration from Skåne or death when censored or end of follow-up. See illustration of study design in Figure 4 and flow chart in Figure 5.

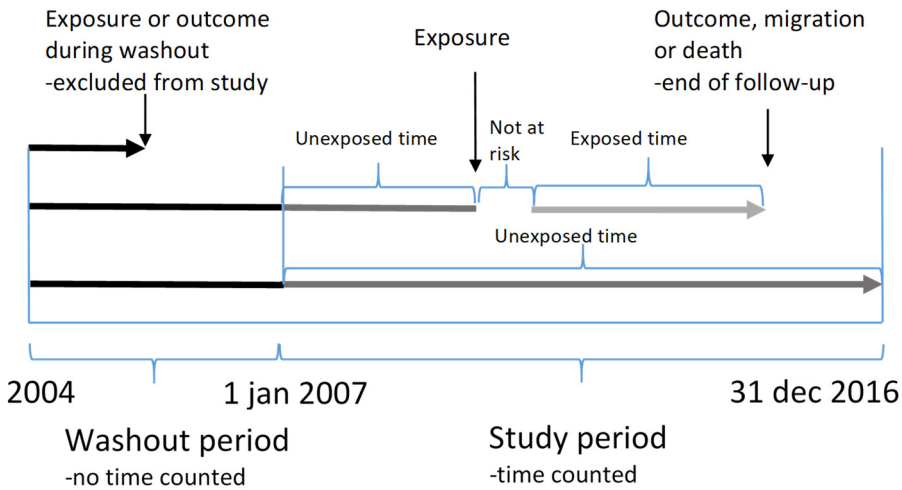

Figure 4.
Illustration of the study design in study II.

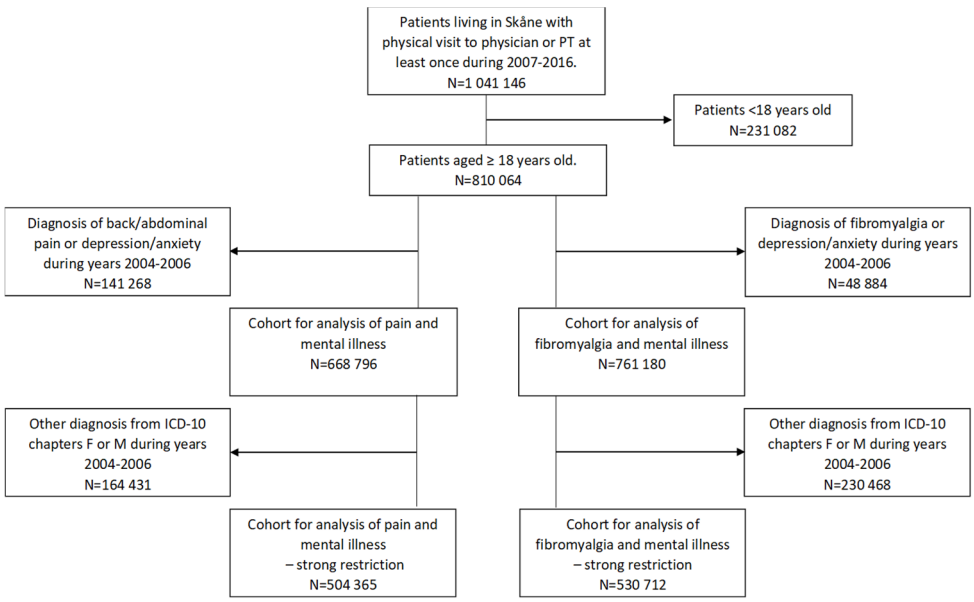

Figure 5.
Flow chart in study II.

Analyses

We calculated incidence rates for pain (back/neck pain and fibromyalgia) and mental illness (depression/anxiety). Further, using Poisson's regression with calendar year as the underlying time scale, hence adjusting for calendar time, we calculated incidence rate ratios for pain and mental illness respectively, both crude and adjusted for sex, age and level of education. We performed analyses with two different restrictions of the washout period. In the main analysis the restriction was excluding patients with any ICD-10 diagnosis in the F and/or M chapters, that is *all* mental and musculoskeletal disorders. In the sensitivity analysis the restriction was excluding patients with the investigated diseases (back/abdominal pain or fibromyalgia and depression/anxiety).

Utilisation of healthcare and prescription medicines after interventions for depression (Study III)

Study design

Study III is a register-based long-term follow-up cohort study, based on a randomised controlled trial (RCT), REGASSA (Figure 6).

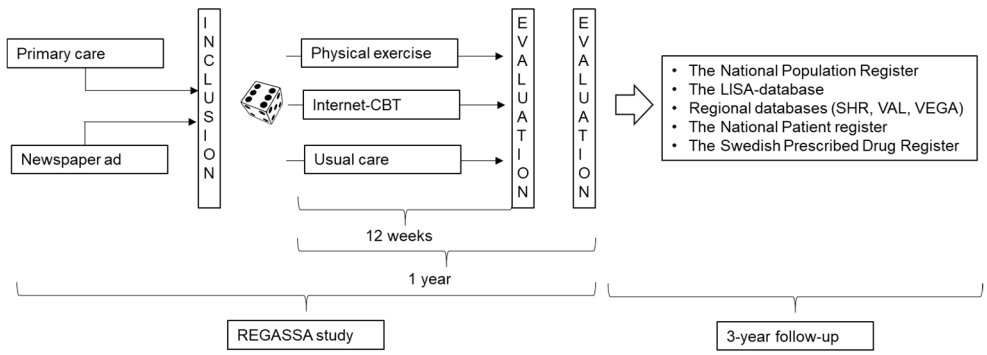

Figure 6.
Illustration of the study design in study III.

Study population and procedure of the original RCT-study

The original trial was performed in primary care, where twenty healthcare units in six different counties in Sweden participated. The trial took place between 2011 and 2013 and was an RCT with three arms, aimed at patients with mild to moderate depressive disorders. Patients were enrolled at the different primary healthcare units and by advertising in newspapers. The Patient Health Questionnaire (PHQ-9) (134) was used to screen for depression and those who scored >9 on PHQ-9 and were ≥18 years of age, were eligible to take part in the trial. Patients with severe somatic

illness, a primary alcohol or drug use disorder or a psychiatric diagnosis that required specialist treatment (such as psychosis) were excluded. Included patients (n=945) were randomised to two different treatment arms, physical exercise (n=316) or internet-CBT (n=317), or to usual care (n=312). The main outcome in the trial was depression severity. There were no limitations in the study design regarding ongoing care for any of the groups, patients could e.g. remain on or be prescribed new medicines. Internet-CBT and physical exercise were provided in addition to usual care and free of charge.

Interventions in the original RCT-study

During the first weeks of Internet-CBT treatment, the patients worked with problems related to depressive symptoms in general, for instance inactivity and avoidance behaviours. These mandatory modules also included identification of patient-specific mental health concerns and problems related to work. Later on, modules were adapted to the specific problems for each patient, e.g. worry, panic attacks, stress, insomnia, social anxiety, pain and work-related problems (135). The assigned psychologist gave feedback to the patient and inactive patients were contacted and urged to continue. The patients accessed, on average, eight internet-CBT modules out of an expected 13 (adherence rate 60%) (136).

Within the exercise group, the patients were randomised to one of three groups with different training intensity: light exercise such as yoga or stretching classes, moderate exercise such as low-intermediate aerobics classes, and vigorous exercise which consisted of middle-intensity aerobics. The classes took place at "Friskis och Svettis" and were led by qualified trainers. The patients were asked to complete three 60-minutes sessions per week for 12 weeks. Those who did not show up for classes were contacted by telephone or text-messages. The average attendance was 14.5 sessions out of 36 possible, i.e. approximately 40% of the recommended classes (137).

The usual care group received standard treatment for depression as prescribed by their primary care physician. This group had, on average, between one and two consultations with a primary care physician, which was comparable to the number of consultations for patients in both the internet-CBT and the physical exercise group. Among the patients in the usual care group, 20% had counselling and 9% had individual CBT. In comparison, the figures for the internet-CBT group were 6% and 3% and for the physical exercise group 13% and 3% (138). In the usual care group, almost 25% of the patients reported that they received no treatment at all (137).

Study population in the cohort study

The original REGASSA study included 945 patients. Ten patients died or migrated during the three-year follow-up period, which left 940 patients for analyses year 1-

2 after inclusion and 935 patients for year 2-3. We had data regarding healthcare consultations from 841 participants year 1-2 and 837 year 2-3 (Figure 7).

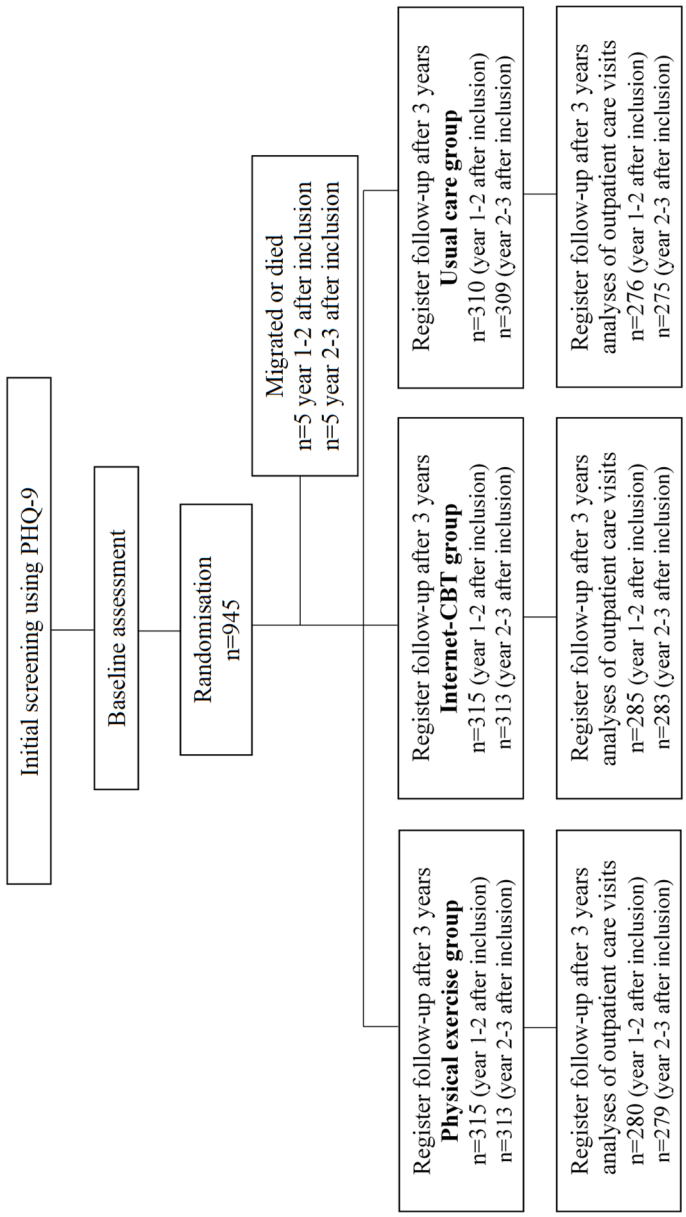

Figure 7.
Flow chart in study III.

Outcomes

Proportion and number of healthcare consultations, where consultations in primary care and outpatient specialised care were summed together because of few outpatient visits, and proportion and number of dispensed prescription medicines were used as outcomes. Healthcare consultations for mental illness were defined as having a registered ICD-10 code in the 'F' chapter or consulting a psychologist, psychiatrist or counsellor. A consultation for pain was defined according to Table 2. Among dispensed prescription medicines we investigated the use of antidepressants (ATC=N06A), anxiolytics (ATC=N05B), hypnotics/sedatives (ATC=N05C) and opioids (ATC=N02A).

Analyses

Independent samples t-tests for continuous data and chi-squared tests for categorical data were used to assess differences in baseline characteristics. When estimating the effect of the interventions, the comparison was based on the intention-to-treat (ITT) principle, i.e. patients are analysed according to the group they were randomised to.

We transformed data on dispensed daily doses to count data by rounding summed daily doses per individual to nearest integer. Extreme values, defined as values over the 99 percentile, were converted to the 99 percentile value, both for healthcare consultations and dispensed daily doses. We performed the comparison between the three groups in a two-step manner because the outcome variables had a zero-inflated and over-dispersed distribution. First, we used modified Poisson regression to assess whether the participants had a) any healthcare consultation for mental illness/pain or not and b) any dispensed prescription of antidepressants/anxiolytics/hypnotics and sedatives/opioids or not, i.e. a binary outcome. Secondly, we used Pearson-scale-adjusted negative binomial regression to model the continuous variables: a) mean number of healthcare consultations among those with any consultation and b) mean number of dispensed daily doses of antidepressants, anxiolytics, hypnotics and sedatives or opioids among those with any dispensed prescription.

Dying with unrelieved pain – risk and risk factors (Study IV)

Study population and design

To quantify occurrence of pain, risk of and risk factors for dying with unrelieved pain, we linked data from all expected deaths between years 2011 to 2015 (n=236, 527) to data about cause of death. Death is classified as *expected* if preceded by diseases such as disseminated cancer or other chronic illnesses without cure, as decided by the treating physician/nurse. The main outcome was unrelieved pain during the final week in life. In the SRPC, pain experienced by patients is classified into ''completely,'' ''partly,'' or ''not at all'' relieved. We combined the latter two categories into the category unrelieved, as less than 1% had ''not at all'' relieved

pain, and this was contrasted to ‘‘completely’’ relieved pain. We then investigated four risk factors available in the SRPC (Table 3).

Table 3.
Risk factors for dying with unrelieved pain.

Risk factor	Description
Cause of death	Noncancer
	Five groups of cancer (bone, brain, lung, liver, other)[a]
Place of death[b]	Specialist palliative care (specialist palliative care ward or at home, with care provided by the specialist palliative care unit)
	General in-hospital care (all wards excluding inpatient specialist palliative care)
	Community-based care (all other: resident nursing home; private home with or without support from home care services etc.)
Absence of an end of life conversation	No documentation in the medical record of a dialog with neither the patient nor a family member regarding the patient's imminent death
Lack of contact with pain management expertise	No contact with the pain management or palliative unit was reported

[a]The classification was based on both underlying and contributing cause of death. The fifth group included patients with cancer in any other site as the underlying cause of death.

[b]Place of death was reported in seven categories, reclassified into three categories for this study.

Confounding factors

Information in the SRPC about diagnoses contributing to death was used to define a dichotomous variable: multiple illnesses, ≤ 2 vs. ≥ 3 diagnoses. Information about the symptoms pain, wheeziness, nausea, anxiety, respiratory distress, and confusion experienced during the final week of life was tallied in an attempt to summarise the dying experience. The resulting variable, *number of symptoms*, was scored from 1 to 6, where 1=one prevalent symptom and 6=all six symptoms. A corresponding variable was created for *number of symptom-relieving prescriptions PRN*, ranging from 0 to 4.

Analyses

Descriptive data analysis was performed, including chi-squared test, to obtain the distribution of a number of factors by pain status (relieved vs. unrelieved) during the final week of life. Risk ratios (RRs) associated with each risk factor were estimated using modified Poisson regression. All models were adjusted for age and sex and also for additional confounding factors specified in each model. Complete case analysis was performed. To define a patient group in need of additional expert knowledge, the data set we used to evaluate contact with pain management expertise was restricted to individuals in hospital or community-based care reported to have had intense pain.

Ethics

This thesis and the studies herein were conducted in compliance with the Declaration of Helsinki and were approved by Swedish ethical review authority and regional ethical review boards. (study I: Dnr 2018/376, study II: Dnr 301/2007 and 2011/432, study III registration number 2010/1779-31/4 and Dnr 2015/2112-31).

Since all four studies include register data, approval has also been obtained from the authorities holding the different registers.

Regarding study IV, when a person is deceased their data are no longer classified as ‘‘personal data’’ by the legal authorities in Sweden. Therefore, there is no automatic requirement to obtain ethical approval from the Swedish ethical review authority. Nevertheless, data were stored and handled in accordance with existing recommendations for research data.

Data on disease, socioeconomics and drug utilisation are sensitive personal data for the individual and must be handled with the greatest care and confidentiality according to the General Data Protection Regulation (GDPR). All data was pseudo-anonymised during processing and data analysis.

Results

Consultation prevalence of pain conditions in a young population (Study I)

In study I, where we investigated the consultation prevalence of pain during 2017, 58, 981 youths under the age of 25 consulted at least once for pain, corresponding to a consultation prevalence of 15.8% (95% CI 15.7%–15.9%). The consultation prevalence was higher among females than males, 17.6% versus 14.1% and abdominal pain was the most common pain site (Table 4). Overall consultation prevalence increased with age (Table 4 and Figure 8, panel A).

Different pain conditions had different patterns in relation to sex and age as seen in Table 4 and Figure 8, panel B. Abdominal pain had the steepest age-related increase within the younger age groups. For males in older age groups, a decreased consultation prevalence was seen for abdominal pain and headache, whereas for females, headache levelled out from age 17. For all pain conditions and both sexes, a decrease in prevalence was seen between the ages of 17-19 (Figure 8, panel B).

Table 4.
Prevalence, % (95% confidence interval), of pain diagnoses in SHR in 2017, by sex and age (children adolescents and young adults).

	Sex	Abdominal pain	Headache	Back/neck pain	Joint pain/ Myalgia
Children Aged 1-12	Females	6.1 (6.0-6.3)	1.8 (1.7-1.9)	0.5 (0.4-0.5)	1.7 (1.6-1.7)
	Males	5.2 (5.0-5.3)	1.6 (1.5-1.7)	0.4 (0.4-0.4)	1.7 (1.6-1.8)
Adolescents Aged 13-18	Females	7.5 (7.2-7.7)	4.9 (4.7-5.1)	3.0 (2.9-3.2)	4.7 (4.5-4.9)
	Males	4.4 (4.2-4.6)	3.1 (2.9-3.2)	2.4 (2.3-2.5)	3.9 (3.8-4.1)
Young adults Aged 19-24	Females	9.2 (8.9-9.4)	5.4 (5.2-5.6)	4.3 (4.1-4.5)	4.6 (4.5-4.8)
	Males	3.3 (3.2-3.5)	2.2 (2.1-2.3)	3.3 (3.1-3.4)	3.6 (3.4-3.8)
All ages Aged 1-24	Females	7.2 (7.1-7.3)	3.4 (3.3-3.5)	2.0 (2.0-2.1)	3.1 (3.0-3.2)
	Males	4.5 (4.4-4.6)	2.1 (2.0-2.1)	1.6 (1.5-1.6)	2.7 (2.6-2.8)
Total	Total	5.8 (5.7-5.9)	2.7 (2.7-2.8)	1.8 (1.8-1.9)	2.9 (2.8-3.0)

[a]Pain diagnoses according to Table 2.

Table 4. (continued)
Prevalence, % (95% confidence interval), of pain diagnoses in SHR in 2017, by sex and age (children adolescents and young adults).

	Sex	Pain-not specified	Persistent pain	All pain disorders
Children Aged 1-12	Females	4.7 (4.6-4.9)	0.02 (0.01-0.03)	12.7 (12.5-12.9)
	Males	5.0 (4.9-5.1)	0.01(0.01-0.02)	12.1 (11.9-12.3)
Adolescents Aged 13-18	Females	7.7 (7.4-8.0)	0.11 (0.07-0.14)	21.6 (21.2-22.0)
	Males	7.6 (7.4-7.8)	0.04 (0.02-0.06)	17.4 (17.1-17.8)
Young adults Aged 19-24	Females	8.9 (8.7-9.2)	0.20 (0.15-0.24)	23.9 (23.5-24.2)
	Males	7.1 (6.9-7.3)	0.07 (0.05-0.09)	15.4 (15.0-15.7)
All ages Aged 1-24	Females	6.5 (6.4-6.6)	0.08 (0.07-0.10)	17.6 (17.4-17.7)
	Males	6.1 (6.0-6.2)	0.03 (0.03-0.04)	14.1 (14.0-14.3)
Total	Total	6.3 (6.2-6.4)	0.06 (0.05-0.07)	15.8 (15.7-15.9)

[a]Pain diagnoses according to Table 2.

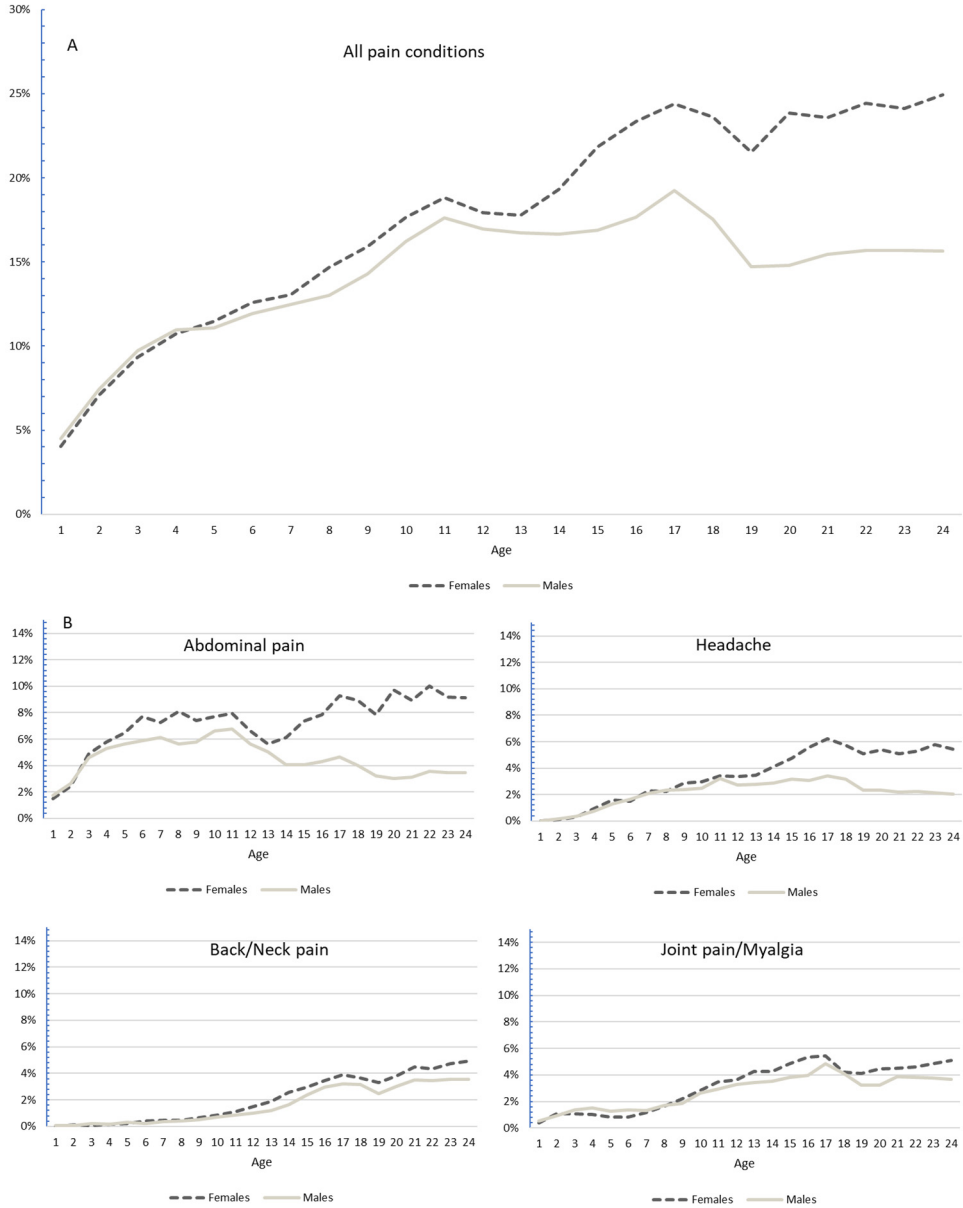

Figure 8.

a) Consultation prevalence of pain conditions in total in 2017, by age and by sex (females=black dotted line and males=beige line).
b) Consultation prevalence of different pain conditions in 2017, by age and by sex (females=black dotted line and males=beige line).

Frequent consulters

In total, 13.5% (95% CI 13.2%–13.8%) of the pain cases were frequent consulters i.e., had four or more consultations for pain during the year, this was more common among females (15.5%) than males (11.1%; $p < .0001$) and there was a marked increase with age (Figure 9).

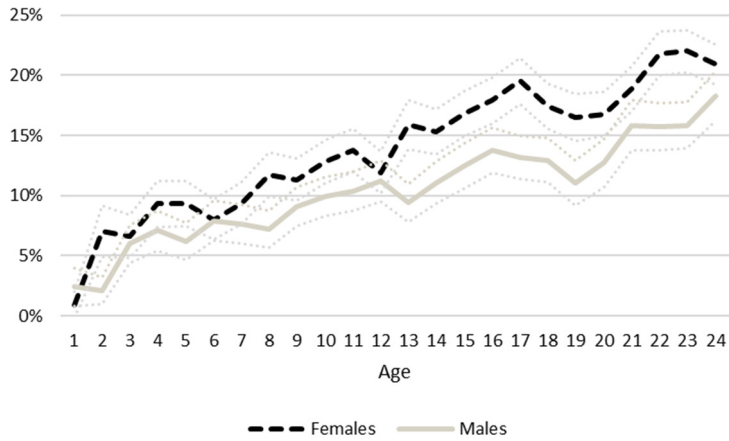

Figure 9.

Frequent consulters. Proportion of individuals with any pain condition who consulted healthcare services four or more times for pain in 1 year (2017), by age (1–24) and by sex (females=black dotted line) and males=beige line) separately, dotted lines 95% CI.

The patient group with persistent pain had the highest proportion of frequent consulters, 27.1% (95% CI 21.1%–33.1%). The patient groups with unspecific pain and joint pain/myalgia had the least proportions of frequent consulters (Table 5).

Table 5.

Percentage (95% confidence interval) of frequent consulters within each pain condition.

Pain condition[a]	Females	Males	Total
Abdominal pain	10.6 (10.1-11.1)	8.1 (7.5-8.7)	9.6 (9.2-10.0)
Back/neck pain	16.8 (15.5-18.0)	14.7 (13.4-15.9)	15.8 (14.9-16.7)
Headache	11.8 (11.0-12.6)	8.9 (8.0-9.8)	10.7 (10.1-11.3)
Joint pain/myalgia	8.3 (7.6-9.0)	5.7 (5.1-6.4)	7.1 (6.6-7.5)
Pain – not specified	5.1 (4.7-5.5)	4.4 (4.0-4.7)	4.7 (4.5-5.0)
Persistent pain	27.5 (20.3-34.7)	26.2 (15.5-36.8)	27.1 (21.1-33.1)
All pain conditions	15.5 (15.1-15.9)	11.1 (10.7-11.5)	13.5 (13.2-13.8)

[a]Pain diagnoses according to Table 2.

Overall healthcare consultations (SMR)

Individuals who had consulted for a pain condition in 2017 also had higher overall healthcare utilisation that year, compared to those without a pain condition but who had still consulted healthcare that year. Standardised morbidity ratio (SMR) was

1.82 (95% CI 1.74–1.87) for females and 1.51 (95% CI 1.42–1.56) for males. The SMR was higher among females in all ages (Figure 10). Among pain cases, 74% of their consultations were for reasons other than pain, that is, the increased SMR was only partly explained by consultations directly connected to the pain conditions.

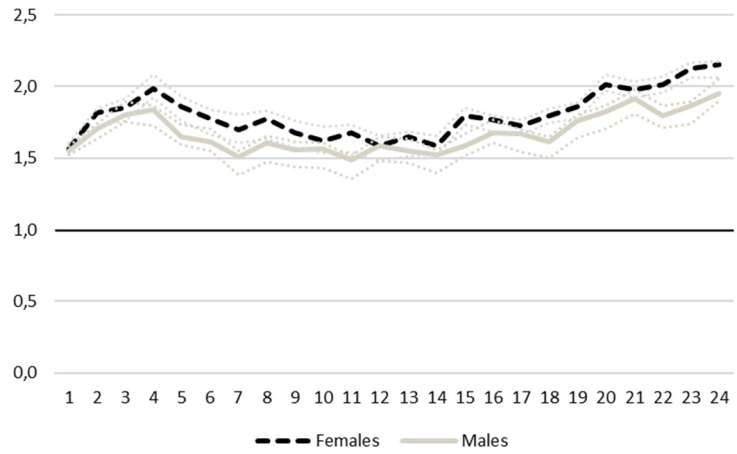

Figure 10.
SMR (standardised morbidity ratio) of number of consultations in 2017 among those diagnosed with any pain condition as compared to the rest of the patients in the healthcare cohort (who consulted healthcare at least once in 2017), by age (1–24) and by sex (females=black dotted line) and males=beige line) separately, dotted lines 95% CI.

Comorbidity between pain and mental illness (Study II)

In study II, we investigated the risk for mental illness after pain compared to having no pain, and the reverse, the risk for pain after mental illness compared to having no mental illness. In total, 32% of patients were diagnosed with pain and 14% were diagnosed with mental illness. Most diagnoses were recorded in primary care, with the exception of fibromyalgia. In all, 6% of patients were diagnosed with both pain and mental illness. The mean age at study start was 47 years (SD = 18) and 48% were women. The most common level of education was 10-12 years. The risk of mental illness after pain (back/abdominal pain) and the risk of pain after mental illness were distributed evenly and decreasingly over the first 10 years after first diagnosis (Figure 11, Panel A and B).

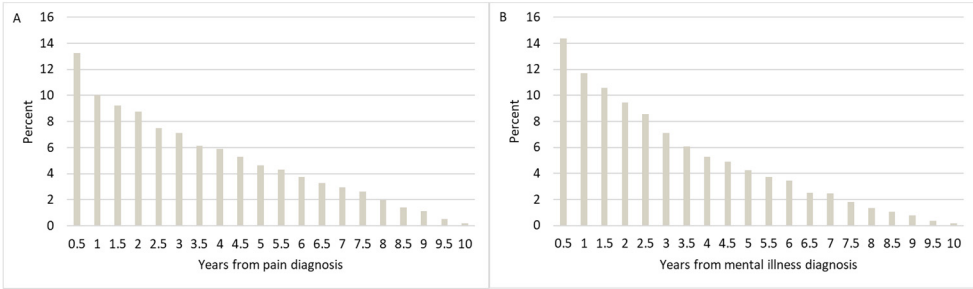

Figure 11. (A) Time to diagnosis of mental illness, in six-month intervals, after pain diagnosis, N = 29,053. (B) Time to pain diagnosis, in six-month intervals, after diagnosis of mental illness, N = 21,556.

During the 10-year study period, the incidence of mental illness was 1,6/100 person years while the incidence of pain was 4,1/100 person years.

The incidence rate ratio (IRR) for developing mental illness after pain was 2.18 (95% CI 2.14–2.22) compared to not having pain, adjusted for sex, age and education level (Table 6). Adjusted IRR for developing pain after mental illness, compared to not having mental illness was 2.02 (95% CI 1.98-2.06). The risk for the outcome diagnosis was thus approximately doubled regardless of whether pain or mental illness was the exposure (Table 6).

The IRR for developing mental illness after fibromyalgia compared to not having fibromyalgia was 4.05 (95% CI 3.58–4.59), while the IRR for developing fibromyalgia after mental illness, compared to not having mental illness was 5.54 (95% CI 4.99–6.16) (Table 6). In the sensitivity analyses where only patients with any of the investigated diseases were excluded during the washout, we found slightly decreased IRRs for all four analyses (Table 6).

Table 6.
Incidence rate ratios (IRR) for mental illness after pain/fibromyalgia and for pain/fibromyalgia after mental illness respectively during years 2007-2016 using Poisson regression.

	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 and only restricted to patients with any of the investigated diseases during the washout.
[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.

Utilisation of healthcare and prescription medicines after interventions for depression (Study III)

In the three-year follow-up of utilisation of healthcare and prescription medicines after interventions for depression we included 940 participants and most of them were female (73%). The mean age was 43 years (sd.= 12) and most had a combined depressive and anxiety disorder (77%). Many patients were highly educated, and the majority was working (80%). At baseline, a significant proportion reported physical pain (68%) and physical activity level was mainly light. Alcohol (hazardous level) and tobacco was used by 16% and 21%, respectively.

On average 43% had one or more annual consultations for mental illness during the follow-up period (year 2 and 3 after inclusion). The average number of consultations was 5 per year, among those with any consultation and the majority (76%) were primary care consultations. There was no difference between the groups, neither regarding proportion of participants with healthcare consultations for mental illness, nor regarding the number of healthcare consultations, during the follow-up periods (Table 7).

Table 7.
Estimates of healthcare consultations.

Participants with visits to outpatient care for mental illness, 1-2 years and 2-3 years after inclusion, per intervention group.

Mental illness	**Proportions**			**RR[a] (95% CI)**	
	PE	ICBT	UC	PE vs UC	ICBT vs UC
Outpatient care (%)					
Year 1-2	46	44	47	0.98 (0.82-1.17)	0.93 (0.78-1.12)
Year 2-3	40	37	42	0.95 (0.78-1.16)	0.89 (0.72-1.09)

Number of healthcare visits to outpatient care per group among those with one or more healthcare visits for **mental illness**, 1-2 years and 2-3 years after inclusion, per intervention group.

Mental illness	**Mean number**			**RR[b] (95% CI)**	
	PE	ICBT	UC	PE vs UC	ICBT vs UC
Outpatient care					
Year 1-2	4.63	4.85	4.94	0.92 (0.71-1.18)	1.00 (0.78-1.29)
Year 2-3	4.54	5.66	5.74	0.77 (0.59-1.02)	1.02 (0.77-1.34)

PE physical exercise, ICBT Internet-based cognitive behavioural therapy, UC Usual care.

[a]RR relative risk (Modified Poisson regression), CI confidence interval, [b]RR relative risk (Negative binomial regression).

One third of all patients, 33% had consultations related to a pain diagnosis during each year. The average number of consultations was 3 per year among those with any consultation, and most often in primary care, 89%. No difference between groups regarding proportion of participants consulting healthcare for pain were found. However, there were less consultations for both treatment arms compared to usual care during year 2-3 where the physical exercise group had an RR of 0.64

(95% CI: 0.43-0.95) and the internet-CBT group had an RR of 0.61 (95% CI: 0.41-0.90) (Table 8).

Table 8.
Estimates of healthcare consultations.

Participants with visits to outpatient care for **pain**, 1-2 years and 2-3 years after inclusion, per intervention group.

Pain	Proportions			RR[a] (95% CI)	
	PE	ICBT	UC	PE vs UC	ICBT vs UC
Outpatient care (%)					
Year 1-2	31	33	34	0.90 (0.71-1.15)	0.97 (0.77-1.22)
Year 2-3	34	33	33	1.04 (0.82-1.32)	1.00 (0.79-1.27)

Number of healthcare visits to outpatient care among those with one or more healthcare visits for **pain**, 1-2 years and 2-3 years after inclusion, per intervention group.

Pain	Mean number			RR[b] (95% CI)	
	PE	ICBT	UC	PE vs UC	ICBT vs UC
Outpatient care					
Year 1-2	2.99	3.04	3.60	0.72 (0.46-1.13)	0.72 (0.46-1.12)
Year 2-3	3.07	3.05	4.24	***0.64 (0.43-0.95)***	***0.61 (0.41-0.90)***

PE physical exercise, ICBT Internet-based cognitive behavioural therapy, UC Usual care.
[a]RR relative risk (Modified Poisson regression), CI confidence interval, [b]RR relative risk (Negative binomial regression).

Concerning medication during the follow-up, 36% of patients were dispensed antidepressants each year on average, while 16% and 19% were dispensed anxiolytics and hypnotics/sedatives. Regarding proportion of participants being dispensed medicines, we found no difference between groups neither for antidepressants nor anxiolytics, while for hypnotics/sedatives a 28% lower risk of being dispensed a prescription were found for both intervention groups compared to usual care year 2-3 after inclusion (Table 9).

The number of dispensed daily doses among those with medication did not differ between the groups for any of the investigated psychotropic medicines. Dispensed daily doses of antidepressants per person were on average 356 each year, corresponding number for anxiolytics and hypnotics/sedatives were 47 and 162 respectively (Table 9).

Table 9.
Estimates of dispensed prescription medicines.

Participants with dispensed prescription of **antidepressants, anxiolytics, hypnotics and sedatives**, 1-2 years and 2-3 years after inclusion, per intervention group.

Psychotropics	**Proportions**			**RR[a] (95% CI)**	
	PE	ICBT	UC	PA vs UC	ICBT vs UC
Antidepressants (%)					
Year 1-2	35	39	37	0.94 (0.76-1.16)	1.06 (0.87-1.30)
Year 2-3	34	37	36	0.95 (0.77-1.18)	1.03 (0.84-1.27)
Anxiolytics (%)					
Year 1-2	17	15	15	1.20 (0.84-1.73)	1.05 (0.72-1.53)
Year 2-3	18	17	15	1.16 (0.81-1.65)	1.09 (0.76-1.57)
Hypnotics and sedatives (%)					
Year 1-2	17	17	17	0.95 (0.67-1.34)	1.00 (0.71-1.41)
Year 2-3	18	18	25	***0.72 (0.53-0.98)***	***0.72 (0.53-0.98)***

Dispensed daily doses of **antidepressants, anxiolytics, hypnotics and sedatives** among those with medication, 1-2 years and 2-3 years after inclusion, per intervention group.

Psychotropics	**Mean number**			**RR[b] (95% CI)**	
	PE	ICBT	UC	PA vs UC	ICBT vs UC
Antidepressants					
Year 1-2	384	346	330	1.16 (0.96-1.41)	1.05 (0.87-1.26)
Year 2-3	352	378	331	1.06 (0.88-1.28)	1.14 (0.95-1.37)
Anxiolytics					
Year 1-2	62	34	43	1.43 (0.85-2.39)	0.79 (0.46-1.35)
Year 2-3[c]	53	41	51	1.03 (0.61-1.75)	0.81 (0.47-1.38)
Hypnotics and sedative					
Year 1-2	194	171	157	1.23 (0.82-1.86)	1.09 (0.73-1.63)
Year 2-3	151	169	129	1.18 (0.80-1.73)	1.31 (0.89-1.93)

PE physical exercise, ICBT Internet-based cognitive behavioural therapy, UC Usual care.
Antidepressants=ATC-N06A, Anxiolytics=ATC-N05B, Hypnotics and sedatives=ATC-N05C, Opioids=N02A.
[a]RR relative risk (Modified Poisson regression), CI confidence interval, [b]RR relative risk, (Negative binomial regression).
[c] dispensed daily doses missing=1, [d] dispensed daily doses missing=1, [e] dispensed daily doses missing=3.

Looking at pain medication, on average 12% of the patients were dispensed at least one prescription of opioids each year and for those, the average dispensed daily dose for one year was 38. Regarding proportion of participants who had opioids prescribed and number of dispensed daily doses, no differences was found between groups. (Table 10).

Table 10.
Estimates of dispensed prescription medicines.

Participants with dispensed prescription of **opioids**, 1-2 years and 2-3 years after inclusion, per intervention group.

Opioids	**Proportions**			**RR[a] (95% CI)**	
	PE	ICBT	UC	PE vs UC	ICBT vs UC
Opioids (%)					
Year 1-2	11	11	12	0.88 (0.57-1.36)	0.88 (0.57-1.36)
Year 2-3	11	12	13	0.84 (0.55-1.29)	0.87 (0.57-1.32)

Dispensed daily doses of **opioids** among those with medication, 1-2 years and 2-3 years after inclusion, per intervention group.

Opioids	**Mean number**			**RR[b] (95% CI)**	
	PE	ICBT	UC	PE vs UC	ICBT vs UC
Opioids					
Year 1-2 [d]	33	38	42	0.79 (0.46-1.34)	0.90 (0.53-1.53)
Year 2-3 [e]	32	34	49	0.66 (0.36-1.22)	0.70 (0.38-1.28)

PE physical exercise, ICBT Internet-based cognitive behavioural therapy, UC Usual care.
Antidepressants=ATC-N06A, Anxiolytics=ATC-N05B, Hypnotics and sedatives=ATC-N05C, Opioids=N02A.
[a]RR relative risk (Modified Poisson regression), CI confidence interval, [b]RR relative risk, (Negative binomial regression).
[c] dispensed daily doses missing=1, [d] dispensed daily doses missing=1, [e] dispensed daily doses missing=3.

Dying with unrelieved pain – risk and risk factors (Study IV)

In study IV we quantified the occurrence of pain as well as the risk of and risk factors for dying with unrelieved pain. A total of 236, 527 expected deaths were reported between 2011 and 2015. Pain was present during the last week of life in 68.4% of deaths (n=161, 762). Of the patients with pain, 24.7% died with some degree of unrelieved pain, despite opioids PRN (as needed) prescribed to the vast majority (96.7%). Unrelieved pain was common among patients dying of cancer (26.4%) but also in patients dying of other causes (23.3%). Among patients dying in hospital, 37.1% had unrelieved pain, this was significantly more than in specialist palliative care (21.5%, $p<0.0001$) and community-based care (19.6%, $p<0.0001$). Patients with unrelieved pain were on average two years younger and to a larger extent male. A dose-response relation was seen between number of prevalent symptoms during the final week and proportion of patients with unrelieved pain. An inverse dose-response relation was found for number of symptom-relieving medicines prescribed PRN and unrelieved pain (Table 11).

Table 11.
Descriptive data (counts and row percentages) by pain status among expected deaths recorded to have had pain during the last week of life (n =161,762).

	Total	Relieved, n	%	Unrelieved, n	%	p-value
All expected deaths	161,762	121,884	75.3	39,878	24.7	
Age						
<50 years	2878	1892	65.7	986	34.3	<0.0001
50-69 years	23,678	16,724	70.6	6954	29.4	
70-89 years	93,893	70 586	75.2	23,307	24.8	
≥90 years	41,313	32,682	79.1	8631	20.9	
Sex						
Women	89,946	69,134	76.9	20,812	23.1	<0.0001
Men	71,816	52,750	73.5	19,066	26.5	
Cause of death						
Non-cancer	94,537	72,465	76.7	22,072	23.3	<0.0001
Cancer	67,225	49,419	73.5	17,806	26.4	
Cancer in the bones	5643	3962	70.2	1681	29.8	
Cancer in the brain	3534	2768	78.3	766	21.7	
Cancer in the liver	6037	4602	76.2	1435	23.8	
Cancer in the lung	11,971	8543	71.4	3428	28.6	
Other cancer sites	40,040	29,544	73.8	10,496	26.2	
Place of death						
Specialist palliative care	33,882	26,603	78.5	7279	21.5	<0.0001
In-hospital	42,982	27,043	62.9	15,939	37.1	
Community-based care	84,898	68,238	80.4	16,660	19.6	
End-of-life conversation						
Yes	128,353	98,935	77.1	29,418	22.9	<0.0001
No	21,919	15,445	70.5	6474	29.5	
Unknown	11,490	7504	65.3	3986	34.7	
Pain management consultant						
Yes	16,737	11,263	67.3	5474	32.7	<0.0001
No	139,899	107,487	76.8	32,412	23.2	
Unknown	5126	3134	61.1	1992	39.8	
Opioid prescription PRN						
Yes	156,355	119,360	76.3	36,995	23.7	<0.0001
No	5092	2398	47.1	2694	52.9	
Unknown	315	126	40	186	60	
Intense pain						
Yes	43,852	29,369	67	14,483	33	<0.0001
No	91,754	75,592	82.4	16,162	17.6	
Unknown	26,156	16,923	64.7	9233	35.3	
Multiple illnesses						
Yes (≥3)	19,699	14,527	73.7	5172	26.3	<0.0001
No (≤2)	142,063	107,357	75.6	34,706	24.4	

Table 11. (continued)
Descriptive data (counts and row percentages) by pain status among expected deaths recorded to have had pain during the last week of life (n =161,762).

	Total	Relieved, n	%	Unrelieved, n	%	p-value
Number of symptoms (anxiety, confusion, nausea, pain, respiratory distress, wheeziness)						
1	23,496	18,691	79.5	4805	20.5	<0.0001
2	51,145	40,226	78.7	10,919	21.3	
3	47,915	35,712	74.5	12,203	25.5	
4	28,289	19,985	70.6	8304	29.4	
5	9520	6355	66.8	3165	33.2	
6	1397	915	65.5	482	34.5	
Number of symptom relieving prescriptions PRN (for anxiety, nausea, pain and wheeziness)						
0	3630	1689	46.5	1941	53.5	<0.0001
1	6071	3697	60.9	2374	39.1	
2	15,042	10,263	68.2	4779	31.8	
3	29,012	21,338	73.5	7674	26.5	
4	107,779	84,806	78.7	22,973	21.3	
Unknown	228	91	39.9	137	60.1	

Patients dying from cancer as compared to non-cancer had an increased risk of unrelieved pain if dying of cancer in the bones, lung or being in the group with mixed cancers ("Other cancer") while patients with cancer in the brain or liver had a decreased risk (Table 12). Place of death was a significant risk factor for dying with unrelieved pain. Dying in hospital was associated with an 84% increased risk as compared to specialist palliative care (Table 12), while patients in community-based care only had a slightly, but statistical significantly, increased risk of 5%. Not having an end of life conversation was associated with 42% increased risk. Patients who had contact with pain management expertise (analysis restricted to patients with severe pain) had a 19% increased risk of unrelieved pain in the final week of life (Table 12).

Table 12.
Risk ratios (RRs) with 95% confidence intervals (95% CIs) for dying with unrelieved pain. Results from modified Poisson regression models 1-4, crude and adjusted for model-specific confounders.

Risk factor	Crude RR (95% CI)	Adjusted RR (95% CI)
Model 1		
Cause of death (adjusted for: age and sex)		
Non-cancer	1.0	1.0
Cancer in the bones[a]	1.28 (1.22–1.33)	1.13 (1.08–1.18)
Cancer in the brain[a]	0.93 (0.87–0.99)	0.79 (0.74–0.84)
Cancer in the lung[a]	1.23 (1.19–1.26)	1.10 (1.06–1.13)
Cancer in the liver[a]	1.02 (0.97–1.07)	0.91 (0.87–0.95)
Other cancer	1.12 (1.10–1.15)	1.02 (1.00–1.04)
Model 2		
Place of death (adjusted for: cause of death, multiple illnesses, number of symptoms, age and sex)		
Specialist palliative care	1.0	1.0
In-hospital	1.73 (1.69–1.77)	1.84 (1.79–1.88)
Community/other	0.91 (0.89–0.94)	1.05 (1.02–1.08)
Model 3		
EoL conversation (adjusted for: cause of death, pain management team, place of death, multiple illnesses, age and sex)		
Yes	1.0	1.0
No	1.29 (1.26–1.32)	1.42 (1.38–1.45)
Model 4		
Contact with pain management expertise[b] (adjusted for: cause of death, EoL conversation, place of death, multiple illnesses, number of symptoms, age and sex)		
Yes	1.0	1.0
No	0.73 (0.70–0.76)	0.81 (0.78–0.85)

EoL = end of life.
[a]Includes both primary cancer and metastases.
[b]Restricted to patients with intense pain cared for in hospital or a community setting (n=31 970).

Discussion

The overarching aim of this thesis was to increase epidemiological knowledge about pain throughout the course of life, investigating its occurrence and relation to mental illness in the general population with the use of Swedish registers. We have described the occurrence of pain in a young population and at the end of life, studied the comorbidity between pain and mental illness, investigated the long-term effectiveness of non-pharmacological interventions for depression and studied risk factors for dying with unrelieved pain. We conclude that pain is common both in the young population and at the end of life and that pain and mental illness are related in several ways.

Occurrence of pain in the young population and at the end of life

In study I where we investigated the consultation prevalence of pain in a young population, we wanted to capture the burden of the more common pain disorders also seen in the adult population. We found a 1-year consultation prevalence of almost 16% in the young population highlighting the healthcare burden of pain already in the young ages. The consultation prevalence of back/neck pain even approached adult levels by the end of adolescence (19-24 years old) (32). This study is unique, as earlier studies on consultation prevalence have focused on musculoskeletal disorders only (37, 38, 139) or on patterns of consultation (140, 141), while we present comprehensive information on consultation prevalence in both children, adolescents and young adults for several pain conditions. The majority of consultations for our young population took place in primary care, similar to what was shown in a Canadian study on musculoskeletal disorders (37). The same pattern is also seen for healthcare visits for pain among adults (24, 139). Hence, primary care carries the vast burden for pain problems in all age groups. This has impact on the planning of resources at different levels of care, where primary care should be prioritised with regard to resources for necessary staff, training for adequate competence and having sufficient time set aside to be able to assess, give advice, treat and evaluate patients with pain problems (142). In our study, we found similar results to survey studies when it comes to the distribution of pain sites, where abdominal pain and headache were the most common but with less concern of selection bias (25, 26).

We found an overall higher consultation prevalence of pain in females as compared to males, a difference also previously shown in survey studies of chronic pain (25, 26, 143) and among adults (144, 145). Sex differences have been shown both in relation to acute and persistent pain (145, 146) and both biological and psychosocial explanations have been proposed (147-149). However, we found it especially intriguing with the very early sex differences detected in our study. These differences could, as proposed for adults, be due to biological factors, but it could also be speculated that parents and, also healthcare professionals, interpret and react differently on children's pain depending on the child's sex. Girls and boys might also express pain differently. This intricate interplay will have impact on the development and establishment of pain beliefs and behaviours in the young population.

We found that the sex difference in back/neck pain and myalgia/joint pain was much less pronounced than for abdominal pain and headache. This is similar to what has previously been found for back/neck pain (38). Abdominal pain differed markedly between the sexes and this condition also had the steepest raise in consultations in the early ages. In general, we found an increase in consultation prevalence by age, although a decrease was seen between the age of 17 to 19 both generally and in each pain condition and for both sexes. It was not in the scope of our study to investigate mechanisms behind different pain prevalence patterns, but an interesting question is if ending of puberty contributes to the decrease. Pubertal development and growth have been prospectively associated with spinal pain in young people (150) and in a US cross-sectional study, researchers found that for both boys and girls, the probability of experiencing at least one pain condition increased with increasing physical maturity (151). The US study investigated the association between stage of pubertal development and prevalence of different pain conditions among 11–17-year olds but none of the studies investigated individuals after the age of 17. Another possible explanation for the decrease in consultation prevalence is the transition from adolescence to young adults, both in relation to healthcare and parents. Most of the paediatric departments care for young patients until they are 18 years old, after which there may be a gap until adult healthcare is established for the individual. However, primary care has no such age limit, so it is unlikely that this explains our finding of a decrease in consultations, since most studied consultations took place in primary care. Parents probably have less and less influence on care-seeking as the child grows older, which may also influence the amount of care-seeking.

The prevalence of persistent pain was low in our study. Clinical praxis of when and how to use the ICD-10 codes for persistent pain may vary between physicians. In the adult population it takes several years from initial complaints to establishment of a diagnosis of persistent and widespread pain such as fibromyalgia (152, 153). Physicians may also be more reluctant to determine a diagnosis of persistent pain in younger individuals, before all other explanations/possibilities have been ruled out.

We defined cases of persistent pain only when there was a registered diagnosis of persistent pain. However, some individuals could have been in a progress towards persistent pain since e.g. 16.8% of children and young adults with back/neck pain had four or more consultations in one year. Back pain is often involved in widespread and/or persistent pain also in adults (101, 154, 155), so these frequent consulters might already have or be at risk for persistent pain.

Further, in our study population, we found that those consulting for a pain condition had more healthcare consultations overall compared to those consulting for other medical problems, and these excess consultations were in most cases linked to other diagnoses than pain. Children with pain suffer in numerous ways, they have an increased risk of later persistent and/or widespread pain (99-101, 156, 157), and other health impairments (93-95, 158), as well as difficulties with school performance (92, 159, 160). This highlights the vulnerability among the young with pain, but also the high healthcare burden for society.

Our findings, in combination with previous knowledge, emphasize the importance of early interventions in the young population and we support that rehabilitation for persistent pain also among children is based on the biopsychosocial model. The complex interplay of the biological, psychological, social, and environmental factors that contribute to and maintain pain symptoms and related disability needs to be taken into account (161). Besides primary care, the school-setting is a possible arena for interventions for children and adolescents with pain. A Swedish study recently reported results from a brief intervention for adolescents with persistent pain, carried out by school nurses. The results indicated improved self-efficacy beliefs for daily activities among secondary, but not upper secondary, school adolescents with chronic pain (162). Giving young people optimal care and tools to cope with problems early on in life could possibly be protective. Suggested best-evidence interventions are pain education, psychological interventions, and physical and occupational therapies with the ultimate goal of a return to baseline functioning (161). Some studies have shown promising results when interventions are applied on the young population together with their parents (163, 164). However, more research is needed into what specific treatment works for whom (161, 165).

Looking at the other end of the life course, in the final week of life, pain is reported for 68% of patients in the Swedish Register for Palliative Care (SRPC). This is slightly lower than studies from Norway in hospitalised patients (166, 167) but higher than in a US general population study where a pain prevalence of 46% in the last month of life was reported (168). The difference can be due to the stricter definition of pain as “often troubled by pain of at least moderate severity” in the US study and also that patients themselves reported, whereas in the SRPC a nurse or physician reports if pain was present at the end of life, after the patient is deceased.

In the US study, patients were followed during the last two years of life and a steep increase of prevalence of pain towards the end of life was found (168).

In our study, among the patients with pain (68%), almost one-quarter died with some extent of unrelieved pain. This was common both among patients dying of cancer and of other chronic diseases. Estimates of unrelieved pain at the end of life in other studies vary from 10% to 72% depending on the underlying disease and care setting (166, 167, 169, 170). Relief of pain is a complex concept and complete relief might not be compatible with maintained clarity of mind. Opioids were prescribed as needed (PRN) to 97% of patients with pain, which is very close to the target level of 98% established by the National Board of Health and Welfare. Yet, this does not seem to be enough, as almost 25% still die with unrelieved pain to some extent. Even if opioids PRN were documented for the vast majority of patients, pain assessment, administration and evaluation of effect could still be suboptimal. The additional use of non-pharmacological strategies, such as physiotherapy interventions, for managing pain and other distressing symptoms should not be forgotten and can also be of great importance (171, 172).

The risk of dying with unrelieved pain was markedly higher for patients in hospitals compared to dying within specialist palliative care, whereas dying in community-based care only increased the risk slightly. Even if there is an obvious difference in selection of patients to different care settings, the small difference in pain in the last week between community-based and specialist palliative care was surprising, considering the difference in available resources. It is known that having uncontrolled symptoms is a common reason for hospital admissions near end of life (173). Uncontrolled pain could have been one reason for acute hospital admission in our study, but our data lacked this information. However, a Dutch study reported that pain in general was the main reason for hospitalisation at the end of life in only 6% of patients compared to respiratory symptoms (31%), digestive symptoms (17%), and cardiovascular symptoms (14%) that all were more common reasons for admission to hospital (174). Even if the more severe cases concerning pain were admitted to hospital at the end of life, hospitals also have more resources, that should make it possible to provide better care for these patients.

Not having an end of life (EoL) conversation was associated with an increased risk of dying with some degree of unrelieved pain. Talking about and thereby preparing for the imminent death with the patient and/or next of kin therefore seem to be valuable also in the aspect of pain relief. An EoL conversation provides a common ground for all involved (patient, family and healthcare staff) regarding the goal of care. There are studies showing benefits of having EoL conversations, an important one being that less aggressive medical care is given and this in turn is associated with better quality of life for patients approaching end of life (175, 176). Less is known about the effect of EoL conversations on pain outcome, but a Finnish study

reported an increased risk of dying with unrelieved pain when only limited information about the forthcoming death was given, compared to when adequate information was given (177). There was a record of an EoL conversation for 80% of the deceased in our study, either with the patient or with next of kin. The reasons for *not* having an EoL conversation are unknown to us, but an EoL conversation could for some physicians be perceived as a challenging task. Thus, the finding supports the earlier suggestion to increase clinical education about the way difficult news is delivered and how to initiate EoL discussions with seriously ill patients and their families (178).

We can conclude that pain commonly exists both at the beginning and at the end of life and suggest that managing pain problems in the most vulnerable populations should be prioritised.

Relations between pain and mental illness

Another aspect of pain as being present throughout the course of life is the risk of comorbid disease. From study II and III in this thesis we can provide support that pain and mental illness are closely related, both in the sense of being risk factors for one another and that interventions for mental illness affect care-seeking for pain.

We could show that patients with pain (abdominal/back pain), have a two-fold risk of developing mental illness (anxiety/depression) compared to those without pain. But we also found that patients with mental illness have a two-fold risk of developing pain compared to those without mental illness. Even higher estimates were found when analysing fibromyalgia instead of abdominal/back pain. We used new onset of both exposure and outcome to study the relationship between mental illness and pain and this has surprisingly not been done in many studies. In a Taiwanese study, they investigated fibromyalgia and depression exclusively and came to the conclusion that there was a bidirectional relationship (179). In addition to confirming this finding in a different population and healthcare system, we could also show the same reciprocal relationship between abdominal/back pain and depression/anxiety, showing that it is present much earlier in the pain process, before fibromyalgia has developed. This is important knowledge and clinicians have the potential to discover comorbidity earlier in a care process by asking about it when patients seek for only one condition. In a Swedish study it was reported that among patients with anxiety and depression that they did not seek care for, two-thirds had instead sought healthcare for somatic symptoms but avoided to mention the mental illness (180). Further, looking at the young population, a systematic review concluded psychological features to be the most likely risk factors for back pain although the temporal relationship was difficult to establish (181). Given this and the results in study I on the high prevalence of pain in the young population it would be an advantage if patterns of care-seeking for both pain and mental illness

in the young population were studied, and individuals at risk for recurrent or persistent problems identified.

In patients where comorbidity between pain and mental illness is present, interventions should focus on both conditions, since this would reasonably lead to improved outcomes. This might seem like an easy task but there may be several obstacles in the way. Physicians in different levels of care might feel unable to provide both physical and mental healthcare at the same visit because of time constraints (182). Nearly 60% of primary care physicians in Sweden report dissatisfaction with time spent per patient and they state that their practices are not that well prepared to manage the care of patients with comorbidities or complex needs (183). Not having enough time can also impede communication between healthcare providers, communication that is often important when treating patients with comorbidities (183).

In our three-year follow-up on effect of internet-CBT and physical exercise for patients with depression in primary care, we found interesting results both concerning mental illness and pain. Utilisation of healthcare for mental illness did not differ between the three groups but consultations for pain disorders was less in the two treatment arms 2-3 years after inclusion. These results, together with the fact that 68% of our study population reported moderate to severe pain at baseline, underline the comorbidity between mental illness and pain shown in study II as well as in other studies (60, 66, 109). It could further be argued that both internet-CBT and physical exercise have trans-diagnostic effects. Other studies indicate that this is the case both for physical exercise and internet-CBT when treating different mental disorders (87, 184). However, physical exercise can also be used in the treatment of chronic pain (89) and internet-CBT has shown promising effects for chronic pain in children (185) and for adult patients with comorbid chronic pain and depression/anxiety (186). Both physical exercise and internet-CBT focus on providing patients with tools for coping with problems on their own and increasing their self-efficacy in the event of a flare or recurrence. This is important for managing both mental illness and pain disorders, both of which in many cases are life-long diseases.

Methodological discussion

The main strength of this thesis is the use of large prospective population-based cohorts in study I, II and IV. Population-based cohorts are less prone to selection bias which is important both for internal and external validity. The large number of participants enabled us to study rare outcomes such as fibromyalgia and also gave us increased statistical power and subsequently better precision in our estimates. In

this thesis, the focus was on pain and mental illness requiring healthcare. This approach has advantages and disadvantages, among the advantages we see that those seeking care, in most cases have their symptoms confirmed by a diagnosis from a professional clinician. On the other hand, we are aware that not all individuals seek care for their problems, and they were thus not available for inclusion in study I and II. Why some people consult healthcare for their problems while others don't is not entirely clear. However, the need, the symptom itself, i.e. pain, feeling depressed, loss of function or disability evidently plays an important role (144, 187-190). However, also other factors might influence the decision to seek healthcare. Human behaviour is complex, it is influenced by cultural- and social norms, individual attitudes, values and beliefs and can come from learned experiences. Once you have sought care, the probability of seeking again increases (191). How healthcare systems are organised will also affect whether an individual seeks healthcare or not, costs and availability to healthcare services are factors that will influence this decision (192). Therefore, it is important when you compare healthcare utilisation for one patient group that the reference group also have a healthcare seeking behaviour.

When diagnoses are registered in a medical record or a database there is a risk for misclassification. The physician might not identify a diagnosis due to patients failing to present the symptoms or due to not being asked about them. Patients may have several diagnoses and one or more could be unidentified for the same reasons (180). There is also a possibility that the medical secretary registers the diagnosis wrong. However, different studies have validated diagnoses in primary care and found validity to be acceptable or high even if there is room for improvement (193-195).

We used registered diagnoses for identifying different diseases in this thesis. There is a risk that misclassification of diagnoses can have affected results in all four studies. In study I and III, since we chose a strict definition of pain and only used diagnoses with pain, algia and ache in the heading we are likely to have missed some other painful conditions in the ICD-10 M-chapter i.e. some patients could have been misclassified as unexposed when in fact being exposed to a pain diagnosis. This means we could have underestimated the consultations related to pain both in study I and III.

In study II we adjusted for the sex, age and educational level in our analyses. By our study design we also dealt with the most important confounders, earlier pain or mental illness depending on the direction of the analysis, by using the restrictions in the wash-out periods. Further, we adjusted for calendar time when using the Poisson regression analysis. However, earlier care-seeking was not adjusted for and this could have affected our estimates.

In study III we combined the randomised controlled trial (RCT) design with a register-based follow-up. The RCT design allowed control for both measured and

unmeasured confounding and using register-based data on healthcare and dispensed medicines as outcomes enabled a cost-effective long-term follow-up. Utilisation of healthcare and prescribed medicines was thus used as a measure of treatment effect. We are aware of the issue of multiple testing in this study but decided not to correct for this since most of our findings were non-significant. The treatment arms were unrelated and were secondary outcomes to the original RCT (196). The issue of multiple testing is one contributing reason to our cautiousness in drawing conclusions. One limitation in the original RCT study, that also has bearing on the present study, is the low compliance rate to the interventions. This can lead to misclassification, most likely towards-the-null. This complicates the interpretation of the results, especially in relation to previous findings from the same study population; that the overall compliance to the treatment predicted reductions in depression within the internet-CBT arm (135), suggesting a dose-response relationship.

Regarding the study of pain at the end of life (study IV), one limitation was the dichotomization of pain into *relieved and unrelieved pain*. The register data from SRPC contained three levels of pain relief: "completely", "partly" and "not at all" relieved. The reason for using only two groups was that fewer than 1% of observations reported "not at all" relieved, which can be seen as a comforting result and corresponds well to the comprehensive prescription of opioids PRN in 97% of patients. However, the question on pain relief is answered by the caregivers themselves, thus, implying a failure of their own care if reporting that they did not offer any relief of pain at all at the end of life. The concept *partly relieved pain* is wide and uncertain and from a patient perspective "partly" could mean an acceptable or an unacceptable level of pain. The specific level of pain intensity is not reported in the SRPC, however severe pain (>6 on NPRS) was reported in 19% of patients and this is in line with a recent, population-level, Canadian study, where daily pain of severe intensity was reported in 17% of the terminally ill (197).

The result in study IV showing a harmful effect of contact with pain management expertise, on relief of pain, was surprising. However, the plausible explanation for the finding is that of reversed causality, that pain expertise was called on for patients with therapy-resistant pain and/or they were called on to late. Finally, we lacked information about presence of earlier pain which has been seen to reduce the chance of pain relief (198) and also on socioeconomic status which could have affected our estimates. However, we could control for other important confounders since the SRPC contains relevant outcome variables for quality of care at the end of life as perceived by experienced clinicians and researchers within the field (131).

Summary and conclusions

This thesis has deepened the knowledge about pain and mental illness by doing epidemiological studies in the general population using Swedish registers. The occurrence of pain in a young population and at the end of life have been described and the comorbidity between pain and mental illness have been studied. Long-term effect of non-pharmacological interventions for depression in primary care have been investigated and risk factors for dying with unrelieved pain have been described.

- Among individuals under the age of 25, a significant proportion consult for pain already in early ages, and they also have high healthcare consultation rates for conditions other than pain. The even higher consultation rates among young females need additional attention, both in the clinic and in research.

- We found a bidirectional influence of similar magnitude of pain and mental illness, respectively. In monitoring patients with pain or mental illness, a focus on both conditions is thus important to develop appropriate, targeted interventions and may increase the likelihood of improved outcomes.

- Differences between treatment groups regarding healthcare consultations and dispensed prescription medicines were very small but in favour of the treatment arms. Given these results, considering long-term effects, both physical exercise and internet-CBT, being resource-efficient treatments, could be considered as relevant additions for patients with mild to moderate depression in primary care settings and could possibly lead to improved long-term self-management of sleep, anxiety and pain.

- One in four patients with pain die with partly unrelieved pain despite almost complete prescription of opioids PRN. Healthcare providers, hospitals in particular, need to focus more on pain in dying patients and may benefit from better care structures and training. An End of Life conversation ought to be available to most patients and is one intervention that could reduce the number of patients dying with unrelieved pain.

Clinical implications

Patients with pain and mental illness are mainly managed in primary care, therefore resources, education and implementation of evidenced-based care should have a great focus on this level of care. More clinical attention also needs to be focused on pain in our most vulnerable populations, young people and individuals at the end of life. The large proportion of consultations for pain in the young population is important knowledge for planning of future healthcare.

The bidirectional influence of pain and mental illness on one another, that is presented in this thesis, emphasizes the importance of using the biopsychosocial model when assessing and treating patients with these conditions. This model takes into account the complex interplay of the biological, psychological, social, and environmental factors that patients can present with and can help clinicians to tailor interventions, which may then increase the likelihood of improved care. It is vital to organise care in a way that make this possible.

Both physical exercise and internet-CBT, being resource-efficient treatments, could be considered as relevant additions for patients with mild to moderate depression in primary care settings and could possibly lead to improved long-term self-management of sleep, anxiety, and pain. Both treatments are readily available and have few negative side effects.

In pain management at the end of life, opioids are an important intervention, but its use could probably be improved especially in hospitals, concerning assessment, administration and evaluation of effect. A combination of pharmacological and non-pharmacological interventions, such as an end of life conversation, can possibly yield even better pain relief.

Future research

In the young population, the sex difference and corresponding high consultation rates among young females need additional attention. It would also be of value to study if patterns of care-seeking and comorbidities among young patients with pain could be helpful in identifying individuals at risk for recurrent or persistent problems.

How to increase compliance to treatment in complex patient groups such as those investigated in study III needs further exploration, especially for interventions where the patients are responsible for managing the treatment on their own.

It is important to investigate more in detail the mechanisms behind unrelieved pain in hospitals, looking at for example structures of pain assessment and evaluation of treatment and the use of end of life conversations.

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Register studies on pain throughout the course of life

Elisabeth Bondesson is a registered physiotherapist at the Department of Pain rehabilitation at Skåne University Hospital in Lund, Sweden. She has many years of experience in assessment and rehabilitation of patients with persistent pain in primary care and specialist care. Elisabeth is also the national coordinator for the Swedish National Quality Registry for Pain Rehabilitation.

Nearly all of us will experience pain at some stage of our life. Persistent pain affects the individual and the near family as well as society to a great extent. The overall aim of this thesis was to increase epidemiological knowledge about pain throughout the course of life, investigating its occurrence and relation to mental illness in the general population. The four studies in this work are based on Swedish registers, registers that are a unique resource for medical research. The findings provide valuable information on prevalence rates of pain in the young population and at the end of life, information that can facilitate planning of care. We also found that pain significantly increases the risk for mental illness to the same extent as mental illness increases the risk for pain, which is important knowledge for clinicians. Further, in a long-term follow-up, we could show that internet-CBT and physical exercise are relevant additional treatments for patients with depression in primary care. Finally, we could identify areas of improvement when investigating risk factors for unrelieved pain at the end of life. In summary, the findings in this thesis can facilitate planning of care and provide a basis for research, to guide clinicians to better assess patients and tailor interventions based on the individual patient's needs.

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