The way to understanding Chronic Postsurgical Pain

Citation for published version (APA):

Hoofwijk, D. M. N. (2018). *The way to understanding Chronic Postsurgical Pain: From clinical and psychological predictors to incorporating genetics*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20180905dh>

Document status and date:

Published: 01/01/2018

DOI:

[10.26481/dis.20180905dh](https://doi.org/10.26481/dis.20180905dh)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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The background of the cover is a stylized illustration of a neural network. Thick, grey, segmented lines representing axons or dendrites crisscross the frame. Along these lines, several human faces are depicted, showing a progression of emotions from happiness at the top to pain at the bottom. The faces are colored in a gradient: light green at the top, yellow in the middle, and red at the bottom. The text is overlaid on a dark grey rectangular area in the upper half of the image.

The way to understanding

CHRONIC POSTSURGICAL PAIN

From clinical and psychological predictors
to incorporating genetics

D.M.N. Hoofwijk

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Cover design: Daan Janssen Illustrations
Printing: Datawyse | Universitaire Pers Maastricht

ISBN 978-94-93019-20-1

The way to understanding

Chronic Postsurgical Pain

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to incorporating genetics

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof. Dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op woensdag 5 september 2018 om 16.00 uur

door

Daisy M. N. Hoofwijk,
Geboren op 31 juli 1985, Sittard, Nederland

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Chapter 1

General introduction

General introduction

In the Netherlands, approximately one and a half million surgical procedures are performed each year, in a population of 17 million inhabitants.¹ Over 50% of these procedures are relatively minor and take place in an ambulatory setting.¹ Even though many procedures are performed for life threatening disease (such as malignancy or severe cardiovascular disease), a large proportion of the surgical procedures are performed in order to improve the patient's quality of life (QoL), by aiming to treat symptoms such as pain or functional impairment.¹ Examples of surgical procedures to improve patients' QoL are orthopaedic procedures (e.g. knee arthroscopy, joint replacement), ENT-procedures (e.g. removal of tonsils, cochlear implant), neurosurgical procedures (e.g. discectomy) or general surgical procedures (e.g. hemorrhoidectomy, varicose vein surgery).

Many patients know and accept the fact that the acute postoperative phase comes with side effects such as postsurgical pain and diminished functional reserves, which results in a decreased QoL and a decreased capacity to participate in society.^{2,3}

On the other hand, many patients and health care providers do not realise that these acute postsurgical effects may eventually result into long term side effects, as for instance chronic postsurgical pain (CPSP), and then may have major impact on life and society.

Acute postsurgical pain (APSP)

Research has shown that acute pain after surgery is still a serious problem.²⁻⁴ It is estimated that over 80% of all surgical patients experiences not adequately managed pain during the acute postoperative phase.⁴ Negative consequences of APSP have been clearly demonstrated as postoperative pain, along with nausea and vomiting, is one of the most important reasons for delayed hospital discharge, for contact with the general practitioner, and for unanticipated hospital admission.^{4,5} Furthermore, APSP causes discomfort and suffering. This implies that adequate pain management has a moral ground and is an essential part of optimal patient care. For this reason, the effectiveness of postoperative pain management is used as a quality indicator in Dutch hospitals.⁶ APSP is also associated with increased perioperative morbidity and mortality (e.g. myocardial infarction, stroke pulmonary infections, delirium).^{4,7,8} Another important consequence of APSP is an increased risk of developing CPSP.^{9,10}

The prevalence of APSP varies with the type of surgery performed.^{2,11} Inpatient surgery is often more extensive than outpatient surgery, but more frequent pain measurements are possible, and more effective treatment techniques are available (e.g. epidural and neural catheter techniques, patient controlled analgesia). Acute pain treatment after outpatient surgery is more of a challenge and even though procedures are usually less extensive than inpatient procedures, research has shown that

outpatient procedures are not always less painful.¹¹ Some outpatient procedures, such as tonsillectomy and hemorrhoidectomy, are ranked amongst the most painful of all surgical procedures in the very large German 'Quality Improvement in Postoperative Pain Treatment' (i.e. QUIPS) cohort.¹¹ During the last decades, multimodal analgesia techniques (such as loco-regional techniques) and safer analgesics (e.g. combined weak opioid analgesics) have become available for the treatment of pain after outpatient surgery, but has so far not resulted in a significant decrease in the prevalence of acute postsurgical pain.⁴

Chronic postsurgical pain (CPSP)

Initially, a definition for CPSP was proposed by Macrae *et al.* CPSP was defined as pain persisting for more than two months after surgery, and other possible causes for the pain should be excluded (e.g. malignancy, infection).¹² According to this definition it was particularly important to exclude the possibility that the persistent pain was a continuation of pre-existing pain.¹² Because it proved especially difficult to exclude pre-existing pain as a possible cause for CPSP, a refined updated definition has recently been proposed by Werner *et al.*¹³ Pre-existing pain is no longer an exclusion criterion, but the CPSP has to be of increased intensity, and is preferably accompanied by a change in location or characteristic of the pain.¹³ Research has demonstrated that 10-50% of all surgical patients report CPSP,^{9, 12, 14, 15} and in 2-10% of the cases the reported pain is severe.^{9, 15}

The transition from acute to chronic postsurgical pain is a complex process, of which the exact mechanisms are not yet fully understood. Based on the available theories, neurobiological changes in the nociceptive network which are induced during acute postoperative pain play a crucial role.^{9, 16, 17} Surgery and tissue damage lead to an increase in the release of inflammatory mediators at the level of peripheral nociceptors.⁹ This activates intracellular signalling pathways, which leads to a reduced threshold of these peripheral nociceptors and causes hypersensitivity (i.e. peripheral sensitisation). As surgery often causes nerve damage a neuropathic component is likely to be involved as well. Damaged nerves can produce persistent maladaptive plasticity, which finally results in ectopic firing of the remaining axonal sprouts.^{9, 18} Both the increased input of peripheral nociceptors, as well as the continued ectopic firing, will lead to an increased activation of central pain neurons in the spinal dorsal horn and the threshold of the so-called Pain Gate is decreased.¹⁹

This causes altered gene transcription of dorsal horn central sensory pain neurons, and this in turn leads to long-lasting more structural changes of these cells and their connections.^{9, 20} Ectopic firing not only affects the central pain neurons in the dorsal horn, but may also induce the loss of neurons, especially the inhibitory interneurons, which are known to play a pivotal role in the regulation (i.e. opening and closing) of the spinal Pain Gate.^{9, 16} Microglia are activated in the spinal cord and produce increased

excitatory signalling in the dorsal horn.^{9, 21, 22} All these changes in the central nervous system are responsible for the process of central sensitisation, as observed in patients with CPSP. Besides changes at the level of the peripheral nerve and at the spinal cord Pain Gate, changes in function, structure and connectivity are also observed in supraspinal areas like the cortex and cortical grey matter.¹⁷ As there is no one to one relations between the duration and intensity of APSP and the development of CPSP, other mechanisms must play a role as well.

Prediction of CPSP

Researchers have attempted to unravel the risk factors or predictors for the development of CPSP. Since CPSP is associated with negative consequences such as patient suffering and high costs for society (e.g. absenteeism from work, health care costs), it is very important to identify these predictors.^{23, 24} Especially risk factors that can be identified in the preoperative phase are of importance, since this might be able to offer targets for prevention of perioperative peripheral and central sensitisation processes. Research on predictive factors for CPSP has thus far focused on inpatients undergoing major surgery (e.g. cardiac surgery, thoracotomy, joint replacement, caesarean section, etc.).^{9, 25-27}

Among the clinical predictive factors, preoperative pain appears to be one of the most important predictors for the development of CPSP.^{10, 15, 28-30} As is the case with APSP, preoperative pain might lead to peripheral and central sensitization, which leaves the nervous system vulnerable for new pain inducing stimuli.¹⁵ Other described risk factors for the development of CPSP are type of surgery,¹⁰ surgical technique,^{9, 10, 31, 32} younger age,^{30, 31} and female gender.^{9, 33}

As psychosocial factors have proven to play an important role in chronic pain in general,³⁴ the association between psychological risk factors and CPSP has also been extensively studied. Anxiety and more specifically fear for the surgical procedure (i.e. surgical fear), as well as pain catastrophizing have proven to be important risk factors for the development of CPSP.^{9, 28, 35, 36} Other psychological factors, such as depression, pessimism and expectations of pain have also been correlated to CPSP.^{9, 10} More recently it has been suggested that these psychological variables are often correlated to each other, which is why a more general psychological composite variable, such as 'psychological robustness' results in a stronger association with CPSP than all other psychological variables separately.^{37, 38}

Unfortunately, most research in the field of CPSP only focused on demographic, clinical, and psychological predictors has not been able to explain all the variance observed in the prevalence and severity of CPSP. For this reason, genetic factors have become of interest to further improve prediction models which may then allow to better identify patients at risk.

Genetics

Data based on twin studies and human pedigrees estimate that the heritability of chronic pain in general ranges from 30-70%.³⁹ These results suggest that future studies should try to incorporate genetic factors besides clinical and psychological factors, when trying to unravel the predictors for CPSP.

When trying to identify genetic predictors, several research methods are available. An important method is based on the use and analysis of single nucleotide polymorphisms (SNPs), which allows to study the link between genetic factors and clinical syndromes.⁴⁰ In a SNP, a single base is substituted by another base in a specific locus at the chromosome. This substitution leads to different alleles, which can ultimately result in the decoding of a different protein (i.e. 'loss of function'), or of the same protein with other functional capacities (i.e. 'gain of function').⁴¹ Several SNPs in close proximity to each other, often form a haplotype, which implies that they are inherited together.⁴¹ A major limitation of the SNP analysis is based on the fact that most clinical syndromes, especially pain syndromes, are complex and are very rarely caused by only one specific SNP, but rather by many SNPs which act in a concerted action. In order to unravel most potential SNPs correlated with CPSP a genome-wide association study (GWAS) can be performed. In this method an extremely large amount (millions) of SNPs spread over the entire genome, are studied simultaneously.⁴² The downside of performing a GWAS, is that it requires replication of data in multiple very large patient cohorts.⁴³ Another way to acquire more insight into SNPs that could possibly be associated with the development CPSP, is by performing a systematic analysis of the available literature. SNPs that have been associated with CPSP in relatively small and heterogeneous patient cohorts are interesting to research in a larger homogeneous cohort. Finally, identifying SNPs associated with CPSP is only the first step towards a better understanding of the development of CPSP. In light of what we already know about clinical and psychological risk factors for the development of CPSP, it is even more important to explore if the addition of genetic polymorphisms to pre-existing prediction models of CPSP results in an increased accuracy of these models and thus improves the understanding of the complex pain syndrome known as CPSP.

Aims and outline of this thesis

The aim of this thesis is to improve our insight in the complex interaction of clinical, demographic, psychological and genetic factors and the development of CPSP after a wide variety of surgical procedures. In order to achieve this, the following research questions will be addressed:

- RQ 1. What is the prevalence of chronic postsurgical pain (CPSP) after relatively minor procedures in an outpatient setting?

- RQ 2. Which demographic, clinical and psychological factors are associated with the development of CPSP after outpatient surgery?
- RQ 3. Is moderate to severe preoperative pain associated with an increase in hospital costs and postoperative health care utilization after outpatient surgery?
- RQ 4. Which genetic polymorphisms are associated with the prevalence and severity of CPSP?
- RQ 5. Does the addition of genetic risk factors to an existing clinical and demographic prediction model for CPSP after hysterectomy increase the accuracy of this model?

The first and second research questions are answered in chapter II en III respectively. Chapter II describes the results of a large prospective cohort study, which was performed amongst patients undergoing a wide variety of outpatient surgical procedures. These patients were followed during the first postoperative year. Chapter III describes the prevalence and predictive factors of CPSP and in patients after knee arthroscopy. This surgical procedure was chosen because it was one of the most frequently performed outpatient procedures in the Netherlands.¹

RQ 3 is addressed in chapter IV, where we describe whether preoperative pain, an important risk factor for CPSP, was associated with increased hospital costs, health care utilization and absenteeism from work and other activities during the first postoperative year after outpatient surgery.

RQ 4 and RQ 5, both dealing with genetics and CPSP, are addressed in chapter V en VI. In chapter V, the available literature with regard to the genetic polymorphisms associated with CPSP is reviewed. In chapter VI genetic polymorphisms which are associated with CPSP after hysterectomy for benign indication were studied in homogeneous patient cohort. The addition of these genetic polymorphisms to a previously published predictive model for CPSP in the same patient population, is also described. Chapter VII is a general discussion of our findings and describes possible future research directions. The findings of this thesis are summarized in chapter VIII.

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Chapter 2

Prevalence and predictive factors of chronic postsurgical pain and poor global recovery one year after outpatient surgery

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Clin J Pain 2015 Dec;31(12):1017-25

Abstract

Objectives

To prospectively describe the prevalence and predictive factors of chronic postsurgical pain (CPSP) and poor global recovery in a large outpatient population at a university hospital, one year after outpatient surgery.

Methods

A prospective cross-sectional cohort study was performed. During eighteen months, patients presenting for preoperative assessment were invited to participate. Outcome parameters were measured using questionnaires at three timepoints: one week preoperatively, four days postoperatively and one year postoperatively. A value of >3 on an 11-point numeric rating scale (NRS) was considered to indicate moderate to severe pain. A score of $\leq 80\%$ on the Global Surgical Recovery Index (GSR) was defined as poor global recovery.

Results

A total of 908 patients were included. The prevalence of moderate to severe preoperative pain was 37.7%, acute postsurgical pain 26.7%, and CPSP 15.3%. Risk factors for the development of CPSP were surgical specialty, preoperative pain, preoperative analgesic use, acute postoperative pain, lack of optimism and poor preoperative quality of life. The prevalence of poor global recovery was 22.3%. Risk factors for poor global recovery were previous related surgery, preoperative pain, preoperative analgesic use, surgical fear, acute postoperative pain, poor preoperative and acute postoperative quality of life, and related surgery during the first postoperative year.

Discussion

Moderate to severe CPSP after outpatient surgery is common, and should not be underestimated. Patients at risk for developing CPSP can be identified during the preoperative phase.

Introduction

Acute postsurgical pain after outpatient surgery is a common problem, and both the prevalence and risk factors for the development of acute postsurgical pain have been extensively studied.¹⁻⁸ The development of chronic postsurgical pain (CPSP) after outpatient surgery has been less extensively studied, even though it is a burden for the patient and society.

CPSP has been defined as pain persisting longer than two months after surgery.⁹ However, in studies that investigate the problem of CPSP, follow-up times vary widely from several months to years.^{9, 10} The prevalence of moderate to severe CPSP varies from 10% to 50%, whereas 2% to 10% of patients report severe CPSP.¹¹ CPSP is associated with negative outcomes such as a reduced quality of life and increased health care utilization.^{12, 13} Some specific types of surgery such as thoracotomy, lower limb amputation, joint arthroplasty, breast cancer surgery and inguinal hernia repair have been extensively studied and have been associated with severe CPSP.¹¹

The studies that address CPSP have mostly been performed in inpatients.^{11, 14, 15} With the exception of a few studies examining specific outpatient procedures (e.g. inguinal hernia repair, breast cancer surgery), research about the presence of CPSP after outpatient surgery is scarce. The prevalence and risk factors of CPSP after outpatient surgery might be different from those of inpatient surgery for several reasons. First of all, the extent and impact of outpatient surgery can be different with regard to tissue damage and anesthetic techniques. Second, previous studies have shown that the treatment of acute postoperative pain might be less optimal for outpatients than for inpatients.^{16, 17} This might lead to more peripheral and central sensitization and consequently more severe CPSP. Third, the psychological impact of outpatient surgery might be different (e.g. less anxiety and catastrophizing), because the disease which constitutes the indication for surgery may be less severe and because of the absence of hospital admission. In this context it is important and justified to collect specific information about the prevalence and the predictors of CPSP after outpatient procedures. First of all, identifying patients at risk for developing CPSP might lead to better tailored pharmacotherapeutic and psychotherapeutic strategies to decrease the prevalence of CPSP. Secondly, more knowledge about the prevalence of CPSP after outpatient surgery will enable informing patients more accurately about this serious complication.

Global recovery after surgery measures overall functional recovery. CPSP is associated with a negative impact on the cost-effectiveness of outpatient surgery and it may cause absenteeism from work and social activities.¹⁴ However, not all patients experiencing CPSP may be functionally impaired, some may consider themselves fully recovered and participate in regular work and social activities. In contrast, other may experience suboptimal or emotional recovery without experiencing CPSP. Not much

research regarding global recovery has been performed, but predictors for the development of CPSP might not be the same as predictors for a poor global recovery.¹⁸

The aim of this study is to prospectively describe the prevalence and predictive factors of CPSP, as well as the prevalence and predictive factors of a poor global recovery, one year after outpatient surgery, in a large group of outpatients treated at a university hospital.

Materials and methods

Patients

This study was designed as a prospective longitudinal study. It was approved by the institutional Ethics Committee of the Maastricht University Medical Center+, and all patients gave informed consent to participate. Every patient who underwent elective outpatient surgery was eligible for inclusion, regardless of the nature of the procedure. Potential participants were excluded if they were younger than 18 years, were unable to express themselves, were visually impaired, or if their understanding of the Dutch language was insufficient.

Instruments

Information was collected by means of three successive questionnaires; a preoperative pain questionnaire (Q1), an acute postsurgical pain questionnaire (Q2) and a chronic postsurgical pain questionnaire (Q3). Q1 contained questions regarding demographic factors (e.g. age, gender, educational level, work status), average and present pain intensity, the influence of pain on daily activities, prescribed analgesic use, over-the-counter analgesic use, the effect of analgesic use on pain severity, and the number of visits to a medical doctor or other health care professionals. Furthermore, patients were specifically asked to only rate the pain they thought was related to the indication for the surgical procedure. All questions regarding pain were measured on an 11-point numeric rating scale (NRS; where 0 = no pain, and 10 = worst pain imaginable). Q1 also contained parts of four validated questionnaires. For two of these, shortened versions were used to keep the total number of questions within limits and thus avoiding patient refusal due to long questionnaires (i.e. diminishing patient burden). To measure catastrophic thinking, six of the thirteen original items of the Pain Catastrophizing Scale (PCS) were used. These were the two questions loading highest on each of the three subscales (i.e. items 5 and 12 for Helplessness, items 9 and 11 for Rumination, and items 6 and 13 for Magnification). The selection of these items was based on unpublished data from our previous research.^{18, 19} The eight-item Surgical Fear Questionnaire (SFQ) was included to measure fear of potential consequences of

surgery. Four items refer to fear of short-term consequences (e.g. pain, side effects) and four items refer to fear of long-term consequences (e.g. deterioration of health).²⁰ Also, four of the originally ten questions of the Life Orientation Test Revised (LOT-R) were used to measure the personality trait optimism.²¹ The four filler questions were omitted and the four questions (two positively phrased and two negatively phrased) loading highest on, respectively the optimism and pessimism factor in a previous study by our group were selected.¹⁸ Finally, the EuroQol (EQ-5D) was used to measure five dimensions of quality of life (i.e. mobility, self-care, usual activity, pain/discomfort and anxiety/depression).²²

Q2 contained questions regarding average and present pain intensity, the influence of pain on daily activities, prescribed and over-the-counter analgesic use, the effect of analgesic use on pain severity, visits to health care professionals, postoperative side-effects and complications (e.g. nausea, vomiting, wound infections). We specifically asked the patients to only rate the pain they thought was related to the surgical procedure. Q2 also contained the EQ-5D and the 1-item Global Surgical Recovery index (GSR), which represents a single question about the extend to which patients considered themselves recovered from the surgery ("if 100% recovery means your health is back to the same level as it was before the surgery, what percentage of recovery are you at now?").¹⁸ The GSR has been found to correlate well with a more elaborate instrument measuring surgical recovery.²³ Q3 contained the same questions as Q2, as well as a question about the number of sick days during the past year.

Procedure

Between November 2008 and April 2010, patients planned for outpatient surgery and presenting at the outpatient clinic for preoperative assessment at the Maastricht University Medical Center +, were asked to participate in our study. The purpose and methods of the study were explained by the anesthesiologist or physician assistant performing the assessment. If consent was obtained, the patient received an envelope containing an information letter about the study, Q1, Q2, and two return envelopes. If no contraindications were present, the patient also received a standardized prescription for postoperative analgesics (i.e. acetaminophen 1000 mg four times a day, with an upgrade to acetaminophen/tramadol 650/75 mg four times a day). The patient received verbal and written instructions to start with acetaminophen and to switch to acetaminophen/tramadol in case of insufficient analgesia.

Patients were instructed to complete Q1 one week before the surgical procedure. Patients who did not return Q1 were considered to be unwilling to participate, and no further attempts to contact them were made. Q2 had to be completed four days after the surgery. Patients who did return Q1 but did not return Q2, were reminded by regular mail or telephone. One year after the procedure all participants received Q3 by regular mail. All clinical information (e.g. ASA physical status, surgical procedure, type of

anesthesia, duration of the procedure, duration of hospital stay) was acquired by systematic chart review.

Statistical analysis

All patients who returned both Q1 (because this questionnaire contained part of the predictor variables) and Q3 (because this contained the outcome parameters) were included in the analyses. Patient characteristics and mean pain scores were evaluated using descriptive statistics. For Q1 and Q3 average pain intensity during the last week was used, for Q2 the actual pain intensity. An NRS > 3 was defined as a cut-off value to define moderate to severe pain and an NRS > 7 was defined as severe pain.^{24,25} A GSR ≤ 80% was defined as poor global recovery.¹⁸

Before analyzing the database for possible predictors of CPSP and poor global recovery, missing data were imputed using multiple data imputation according to the method described by Van Buuren et al.²⁶ In this method each missing value is replaced by a plausible value based on their predicted distribution. We imputed each of these missing values ten times, leading to ten different data sets. Results are based on the pooled outcome based on these ten data sets. Only predictor values were imputed, missing outcome variables were not. First, univariate logistic regression analyses were performed for each predictive variable. Only variables with a *p*-value < 0.1 were included in the final multiple logistic regression model. Stepwise forward multiple logistic regression analyses were subsequently performed to determine which variables were predictive of CPSP and of poor global recovery. The model was constructed using four successive steps, based on the availability of the variables during the preoperative and postoperative phase. The first step contained the variables that are easiest to obtain, before patients visit the outpatient clinic (i.e. sex, age, and surgical specialty). For the first step a forced entry method was used. The second step contained variables that are easily obtained during the preoperative assessment (i.e. ASA-level, work status, education level, previous surgery, preoperative pain, and preoperative analgesic use). The third step contained variables that are more difficult to obtain, but can still be obtained in the preoperative phase. All psychological variables were added to the model in this step because these variables require patients to fill out multiple questionnaires (i.e. expected postoperative pain, surgical fear, pain catastrophizing, optimism, and preoperative quality of life). The fourth step contained all variables that can only be obtained during or after the surgery (i.e. anesthetic technique, duration of the surgery, duration of the hospital admission, acute postsurgical pain, poor global recovery on the fourth postoperative day, postoperative nausea, postoperative infection, additional surgery during the first postoperative year, and postoperative quality of life). A *p*-value of < 0.05 was considered to be statistically significant. To estimate the models' ability to discriminate between patients with and without CPSP and with good versus poor global recovery, the area under the curve (AUC) was

calculated. In addition, a correlation analysis between CPSP and GSR was performed. All analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL) and STATA version 11.2 (StataCorp, Texas, USA).

Results

During eighteen months, 2500 patients were invited to participate. Of these, 1396 patients (56%) returned Q1. Of all patients that returned Q1, 1282 (92%) returned Q2 and of these patients 906 patients (71%) returned Q3. Of the 114 patients that returned Q1 but not Q2, 26 patients (23%) did return Q3 and were also included. Figure 1 depicts the flowchart of inclusion. Of the 932 patients that were included, 24 patients were excluded because the inclusion had not been in accordance with study protocol; three patients were younger than 18 years at the time of the surgery, one patient was mentally impaired, and 20 patients had undergone a planned inpatient procedure. This resulted in data of 908 patients for the final analyses. Of these patients 908 returned Q1, 883 patients returned Q2, and 908 patients returned Q3.

Procedures performed per surgical specialty are shown in Table 1. Patient characteristics are shown in Table 2. Because the patient characteristics were calculated before missing values were imputed, the results are presented as absolute numbers and percentages, and do not always add up to a total of 908 patients. A small majority of patients were female (56.4%) and the mean age was 53 years (range 18 to 88 years). The average duration of surgery was 49 minutes. Most patients ($n=716$) received general anesthesia, a small number received regional anesthesia (e.g. spinal anesthesia, peripheral nerve blocks, intravenous regional anesthesia, and retrobulbar or sub-Tenon's block) in addition to or instead of general anesthesia. Of all patients, 575 (63.3%) were treated on an ambulatory basis, and 310 (34.1%) in terms of a short-stay admission (< 24 hours). Twenty three patients (2.6%) had to stay in hospital for >24 hours (15 patients stayed for 3 days, 6 patients for 4 days and 2 patients for 5 days) because of unforeseen complications. Of all patients, 67 patients (7.4%) underwent another surgical procedure during the first year after the surgery. This second surgery was related to the original procedure in 42 patients (4.6%).

Figure 1: Flowchart depicting the inclusion and exclusion of the study population.
Q1 = questionnaire one week before the surgery; Q2 = questionnaire four days after the surgery; Q3 = questionnaire one year after the surgery

Table 1: Procedures performed by each surgical specialty

Ophthalmology (n=70) Cataract sugery / vitrectomy (49) Strabismus surgery (11) Dacryocystorhinostomy (5) Other (5)	Urology (n=55) Brachytherapy prostate (26) Scrotal surgery (11) Uterine suspension surgery (11) Other (7)
Gynaecology (n=70) Hysteroscopy (33) Laparoscopic sterilisation / ovariectomy (20) Surgical abortion (7) Vulva condylomata / Bartholin gland (5) Diagnostic laparoscopy (3) Uterine suspension surgery (2)	Plastic surgery (n=96) Dupuytren fasciotomy (25) Breast reduction (11) Surgical correction of scar (9) Tenolysis (9) Replacement of breast implants (8) Carpal tunnel release (7) Skin biopsy / ganglion / lipoma (7) Breast augmentation (6) Liposuction (3)
General surgery (n=271) Inguinal hernia repair (60) Lumpectomy (37)	

Anal surgery (35)	Other (11)
Laparoscopic cholecystectomy (30)	Orthopedic surgery (n=194)
Hardware removal (21)	Arthroscopy knee / meniscectomy (112)
Umbilical / epigastric hernia repair (20)	Shoulder surgery (23)
Skin biopsy / ganglion / lipoma (14)	Hallux valgus correction (17)
Varicectomy (11)	Tenolysis (12)
Mastectomy / axillary lymph node dissection (8)	Hardware removal (5)
Tenolysis (5)	Skin biopsy / ganglion / lipoma (5)
Carpal tunnel release (3)	Other (20)
Other (27)	Other (n=22)
ENT surgery (n=130)	Neurosurgery (1)
Laryngoscopy (31)	Dermatology (4)
Tympanoplasty / stapedectomy (18)	Dental surgery (17)
Cochlear implantation (17)	
Nasal polypectomy (16)	
Tonsillectomy (10)	
Bone anchored hearing aid (9)	
Mastoidectomy (6)	
Nasal septum correction (4)	
Other (19)	

Table 2: Patient characteristics

	<i>N (%)</i>		<i>N (%)</i>
Age (years)		Preoperative pain	
< 45	266 (29.3)	NRS 0-3	553 (62.3)
45-59	295 (32.5)	NRS 4-10	334 (37.7)
> 59	347 (38.2)	Preoperative analgesic use	
Gender		Yes	220 (24.5)
Male	396 (43.6)	No	677 (75.5)
Female	512 (56.4)	ASA physical status	
Educational background		I	444 (50.0)
Elementary school	54 (6.0)	II	405 (45.6)
Intermediate	656 (73.1)	III	39 (4.4)
Higher degree, university	187 (20.8)	Type of anesthesia	
Work situation		General	716 (79.0)
Working	591 (65.2)	Loco-regional	143 (15.8)
Not working	316 (34.8)	General and loco-regional	47 (5.2)

NRS indicates numeric rating scale

Prevalence of pain

A substantial number of patients ($n=334$; 37.7%) experienced moderate to severe pain during the week before completing Q1. Four days after the surgery, 235 patients (26.7%) experienced moderate to severe pain, and one year after surgery this was the case for 139 patients (15.3%). A total of 29 patients (3.2%) experienced severe CPSP.

Figure 2: Prevalence of preoperative, acute postoperative and chronic postoperative pain according to type of surgery. Percentage of patients with a numeric rating scale > 3. CPSP indicates chronic postsurgical pain.

Figure 2 shows the percentages of patients with moderate to severe preoperative, acute postoperative and chronic postsurgical pain for the different surgical specialties. During both the preoperative phase and the postoperative phase, orthopedic and general surgical procedures were most often associated with moderate to severe pain. Preoperative pain was rated as an NRS > 3 by 71.5% of orthopedic patients and by 41.4% of general surgical patients. Postoperatively, 41.2% and 30.5% of these patients scored an NRS > 3. Orthopedic procedures were also most often associated with moderate to severe CPSP; 34.5% of the orthopedic patients scored an NRS > 3 one year after surgery. Other procedures that were relatively often associated with CPSP were general surgical and plastic surgical procedures. Ophthalmologic, urologic and gynecologic procedures resulted in the lowest pain scores at all three measuring points.

The prevalences of moderate to severe CPSP for the more extensively studied outpatient procedures was 13.1% for inguinal hernia repair, 10.0% for breast surgery, 9.6% for general abdominal procedures and 10.0% for laparoscopic cholecystectomy.

Predictors of CPSP

Table 3 shows the logistic regression analysis for CPSP and poor global recovery. No collinearity existed for any of the variables included. ASA-level, work status, educational level, previous surgery, expected postoperative pain, anesthetic technique, duration of the surgery, duration of hospital admission, postoperative nausea, postoperative infection, postoperative analgesic use, surgery during the first postoperative year, and postoperative quality of life, were all nonsignificant in the univariate logistic regression analyses and were therefore not included in this model. The most important predictors for CPSP after outpatient surgery were the surgical specialty, preoperative pain, preoperative analgesic use, surgical fear, and acute postsurgical pain. Of the patients with preoperative analgesic use and no preoperative pain (which is assumed to be adequately treated preoperative pain), the prevalence of CPSP was 8.0% as opposed to 32.0% for patients with moderate to severe preoperative pain (assumed to be inadequately treated preoperative pain). Higher optimism and higher preoperative quality of life were significant protective factors for the development of CPSP.

Prevalence of Poor Global Recovery

The average GSR index one year after outpatient surgery was 84.6% (SD 25.1%). A total of 199 patients (22.3%) scored a GSR of $\leq 80\%$ and were thus defined as poor global recovery. Surgical specialties that were most often associated with poor global recovery were orthopedic surgery (i.e. GSR $\leq 80\%$ in 39.2% of the patients), plastic surgery (24.7%), ophthalmologic surgery (22.9%), ear-nose-throat surgery (21.8%), urologic surgery (20.0%) and general surgery (17.8%). Gynecologic surgery was least often associated with poor global recovery, only 5.9% of these patients scored a GSR $\leq 80\%$.

Predictors of Poor Global Recovery

ASA-level, work status, expected postoperative pain, pain catastrophizing, anesthetic technique, duration of surgery, duration of hospital admission, postoperative nausea, postoperative infection, and postoperative analgesic use, were not statistically significant in the univariate logistic regression analysis and were not included in the final model. Significant predictors for poor global recovery were the surgical specialty (i.e. orthopedic surgery), preoperative pain, preoperative analgesic use, poor global recovery four days postoperative, surgical fear, related surgery during the year before the index surgery and follow-up surgery during the first postoperative year. Furthermore, higher preoperative and postoperative quality of life, as well as higher optimism, protected against a poor global recovery.

Table 3: Results of the logistic regression analysis for CPSP (Numeric Rating Scale > 3) and poor global recovery (Global Surgical Recovery Index < 80%)

Independent variables	Chronic Postsurgical Pain OR (95% CI)	AUC	Poor Global Surgical Recovery OR (95% CI)	AUC
<i>Step 1</i>		0.73		0.65
Age				
Old vs. young	0.99 (0.98-1.00)		1.00 (0.99-1.01)	
Sex				
Male vs. female	0.82 (0.55-1.21)		0.85 (0.62-1.16)	
Surgical specialty (vs. ophthalmology)				
1. Gynaecology	1.21 (0.48-3.09)		0.37 (0.15-0.90)	
2. Ear-nose-throat surgery	2.24 (0.75-6.74)		0.83 (0.42-1.61)	
3. Urology	3.50 (1.48-8.28)		0.84 (0.55-1.27)	
4. General surgery	4.97 (2.37-10.42)		0.86 (0.64-1.16)	
5. Plastic surgery	5.89 (2.72-12.75)		1.14 (0.80-1.61)	
6. Orthopaedic surgery	16.41 (3.88-69.34)		2.67 (1.96-3.62)	
7. Other	2.65 (0.35-20.16)		0.27 (0.12-0.59)	
<i>Step 2</i>		0.80		0.71
Educational level				
Middle vs. low			1.60 (0.83-3.10)	
High vs. low			0.91 (0.42-1.95)	
Previous surgery				
Not related			1.40 (0.86-2.30)	
Related			1.91 (1.25-2.92)	
Preoperative pain (NRS > 3)				
Yes vs. No	4.22 (2.54-7.02)		1.78 (1.22-2.58)	
Preoperative analgesic use				
Yes vs. No	2.16 (1.40-3.34)		1.52 (1.05-2.21)	
<i>Step 3</i>		0.85		0.75
Surgical fear – long term				
Per point (range 0-40 points)	1.04 (1.01-1.06)		1.03 (1.01-1.05)	
Optimism (LOT)				
Per point (range 0-20 points)	0.90 (0.82-0.98)		0.89 (0.83-0.95)	
Preoperative QoL (EQ-5D)				
Per point (range 0.59-1.00 points)	0.09 (0.04-0.22)		0.30 (0.14-0.67)	
<i>Step 4</i>		0.85		0.78
Acute postsurgical pain (NRS > 3)				
Yes vs. No	1.62 (1.02-2.58)			
Poor GSR on day 4 (GSR ≤80%)				
Yes vs. No			2.41 (1.44-4.04)	
Surgery during first postoperative yr				
Not related			0.72 (0.26-1.94)	
Related			2.64 (1.27-5.49)	
Acute postoperative Quality of Life (EQ-5D)				
Per point (range 0.59-1.00 points)			0.24 (0.12-0.50)	

Step 1 used a forced entry method, while in the other steps only significant variables (univariate $p < 0.1$) are entered. Odds ratio's (OR) with 95% confidence interval (CI) and area under the curve (ACU) are presented per step.

Correlation Analysis

Because the data for CPSP and GSR were not parametric, a Spearman ρ was performed to determine the correlation between CPSP and GSR. The correlation coefficient was -0.656 ($p < 0.001$). Furthermore, patients without CPSP have a median GSR index of 100% (interquartile range 90% to 100%), and patients with CPSP have a median GSR index of 50% (interquartile range 25% - 75%).

Discussion

In our study, 15.3% of all patients experienced moderate to severe CPSP after outpatient surgery, and 2.3% experienced severe CPSP. These findings fall in the range of the prevalences previously reported in several review papers. Kehlet et al reported a prevalence of 10% to 50% moderate to severe CPSP, and 2% to 10% severe CPSP.¹¹ Another review article reports even higher incidences; 15% to 60% for moderate to severe CPSP and 4% to 10% for severe disabling CPSP.¹⁵ A recent publication researching only general surgical procedures, reported an incidence of 14.8% for moderate to severe CPSP.²⁷ However, these and several other papers mostly describe surgical procedures that are usually not performed on an outpatient basis (e.g. limb amputation, thoracotomy, coronary artery bypass surgery, caesarean section).^{11, 14, 15, 28, 29} So far, large-scale studies on CPSP after outpatient surgery are lacking; only relatively small studies focusing on specific outpatient procedures are available. There is reason to assume that both the prevalence and predictors of CPSP might be different in outpatients as compared with inpatients. Inpatient procedures are often associated with more extensive tissue damage, longer duration of hospital admission and a longer recovery period. In addition, the treatment of postoperative pain for outpatients might not be as optimal as for inpatients.^{16, 17} Despite these dissimilarities the prevalence of CPSP found in the present study seems to be comparable with the ones reported for inpatient surgery.

One surgical procedure that has been extensively studied in the context of CPSP is inguinal hernia repair. The prevalence of CPSP for these procedures was 13.1% in our study, which is within the range reported by other studies (5% to 35%).^{11, 14, 28, 30, 31} One potentially important predictor for the development of CPSP after inguinal hernia repair is the surgical technique (e.g. mesh vs. non-mesh, open vs. laparoscopic).^{30, 32} Unfortunately, our study did not include and document data about the various surgical techniques.

The prevalence of CPSP after breast surgery has also been extensively studied. We found a CPSP prevalence of 10% after breast surgery, which contrasts to 20% to 50% reported in other major studies.^{11, 14, 28, 33} Most studies have examined CPSP after surgery for breast cancer (i.e. mastectomies and lumpectomies). The procedures in our

study, however, were lumpectomies ($n = 37$), a few mastectomies ($n = 8$), and the remaining were cosmetic surgical procedures ($n = 25$). A small retrospective study focusing uniquely cosmetic breast augmentation, found a CPSP prevalence of 9.5%.³⁴ This might indicate that CPSP is more frequent after surgery for breast cancer than after cosmetic breast surgery. This might be explained by the fact that surgery for breast cancer is often associated with axillary surgery (i.e. nerve damage), chemotherapy and radiotherapy, all of which are risk factors for the development of CPSP.^{14, 33}

A third outpatient procedure that has previously been studied in the context of CPSP is cholecystectomy. In our population, CPSP occurred in 9.6% of the patients after general abdominal procedures and in 10% of patients after laparoscopic cholecystectomy. This is in line with the 5% to 50% previously reported.^{14, 35}

In addition to reporting the prevalence of CPSP after outpatient procedures, another major aim of our study was to identify predictors of CPSP after outpatient surgery. Previous studies on risk factors for the development of CPSP have mostly dealt with inpatient procedures.^{11, 14} As mentioned above, the factors identified for these procedures may not necessarily be the same as those for outpatient procedures. To identify the factors that were related to the presence of CPSP, we performed a stepwise logistic regression analysis. The first step in the logistic regression model contained easily obtainable variables, such as age, sex and surgical specialty. In our model these three variables were capable of a reasonably adequate prediction (AUC 0.73), which was mostly dependent on the surgical specialty. Orthopedic surgery was associated with the most severe CPSP. Orthopedic procedures are often associated with preoperative pain (which is often the reason to operate) and acute postoperative pain. These patients might therefore be prone to peripheral and central sensitization, which might cause the development of CPSP. Age and sex were not found to be significant predictors in our model. Previous studies found inconsistent evidence regarding age and sex as risk factors for CPSP, although various studies suggest that higher age may be associated with a decreased chance of developing CPSP.^{11, 14, 36}

The second step of our model contained variables that can be easily obtained during preoperative assessment. This step significantly improved our model to an AUC of 0.80. The presence of moderate to severe preoperative pain was shown to be the most important predictor of the entire model. Most studies addressing CPSP have also demonstrated this association.^{14, 18, 30, 36} A possible reason for this association is the fact that peripheral and central sensitization may develop more easily in patients with long lasting pain. The presence of CPSP after orthopedic procedures might, however, also be a continuation of the preoperative pain, especially when pain was the indication for the surgery and the surgery was unsuccessful. Another important predictor for CPSP in our model was preoperative analgesic use, which has also been demonstrated before.³⁷ It may, however, not be the use of analgesics in itself that is predictive of CPSP, but rather the efficacy of preoperative analgesic use. Our study demonstrated that patients with preoperative analgesics but without preoperative pain experienced significantly less

CPSP than patients with inadequately treated preoperative pain. Treating preoperative pain with the correct and sufficient dose of analgesics might thus be a way of decreasing the prevalence and severity of CPSP. More research on this topic is needed.

The third step of our logistic regression analysis slightly improved our model by adding the psychological variables. Psychological risk factors for the development of CPSP after inpatient surgery have been extensively studied and especially anxiety and pain catastrophizing have been demonstrated to be associated with the risk of developing CPSP.^{10, 14, 18} In our study, all psychological variables included were associated with CPSP in the univariate analyses. In the multivariate analysis, long-term surgical fear, optimism, and quality of life remained in the model. Pain catastrophizing was no longer significant in the multivariate analyses. It might be speculated that patient undergoing minor outpatient procedures are less prone to catastrophize compared with patients undergoing more extensive inpatient procedures. Another explanation might lie in the use of a shortened version of the Pain Catastrophizing Scale, which might be less reliable. An alternative interpretation for the different findings amongst studies might be that anxiety, pain catastrophizing and optimism are to some extent correlated with each other. Letting them compete in a multivariate regression analysis might thus be artificial and lead to unstable results. In that case, another approach could be to identify broader psychological profiles, such as was done by Bruce et al.³³ A composite variable consisting of high optimism, high positive affect, and low trait anxiety and depression, which they called 'psychological robustness' was associated with a decreased risk of developing CPSP after breast cancer surgery.

The fourth step added all perioperative and postoperative variables. The only statistically significant predictor for CPSP after outpatient surgery in this step was the presence of acute postoperative pain. Acute postoperative pain has been reported to be an important predictor for CPSP in other studies.^{11, 14, 18, 32} In our population acute postoperative pain also predicted CPSP, but our model improved only slightly. Hence, acute postoperative pain seems less important than preoperative pain in predicting CPSP. It might be speculated that neuroplastic changes related to the development of CPSP, like peripheral and central sensitization, are more extensive and severe after long lasting preoperative pain than after relatively brief acute postoperative pain.

In addition to identifying predictors for CPSP, we also examined predictors of global perceived recovery. Some predictors for poor global recovery were identical to those for CPSP. This is not surprising, as pain is part of overall functional recovery and the two outcomes showed a substantial correlation. Nevertheless some additional predictors were identified: related surgery in the year before the surgical procedure, as well as preoperative and postoperative quality of life. Undergoing multiple operations within a relatively short timeframe and already being in a suboptimal condition as indicated by lower quality of life scores, may negatively impact the recovery process. Our model for predicting poor global recovery was fairly good (AUC 0.76), even though all four steps

were necessary to achieve this predictability. However, more research on this subject is needed.

Our study included all outpatient procedures performed in our hospital, which has led to a heterogeneous study population. However, so far hardly any research on CPSP in a general outpatient population had been performed and the aim of this study was to examine whether CPSP is an important problem in this population as well. The heterogeneity was statistically corrected for by adding the surgical specialty to our regression model. Unfortunately, the groups of patients were too small to perform sparse regression analyses for all the different kind of procedures performed. The results do demonstrate that some procedures are more often associated with CPSP than others (e.g. orthopedic surgery). However, when other possible predictors were added to the model, such as preoperative pain and analgesic use, the contribution of the surgical specialty became less prominent. This demonstrates that there may be common factors predicting outcome of various surgical procedures.

Our study has several limitations. The first limitation of our study might be that it is not possible to determine whether CPSP was a new problem or whether it was a continuation of already existing preoperative pain. The proposed definition by Macrae states that this should be ruled out.⁹ Nevertheless, the aim of our study was to identify patients at risk for developing CPSP and preoperative pain seemed to be the single most important risk factor. For the individual patient it does not matter whether it is a new problem or not, they simply want to be able to prevent it or treat it. Future studies, however, should try to establish detailed assessment to determine whether the postsurgical pain is indeed newly developed pain. Another limitation is that patients were not asked to differentiate between pain at rest and pain with movement. Several previous studies have made this distinction and have shown that there can be a difference.^{33, 35} We recommend that future studies do differentiate between pain at rest and pain with movement.

An important next step will be to investigate if and how it is possible to prevent CPSP, especially in patients at risk. As preoperative pain seems to be the single most important risk factor, one might hypothesize that a strategy of effectively treating this pain might reduce the incidence of CPSP. Whether it is possible to reverse the central sensitization that has already taken place, is a topic for future research. We feel that patients undergoing surgery should be informed that CPSP is an important problem, even after outpatient procedures and this information should be used as one of the determinants as to whether an elective surgical procedure should take place or not.

In conclusion, our study demonstrates that CPSP after outpatient surgery is an important problem, with 15.3% of all patients experiencing moderate to severe pain one year after the surgery. The preoperative phase proved to be extremely important in identifying patients at risk. By asking patients about preoperative pain and analgesic use, and determining the surgical specialty, it may be possible to reasonably accurately predict the chance of developing CPSP. This prediction might be somewhat improved by

identifying patients with an unfavorable psychological profile, exemplified by a lack of optimism, high levels of surgical fear, and a low preoperative quality of life in this study. Although acute postoperative pain has previously been found to be an important risk factor, the addition of this factor only slightly improved our predictive model.

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Chapter 3

Prevalence and predictive factors of chronic postsurgical pain and global surgical recovery one year after outpatient knee arthroscopy; a prospective cohort study

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Medicine (Baltimore) 2015 Nov;94(45):e2017

Abstract

Introduction

Outpatient knee arthroscopy is one of the most commonly performed surgical procedures. Previous research has demonstrated that chronic postsurgical pain (CPSP) after outpatient surgery is prevalent. Our objective was to determine the prevalence and predictive factors of CPSP and Global Surgical Recovery (GSR) one year after knee arthroscopy.

Methods

A prospective longitudinal cohort study was performed. Patients were included during an eighteen month period. Data were collected by using three questionnaires: at one week preoperatively, four days postoperatively and one year postoperatively. A value of >3 on an 11-point numeric rating scale (NRS) was defined as moderate to severe pain. A score of $\leq 80\%$ on the Global Surgical Recovery Index was defined as poor GSR. Stepwise logistic regression analysis was performed to determine which variables were predictors for CPSP and poor GSR.

Results

The prevalence of moderate to severe preoperative pain in patients undergoing knee arthroscopy ($n=104$) was 71.2%, of acute postsurgical pain 37.5%, and of CPSP 32.7%. Risk factors for CPSP were the presence of preoperative pain and preoperative analgesic use, with odds ratios of 6.31 (1.25-31.74) and 4.36 (1.58-12.07) respectively. The prevalence of poor GSR one year after outpatient knee arthroscopy was 50.0%. Poor GSR four days after the surgery was a risk factor with an odds ratio of 8.38 (0.92-76.58) and quality of life four days after surgery was a protective factor with an odds ratio of 0.10 (0.02-0.64).

Discussion

Both CPSP and poor GSR are common one year after knee arthroscopy. Patients at risk for CPSP can be identified during the preoperative phase. Prediction of poor GSR one year after surgery is mainly related to early postoperative recovery.

Introduction

Arthroscopic knee surgery is one of the most commonly performed surgical procedures, especially in the outpatient setting. Indications for performing this procedure include functional complaints, as well as acute or persisting pain. Recently, the effectiveness of arthroscopic knee surgery has been questioned for various indications and is now considered controversial.¹ Several randomized studies have been performed to compare optimal conservative treatment or sham surgery with arthroscopic knee surgery for various diagnoses, but were not able to demonstrate a benefit of surgical intervention.²⁻⁵ Nevertheless, due to methodological constraints, correct interpretation of the results is difficult. First of all, no study has yet been performed to determine which variables, besides the presence of osteoarthritis, might predict whether a patient might benefit from surgical intervention or not. In this respect, variables like those related to socio-demographic, clinical and psychological predictors are of main interest. Second, most studies determine the effectiveness of arthroscopic knee surgery in terms of functional complaints. In this context, the question of both acute and chronic postsurgical pain (APSP and CPSP) should not be overlooked, since pain is most often the major indication for surgery, and at the same time pain is also considered to be an important complication of the surgical procedure.^{6,7} Both APSP and CPSP have been associated with several negative consequences for the patient's general health, the cost-effectiveness of the surgical procedure and for society in general.⁸⁻¹⁰ Another important outcome parameter is global surgical recovery (GSR), measuring the patient's satisfaction and overall success of the procedure.¹¹ Patients who experience CPSP might consider themselves fully recovered and participate in regular work and social activities. In contrast, some patients without CPSP, might experience suboptimal overall recovery. Interestingly, previous studies have demonstrated that predictors of poor GSR might not be identical to predictors of CPSP.^{7,12}

The aim of this study is to describe the prevalence and predictive factors of chronic postsurgical pain and poor global surgical recovery one year after outpatient knee arthroscopy in order to be able to identify the patients who are at risk.

Methods

Subjects

This study is a subgroup analysis of a previously published prospective longitudinal cohort study performed to collect information about the prevalence and predictive factors of APSP and CPSP, and GSR in patients undergoing outpatient surgery.⁷ Approval to perform this study was given by the Ethics Committee of the Maastricht University

Medical Center+ (MUMC+), and all patients gave written informed consent to participate. The study included all adult patients undergoing outpatient surgery, regardless of the nature of the procedure. Patients were excluded if they were younger than 18 years, were unable to express themselves, were visually impaired, or if their understanding of the Dutch language was insufficient. In this present article, only patients who underwent arthroscopic knee surgery are described.

Instruments

Information was collected by using three questionnaire packages; a preoperative pain questionnaire package (Q1), an acute postsurgical pain questionnaire package (Q2) and a chronic postsurgical pain questionnaire package (Q3). Q1 contained questions about preoperative pain intensity, analgesic use, health care utilization, quality of life, as well as questions about demographic and psychological candidate predictors. Q2 and Q3 contained questions about pain intensity, analgesic use, health care utilization, quality of life, global recovery, and postoperative side effects.^{7,12} All questions regarding pain were measured on an 11-point numeric rating scale (NRS; where 0 = no pain, and 10 = worst pain imaginable). Furthermore, patients were specifically asked if they thought the pain they were experiencing was related to the surgery. Global surgical recovery (GSR) was measured by using the Global Surgical Recovery index, which represents a single question about the extend to which patients considered themselves recovered from the surgery ("if 100% recovery means your health is back to the same level as it was before the surgery, what percentage of recovery are you at now?").¹² In order to measure the patient's psychological status four validated questionnaires were used (i.e. Pain Catastrophizing Scale, Surgical Fear Questionnaire, Life Orientation Test Revised and the EuroQol).¹³⁻¹⁶ A detailed description of the questions asked and the questionnaires used, can be found elsewhere.⁷

Study design

Between November 2008 and April 2010, patients scheduled for elective outpatient surgery at the MUMC+ were asked to participate if they were planned for outpatient surgery. In case of consent, patients received an envelope with the first two questionnaires and a standardized prescription for postoperative analgesics (i.e. acetaminophen 1000 mg four times a day, with an upgrade to acetaminophen/tramadol 650/75 mg four times a day in the case of insufficient analgesia). Patients were asked to complete Q1 one week before the surgery and Q2 four days after the surgery. Patients who returned Q1, but not Q2, were reminded to complete Q2 by telephone or mail. Patients received Q3 one year after the surgery. All clinical information (e.g. ASA physical status, type of anesthesia, duration of the procedure, duration of hospital stay) was acquired by systematic chart review. The severity of osteoarthritis was graded

during the arthroscopic procedure, according to the Outerbridge Classification.¹⁷ This classification consists of a 5-point scale, where 0 is no osteoarthritis, 1 is softening and swelling of articular cartilage, 2 is fragmentation and fissuring of articular cartilage affecting < 0.5 inches, 3 is fragmentation and fissuring of articular cartilage affecting > 0.5 inches, and 4 is cartilage erosion to the bone.

Outcome measures

The main outcome variables in this study were chronic postsurgical pain and global surgical recovery. In accordance with previous studies, NRS > 3 was used to define moderate to severe pain.^{7,18,19} Global surgical recovery was defined as poor when the GSR-index was ≤80%.^{7,12}

Statistical analysis

Only patients who returned all three questionnaires were included in the analyses. In order to evaluate patient characteristics and mean pain scores, descriptive statistics were used. For Q1 and Q3 the average pain intensity during the last week was used, for Q2 the actual pain intensity.

We recently identified variables that were relevant predictors for the development of CPSP or poor GSR.⁷ The following variables were included in the analyses: age, gender, preoperative pain, preoperative analgesic use, expected postoperative pain, surgical fear, preoperative quality of life, early postoperative quality of life, acute postoperative pain, acute postoperative global recovery, comorbid osteoarthritis, and additional surgery during the first postoperative year. Missing data were imputed using multiple data imputation according to the Van Buuren method.²⁰ Only missing predictors variables were imputed, missing outcome variables were not.

Predictor variables were initially tested in a univariate logistic regression analysis. If the *p*-value was <0.1, the variable was also included in the multiple logistic regression model. Stepwise forward four-step multiple logistic regression analysis was performed. The steps were based on the availability of the variables during the perioperative phase. The first step contained variables that were easiest to obtain; before the patient visits the outpatient clinic (i.e. gender and age). A forced entry method was used for the first step. The second step contained variables that can easily be obtained during the preoperative visit (i.e. preoperative pain and preoperative analgesic use). The third step contained variables that can be obtained preoperatively, but require more detailed questionnaires (i.e. expected postoperative pain, surgical fear and preoperative quality of life). The fourth step consisted of variables that can only be obtained during or after the surgery (i.e. comorbid osteoarthritis according to the Outerbridge Classification, acute postoperative pain, acute postoperative global recovery, additional surgery during the first postoperative year, acute postoperative quality of life). A *p*-value of

<0.05 was considered to be statistically significant. The area under the curve (AUC) was calculated to determine the models' ability to discriminate. All analyses were performed by SPSS version 20.0 (SPSS Inc, Chicago, IL) and STATA version 11.2 (StataCorp, College Station, TX)

Results

Of the 908 patients that underwent outpatient surgery and were included into our database, 104 patients fulfilled the inclusion criteria of the current substudy. For the flowchart of the original 908 patients we would like to refer to our previous publication.⁷ Patient characteristics of the 104 patients are given in Table 1. Because the patient characteristics were calculated before multiple imputation, the results do not always add up to a total of 104 patients. The mean age of the patients was 53.1 years (standard deviation 13.6 years) and there were 54 male and 50 female patients. Forty patients (38.5%) used analgesics during the week before the surgery, and 62 patients (59.6%) did not. A total of 8 patients (7.7%) underwent another surgical procedure during the first postoperative year (i.e. 6 patients underwent total knee arthroplasty, 1 patient underwent a different arthroscopic procedure of the same knee, and 1 patient underwent anterior cruciate ligament reconstruction).

Table 1: Baseline patient characteristics.

	N (%) /		N (%)
Age (years)		Type of surgery	
< 45 years	28 (26.9)	Lavage and debridement	21 (20.2)
≥ 45 years	76 (73.1)	Partial meniscectomy	81 (77.9)
Gender		Microfracture chondral defect	2 (1.9)
Male	54 (51.9)	Indication for surgery	
Female	50 (48.1)	Pain	98 (94.2)
Educational background		Symptoms of locking	15 (14.4)
Elementary school	8 (7.7)	Instability	7 (6.7)
Intermediate	80 (76.9)	Effusion	5 (4.8)
Higher degree, university	16 (15.4)	Outerbridge Classification	
Work situation		0 and 1 (no osteoarthritis)	30 (28.8)
Paid work	53 (51.0)	2 and 3 (mild osteoarthritis)	39 (37.5)
Unpaid work	23 (22.1)	4 (severe osteoarthritis)	16 (15.4)
Not working	28 (26.9)	Type of anesthesia	
ASA physical status		General	50 (48.1)
I	52 (50.0)	Spinal	44 (42.3)
II	46 (44.2)	Combination	10 (9.6)
III	3 (2.9)		

NRS = Numeric Rating Scale

Prevalences of acute and chronic postsurgical pain and poor global recovery

The prevalences of preoperative pain, APSP and CPSP, as well as the GSR of patients undergoing knee arthroscopy are demonstrated in Table 2. Seventy-four patients (71.2%) experienced moderate to severe pain during the week before surgery. In 72 patients (69.2%) pain interfered with usual activities. Thirty-nine patients (37.5%) experienced moderate to severe APSP on the fourth postoperative day. Pain interference had not decreased. Thirty-four patients (32.7%) experienced moderate to severe CPSP one year after the procedure, and in 32 patients (30.8%) pain interfered with daily activities. One year after the knee arthroscopy, 17 patients (16.4%) reported more pain than preoperatively, 13 patients (12.5%) reported the same amount of pain, and 74 patients (71.1%) reported less pain than preoperatively. Table 3 demonstrates the percentage of patients with APSP and CPSP for patients with and without moderate to severe preoperative pain.

Ninety-two patients (88.5%) scored a GSR $\leq 80\%$ four days after the surgery, 9 patients (8.7%) scored GSR $>80\%$ and thus showed good recovery, and of 3 patients data were missing. One year after surgery, 52 patients (50.0%) presented a GSR $\leq 80\%$, 48 patients (46.2%) a GSR $>80\%$, and the data of 4 patients were missing.

Table 2: Preoperative, acute postoperative and chronic postoperative pain intensity and global surgical recovery index.

	Preoperative N (%)	4 days postoperative N (%)	1 year postoperative N (%)
Global Surgical Recovery Index (%)			
Median (IQR)		50 (40 – 70)	80 (60-99)
Mean pain intensity¹ (NRS 0 – 10)			
Median (IQR)	5 (3 – 7)	4 (2 – 6)	2 (0 – 5)
NRS 0-3	29 (27.9)	46 (44.2)	70 (67.3)
NRS 4-10	74 (71.2)	58 (55.8)	34 (32.7)
Information missing	1 (1.0)	-	-
Present pain intensity (NRS 0 – 10)			
Median (IQR)	5 (2 – 6)	3 (1 – 4)	1 (0 – 3)
NRS 0-3	41 (39.4)	65 (62.5)	80 (76.9)
NRS 4-10	62 (59.6)	39 (37.5)	24 (23.1)
Information missing	1 (1.0)	-	-
Pain interference with usual activities (NRS 0 – 10)			
Median (IQR)	5 (3 – 7)	5.5 (3 – 7)	2 (0 – 4)
NRS 0-3	30 (28.8)	32 (30.8)	72 (69.2)
NRS 4-10	72 (69.2)	72 (69.2)	32 (30.8)
Information missing	2 (1.9)	-	-

IQR = Interquartile Range. NRS = Numeric Rating Scale.

Table 3: Number and percentages of patients with acute postsurgical pain (APSP) and chronic postsurgical pain (CPSP) for patients with and without moderate to severe preoperative pain.

Preoperative NRS	APSP <i>n</i> (%)	CPSP (%) <i>n</i> (%)
NRS 0-3 (<i>n</i> = 29)	5 (17.2)	2 (6.9)
NRS 4-10 (<i>n</i> = 75)	34 (45.6)	32 (42.7)

NRS = numeric rating scale

Predictors of CPSP and poor global recovery

Based on a logistic regression analysis for CPSP and poor GSR no colinearity for any of the variables was observed (Table 4). Surgical fear, acute postoperative GSR, the presence of osteoarthritis and additional surgery in the year after the index procedure, were not statistically significant predictors for CPSP in the univariate analysis and were thus not added to the final model. Variables predictive of CPSP in the multiple regression model were the presence of preoperative pain and the preoperative use of analgesics (AUC of 0.78). The only significant predictors for poor GSR one year after surgery, were poor GSR four days after the surgery and poor quality of life four days after the procedure (AUC of 0.70). Surgical fear, the presence of comorbid osteoarthritis and additional surgery in the year after the index procedure were no predictors for poor GSR.

The severity of osteoarthritis according to the Outerbridge Classification versus the GSR and pain intensity one year after knee arthroscopy is shown in figure 1 and figure 2.

Table 4: Results of the linear regression analysis for chronic postsurgical pain (CPSP) and global surgical recovery (GSR).

Independent variable	CPSP OR (95% CI)	AUC	Poor GSR 1 yr after surgery OR (95% CI)	AUC
<i>Step 1</i>		0.57		0.52
Age				
≥45 yrs vs. <45 yrs	0.80 (0.32 – 2.02)		1.00 (0.42-2.43)	
Gender				
Male vs. female	0.68 (0.29-1.56)		0.84 (0.38-1.85)	
<i>Step 2</i>		0.78		-
Preoperative pain (NRS > 3)				
Yes vs. no	6.31 (1.25-31.74)			
Preoperative analgesic use				
Yes vs. no	4.36 (1.58-12.07)			
<i>Step 3</i>		-		-
<i>Step 4</i>		-		0.70
GSR 4 days after surgery				
>80% vs. ≤80%			8.38 (0.92 – 76.58)	
QOL 4 days after surgery				
Per point (range -0.59-1.00 points)			0.10 (0.02 – 0.64)	

Step 1 used a forced entry method, while in other steps only significant variables (univariate $p < 0.1$) are entered. Area under the curve (AUC) are presented per step. NRS = numeric rating scale. QOL = quality of life.

Figure 1: Presence of chronic postsurgical pain (CPSP) versus the severity of osteoarthritis according to the Outerbridge Classification. NRS = numeric rating scale, OA = osteoarthritis

Figure 2: Presence of poor global surgical recovery (GSR) versus the severity of osteoarthritis according to the Outerbridge Classification. OA = osteoarthritis

Discussion

In this study we report a prevalence of preoperative pain in patients that underwent arthroscopic knee surgery of 71.2%, a prevalence of acute postsurgical pain of 37.5% and a prevalence of chronic postsurgical pain one year after surgery of 30.8%. During the last decade, the prevalence of CPSP after several inpatient procedures was reported to vary between 10% and 60%.²¹⁻²³ A more recent large cross-sectional study reported a prevalence of 18.3% of moderate to severe CPSP after various surgical procedures.²⁴ With respect to knee arthroscopy a CPSP prevalence of 30% (NRS ≥ 1) was reported one year after surgery.²⁵ The prevalence of CPSP after knee arthroscopy as reported in our study is higher than reported by Rosseland and colleagues, but it should be noted that in their study only patients with moderate acute postoperative pain were included, whereas all patients with preoperative pain or severe acute postoperative pain were excluded. For that reason, the results of Rosseland and colleagues and our results regarding the prevalence of CPSP one year after knee arthroscopy are difficult to compare. Closely related, but not identical, data on the prevalence of CPSP in patients

after joint arthroplasty have been published.²⁶⁻²⁸ It should be taken into account that arthroscopic knee surgery is a relatively minor outpatient procedure, which causes less tissue damage and no or even shorter hospital admission compared to joint arthroplasty. Nevertheless, the prevalence of CPSP after joint arthroplasty, varying between 37.5% six months after total hip replacement, 50.5% three months after total knee replacement, and 37.5% one year after total shoulder replacement, does not significantly differ from our data in patients after arthroscopic knee surgery.²⁶⁻²⁸ This might indicate that, in case of orthopedic surgery, the extent of tissue damage and the duration of hospital admission are no reliable predictors for CPSP compared to other variables.

We previously reported a CPSP prevalence of 15.3% after various surgical outpatient procedures.⁷ This suggests that CPSP occurs more often after knee arthroscopy (32.7%) compared to other outpatient procedures. This increased prevalence might be explained by a high prevalence of preoperative pain in these patients populations (71.2% for arthroscopic knee surgery versus 37.7% for various outpatient procedures). Preoperative pain has proven to be one of the most important risk factors for the development of CPSP.^{7,12,21,23,28,29}

Another aim of this study was to analyze risk factors of CPSP after outpatient knee arthroscopy. Age and gender were included into the first step of the logistic regression model. Neither age nor gender proved to be a significant predictor of CPSP in our model. Large recent studies on CPSP in a general population, as well as smaller studies performed in a specific orthopedic population, could not identify gender as a predictable risk factor for CPSP.^{7,12,24,26,28} In contrast, conflicting results have been reported for age. Some studies have not been able to find an effect, while other large studies observed an increasing chance of developing CPSP with decreasing age.^{7,12,24,26,28} This finding is not supported by the results of the present study in patients undergoing knee arthroscopy.

Significant predictors in the second step of our model were the presence of preoperative pain and preoperative analgesic use. The addition of these variables into the regression model resulted in an AUC of 0.78. As mentioned before, preoperative pain has been proven to be an important predictor of CPSP.^{7,12,21,23,28,29} This is most probably related to the fact that preoperative pain causes both peripheral and central sensitization, which in turn can cause CPSP to develop more easily. Preoperative analgesic use was also an important predictor of CPSP. We previously demonstrated that patients with preoperative analgesic use and preoperative pain were more likely to develop CPSP than patients with adequately treated preoperative pain.⁷ We therefore hypothesize that it is not analgesic use in itself that is the risk factor for CPSP, but rather the inefficacy of the analgesic use.

Psychological variables were added to the regression model in the third step. As these variables were not statistically significant in predicting CPSP, they were discarded from the model. Psychological traits have been extensively studied and previous

research has demonstrated that these variables (e.g. surgical fear, pain catastrophizing, depression, pessimism) are important risk factors for the development of CPSP.^{7,12,27,29,30} We hypothesize that these variables were not significant in this study because knee arthroscopy is a relatively minor procedure without a large emotional aspect, as opposed to other surgical procedures (e.g. oncologic surgery).

All further perioperative and postoperative variables were added to the regression model in the fourth step, but none of these variables were statistically significant. Acute postoperative pain has been proven to be an important predictor for the development of CPSP after varying procedures.^{7,12,21,29} One small scale study did not report a predictive effect of acute postoperative pain on CPSP in patients that underwent total hip arthroplasty.²⁶ The conclusion of this study is at least debatable as the absence of a significant effect might be related to the small amount of patients included. In our previous large-scale study, acute postoperative pain was shown to be a significant predictor of CPSP, although it only slightly improved the prediction model.⁷ We speculated that long-lasting preoperative pain is a more relevant predictor, because long-lasting preoperative pain might cause more extensive neuroplastic changes compared to brief acute postoperative pain. Additional related surgery in the first postoperative year was also added to the regression model in the fourth step, but was not a predictor. One could argue that this was not statistically significant because of the small number of patients that actually underwent a second procedure ($n = 8$). However, the prevalence of CPSP in these patients was 37.5% as opposed to 32.3% in the patients that did not undergo another related surgical procedure.

Another important variable that was added to the regression model was the severity of osteoarthritis according to the Outerbridge Classification. The degree of osteoarthritis was not a significant predictor, although we did observe a trend towards an increasing prevalence of CPSP in patients with concomitant grade 4 osteoarthritis. In this respect two relevant studies have been published.^{3,4} The first study described patients with a meniscal tear and concomitant osteoarthritis, and could not demonstrate any benefit of arthroscopy versus optimized physical therapy.⁴ The second study studied patients with a meniscal tear without osteoarthritis, and could also not find any benefit of arthroscopy versus sham surgery.³ The authors hypothesize that a meniscal tear could be an early sign of knee osteoarthritis rather than a separate clinical problem. It should, however, be noted that in this study patients with a traumatic meniscal rupture were excluded, while specifically this subpopulation might benefit from arthroscopy surgery. Unfortunately, in both studies no subgroup analysis was done in order to determine which patients might benefit from surgery and which patients might not. Here we did not observe a predictive effect of osteoarthritis on CPSP, but the present study was not powered for this secondary outcome. On the other hand, we observed a trend of an increased risk for the development of CPSP in patients with grade 4 osteoarthritis (figure 1a). In order to better answer the question whether the degree of osteoarthritis is a predictor of CPSP after knee arthroscopy, an adequate

trial comparing knee arthroscopy with nonsurgical intervention in patients with a meniscal tear, with and without osteoarthritis and patients with and without a traumatic cause should be performed. Then subgroup analyses would have to be performed to determine which patients might benefit from surgical intervention.

The second outcome parameter of this study was global surgical recovery (GSR). This parameter was chosen because it measures overall recovery and previous studies have demonstrated that the risk factors for developing CPSP might not be identical to those for poor GSR.^{7,12} A substantial amount of patients in this study (i.e. 50.0%) experienced poor GSR one year after knee arthroscopy. This percentage of 50.0% is relatively high as compared to those reported in other studies. The study of Peters and colleagues reported a prevalence of 34.4% six months after various inpatient procedures.¹² Recently, we reported a prevalence of 22.3% one year after various outpatient procedures, and 39.2% in the subset of patients undergoing ambulatory orthopedic surgery.⁷ Clearly, the prevalence of poor GSR after outpatient knee arthroscopy is amongst the highest of all procedures, including other orthopedic procedures. It would be interesting to know in which domain knee arthroscopy patients experience suboptimal recovery (e.g. functional, emotional, daily activities, social activities). We were able to define two significant risk factors for poor GSR one year after knee arthroscopy. First, poor GSR four days after surgery and second poor quality of life four days after surgery. Unfortunately, this implies that patients at risk for a long-term poor GSR after knee arthroscopy can only be identified after surgery. Hence the model cannot be used to predict preoperatively which patients might benefit from the surgery. Nevertheless, it would be of major interest to study whether modifications in postoperative therapy in patients with poor GSR four days after surgery, can change the one-year outcome.

The present study has a number of limitations. The most important limitation is that we were not able to determine if the CPSP was a newly developed postoperative problem, or rather a continuation of pre-existing preoperative pain. This might result in an overestimation of the incidence of CPSP after arthroscopic knee surgery. Table 3 shows that the prevalence of CPSP in patients without preoperative pain was 6.9%. In these patients it is fairly certain that the newly acquired pain is CPSP and thus a complication of the procedure. Furthermore, we have demonstrated that 16.4% of the patients reports worse pain after one year than before the procedure. In patients with moderate to severe preoperative pain, the prevalence of CPSP was 42.7%. One could argue that most of these patients have benefitted of the arthroscopic procedure, because fewer patients are in moderate to severe pain after one year. However, since the natural cause of the pain without arthroscopic knee surgery is unknown, our study is not able to either support or reject that theory either. Future studies should therefore focus on trying to establish whether CPSP is indeed newly developed pain. The second limitation of the present study is the fact that the performed arthroscopies were quite heterogeneous (i.e. lavage and debridement, partial meniscectomy, microfracture

chondral defect). Variable procedures might result in small but significant changes in predicting CPSP and poor GSR, and this can lead to instabilities in the logistic regression model. However, we accepted this variability, because it reflects clinical reality much better than focusing on a specific group of arthroscopic treatments (e.g. meniscal tear). A third limitation of the present study was the fact that certain parameters were acquired by retrospective systematic chart review (i.e. performed arthroscopic procedure, indication for the surgery). This was necessary because the present study is based on a subgroup analysis of a previously performed study.⁷ For this reason we are not able to clarify the discrepancy between the prevalence of pain as the indication for the procedure (94.2%) and preoperative pain as measured by our questionnaire (71.2%). A possible explanation might be that orthopedic surgeons are more likely to look at a composite endpoint (e.g. consisting of pain, annoyance, bad feeling, functional complaints, etc.) instead of standardized pain questionnaires. A second possible explanation for the discrepancy could be the natural course of the pain. Patients may experience serious pain when visiting the orthopedic outpatient clinic, but the pain could have diminished by the time the surgery is performed, usually several weeks later. This would require a re-evaluation of the pain complaints immediately before performing the surgery.

In conclusion, our study demonstrates that a substantial amount of patients experienced CPSP after outpatient knee arthroscopy. Patients with preoperative pain and patients with preoperative analgesic use were at risk for experiencing CPSP. The prevalence of poor GSR one year after outpatient knee arthroscopy was 50%. A poor GSR four days after surgery and poor quality of life four days after surgery were strong predictors for poor GSR one year after surgery. Even though increasing severity of osteoarthritis according to the Outerbridge Classification was not a significant predictor for either CPSP or poor GSR one year after surgery, we did demonstrate a trend towards a bad outcome.

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Chapter 4

Severity of preoperative pain is associated with the amount of postoperative hospital-based health care costs during the first year after outpatient surgery

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Submitted

Abstract

Objectives

The aim of the study is to determine whether there is an association between the severity of preoperative pain and the amount of postoperative hospital-based health care costs during the first year after outpatient surgery. Identifying patients at risk for high postoperative health care costs during the preoperative phase might create possibilities for developing cost-effective interventions.

Methods

A prospective longitudinal cohort study was performed. The amount of postoperative hospital-based health care costs was gathered from our data management system. Patient characteristics and pain scores were measured by three questionnaires (1 week preoperatively, 4 days postoperatively and 1 year postoperatively). Multiple linear regression analysis was used to test the association between preoperative pain severity and postoperative hospital-based health care costs.

Results

1353 patients were included. The average amount of postoperative hospital-based health care costs was €1.520 (CI €1.406-€1.633). Increasing preoperative pain severity was associated with higher postoperative hospital-based health care costs ($p < 0,001$), especially after orthopaedic and urologic surgery. Patients with moderate to severe preoperative pain (Numeric Rating Scale (NRS) > 3) visited their general practitioner, medical specialist or other health care professional significantly more often during the first postoperative year. These patients were also more often absent from paid work.

Discussion

Preoperative pain severity is positively associated with postoperative hospital-based health care costs during the first year after outpatient surgery. Future studies have to be performed to determine whether preoperative interventions are able to reduce postoperative health care expenditures in patients with preoperative pain.

Introduction

Pain in general is an important health problem in the developed world, which is associated with increased consumption of health care resources, absenteeism from paid work and a substantial economic burden.¹⁻⁵ Health care costs associated with chronic pain after surgery have been less extensively studied, even though previous studies have demonstrated that 10-60% of all surgical patients suffer from chronic postsurgical pain (CPSP).⁶⁻⁸ A small study reports that patients with severe neuropathic CPSP or post-trauma pain visit physicians more frequently and use more prescribed medication than patients with less severe neuropathic CPSP or post-trauma pain.⁹ Another small study reports that CPSP after kidney transplantation is associated with increased health care utilization.¹⁰ Even though these studies report an association between CPSP and health care utilization, they do not actually demonstrate an association between CPSP and increased health care costs.

We do know that preoperative pain is very strongly associated with the severity of CPSP.¹¹⁻¹⁴ The general prevalence of preoperative pain is approximately 40%, but varies widely between surgical specialties; from 9% for ophthalmologic surgery to 71% for orthopaedic surgery.¹¹ A causal relationship between the severity of preoperative pain and CPSP, through neuroplastic changes, is likely.⁶ It is therefore thought that treating preoperative pain might lead to a decrease in the prevalence and severity of CPSP, and might thus lead to decreased postoperative health care utilization. There is some evidence suggesting that postoperative health care consumption could be reduced by preoperative neuroscience education in patients with preoperative pain.¹⁵ However, no literature is available that demonstrates a clear relationship between the severity of preoperative pain and postoperative health care consumption.

The primary aim of this study is to determine the amount of hospital-based health care costs during the first postoperative year after outpatient surgery and to determine whether there is an association between the severity of preoperative pain and the postoperative hospital-based health care costs. This study will be the first to explore this association. The first secondary aim is a subgroup analysis of this association between the severity of preoperative pain and the postoperative hospital-based health care costs per surgical specialty. Another secondary aim is the determination of other health care costs (e.g. primary care costs, paramedical costs) and indirect costs based on the loss of productivity for both patients with and without preoperative pain.

Materials and methods

Subjects

This study was designed as a prospective longitudinal cohort study. It was approved by the Ethics Committee of the Maastricht University Medical Center+ (MUMC+), and all patients gave informed consent. All adult patients who were planned for elective outpatient surgery were eligible to participate, except patients with visual impairment, inability to express themselves or insufficient understanding of the Dutch language were excluded.

Outcome measures

The primary outcome measure was the amount of hospital-based health care costs during the first year after outpatient surgery and the relationship between the costs and the severity of preoperative pain. The first secondary outcome measure was the relationship between the costs and the severity of preoperative pain per surgical specialty. The other secondary outcome measures were the number of visits to a general practitioner, medical specialist, emergency department or other health care professional and the costs associated with these visits, as well as the number of absent days from paid work, school and regular activities, and the indirect costs associated by absenteeism from paid work (i.e. loss of productivity).

Study design

A large prospective cohort study was performed. The aim of the study was to identify the prevalence and risk factors of preoperative, acute postoperative and chronic postoperative pain after outpatient surgery, as well as the costs associated with these procedures and the severity of pain. The data regarding prevalence and risk factors for acute and chronic postsurgical pain have been published in another paper.¹¹

An elaborate description of the study design is presented elsewhere.¹¹ Patients planned for outpatient surgery were asked to participate when presenting at the outpatient clinic for preoperative assessment at the Maastricht University Medical Center+. Participating patients received three questionnaires. The first questionnaire (Q1) was to be completed one week before the surgery, the second questionnaire (Q2) on the fourth postoperative day and the third questionnaire (Q3) one year after the surgery. If no contraindications were present, patients received a standardized prescription for postoperative analgesics (acetaminophen 1000 mg 4 times a day, with an upgrade to acetaminophen/tramadol 650/75 mg 4 times a day).

Q1 was the baseline questionnaire and contained questions about demographic characteristics (e.g. age, gender, educational level, and work status), average and

present pain intensity, the influence of pain on daily activities, analgesic use and the effect of analgesic use on pain severity, the number of visits to a healthcare professional during the past twelve months (i.e. general practitioner, medical specialist, emergency department, or other medical professional), as well as the number of days of absenteeism from work, school or other regular activities during the past twelve months. Q1 also contained parts of four validated questionnaires to evaluate psychological characteristics (i.e. Pain Catastrophizing Scale, Life Optimism Trait, Surgical Fear Questionnaire and EuroQol-5D).¹⁶⁻¹⁹

Q2 and Q3 were two similar questionnaires with questions about pain intensity, the influence of pain on daily activities, and analgesic use. Patients were asked about the number of postoperative visits to a medical professional because of pain, as well as the number of absent days from work, school or other regular activities since the surgical procedure. These questionnaires also contained the EuroQol-5D and the Global Surgical Recovery Index.^{19, 20}

Data about hospital-based health care costs (i.e. the primary outcome) were collected from the patient data management system of the MUMC+. We collected data about the health care use for each patient and calculated the associated costs, by using the standardized prices charged by the hospital in 2009. Data collection started the moment the patient left the hospital after the index surgery, until exactly one year after the surgery. The index surgery and the day admission were not included, because these were assumed to be the same for all patients. All hospital-based costs were included (e.g. visits to outpatient clinics, admissions, imaging techniques, etc.), with the exception of laboratory tests and histologic examinations.

Data about the number of visits to health care professionals and associated costs, as well as indirect costs (i.e. the secondary outcomes) were collected via the study questionnaires. Patients reported the number of visits with questions about pain to a general practitioner, medical specialist in any hospital, emergency department of any hospital, or other medical professional (e.g. physical therapists, chiropractor, etc.) since the surgery. Patients also reported the number of days they were absent from regular work activities, school or other social activities. Costs for these secondary outcomes were calculated by using Dutch standardized prices for 2009.²¹

Statistical analysis

Patients who returned Q1 were included in the analyses of the primary outcome parameter. For the secondary outcome parameters, only patients who returned both Q1 and Q3 were included, because these outcomes were reported by the patients in Q3. In accordance with previous publications, an NRS >3 was defined as moderate to severe pain.^{11, 22, 23} Patient characteristics were evaluated by using descriptive statistics. Differences in patient characteristics between patients with and without preoperative pain were evaluated by using the Mann-Whitney U test and the Kruskal-Wallis test for

continuous variables that were not normally distributed, and the Chi-square test for categorical variables.

Before performing the analyses for the primary and secondary outcomes, missing data were imputed using multiple imputation. The number of imputations was set to 5, and we used predictive mean matching to draw values. This method ensures no values beyond the range of observed values can be imputed, and is robust to non-normal distribution of variables. The results were pooled using Rubin's Rules if possible, with the exception of *p*-values. These are reported as a range because no universally valid method exists to pool *p*-values after multiple imputation. If no range is reported, all *p*-values were the same in the five datasets.

In order to analyse the association between the severity of preoperative pain and postoperative hospital-based health care costs, a multiple linear regression analysis was performed. Gender, age and severity of preoperative pain were included in the multiple linear regression model. Other preoperative variables were one by one included into the model. If, after inclusion of a variable, the regression coefficient of preoperative pain changed more than 10%, the variable was considered to be a confounder and remained in the model. Preoperative variables that we tested were ASA physical status, educational level, work status, and psychological variables (i.e. optimism, pain catastrophizing and surgical fear).

For the first secondary outcome, subgroup multiple linear regression analyses were performed for each surgical specialty. For the other secondary outcomes descriptive statistics were used. In order to differentiate between patients with and without moderate to severe preoperative pain, the Mann-Whitney U test and the Kruskal-Wallis test for nonparametric data were used.

A *p*-value of <0.05 was considered to be statistically significant. All analyses were performed using SPSS version 24.0 (SPSS Inc, Chicago IL).

Results

Flowchart and patient characteristics

Between November 2008 and April 2010, 2500 patients were invited to participate. The flowchart of included and excluded patients is demonstrated elsewhere.¹¹ Of all invited patients 1396 patients (56%) returned Q1. Of these patients, 1353 patients did not meet any exclusion criteria and for these patients postoperative hospital based health care costs were calculated. These patients were used for the analyses of the primary outcome. A total of 912 patients (67,4%) returned Q3 and were used for the analysis of the secondary outcomes.

The patient characteristics are shown in Table 1. Because the patient characteristics were calculated on the raw data (before the multiple imputation), the numbers do not

always add up to a total of 1353 patients. A total of 508 patients (38,3%) experienced moderate to severe preoperative pain during the week before the surgery, and 818 patients (61,7%) did not. A small majority was female. Most patients were ASA physical status class I or II. Most procedures were performed by the following specialties: general surgery (395 patients, 29,2%), orthopaedic surgery (289, 21,4%) and ear-nose-throat surgery (204, 15,1%). A list of the included procedures per specialty has been published elsewhere.¹¹

Table 1: Patient characteristics for patients with and without moderate to severe preoperative pain.

	All patients (<i>n</i> = 1353)	NRS 0-3 (<i>n</i> = 818)	NRS 4-10 (<i>n</i> = 508)	<i>p</i> -value
Age (years, SD)	51,3 (14,9)	52,4 (14,9)	49,5 (14,6)	< 0,001
Gender (<i>n</i>, %)				0,06
Male	589 (43,5)	378 (46,2)	208 (40,9)	
Female	764 (56,5)	440 (53,8)	300 (59,1)	
Surgical specialty (<i>n</i>, %)				< 0,001
General surgery	395 (29,2)	227 (27,8)	164 (32,3)	
Orthopaedic surgery	289 (21,4)	79 (9,7)	207 (40,7)	
ENT-surgery	204 (15,1)	169 (20,7)	31 (6,1)	
Plastic surgery	142 (10,5)	86 (10,5)	53 (10,4)	
Gynaecology	112 (8,3)	83 (10,1)	26 (5,1)	
Ophthalmology	96 (7,1)	83 (10,1)	8 (1,6)	
Urology	76 (5,6)	64 (7,8)	11 (2,2)	
Dental surgery	29 (2,1)	20 (2,4)	6 (1,2)	
ASA physical status (<i>n</i>, %)				0,26
I	707 (52,3)	430 (52,6)	267 (52,6)	
II	567 (41,9)	333 (40,7)	220 (43,3)	
III	55 (4,1)	38 (4,6)	15 (3,0)	
Educational level (<i>n</i>, %)				< 0,001
Elementary school	81 (6,0)	34 (4,2)	43 (8,5)	
Intermediate	886 (65,5)	513 (62,7)	358 (70,5)	
Higher degree, university	262 (19,4)	201 (24,6)	56 (11,0)	
Work status (<i>n</i>, %)				< 0,001
Paid work	633 (46,8)	392 (47,9)	231 (45,5)	
Unpaid work	194 (14,3)	109 (13,3)	76 (15,0)	
No work	160 (11,8)	76 (9,3)	83 (16,3)	
Retired	255 (18,8)	177 (21,6)	72 (14,2)	
Expected postoperative pain on the fourth postoperative day (NRS, SD)	3,9 (2,4)	3,2 (2,2)	5,1 (2,4)	< 0,001
N of patients that visited at least once (%)				
General practitioner	64,4%	53,5%	81,8%	< 0,001
Medical specialist	59,8%	43,4%	84,9%	< 0,001
Emergency department	19,0%	14,5%	25,2%	< 0,001
Other health care professionals	28,5%	24,2%	35,2%	< 0,001
Missed activities during the last year (median, IQR)	29,7%	20,2%	44,3%	< 0,001

p-value demonstrates the significance level of the difference of the preoperative variable between patients with and with moderate to severe preoperative pain.

Hospital-based health care costs

For the analyses of this outcome 1353 patients were included. The average amount of hospital-based health care costs during the first postoperative year after outpatient surgery was €1.520 (Confidence Interval (CI) €1.406-€1.633), with a minimum of €39 and a maximum of €26.920. The amount of hospital-based health care costs was statistically significantly different between the surgical specialties ($p < 0,001$). Table 2 demonstrates the average amount of health care costs per surgical specialty for all patients and for patients with and without moderate to severe preoperative pain. Most of the costs were created by patients after ENT-surgery (€1.768, CI €1.337-€2.199), dental surgery (€1.697, CI €170-€3.224), and orthopaedic surgery (€1.589, CI €1.372-€1.805).

Table 2: Average hospital-based health care costs in euros per surgical specialty during the first postoperative year for patient with and without moderate to severe preoperative pain. (NRS = numeric rating scale, CI = confidence interval).

Surgical specialty	Average hospital based health care costs in euros			<i>p</i> -value
	Mean (95% CI)	NRS 0-3 (<i>n</i> = 832)	NRS 4-10 (<i>n</i> = 521)	
All specialties (<i>n</i> = 1353)	€1.520 (1.406-1.633)	€1.431 (1.291-1.570)	€1.662 (1.468-1.856)	0,001
General surgery (<i>n</i> = 394)	€1.551 (1.346-1.756)	€1.651 (1.376-1.927)	€1.412 (1.108-1.717)	0,42-0,56
Orthopaedic surgery (<i>n</i> = 289)	€1.589 (1.372-1.805)	€1.157 (944-1.370)	€1.751 (1.467-2.035)	0,012
ENT-surgery (<i>n</i> = 204)	€1.768 (1.337-2.199)	€1.584 (1.177-1.991)	€2.756 (1.113-4.400)	< 0,01
Plastic surgery (<i>n</i> = 142)	€1.547 (1.341-1.753)	€1.530 (1.275-1.785)	€1.574 (1.225-1.924)	0,84-0,96
Gynaecology (<i>n</i> = 112)	€1.252 (966-1.538)	€1.202 (860-1.543)	€1.417 (917-1.916)	0,05-0,06
Ophthalmology (<i>n</i> = 96)	€1.228 (905-1.551)	€1.264 (907-1.621)	€947 (381-1.514)	0,12-0,40
Urology (<i>n</i> = 76)	€1.005 (771-1.238)	€873 (717-1.029)	€1.782 (509-3.054)	0,033
Dental surgery (<i>n</i> = 29)	€1.697 (170-3.224)	€1.729 (0-3.666)	€1.598 (0-3.543)	0,48-0,86

p-value demonstrates significance between patients with and without moderate to severe preoperative pain.

The average amount of postoperative hospital-based health care costs was €1.431 euros (CI €1.291-€1.570) for patients with a preoperative NRS of 0-3 and €1.662 (CI €1.468-€1.856) for patients with a preoperative NRS of 4-10. This difference was statistically significant ($p < 0,001$). Linear regression analysis demonstrated that age and work status were confounders, but even with these variables in the model, preoperative pain remained statistically significantly associated with the amount of postoperative hospital-based health care costs. Other preoperative variables (i.e. ASA physical status, educational level, life optimism trait, pain catastrophizing and surgical fear) were not statistically significant confounders.

In patients who underwent orthopaedic surgery, urologic surgery or ENT-surgery the amount of postoperative hospital-based health care costs was statistically significantly different between patients with and without moderate to severe preoperative pain. For these specialties multiple linear regression analyses were performed. In orthopaedic surgery, life optimism trait was a confounder, but even with this confounder in the model, preoperative pain remained associated with postoperative hospital-based health

care costs. In patients after urologic surgery no confounders were identified. In patients who underwent ENT-surgery, the severity of preoperative pain was no longer significantly associated with the amount of postoperative hospital-based health care costs after addition of the patient's age into the model.

Other health care costs

Table 3a demonstrates the average amount of visits to health care providers for patients with and without moderate to severe preoperative pain. Table 3b demonstrates the costs associated with these visits. Most patients did not visit their general practitioner (840 patients, 62,1%), a medical specialist (895 patients, 66,1%), an emergency department (1193, 88,2%) or other health care professional (1081, 79,9%) with questions about pain during the first postoperative year. Patients with moderate to severe preoperative pain visited their general practitioner ($p < 0,001$), medical specialist ($p < 0,001$), or other health care professional ($p < 0,001$), significantly more often than patients without moderate to severe preoperative pain. This was also associated with increased costs ($p < 0,001$). The number of visits to an emergency department did not differ between the two groups

Indirect costs

Table 3a shows the amount of absent days from paid and unpaid work for the two groups. Table 3b shows the indirect costs associated with absenteeism. At the time of the surgical procedure 437 patients (47,9%) had a paid job. The median amount of absent days was 0 (IQ-range 0-14). Patients with moderate to severe preoperative pain were significantly more often absent from work than patients without moderate to severe preoperative pain ($p < 0,01$). The average costs associated with absenteeism from a paid job were €4.789. These costs were significantly higher for patients with moderate to severe preoperative pain (€6.643, 95% CI €4.477-€8.809) compared to patients without preoperative pain (€3.646, 95% CI €2.497-4.794, $p < 0,01$). Patients with unpaid work (e.g. students, volunteers, etc) at the time of the surgical procedure were not significantly more often absent during the first postoperative year.

Table 3a: Secondary outcome parameters: percentage of patients that visited health care professional at least once, or were absent from work and regular activities at least once during the first postoperative year. Table also shows the median amount of visits or absent days for patients with at least one visit or one absent day.

	NRS 0-3 (n=564)	NRS 4-10 (n=348)	P-value
Visits to health care professionals (% that visited at least once, median <i>n</i> of visits for these patients)			
General practitioner	20,2% (2)	36,2% (2)	< 0,001
Medical specialist	17,2% (2)	39,1% (3)	< 0,001
Emergency department	6,9% (1)	10,1% (1)	0,05-0,19
Other health care professionals	9,9% (13)	25,0% (15)	< 0,001
Absenteeism from work (% that was absent at least one day, median <i>n</i> of days for these patients)			
Paid work	38,1% (14)	50,9% (25)	<0,01
Unpaid work	2,3% (2)	9,7% (76)	0,01-0,36
Missed activities during the first postoperative year (% that missed at least one activity, median <i>n</i> missed activities for these patients)			
	13,1% (14)	54,1% (41)	< 0,001

Table 3b: Secondary outcome parameters: average costs in euros of visits to health care professionals and absenteeism from paid work during the first postoperative year. (NRS = numeric rating scale, CI = confidence interval)

	NRS 0-3 (n=564)	NRS 4-10 (n=348)	P-value
Costs of visits during the first postoperative year (costs, 95% CI)			
General practitioner	€16 (19-27)	€33 (25-40)	< 0,001
Medical specialist	€67 (46-87)	€227 (164-289)	< 0,001
Emergency department	€13 (9-17)	€19 (12-27)	0,05-0,19
Other health care professionals	€80 (46-113)	€255 (172-338)	< 0,001
Costs of absenteeism from paid work (costs, 95% CI)			
	€3.646 (2.497-4.794)	€6.643 (4.477-8.809)	<0,01

Discussion

Our study demonstrates for the first time, that the severity of preoperative pain is associated with an increased amount of hospital-based health care costs during the first year after outpatient surgery. As it is reported that the severity of preoperative pain is one of the most important risk factors for the development of chronic postsurgical pain (CPSP),¹¹⁻¹⁴ it is far from unlikely to assume that patients with CPSP use more health care resources and thus generate more health care costs than patients without CPSP. A study by Parsons et al. demonstrated that patients with more severe post-trauma or post-surgical neuropathic pain create higher direct and indirect postoperative expenditures.⁹ The average annual calculated costs in this study were much higher than the average costs in our study. This difference can be explained by differences in the

structure of health care systems (i.e. The Netherlands versus the United States) and by underreporting of costs in our study. For example, costs generated by prescription of medications were not measured in our study, but a significant percentage of the total costs in the study by Parsons et al was due to prescription medication.⁹

From our results we conclude that the association between the severity of preoperative pain and the amount of hospital-based health care costs was most clear for patients after orthopaedic and urologic surgery. Previous studies have shown that orthopaedic surgery is a risk factor for the development of acute and chronic postoperative pain.^{11, 24} The prevalence of moderate to severe preoperative pain was much higher in this group of orthopaedic patients as compared to the total population (72,7% versus 38,3%). In many of these patients the severity of preoperative pain is the reason to perform the surgical procedure. We hypothesize that in many of these orthopaedic patients the pre-existing pain continues into the postoperative phase, due to failure of the surgical procedure to relieve this pain (e.g. knee arthroscopy). In addition to this, many of these patients undergo an expensive second surgical procedure during the first postoperative year (e.g. total knee replacement). This might account for the high amount of health care costs after orthopaedic surgery. Future studies are necessary to confirm these results and will hopefully be able to identify other risk factors for high hospital-based health care costs after orthopaedic surgery.

Future studies are needed to confirm preoperative pain as a risk factor for increased postoperative health care costs, as well as to identify other risk factors. The next step will be to determine if it is possible to reduce these costs by optimizing preoperative risk factors. Optimizing treatment of preoperative pain, might lead to a reduction in postoperative health care costs, as well as other negative outcomes (e.g. the prevalence CPSP). This might be achieved by conventional analgesics, but also via treatment of psychological risk factors and by improving preoperative patient education. In this respect it is interesting to note that preoperative neuroscience education by a physical therapist, in patients with preoperative pain due to radiculopathy, resulted in less health care expenditure during the first year after lumbar surgery as compared to routine preoperative care.¹⁵ A study to evaluate the effect of mindfulness training prior to hip or knee arthroplasty on physical function and postoperative health care consumption is being performed.²⁵ No studies are available that test the association between the optimization of conventional analgesics during the preoperative period and postoperative health care expenditures.

Our study has several limitations. First of all, the calculated amount of hospital-based health costs was based on the procedures and visits performed in our own hospital. It is unknown if patients visited other hospitals during the first year after the surgery. Because our hospital is a large university hospital, where patients from a large area are treated, it is possible that patients visited smaller local hospitals for other medical problems. This might lead to underreporting of the actual use of health care facilities and thus to lower calculated overall hospital-based health care costs. In case of

future studies, data should be collected via the patients insurance companies in order to overcome this limitation. A second limitation is the self-reporting of the number of visits to their general practitioner, medical specialist, emergency department or other health care professional during the last year. Previous studies have shown that the validity of self-reported visits to outpatient clinics is low.²⁶⁻²⁸ Whether the accuracy of the self-reported number of visits decreases with time is controversial.^{26, 27} Even though self-reported number of visits might seem more accurate with shorter recall periods, this is probably not due to more accurate reporting, but rather related to relatively more over-reporting and less under-reporting.²⁷

In conclusion, our study demonstrates that the severity of preoperative pain is statistically significantly associated with the amount of hospital-based health care costs during the first year after outpatient surgery. This association is strongest for patients after orthopaedic or urologic surgery. Patients with moderate to severe preoperative pain visited their general practitioner, medical specialist or other health care professional more often, than patients with mild to no pain. This study demonstrates that it is of utmost importance to treat preoperative pain. Future studies will have to be performed in order to determine which preoperative interventions (e.g. optimizing analgesic therapy, psychological interventions, etc). will be able to reduce postoperative health care expenditures in patients with preoperative pain.

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The background of the page features a stylized, light gray illustration of a DNA double helix structure. Overlaid on this are several faint, overlapping outlines of human faces, suggesting a focus on genetics and human health. The overall design is clean and modern, with a light gray color scheme.

Chapter 5

Genetic polymorphisms and their association with the prevalence and severity of chronic postsurgical pain - A systematic review

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Br J Anaesth 2016 Dec;117(6):708-719

Abstract

Background

Although several demographic, clinical and psychological risk factors for chronic postsurgical pain (CPSP) have been identified, genetic variants including single nucleotide polymorphisms have also become of interest as potential risk factors for the development of CPSP. The aim of this review is to summarize the current evidence on genetic polymorphisms associated with the prevalence and severity of CPSP in adult patients.

Methods

A systematic review of the literature was performed, and additional literature was obtained by reference tracking. The primary outcome was CPSP, defined as pain at least two months after the surgery. Studies performed exclusively in animals were excluded.

Results

Out of the 1001 identified studies, 14 studies were selected for inclusion. These studies described 5269 participants in 17 cohorts. A meta-analysis was not possible because of heterogeneity of data and data analysis. Associations with the prevalence or severity of CPSP were reported for genetic variants in the *COMT* gene, *OPRM1*, potassium channel genes, *GCH1*, *CACNG*, *CHRNA6*, *P2X7R*, cytokine associated genes, *HLA*, *DRD2*, and *ATXN1*.

Discussion

Research on the topic of genetic variants associated with CPSP is still in its initial phase. Hypothesis-free, genome-wide association studies on large cohorts are needed in this field. In addition, future studies may also integrate genetic risk factors and patient characteristics, clinical and psychological predictors for CPSP.

Introduction

Chronic postsurgical pain (CPSP) is a common problem that can occur after any type of surgery.^{1, 2} The prevalence of moderate to severe CPSP varies between 10 and 60%.^{1, 3, 4} Chronic postsurgical pain not only has a negative influence on the quality of life of the patient, but it also has major socioeconomic consequences.^{5, 6} Several studies have been performed to determine the risk factors for the development of CPSP, and a number of patient characteristic, clinical and psychological risk factors have already been identified.^{1, 2, 7-9} However, these studies have also demonstrated that a substantial amount of the variance in CPSP cannot be explained by these predictors.^{1, 2, 9}

Recently, polymorphisms of several genes have also become of interest as potential risk factors for the prevalence and severity of CPSP. It is suspected that some genes predispose to CPSP whereas others are associated with a protective effect. Data from twin studies and human pedigrees estimate that the heritability of chronic pain ranges from 30 to 70%.¹⁰ Research has focused on variants in genes that encode for proteins involved in nerve conduction and transmission, opioid receptor signalling and inflammatory processes.¹¹⁻¹⁵

The lack of ability of patient characteristic, clinical and psychological factors to explain all the variance in the prevalence and severity of CPSP, coupled with the interest in genetic polymorphisms as predictors of other chronic pain states, leads to two questions. Are genetic polymorphisms associated with the prevalence and severity of CPSP? If this is the true, does adding these polymorphisms to the existing prediction models improve their accuracy?

Therefore, the objective of this systematic review is to summarize the current evidence with respect to genetic polymorphisms as predictors for the prevalence (i.e. the number of patients in the study population that develop CPSP) and severity of CPSP after any type of surgery in adult patients. Finding consistent and reliable genetic predictors might improve the understanding of the molecular mechanisms underlying the development of CPSP and reveal therapeutic targets, and might also improve preoperative prediction models and thus offer surgeons and anaesthetists the possibility to identify patients at risk for developing CPSP.

Methods

Search strategy

This review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. A systematic literature review was conducted, using the databases of PubMed, Embase and PsychINFO. The final search

strategy was as follows: ("Pain, Postoperative"[Mesh] OR ("persistent pain" AND surgery) OR ("chronic postsurgical pain") OR ("chronic post surgical pain") OR cpSP OR ("persistent postoperative pain") OR ("chronic postoperative pain") OR ("chronic pain" AND surgery)) AND (genetic* OR gene OR genes OR snp OR snps OR polymorphism*) NOT "pain treatment" NOT "pain therapies" NOT "pain management" NOT "pain control". Electronic searches were limited to the availability of abstracts, and to studies published in the English, French, German or Dutch language. Additional searches were carried out by reference tracking and expert consultation.

Study selection and inclusion criteria

Studies eligible for inclusion were observational cohort studies, case-control studies and randomized controlled trials, performed in adult patients undergoing any type of surgical procedure. Conference abstracts and case reports were excluded, as were studies performed exclusively in animals. Studies were included if the study population had already undergone surgery and the follow-up time was at least two months. This time frame was chosen in line with the definition of CPSP.¹⁶ Pain had to be the primary outcome parameter, but the method by which pain was measured was not a specific inclusion or exclusion criterion. All included studies had to measure genetic polymorphisms directly. Indirect measurement, via the analysis of gene products, resulted in exclusion of the study. The abstracts retrieved from the search were all read and assessed independently by two authors (D.M.N.H. and R.R.I.v.R.). If an abstract fulfilled all inclusion criteria, or if any aspect of the abstract was unclear, the full text was obtained and assessed by the two reviewers (D.M.N.H. and R.R.I.v.R.). Differences in opinion were resolved through structured discussion.

Data extraction and data analysis

The following information was extracted from each study: reporting author, publication year, study design, number of participants, ethnicity of participants, type of surgery, primary and secondary outcome measures, follow-up time, polymorphisms studied, and type of statistical analyses used. The quality of the studies was assessed using an eight-item checklist (scores 0-8), based on the Critical Appraisal Checklist for Cohort/Case Control of the Joanna Briggs institute,¹⁷ and the checklist for measuring study quality developed by Downs and Black.¹⁸ The quality of each study was assessed independently by two authors (D.M.N.H. and R.R.I.v.R.) This eight-item checklist was used in previous research, where substantial agreement between raters was demonstrated.⁸ An explanation of this quality checklist is available elsewhere.⁸ We considered performing a meta-analysis for polymorphisms that were reported by more than one study. Unfortunately, an accurate and reliable meta-analysis could not be performed because only a few polymorphisms were reported by more than one study. Furthermore, study

design (e.g. included surgical procedures, definition of CPSP, follow-up time), statistical analysis, and the manner of reporting the results (e.g. odds ratios (ORs) versus only *p*-values) varied too much between authors.

Results

The systematic search and reference tracking resulted in 1002 publications (Figure 1). Of these initial 1002 articles, 49 duplicates were removed and 920 articles were excluded after screening of the abstracts. Most of these 920 articles were either conference abstracts or animal studies. Hence, a total of 33 full-text articles were screened, of which 18 were excluded (in four articles pain was not an outcome parameter, 12 articles did not measure CPSP, two articles did not include genetic analyses, and one article included patients younger than 18 years old). A total of 14 articles, including 5269 participants in 17 cohorts, were finally used for the analyses.

Figure 1: Flowchart of the process of article selection.

The characteristics of the patient cohorts are summarized in Table 1. The most common surgical procedures were breast surgery and inguinal hernia repair. In all studies CPSP was measured at three months or more after the surgical procedure. Seven of the cohorts studied a Caucasian population, three cohorts studied an Israeli population (of Ashkenazi and non-Ashkenazi descent), one cohort studied a Chinese population and the remaining studies included participants of diverse ethnicities or did not report the ethnicity of the participants. The sample size of the included cohorts varied between 42

and 1005 participants. The relatively low sample size of many studies, combined with the number of polymorphisms investigated, resulted in low statistical power in most studies. Moreover, the statistical analyses used in the studies differed considerably; one study used multiple testing corrections by the Bonferroni method,¹¹ two other studies chose not to correct for multiple testing because they considered their investigation to be of exploratory nature, and the remaining studies did not report whether they performed multiple testing correction.^{13, 15} The quality of the studies varied between four and seven points on the eight-item quality checklist. Most points were lost because of the quality of the statistical analyses (i.e. lack of statistical power), and because of data dredging (i.e. retrospective studies).

Table 2 lists the results of each cohort, including the association between the studied polymorphisms and the prevalence or severity of CPSP. Only polymorphisms that were reported as significantly associated with CPSP in at least one study are mentioned in Table 2. A complete table of all polymorphisms studied is available as additional content (supplemented data). Only statistically significant results will be mentioned in the text. Numerical outcomes, effect sizes, confidence intervals (CI's) and information on multiple testing correction are listed in the text if they were mentioned in the original studies. Unfortunately, many studies did not provide numerical outcomes, but stated only whether an association between the polymorphism and prevalence or severity of CPSP was found or not.

COMT

The *COMT* gene encodes for the catechol-o-methyl transferase enzyme, which is involved in the inactivation of catecholamines.^{19, 20} Polymorphisms in the *COMT* gene in relation to CPSP, have been studied in six investigations.^{11, 21-25} Two studies reported a significant association between polymorphisms in the *COMT* gene and CPSP.^{21, 25} The minor allele of rs4818 ($p = 0.031$) and rs4633 ($p = 0.01$) and the major alleles of rs6269 ($p = 0.02$) and rs4680 ($p = 0.018$) were associated with an increased severity of CPSP in a Caucasian population 12 months after lumbar discectomy.²¹ This difference was reported as statistically significant only for pain measured by the 6-point Likert scale used in the Oswestry Disability Index, and not when measured by the Visual Analogue Scale (VAS). The high pain sensitivity haplotype (rs6269A, rs4633C, rs4818C, rs4680G) as described by Diatchenko and colleagues²⁶ was associated with lower VAS scores 12 months after lumbar discectomy (OR 1.45, $p = 0.046$).²¹ This was in contrast to previous findings in experimental pain studies, but the authors did not offer an explanation for these findings.²¹ Furthermore, an association was reported between COMT diplotype (rs4633 and rs4818), pain catastrophizing scale and the severity of CPSP, measured at three, four and five months after arthroscopic shoulder surgery.²⁵ Patients with low *COMT* activity (average and high pain sensitivity diplotype) and high pain catastrophizing scale scores experienced higher pain ratings than patients with other combinations.

Table 1: Characteristics of the included cohorts

Cohort	Study design	N	Ethnicity	Type of surgery	Primary outcome	Study quality	Confounders	Time since surgery
Montes et al., 2015 ¹¹	Prospective cohort study	1005	Spanish	Hernia repair, hysterectomy (vaginal/abdominal), thoracotomy	Prevalence of CPSP (NRS > 3)	6	None	4 months after surgery
Wieskopf et al., 2015 ¹²	Prospective cohort study	429	Danish and German Caucasian	Open or laparoscopic elective groin hernia repair	Prevalence of CPSP (yes or no)	6	Age, type of surgery, activity assessment scale	6 months after surgery
Langford et al., 2015 ¹³	Prospective cohort study	398	Diverse	Breast cancer surgery on one breast	Prevalence of CPSP (NRS)	7	Ethnicity, preoperative pain	6 months after surgery
Stephens et al., 2014 ¹⁵	Prospective cohort study	398	Diverse	Breast cancer surgery on one breast	Prevalence of CPSP (NRS)	7	Ethnicity, preoperative pain, postoperative pain	6 months after surgery
Rut et al., 2014 ²¹	Prospective cohort study	176	Caucasian	Lumbar discectomy on one level from L3-S1	Severity of CPSP of back and leg (VAS and 6-point Likert scale in Oswestry Disability Index)	7	Age, gender	12 months after surgery
Kolesnikov et al., 2013 ²²	Prospective cohort study	102	Caucasian	Abdominal radical prostatectomy or abdominal radical hysterectomy	Prevalence and severity of CPSP (NRS)	6	Age, gender, baseline pain score	3 months after surgery
Dominguez et al., 2013 ⁴⁰	Retrospective study	189	Swedish	Inguinal hernia repair	Prevalence of CPSP (VAS)	4	None	6 months after surgery
Sorge et al., 2012 ³⁶	Retrospective study	354	Israeli	Breast surgery for tumor removal with axillary lymph node resection.	Severity of CPSP (20-point NRS)	4	None	At least 6 months after last surgical or adjuvant treatment
Hickey et al., 2011 ²³	Retrospective study	42	Unknown	Breast reconstruction following mastectomy	Prevalence of CPSP (yes or no)	5	None	Average of 25.5 months postoperative (range 3-84)
Lee et al., 2011 ²⁴	Prospective cohort study	98	Caucasian of Irish descent	M3 extraction	Prevalence of CPSP (VAS)	6	None	3 months after surgery

Cohort	Study design	N	Ethnicity	Type of surgery	Primary outcome	Study quality	Confounders	Time since surgery
Sia et al, 2010 ⁶¹	Prospective cohort study	503	Han Chinese	Elective caesarean section under spinal anesthesia	Prevalence of CPSP (yes or no)	5	None	6 months after surgery
Costigan et al, 2010 ³⁰ Cohort 1	Prospective cohort study	151	Caucasian	Surgical disectomy for intervertebral disc herniation	Severity of CPSP (mean of pain scores over one year)	4	Age, gender, worker's compensation status, delay in surgery, SF-36 General Health	Baseline, 3 months, 6 months and 12 months after surgery
Costigan et al, 2010 ³⁰ Cohort 2	Retrospective study	199	Ashkenazi and non-Ashkenazi Jews	Limb amputation	Severity of CPSP	4	Ethnicity	Between 1 and 35 years after surgery
Costigan et al, 2010 ³⁰ Cohort 3	Retrospective study	100	Unknown	Upper and lower limb amputation	Severity of CPSP (VAS)	5	Age, gender	Unknown
Costigan et al, 2010 ³⁰ Cohort 4	Retrospective study	529	Ashkenazi and non-Ashkenazi Jews	Mastectomy with axillary lymph node dissection, and lumpectomy with axillary lymph node resection.	Severity of CPSP (NRS)	5	Surgery type, age, years since operation, type of adjuvant treatment, ethnicity	At least one year after surgery
Nissenbaum et, 2010 ¹⁴	Retrospective study	549	Ashkenazi and non-Ashkenazi Jews	Mastectomy with axillary lymph node dissection, and lumpectomy with axillary lymph node resection.	Prevalence of CPSP during the last year (yes or no)	6	Ethnicity, years since operation, type of surgery	Average of 6.6 years postoperative (rang 0.5-10 years)
George et al, 2008 ⁵	Prospective cohort study	47	Diverse	Arthroscopic shoulder surgery	Severity of CPSP (NRS)	7	Age, gender, ethnicity	3-5 months after surgery

Table 2: Results of the individual studies. The table demonstrates the effect of the minor allele of the polymorphism on the prevalence and/or the severity of chronic postsurgical pain (CPSP). Genes without statistically significant associations were omitted. + = minor allele associated with more CPSP, - = minor allele associated with less CPSP, 0 = no effect was found, Yes = effect found, but directionality unknown. 0/+ = association only before multiple testing correction.

		Montes, 2015 n = 1005	Wieskopf, 2015 n = 429	Langford, 2015 n = 398	Stephens, 2014 n = 398	Rut, 2014 n = 176	Kolesnikov, 2013 n = 102	Dominguez, 2013 n = 189	Sorge, 2012 n = 354	Hickey, 2011 n = 42	Lee, 2011 n = 98	Sia, 2010 n = 503	Costigan, 2010, cohort 1 n = 151	Costigan, 2010, cohort 2 n = 199	Costigan, 2010, cohort 3 n = 100	Costigan, 2010, cohort 4 n = 529	Nissenbaum, 2010 n = 549	George, 2008 n = 47
COMT	rs4818					+					0							
	rs6269	0				-					0							
	rs4680	0				-	0		0	0								
	rs4633					+												
	Haplotype Diatchenko # Haplotype 1 #					-												Yes
OPRM1	rs1799971	0					+				0							
KCNA1	rs4766311		-															
KCND2	rs17376373		-															
	rs702414		Yes															
	rs802340		Yes															
	rs12706292		Yes															
	rs1072198		+															
KCNS1	rs734784		Yes									+	+	+	0			
	rs13043825											+	0					
KCNJ3	rs6435329		Yes															
	rs11895478		Yes															
	rs3106653		Yes															
	rs3111006		Yes															
	rs12471193		Yes															
	rs7574878		Yes															
	rs12995382		-															
	rs13398937		Yes															
	rs2591157		Yes															

		n = 1005	Montes, 2015	n = 429	Wieskopf, 2015	n = 398	Langford, 2015	n = 398	Stephens, 2014	n = 176	Rut, 2014	n = 102	Kolesnikov, 2013	n = 189	Dominguez, 2013	n = 354	Sorge, 2012	n = 42	Hickey, 2011	n = 98	Lee, 2011	n = 503	Sia, 2010	n = 151	Costigan, 2010, cohort 1	n = 199	Costigan, 2010, cohort 2	n = 100	Costigan, 2010, cohort 3	n = 529	Costigan, 2010, cohort 4	n = 549	Nissenbaum, 2010	n = 47	George, 2008	
KCNJ6	rs17641121				+																															
	rs4467223				Yes																															
	Haplotype 2 [#]				-																															
	rs860795				Yes																															
	rs857967				Yes																															
	rs858010				Yes																															
	rs858003				+																															
	rs2835914				Yes																															
KCNK3	rs858035				Yes																															
	rs2835925				+																															
	rs1662988				Yes																															
KCNK9	rs7584568				Yes																															
	rs2542424				-																															
	rs2014712				+																															
	rs2545457				+																															
GHC1	rs888349				Yes																															
	rs4411417	0/+																																		
CACNG	rs4820242																																	+		
	rs2284015																																	+		
	rs2284017																																	+		
	rs2284018																																	+		
	rs1883988																																	+		
	Haplotype 3 [#]																																	+		
CHRNA6	rs7828365		+																																	
P2X7R	rs208294																+																			
	rs208296																-																			
	rs7958311																-																			
IFNG1	rs2069727								Yes																											
	rs2069718								Yes																											

		Montes, 2015 n = 1005	Wieskopf, 2015 n = 429	Langford, 2015 n = 398	Stephens, 2014 n = 398	Rut, 2014 n = 176	Kolesnikov, 2013 n = 102	Dominguez, 2013 n = 189	Sorge, 2012 n = 354	Hickey, 2011 n = 42	Lee, 2011 n = 98	Sia, 2010 n = 503	Costigan, 2010, cohort 1 n = 151	Costigan, 2010, cohort 2 n = 199	Costigan, 2010, cohort 3 n = 100	Costigan, 2010, cohort 4 n = 529	Nissenbaum, 2010 n = 549	George, 2008 n = 47
IL1R1	rs3917332				Yes													
IL1R2	rs11674595				+													
IL4	rs2243248				Yes													
IL10	rs3024498				Yes													
	rs1878672				Yes													
	rs3024491				Yes													
	Haplotype 4 [#]				-													
IL13	rs1881457				Yes													
	rs1800925				Yes													
	rs1295686				Yes													
	rs20541				Yes													
NFKBIA	rs8904	0/+																
NFKB1	rs4648141				Yes													
HLA	DRB1*04																	+
	DQB1*03:02																	+
	Haplotype 5 [#]																	+
DRD2	rs4648317	0/+																
	rs12364283	0/+																
ATXN1	rs179997	0/+																

[#]Haplotype of Diatchenko: rs6269A, rs4633C, rs4818C, rs4680G; [#]Haplotype 1: rs4633C, rs4818C; [#]Haplotype 2: rs3111020G, rs11895478A; [#]Haplotype 3: rs4820242A, rs2284015C, rs2284015C; [#]Haplotype 4: rs3024505C, rs3024498A, rs3024496T, rs1878672C, rs1518111A, rs1518110T, rs3024491G; [#]Haplotype 5: DRB1*04, DQB1*03:02.

Opioid receptors

Three families of opioid receptors (μ , κ , and δ) have been identified and have been investigated in the context of CPSP.²⁷ The most extensively studied receptor is the μ -opioid receptor, which is encoded by the *OPRM1* gene. The importance of this receptor in mediating the actions of endogenous opioids, morphine and other morphine-like drugs has been well established.²⁸ The association between two polymorphisms of the

OPRM1 gene (rs1799971 and rs563649) and the prevalence of CPSP has been studied in three patient cohorts.^{11, 22, 24} Carriers of at least one copy of the minor allele of rs1799971 experienced increased pain scores three months after abdominal surgery as compared to patients homozygous for the major allele ($p = 0.02$), even though the prevalence of CPSP was not increased ($p = 0.22$). The other cohorts did not show an association between polymorphisms of the *OPRM1* gene and the prevalence or severity of CPSP.^{11, 24} Polymorphisms of the *OPRD1* and *OPRK1* gene were studied in only one study and no association with the prevalence of CPSP was found.¹¹

Potassium channels

Potassium channels are a vital part of the action potential and may influence pain conduction and transmission. They are tetrameric proteins, of which each subunit may harbour structural differences based on genetic variants.²⁹ Structurally different subunits, encoded by seven different genes, have been studied in relation to CPSP (*KCNA1*, *KCND2*, *KCNS1*, *KCNJ3*, *KCNJ6*, and *KCNK9*).^{13, 30} A statistically significant association was reported between the prevalence of CPSP six months after surgery for breast cancer and 31 polymorphisms located across all seven genes.¹³ However, no correction for multiple testing was performed. The minor alleles of rs4766311 ($p = 0.003$), rs17376373 ($p = 0.009$), rs12995382 ($p = 0.017$) and rs2542424 ($p = 0.023$) were associated with a lower prevalence of CPSP. For rs1072198 ($p = 0.048$), rs17641121 ($p = 0.011$), rs858003 ($p = 0.03$), rs2835925 ($p = 0.002$), rs2014712 ($p = 0.041$), and rs2545457 ($p = 0.022$) the minor allele was associated with a higher prevalence of CPSP.¹³ For the remaining polymorphisms, it was not mentioned whether the minor allele was associated with an increased or decreased prevalence of CPSP.

The association between two polymorphisms of the *KCNS1* and the severity of CPSP gene was analysed in four postsurgical patient cohorts.³⁰ The minor allele of rs13043825 was studied in two of these cohorts and was found to be associated with more severe CPSP after lumbar surgical discectomy ($p = 0.03$), but not after limb amputation. The minor allele of rs734784 was studied in all four cohorts and was associated with more severe CPSP after lumbar surgical discectomy ($p = 0.003$), and limb amputation ($p = 0.00012$ for phantom limb pain and $p = 0.0033$ for stump pain), but not after mastectomy.³⁰

GCH1

GCH1 encodes for the enzyme GTP cyclohydrolase 1, which is an important enzyme in the biosynthesis of catecholamines, serotonin and nitric oxide.³¹ Fourteen polymorphisms and two haplotypes of this gene were studied, of which only one was statistically significant before multiple testing correction.¹¹ The minor allele of rs4411417 was associated with an increased prevalence of CPSP after several surgical procedures (OR 1.27, 95% CI 1.00-1.62, $p = 0.046$). Polymorphisms in the *GCH1* gene

were also investigated in two other studies, but these studies did not find a statistically significant association with the prevalence of CPSP.^{23, 24}

CACNG2

This gene encodes for the γ -2 transmembrane AMPA receptor regulatory protein stargazin, and is known for its role in cerebellar function and development of epilepsy.¹⁴ In only one study, the association between the *CACNG2* gene and CPSP was investigated. Twelve polymorphisms and one haplotype of the *CACNG2* gene were studied in a retrospective cohort of Israeli women after mastectomy or lumpectomy.¹⁴ The minor alleles of five of these polymorphisms (rs4820242, rs2284015, rs2284017, rs2284018, and rs1883988) were associated with an increased prevalence of CPSP. Three of the polymorphisms (rs4820242, rs2284015, rs2284017) were combined in a haplotype (containing nucleotides A-C-C respectively), that was associated with an increased prevalence of CPSP (OR = 1.65, p = 0.001).

CHRNA6

CHRNA6 codes for the α 6 subunit of nicotinic acetylcholine receptors, which is expressed by dopamine-releasing neurons in the midbrain.³² Only one study investigated the *CHRNA6* polymorphisms in relation to CPSP.¹² Of the three polymorphisms, only one (rs7828365) was associated with CPSP.¹² Patients carrying the minor allele showed an increased risk of developing CPSP six months after inguinal hernia repair (OR 12.0, p = 0.03).

P2X7R

P2X7R codes for an ionotropic ATP-gated purinoceptors.³³ This is a ligand-gated receptor that is located in the central and peripheral nervous system and immune cells.³⁴ It is involved in mediating cell death, regulation of receptor trafficking, and inflammation.³⁵ An association was reported between 23 polymorphisms in the *P2X7R* gene and the severity of CPSP in patients after breast surgery for tumour removal and axillary lymph node dissection.³⁶ The minor allele of rs208294 (p = 0.003) was associated with more severe CPSP and the minor alleles of rs7958311 (p = 0.003) and rs208296 (p = 0.006) were associated with less severe CPSP.

Cytokines

Cytokines are key messengers in the human body, and are important in the paracrine and autocrine signalling, and regulation of an inflammatory response.³⁷ An association between 84 polymorphisms across 15 cytokine-affiliated genes and the prevalence of CPSP in women after surgery for breast cancer has been described.¹⁵ Thirteen of these polymorphisms showed a statistically significant association with the prevalence of

severe CPSP (vs. no CPSP), but correction for multiple testing was not performed. The *IFNG1* gene encodes for cytokine interferon γ . Two polymorphisms in this gene; rs2069727 ($p = 0.025$) and rs2069718 ($p = 0.006$) were significantly associated with the prevalence of CPSP. The *IL1R1* and *IL1R2* genes encode for interleukin receptors. Rs3917332 was significantly associated with CPSP ($p = 0.037$), but it was not mentioned whether the minor allele was associated with an increased or decreased prevalence. The minor allele of rs11674595 was associated with an increased prevalence of CPSP (OR 36.0, 95% CI 2.02-643.37, $p = 0.015$). Polymorphisms in interleukin genes were also reported to be associated with CPSP.¹⁵ Rs2243248 ($p = 0.033$) in IL4, rs3024498 ($p = 0.015$), rs1878672 ($p = 0.029$) and rs3024491 ($p = 0.035$) in IL10 and rs1881457 ($p = 0.043$), rs1800925 ($p = 0.007$), rs1295686 ($p = 0.014$) and rs20541 ($p = 0.017$) in *IL13* were all associated with the prevalence of CPSP, but once again it was not mentioned whether the minor allele was associated with an increased or decreased prevalence. The *NFKB1* encodes for the DNA binding subunit of nuclear factor- κ B.³⁸ The polymorphism rs4648141 was also reported to be associated with either an increased or decreased prevalence of CPSP.¹⁵ The *NFKBIA* gene encodes for an inhibitor of nuclear factor- κ B transcription factor.³⁹ The minor allele of the rs8904 polymorphism was associated with an increased prevalence of CPSP (OR 1.21, 95% CI 1.01-1.44, $p = 0.039$), but it was no longer statistically significant after multiple testing correction.¹¹

Human leukocyte antigens

The human leukocyte antigens play an important role in the immune system.³⁷ Twenty-three polymorphisms and one haplotype were studied in relation to the prevalence of CPSP after inguinal hernia repair.⁴⁰ Two polymorphisms; DRB1*04 (OR 2.28, 95% CI 1.32-3.96, $p = 0.004$) and DQB1*03:02 (OR 3.16, 95% CI 1.61-6.22, $p = 0.009$) were significantly more frequent in patients with CPSP. Both polymorphisms were combined into a haplotype, which was also associated with an increased prevalence of CPSP (OR 3.16, 95% CI 1.61-6.22).

DRD2

The *DRD2* gene encodes for the dopamine receptor. Dopamine is an important neurotransmitter involved in the transmission of nerve impulses, and is associated with many psychiatric disorders.⁴¹ Nine polymorphisms in the *DRD2* gene were studied, two of which were associated with the prevalence of CPSP, but only before multiple testing correction.¹¹ The minor alleles of rs4648317 (OR 1.35, 95% CI 1.05-1.74, $p = 0.019$) and rs12364283 (OR 1.58, 95% CI 1.11-2.23, $p = 0.0102$) were associated with a higher prevalence of CPSP.

ATXN1

The *ATXN1* encodes for the protein ataxin-1, which has been associated with neuronal death in spinocerebellar ataxia type 1.⁴² In the one study that analysed the *ATXN1* gene, an association was reported between the minor allele of rs179997 and an increased prevalence of CPSP, but this was statistically significant only before multiple testing correction (OR 1.20, 95% CI 1.00-1.44, $p = 0.0473$).¹¹

Discussion

In this systematic review, we summarize those studies that have focused on the association between genetic polymorphisms and the prevalence and severity of chronic postsurgical pain. Our results demonstrate that the overlap of the polymorphisms analysed between studies is minimal. Only a few polymorphisms within the *COMT* gene, the *OPRM1* gene, potassium channel genes, *GCH1*, and the *IL10* gene, have been investigated by two or more studies. Most studies analysed a wide array of polymorphisms, and did not correct for multiple testing.^{11, 13, 15} From a methodological point of view, we therefore conclude that research on polymorphisms and the prevalence and severity of CPSP is still in its infancy. Nevertheless, in answer to our first research question, several genes might be associated with the prevalence and severity of CPSP, based on the studies included in this systematic review; *COMT* gene, *OPRM1*, potassium channel genes, *GCH1*, *CACNG*, *CHRNA6*, *P2X7R*, cytokine-associated genes, human leukocyte antigens, *DRD2*, and *ATXN1*.

In the context of pain, the *COMT* gene has been studied most extensively. The *COMT* gene has been shown to play an important role in experimental pain, non-surgical chronic pain and even acute postoperative pain.^{26, 43-47} *COMT* haplotypes which link the activity of the COMT enzyme to the sensitivity of pain, are still used today.²⁶ Based on this systematic review the role of the *COMT* gene in CPSP is not fully clear; although a statistically significant association was reported, other studies were not able to confirm this finding.^{11, 21-24} A recent study reported a significant association between *COMT* polymorphisms and pain-related functional impairment in the chronic postoperative phase.⁴⁸ Strictly, this is not identical to CPSP, but these findings might suggest a role of *COMT* during the postoperative phase. A statistically significant association between a *COMT* diplotype and both pain and pain catastrophizing was noted.²⁵ Psychological factors, such as pain catastrophizing, surgical fear, and depression, have been shown to play an important role in the development of CPSP, and the *COMT* gene might be the common moderating factor.^{2, 8, 9} More research on the association between the *COMT* gene, pain and psychiatric disorders such as depression, anxiety and catastrophizing, might be of interest and might lead to preventive measure in the preoperative phase.

The opioid receptor genes have also been extensively studied. Several studies have shown an association between polymorphisms within these genes and morphine use in the acute postoperative phase, especially for rs1799971 in the *OPRM1* gene.^{49, 50} This is not surprising, as polymorphisms in these genes might influence the expression of opioid receptors and reduce the affinity for exogenous opioids, and thus the magnitude of the expected analgesic effect. The role of opioid receptors in the chronic postoperative phase is more complex. Laboratory studies suggest that the receptor variant of the minor allele might be more sensitive to endogenous opioids (e.g. β -endorphins), increasing the pain threshold, whereas the sensitivity to exogenous opioids is reduced.⁵¹ The rs1799971 polymorphism was found to be associated with an increased pain intensity in the chronic postoperative phase.²² This finding was not confirmed by two other studies.^{11, 24} Although one of these studies was clearly underpowered to detect any effect, the other study included over a thousand patients and might have been powerful enough.

Potassium channels are also known to play an important role in nociceptive signalling, and polymorphisms in genes encoding for potassium channels are associated with different sorts of pain (e.g. postoperative pain, cancer pain, inflammatory pain, neuropathic pain).^{52, 53} The *KCNS1* gene is the most studied potassium channel gene in relation to CPSP. The minor allele of the rs734784 polymorphism in this gene has been associated with more severe CPSP in several cohorts.^{13, 30} Other potassium channel genes have been studied and associations with CPSP were reported.¹³ Even though more research is necessary, *KCNS1* is an interesting target for future therapeutic strategies.

Polymorphisms in the *GCH1* gene and the relation with CPSP was analysed in various studies. However, only one study reported a statistically significant association before multiple testing correction.¹¹ Even though other studies have demonstrated a relationship between the *GCH1* gene, and experimental and chronic non-surgical pain, more research will be necessary to determine whether an association between *GCH1* and CPSP exists.^{31, 54}

Unfortunately, the included studies were not able to answer our second research question (Does adding the associated polymorphisms to existing prediction models improve their accuracy?) Even though almost all included studies corrected for one or several confounding factors, the confounders differed between the studies and none of the studies included all major known patient characteristic, clinical and psychological predictors.^{1, 2, 55, 56} The results of this systematic review indicate that some polymorphisms might be interesting predictors for CPSP, but it would be interesting to know whether these polymorphisms can genuinely increase the reliability of the pre-existing models. For instance, polymorphisms in the *COMT* gene were shown to be significantly associated with persistent post-herniotomy-related functional impairment, but when included into a general prediction model, the discriminatory power of the model did not significantly improve.⁴⁸ Given that determination of polymorphisms on a

per-patient basis is still relatively expensive, an increased discriminatory power of the prediction model is obviously needed before including genotyping into the analysis of preoperative patients.

A major limitation of this systematic review is the absence of a meta-analysis. After a careful analysis of the available literature, we decided not to perform a meta-analysis, because the studies were too heterogeneous, and too few per genetic variant. We noted a wide variety in the included surgical procedures, the instrument by which pain was measured and the follow-up time. Furthermore, various statistical tests were performed, which resulted in different ways of data presentation. The studies were also methodologically different. Most studies did not mention the use of multiple testing correction, and the presented *p*-values suggest that the results would no longer be statistically significant if multiple testing correction had been applied. Another research strategy might be more appropriate for the future.

Future research strategies might benefit from approaches used in other complex diseases, such as psychiatric disorders, where genetic vulnerability is characterized by many contributing polymorphisms, each with low effect size. By increasing the number of samples, genome-wide association studies (GWAS) have proved capable of reliably identification of common genetic risk variants for schizophrenia.^{57, 58} Although the neurobiological effects of these variants are on the verge of being explored, this research has already yielded new biological hypothesis. In addition, polygenic risk scores, constructed based on explorative GWAS, successfully predict liability to schizophrenia, enabling researchers to estimate genetic liability at the individual level, and to use this information when studying for gene-environment interactions.^{59, 60}

Genome wide association studies of CPSP are still lacking. Only by performing these GWAS, can we identify accurately all the polymorphisms associated with the prevalence and severity of CPSP. Performing such studies would require the collection of large clinical samples, with clearly defined phenotypes. This can be achieved only through international consortia.¹⁰ It would certainly advance the knowledge on the genetic background of CPSP and other pain related phenotypes, and would create opportunities and targets for future hypothesis driven research.

In addition to this, as we explained before, we strongly suggest that future research should focus on incorporating genetic risk factors in general predictor models on the prevalence of CPSP.

In conclusion, many studies have investigated the association between several polymorphisms and the prevalence and severity of chronic postsurgical pain. The methodology of the included studies was too heterogeneous to enable accurate conclusions to be drawn. Another approach might be more appropriate in the future. Genome-wide association studies are still lacking in this field. Larger sample sizes, more replication efforts and alignment of primary outcome measures and confounding variables will be necessary. Based on this systematic review, promising genes include the *COMT* gene, opioid receptor genes, potassium channel genes, *GCH1*, *CACNG*,

CHRNA6, *P2X7R*, cytokine-associated genes, human leukocyte antigens, *DRD2*, and *ATXN1*. Future research should be aimed at incorporating genetic risk factors with patient characteristic, clinical and psychological predictors for CPSP.

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Chapter 6

Genetic polymorphisms and prediction of chronic postsurgical pain 3 and 12 months after hysterectomy

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Submitted

Abstract

Chronic postsurgical pain (CPSP) is a serious problem. Clinical and psychological variables have not been able to explain all observed variance in prevalence and severity of CPSP. The first objective is to determine the association between genetic polymorphisms and the prevalence of CPSP after hysterectomy. The second objective is to analyze if the implementation of genetic polymorphisms into a previously performed clinical and psychological predictor analysis on the development of CPSP after hysterectomy will improve its discriminatory power. A prospective multicenter cohort study was performed in patients undergoing hysterectomy for benign indication. Clinical and psychological variables were collected by questionnaires in the week before surgery, postoperatively up to day 4, three and twelve months after hysterectomy. Blood was collected and 16 polymorphisms previously suggested to be correlated to CPSP (*COMT*, *GCH1*, *KCNS1*, *CACNG2* and *OPRM1*) were genotyped. Logistic regression analyses were performed. A total of 345 patients were available for the genetic analyses. The prevalence of CPSP three months postoperatively was 10.5% and after twelve months 7.9%. The polymorphism rs4818 within the *COMT*-gene was associated with the prevalence of CPSP after three months. No polymorphisms were associated with CPSP after twelve months. The addition of rs4818 to the prediction model did not change its discriminatory power significantly.

Introduction

Chronic postsurgical pain (CPSP) is a common problem affecting up to 60% of surgical patients and is associated with negative outcomes such as a reduced quality of life and socio-economic consequences.¹⁻⁶ Demographic, clinical and psychological risk factors for the development of CPSP have been well documented and include young age, procedure related risk factors, preexisting pain, acute postoperative pain, pain catastrophizing, surgical fear and lack of optimism.^{1, 2, 7-9} Unfortunately, these factors have not been able to explain all the observed variance in the prevalence and severity of CPSP. For this reason, the study and implementation of these polymorphisms have become of interest to further improve prediction models for CPSP. Data from twin studies and human pedigrees have estimated that the heritability of chronic pain generally ranges from 30-70%.¹⁰ Especially polymorphisms in genes that encode for proteins involved in nerve conduction and transmission, opioid signaling and inflammatory processes have been suggested to play an important role in the development of CPSP.¹¹⁻¹⁴ Identifying these genes could play an important role in finding targets for treatment.

Multiple studies have been performed that describe the association between genetic polymorphisms and the prevalence or severity of CPSP.¹¹⁻¹⁷ Based on a systematic review an association between the prevalence or severity of CPSP and single nucleotide polymorphisms (SNPs) within the *COMT* (catechol-O-methyl transferase) gene, opioid receptor genes, potassium channel genes, *GCH1* (GTP cyclohydrolase 1) gene, *CACNG2* (calcium channel voltage gate dependent gamma subunit 2) gene, *CHRNA6* (cholinergic receptor nicotinic alpha 6) gene, *P2X7R* (P2X purinoceptor 7) gene, cytokine-associated genes, human leukocyte antigens, *DRD2* (dopamine receptor D2) gene and *ATXN1* (ataxin 1) gene was suggested.¹⁸ Nevertheless, most of these polymorphisms were researched by only one study, with the exception of polymorphisms within the *COMT*, *OPRM1*, *GCH1*, and *KCNS1* genes.^{16, 19-22} Furthermore, this systematic review revealed that several studies were of retrospective design, and most studies lacked statistical power and had only performed exploratory statistical analyses without correcting for multiple testing or known confounders.¹⁸ Interestingly, none of the studies used in the systematic review incorporated genetic polymorphisms in pre-existing prediction models for CPSP (i.e. based on demographic, clinical and psychological factors). As a result, it is unknown whether the inclusion of associated genetic polymorphisms will improve the discriminatory power of the existing clinical and psychological prediction models for the development of CPSP. It needs no further explanation that the latter is of significant clinical importance.

This study has two objectives. The first objective is to determine if genetic polymorphisms in the *COMT*, *OPRM1*, *GCH1*, *CACNG2* and *KCNS1* genes are associated with the prevalence of CPSP after hysterectomy. The second objective is to determine if the implementation of these genetic polymorphisms into a previously performed

clinical and psychological predictor analysis for CPSP in this population will be able to improve its discriminatory power.²³

Methods

Study population

The study was registered at the Dutch Trial Register under the number NTR2702 (<http://www.trialregister.nl/trialreg/index.asp>). An elaborate description of the study protocol has been published elsewhere.²³ In short, a multicenter prospective cohort study was performed. Patients planned to undergo hysterectomy for a benign indication were included in one of 4 hospitals in the Netherlands: Maastricht University Medical Center+ (MUMC+) Maastricht, the Catharina Hospital (CzE) Eindhoven, the Máxima Medical Center (MMC) Veldhoven and the Orbis Medical Center (OMC) Sittard-Geleen. Inclusion took place between September 2010 and January 2014. Inclusion criteria were age between 18 and 65 years, good command of the Dutch language, elective surgery and total or subtotal hysterectomy with or without oophorectomy, and all types of surgical approach. Exclusion criteria were history of cancer, illiteracy and cognitive impairment. Patients who reported a malignancy or underwent another surgical procedure during the first postoperative year were also excluded. Approval of the local Medical Ethical Committee was obtained in all hospitals and all patients gave informed consent before participation.

Collection of preoperative variables and predictors

Patients were asked to fill out a baseline questionnaire before undergoing the hysterectomy. This questionnaire contained questions about demographics, (i.e. age, educational level, employment status, marital status, number of children, ethnicity), general health status and comorbidity, preoperative pain, and several psychological predictors. Preoperative pain was measured by using an adapted version of the Brief Pain Inventory, which determines the severity, location, duration and intensity of pain during the last week.²⁴ An 11-item Numeric Rating Scale (NRS; where 0 = no pain, and 10 = worst pain imaginable) was used to measure pain intensity. Patients were asked to rate preoperative pain related to the planned hysterectomy and non-hysterectomy related pain separately. The Douleur Neuropathique 4 (DN4) was used to assess the neuropathic character of the pain. This instrument originally consists of 10 items, but only the 7 self-reported items were used (DN4-interview). Previous literature has demonstrated a sensitivity of 78% and specificity of 81% if only these 7 self-reported items are used.^{23, 25} In agreement with previous literature a score of ≥ 3 was defined as neuropathic pain.²⁵

Psychological predictors included expected pain at the fourth postoperative day, surgical fear, pain catastrophizing, optimism, social support, depression, well-being and childhood abuse. Surgical fear was measured by the 8-item surgical fear questionnaire, of which four items measure short-term aspects of surgical fear and four items measure long-term aspects of fear.²⁶ The 13-item Pain Catastrophizing Scale (PCS) was used to measure pain catastrophizing on three subscales; helplessness, rumination, and magnification.²⁷ Optimism was assessed by using the 10-item revised Life Orientation Test (LOT-R).²⁸ Social support was measured by the 19-item Medical Outcomes Study – social support survey (MOS-SSS), and by asking the patient for the number of close friends and relatives available for support.²⁹ Depression was assessed with the Center for Epidemiological Studies – Depression (CES-D) questionnaire.³⁰ Psychological well-being was assessed by the 12-item Well-Being Questionnaire (W-BQ12), which measures positive well-being, energy and negative well-being.³¹ To avoid overlap with the CES-D, the subscale of negative well-being was left out.

Collection of perioperative variables and predictors

Surgery-related and anesthesia-related variables were collected at the time of the procedure. These included type of incision, total or subtotal hysterectomy, with or without oophorectomy, indication for the hysterectomy, type of anesthesia, postoperative analgesic use, duration of the surgery, amount of blood loss, complications, and the amount of years of experience of the attending gynecologist.

Acute postoperative pain was assessed each day during the first four postoperative days. Patients were asked to rate their average and highest pain at rest and during movement, as well as the use of any analgesics. At the fourth postoperative day the DN4-interview was used to assess neuropathic pain.

Collection of outcomes measures

Questionnaires were used to measure pain severity at 3 and 12 months after hysterectomy. Patients were asked to rate hysterectomy related and non-hysterectomy related pain separately. Predictor analysis was performed with the highest hysterectomy related pain during the last week. In accordance with previous research an NRS >3 was defined as moderate to severe pain.^{2, 23, 32, 33}

Genotyping and quality control

Peripheral blood samples were obtained from the included patients. DNA was extracted from these samples at the Department of Clinical Genetics of the Maastricht University Medical Center+ (Maastricht, The Netherlands). Genotyping of SNPs within the following genes was performed at the Institute of Human Genetics at the UniKlinikum

(Bonn, Germany) using the Infinium PsychArray v1.2 BeadChip (Illumina Inc., San Diego, CA, USA) and a customized Iplex array: *COMT* (rs4633, rs6269, rs4818, rs4680), *GCH1* (rs10483639, rs3783641, rs8007267), *KCNS1* (rs13043825, rs734784), *CACNG2* (rs2284015, rs2284017, rs2284018, rs4820242, rs1883988) and *OPRM1* (rs563649, rs1799971). These genes and polymorphisms were selected because they have previously been reported to be linked to CPSP.¹⁸

Genotypes were called using BeadStudio (Illumina Inc.). Quality control parameters included SNP callrate < 95%, subject callrate < 95%, deviation of the Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$) and removal of rare variants with a minor allele frequency < 0.01. After basic quality control heterozygosity was tested and outliers (> 3 standard deviations) were removed. Relatedness between the subjects was tested and one member of each pair was removed at random if relatedness was detected. All SNPs with A <> T or C <> G polymorphisms were removed from the set. After these control steps the SNPs were pruned to remove SNPs in LD ($r^2 > 0.02$). Principal components analysis was performed and the first two principal components were analyzed. The ancestry of the subjects was determined using HapMap, which showed that the outliers in the principal component analysis had a background other than Caucasian and were therefore removed from the sample.

Genotype imputation was performed using the imputation stepwise approach implemented in Minimac3³⁴ and Eagle v2.3³⁵. HRC r1.1 2016 panel was the reference panel, with population set to European.³⁶ The output of the imputation was checked with the Will Rayner tool. Afterwards additional quality control was performed with genotype probability >0.9, quality threshold was set at 0.5, INFO-score >0.4 and minor allele frequency and genotyping rate was checked again.

Statistical analysis

Patient characteristics and mean pain scores were evaluated using descriptive statistics. Before performing any other analyses, missing data were imputed by predictive mean matching. This method imputes values within the range of observed values in the data set, and is therefore robust to non-normal distribution of variables. The number of imputations was set to 5. The results demonstrated are the pooled results based on these 5 datasets. In order to reduce the number of psychological predictors, a factor analysis with oblimin rotation was performed. Principal component analyses revealed 2 factors, which were named surgery-related worries (based on the SFQ and PCS) and general psychological robustness (based on the LOT-R, CES-D and W-BQ12).²³

The association between the genetic polymorphisms and CPSP at 3 and 12 months was tested by univariate logistic regression analyses. An additive genetic model was tested, in which the number of minor alleles (0, 1 or 2) was defined as the candidate predictor. A p -value of <0.05 was considered statistically significant.

In order to evaluate the effect of addition of genetic polymorphisms to a previously performed predictor analysis based on clinical and psychological variables, analyses were repeated using the same data.²³ Separate analyses were performed for CPSP after 3 and 12 months. We first performed univariate logistic regression analyses on the same candidate predictors as were used in our previous publication (i.e. participating hospital, age, type of anesthesia, type of incision, paid job, educational level, American Society of Anesthesiology (ASA) physical status, number of pregnancies, surgery-related worries, general psychological robustness, history of sexual abuse, hysterectomy related baseline pain, non-hysterectomy related baseline pain, neuropathic pain at postoperative day 4, training of attending gynecologist, surgery related infection during the first three postoperative months). For clinical and psychological predictors, the variable was only included in the multivariate logistic regression analysis if the univariate *p*-value was < 0.1. Before including any of the genetic predictors in the regression model, correction for multiple testing was performed. This was done according to the method described by Galwey et. al., in which the effective number of tests is used instead of the actual number of tests.^{37, 38} In our study the effective number of tests was 11, which means that the SNP was only included in the regression model if the *p*-value in the univariate analysis was <0.0091 (0.1/11). After inclusion of all predictor variables in the regression model, a backward elimination analysis was performed until all remaining *p*-values were < 0.05 for clinical and psychological variables or < 0.0045 (0.05/11) for genetic variables.

For the variables hospital, age, type of anesthesia and type of incision a forced entry method was used in our previous publication, but because they were all non-significant, we did not use a forced entry in this analysis. After the final clinical and psychological prediction model was determined, the area under the curve (AUC) was calculated to investigate the model's discriminatory accuracy. After that, the genetic polymorphisms that were statistically significant in univariate logistic regression analyses were added to the multivariate prediction model, after which a backward elimination analysis was performed until all *p*-values were < 0.05. The AUC was calculated for this final prediction model, and allows for determination whether the use of genetic analysis in clinical prediction models improves the chance of identifying patients at risk for CPSP after hysterectomy.

Results

Flowchart and patient characteristics

Figure 1 demonstrates the flowchart of inclusion and follow-up, which is an extension of the flowchart of our previous publication.²³ Of the 517 patients that provided informed consent, 428 patients (82.8%) provided baseline data and returned at least one of the

follow-up questionnaires. Of these patients, 3 patients were excluded because no blood was available for genotyping and 80 patients were excluded because of insufficient quality of the isolated DNA, leaving 345 patients (80.6%) with useful data for the genetic analyses. Of these 345 patients, 332 patients (96.2%) returned the 3 month follow-up questionnaire, and 305 patients (91.9%) returned the 12 month follow-up questionnaire.

Figure 1. Flowchart of patient inclusion.

Baseline patient characteristics are displayed in Table 1 and perioperative data are shown in Table 2. All patients included were females of European descent. The average age at the time of hysterectomy was 46,9 years (SD 7.2). The most frequently performed procedure was vaginal hysterectomy (65.8%), and the most frequently performed anesthetic technique was general anesthesia (88.4%). Most patients were ASA physical class I (54.8%) or II (40.3%). The prevalence of moderate to severe preoperative pain (NRS > 3) was rather high; 49.3% reported pain related to the planned hysterectomy and 34.2% reported non-hysterectomy related pain. Pain at the fourth postoperative day was also common; 62.5% of patients scored an NRS >3, and 20.8% of all patients scored ≥ 3 at the DN4-interview.

Table 1. Baseline patient characteristics.

	Baseline sample (n = 345)
Center	
Maastricht UMC+	116 (33.6%)
CzE	106 (30.7%)
MMC	87 (25.2%)
OMC	36 (10.4%)
Age (mean, SD)	46.9 (7.2)
Employment	
Paid job	252 (73.3%)
No paid job	92 (26.7%)
Educational level	
No/lower	51 (14.8%)
Intermediate	214 (62.2%)
University/higher	79 (23.0%)
ASA physical class	
I	189 (54.8%)
II	139 (40.3%)
III	5 (1.4%)
Preoperative pain	
Hysterectomy related pain (highest NRS > 3)	170 (49.3%)
Non-hysterectomy related pain (highest NRS > 3)	118 (34.2%)
History of sexual abuse	
No	272 (79.5%)
Yes	70 (20.5%)
Number of pregnancies (mean, SD)	2.5 (1.2)
Indication for hysterectomy (more than 1 possible)	
Leiomyoma	105 (30.4%)
Prolapse	64 (18.6%)
Menorrhagia/metrorrhagia	170 (49.3%)
Dysmenorrhoea	22 (6.4%)
Endometriosis/adenomyosis	18 (5.2%)
Abdominal pain	18 (5.2%)
Cervical dysplasia	20 (5.8%)
Other	19 (5.5%)

ASA = American Society of Anesthesiologist, Maastricht UMC+ = Maastricht University Medical Center+, CzE = Catharina Hospital Eindhoven, MMC = Máxima Medical Center Veldhoven, OMC = Orbis Medical Center Sittard-Geleen, NRS = Numeric Rating Scale, SD = Standard Deviation.

Table 2. Perioperative data

	Baseline sample (<i>n</i> = 345)
Anesthesia type	
General	296 (85.8%)
Spinal	40 (11.6%)
General & epidural	9 (2.6%)
Hysterectomy procedure	
Total hysterectomy	328 (95.1%)
Subtotal hysterectomy	14 (4.1%)
Oophorectomy	
No	317 (93%)
Unilateral oophorectomy	10 (2.9%)
Bilateral oophorectomy	14 (4.1%)
Incision type	
Total laparoscopic	65 (18.8%)
Vaginal or laparoscopic assisted vaginal	227 (65.8%)
Abdominal incision	53 (15.4%)
Years of training of gynecologist (mean, SD)	14.2 (9.9)
Pain at rest at PACU (1 hour after hysterectomy)	
NRS 0-3	168 (54.5%)
NRS 4-10	140 (45.5%)
Pain at postoperative day 4 (highest NRS last 24 hours)	
NRS 0-3	188 (62.5%)
NRS 4-10	113 (37.5%)
DN4 at day 4	
0-2	228 (79.2%)
≥ 3	60 (20.8%)

PACU = Post Anesthesia Care Unit, NRS = Numeric Rating Scale, SD = Standard Deviation, DN4 = Douleur Neuropathique 4

Genetic polymorphisms and CPSP

Three months after hysterectomy, 35 of 332 patients (10.5%) experienced moderate to severe hysterectomy related pain (NRS > 3). Twelve months after hysterectomy, the prevalence decreased to 24 of 305 patients (7.9%).

Table 3 shows the location, minor alleles and minor allelic frequencies of all included SNPs. Almost all SNPs followed Hardy Weinberg equilibrium, with the exception of rs2284018. This is probably caused by the fact that the genotype TT was not present in our population. Therefore, the results of polymorphism rs2284018 need to be interpreted with caution. Table 4 demonstrates the results of the univariate regression analyses without correction for multiple testing. CPSP three months after hysterectomy was statistically significantly associated with the minor allele of rs4818 (OR [95%CI] 1.99 [1.19-3.33], *p*-value 0.009) and rs6269 (1.97 [1.18-3.28], *p*-value 0.01) within the *COMT*-gene. After correction for multiple testing only rs4818 was eligible for inclusion in the prediction model for CPSP. All other tested SNPs, within the *GCH1*, *CACNG*, *KCNS1* and *OPRM1* genes, were not significantly associated with the presence of moderate to severe

hysterectomy related pain three months after the surgery. No association was found between the included SNPs and the severity of pain 12 months after hysterectomy.

Table 3. Description of included polymorphisms within our patient population

Gene	SNP	Chromosome	Major/minor allele	MAF	HWE p^*
COMT	rs4633	22	T/C	0.44	0.01
	rs6269	22	A/G	0.36	0.01
	rs4818	22	C/G	0.36	0.04
	rs4680	22	A/G	0.44	0.01
GCH1	rs10483639	14	G/C	0.18	0.49
	rs3783641	14	T/A	0.18	0.02
	rs8007267	14	C/T	0.17	0.01
KCNS1	rs13043825	20	C/T	0.28	0.21
	rs734784	20	T/C	0.45	0.58
CACNG	rs2284015	22	C/G	0.27	0.76
	rs2284017	22	C/T	0.47	0.32
	rs2284018	22	C/T	0.22	<0.001
	rs4820242	22	A/G	0.37	0.48
	rs1883988	22	G/A	0.28	0.95
OPRM1	rs563649	6	C/T	0.10	0.52
	rs1799971	6	A/G	0.14	0.06

SNP = Single Nucleotide Polymorphism, MAF = Minor Allelic Frequency, HWE = Hardy Weinberg equilibrium.

Table 4. Association between included polymorphisms and chronic postsurgical pain (CPSP) at 3 and 12 months after hysterectomy

Gene	SNP	CPSP at 3 months ($n = 332$)		CPSP at 12 months ($n = 305$)	
		OR (95% CI)	p	OR (95% CI)	p
COMT	rs4633	1.59 (0.95-2.66)	0.08	1.09 (0.59-2.02)	0.78
	rs6269	1.97 (1.19-3.26)	0.01	1.22 (0.67-2.24)	0.52
	rs4818	1.99 (1.19-3.33)	0.009	1.35 (0.73-2.48)	0.34
	rs4680	1.58 (0.94-2.65)	0.08	1.20 (0.65-2.22)	0.57
GCH1	rs10483639	1.11 (0.61-2.03)	0.74	1.11 (0.54-2.31)	0.77
	rs3783641	1.04 (0.57-1.90)	0.90	1.13 (0.56-2.30)	0.73
	rs8007267	1.34 (0.76-2.36)	0.32	1.08 (0.52-2.26)	0.84
KCNS1	rs13043825	0.86 (0.48-1.53)	0.61	0.91 (0.46-1.77)	0.77
	rs734784	0.77 (0.47-1.29)	0.32	0.85 (0.47-1.55)	0.60
CACNG	rs2284015	0.86 (0.49-1.14)	0.61	0.80 (0.40-1.58)	0.51
	rs2284017	1.15 (0.90-1.47)	0.57	0.89 (0.50-1.60)	0.70
	rs2284018	0.75 (0.36-1.56)	0.45	0.77 (0.32-1.84)	0.56
	rs4820242	1.35 (0.81-2.26)	0.25	1.19 (0.65-2.18)	0.57
	rs1883988	0.83 (0.47-1.47)	0.53	0.75 (0.38-1.49)	0.41
OPRM1	rs563649	1.40 (0.63-3.12)	0.41	0.37 (0.09-1.62)	0.19
	rs1799971	1.25 (0.60-2.60)	0.56	0.54 (0.18-1.62)	0.27

SNP = Single Nucleotide Polymorphism, OR = Odds ratio.

Discriminatory power of prediction models

Because no SNPs were significantly associated with CPSP 12 months after hysterectomy in the univariate logistic regression analyses, we will only describe the prediction model for CPSP 3 months after hysterectomy. The following demographic, clinical and psychosocial variables were not associated with CPSP at 3 months in the univariate analyses and were therefore not used in the clinical prediction model: participating hospital, type of anesthesia, type of incision, educational level, ASA physical status, general psychological robustness, history of sexual abuse, and training of attending gynecologist.

The results of the logistic regression analysis for CPSP after three months are shown in Table 5. After performing the backward elimination analysis the following variables were included in the clinical prediction model: employment status, preoperative hysterectomy related pain, neuropathic pain at the fourth postoperative day, and self-reported infection during the first three postoperative months. The area under the receiver operating characteristic curve (AUC) for this clinical model was 0.78.

In step 2, *COMT* rs4818 was added to the model. Rs4818 remained significant in the model, with an odds ratio of 2.50 (1.36-4.60). The addition of this variable increased the AUC of the prediction model from 0.78 (95% CI 0.69-0.86) to 0.82 (0.74-0.91), but this was not statistically significant.

Table 5. Prediction model for CPSP 3 months after hysterectomy, based on demographic, clinical, psychological and genetic factors

Independent variable	OR (95% CI)	P-value	AUC
<i>Step 1</i>			0.78
Age			
Per year	NS	N/A	
Employment			
Paid job vs. no paid job	0.39 (0.17-0.91)	0.03	
Pregnancies			
Per number	NS	N/A	
Surgery-related worries			
Per point (range -1.68 – 2.60)	NS	N/A	
Preoperative hysterectomy related pain			
Per point on NRS (rang 0 - 10)	1.18 (1.04-1.35)	0.01	
Preoperative non-hysterectomy related pain			
Per point on NRS (rang 0 - 10)	NS	N/A	
DN4-interview at postoperative day 4			
≥ 3 vs. 0-2	4.65 (1.77-12.18)	0.002	
Self-reported infection first 3 postoperative months			
Yes vs. no	6.81 (2.66-17.45)	<0.001	
<i>Step 2</i>			0.82
rs4818 (<i>COMT</i> gene)			
Per number of minor alleles	2.50 (1.36-4.60)	0.003	

NRS = Numeric Rating Scale, DN4 = Douleur Neuropathique 4, OR = Odds Ratio, CI = Confidence Interval, AUC = Area Under the Curve, NS = Not significant.

Discussion

The first objective of this study was to determine if genetic polymorphisms in the *COMT*, *OPRM1*, *GCH1*, *CACNG2* and *KCNS1* genes are associated with the prevalence of CPSP after hysterectomy. This study shows that the rs4818 polymorphism within the *COMT* gene is associated with the presence of moderate to severe chronic postsurgical pain, three months after hysterectomy. The *COMT* gene encodes for the enzyme catechol-O-methyl transferase, which is essential in the breakdown of catecholamines. Polymorphisms within this gene can cause altered *COMT* enzyme activity.^{39, 40} The *COMT* gene has been studied extensively in relation to several pain syndromes. Associations have been found for experimental pain, for non-surgical chronic pain, for acute postoperative pain and for CPSP.⁴¹⁻⁴⁶ In line with our findings, Rut et. al. reported a relationship between increasing severity of CPSP after lumbar discectomy and the minor allele (G) of rs4818, the minor allele (G) of rs4680, and homozygosity for the minor allele (T) of rs4633.¹⁶ On the other hand, in contrast to our findings, Rut and colleagues also described an association between less severe CPSP and the minor allele (G) of rs6269. Patients with the minor allele of rs6269 have been reported to experience more severe preoperative pain in their study.¹⁶ Two studies that investigated pain in the acute postoperative phase, demonstrated a relationship between increased pain severity and the presence of one or two minor alleles of rs4818 in patients after third molar extraction or surgery for breast cancer.^{21, 43} An association between pain sensitivity in an experimental setting and several polymorphisms within the *COMT* gene in women with temporomandibular joint disorder has been reported, as patients with the major allele (A) of and the major allele (C) of rs4818 are more sensitive to pain.⁴¹ An association between several *COMT* polymorphisms and pain related functional impairment six months after inguinal hernia surgery has been described, as the presence of one or more minor alleles of rs4633 and rs6269 were associated with a protective effect.⁴⁷

In sum, many studies reported associations between pain and polymorphisms within the *COMT* gene. However, the allele responsible for an increase in pain sensitivity or severity is not identical in all studies. Polymorphisms associated with increased pain severity in some studies were associated with a protective effect in other publications.^{16, 21, 41, 43, 46} Differences in types of pain (e.g. postoperative pain versus experimental pain and functional impairment) might be a possible explanation for these variations. Future studies are needed to further analyze the relation between types of pain, pain sensitivity or severity and polymorphisms in the *COMT* gene. Obviously it is very important to know the allele responsible for an increase in pain severity before these *COMT* polymorphisms can be included in general pain prediction models.

In this study, we were unable to demonstrate an association between the prevalence of CPSP after hysterectomy and polymorphisms within the *GCH1*, *KCNS1*,

CACNG, and *OPRM1* genes. Associations between CPSP and these polymorphism have been found in previous publications.^{11, 13, 14, 17, 18, 22} It is very likely that our present study lacks statistical power to find an association between these polymorphisms and the presence of CPSP three and twelve months after hysterectomy. Future studies, in larger patient cohorts, are necessary to determine whether an association between these genes and CPSP exists.

The second objective of our study was to determine if the addition of genetic polymorphisms to the pre-existing clinical and psychological prediction model for CPSP after hysterectomy, would be able to improve the discriminatory power of the model. Our study demonstrates, for the first time, that the addition of polymorphisms within the *COMT* gene to the pre-existing prediction model improved the discriminatory power of the model from 'fair' (AUC 0.7-0.8) to 'good' (AUC 0.8-0.9). Even though the difference in AUC between a clinical prediction model and a prediction model with additional genetic factors was not statistically significance, we did show a trend towards improvement, and even small improvements in prediction value can be of clinical relevance in personalizing risk profiles and tailoring preventative strategies.⁴⁷ Although many studies have found associations between polymorphisms in several genes and the prevalence and severity of CPSP,¹⁸ until now the additional value of using genetic polymorphisms in predicting CPSP has not been described. The additional value of using polymorphisms in pain related functional impairment after inguinal hernia repair has been reported, but pain related functional impairment is a different outcome than CPSP.⁴⁷ Nevertheless, comparable findings between the two studies suggest that *COMT* polymorphisms play an important role in mediating pain processes during the chronic postoperative period.^{18, 47} Future studies will be needed to determine whether polymorphisms within other genes might be able to even further improve clinical and psychological prediction models.

Many studies have shown that psychological predictors, such as pain catastrophizing, surgical fear and lack of optimism are associated with the prevalence and severity of CPSP, but we were not able to confirm these findings in the present study.^{2, 7, 48} For this study the considerable number of psychological predictors was reduced to two variables (i.e. general psychological robustness and surgery-related worries) based on a factor analysis.²³ Combining multiple psychological predictors into a single variable might explain why we did not find a significant association between psychological robustness and CPSP. On the other hand, lack of statistical power might also be a reason for the absence of a association between psychological predictors and CPSP. However, there was to be enough power to detect an association between genetic polymorphisms and CPSP. Future studies are needed to determine the role of simultaneous use of psychological and genetic variables for the prediction of CPSP.

Important strengths of our study are both its prospective longitudinal design, as well as the homogeneity of the patient sample. All patients were of female gender, the same ethnicity and underwent the same surgery for benign indication. However, our study

also has limitations. First of all, the sample size was relatively small for genetic research. The study was powered to perform a regression analysis with clinical and psychological variables. It is likely that larger sample sizes are necessary to detect the association between individual genetic polymorphisms and the prevalence of CPSP. In addition to this, the prevalence of CPSP was relatively low (only 35 patients after three months, and 24 patients after 12 months), which further decreases the statistical power. This could explain why we did find an association between polymorphisms and pain three months after hysterectomy, but not 12 months. The second limitation is that we only studied polymorphisms that have already been studied by other authors. No genome wide association studies (GWAS) have been performed yet with regard to CPSP.

Future studies on CPSP and genetics should focus on GWAS. This is the only way to identify all polymorphisms that can possibly be associated with the development of CPSP. This approach would require larger sample sizes and preferably homogeneous patient populations with a clearly defined pain phenotype. At the moment, our research group is working on a GWAS to determine if other polymorphisms are associated with CPSP after hysterectomy. After promising polymorphisms have been identified by GWAS, these polymorphisms can be tested and validated in large groups of patients, and various surgical procedures. We hypothesize that individual genes explain only a small part of the variation in pain phenotype, whereas a combination of multiple genes of interest might be able to explain a larger portion. This combination of polymorphisms can then be combined with clinical and psychological predictors to compose personalized risk profiles for standard procedures.

In conclusion, our study demonstrates that two polymorphisms within the *COMT* gene are associated with the prevalence of moderate to severe CPSP three months after hysterectomy. In line with recent literature, our results further indicate that polymorphisms within the *COMT* gene play an important role in postoperative mechanisms of pain processing. Addition of the rs4818 polymorphism to the prediction model showed a trend towards improvement. In order to determine the role of other genes on the development of CPSP, more research in larger patient cohorts is needed.

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Chapter 7

General discussion

General discussion

Every surgeon and anesthesiologist is aware of the fact that good perioperative patient care is unmistakably important to ensure optimal patient outcome. Outcome is often defined in terms of improvement of health status (e.g. curation of malignant disease, improvement of vascular status, etc) or improvement of functional status (e.g. return of joint mobility, improvement of vision), but outcome in terms of the patient's quality of life (QoL) should not be forgotten. Research has demonstrated that the presence of pain has a significant burden on quality of life, by affecting both physical and mental health status.^{1, 2} Pain also has a significant influence on the patient's ability to participate in society, causes work impairment and increases use of health care resources.^{1, 3, 4}

In order to ensure optimal patient outcome it is therefore paramount to make every possible effort to prevent the development of both acute and chronic postsurgical pain. A lot of literature is available with regard to acute postsurgical pain (APSP), and anesthesiologist are proficient at preventing and treating APSP by using multimodal analgesia techniques (e.g. combining analgesics, peripheral and neuraxial blocks, etc).⁵⁻⁷ Most hospitals have protocols in place to identify patients with APSP as early as possible, so that optimal treatment can be promptly initiated.⁸ However, with regard to the prevention and treatment of chronic postsurgical pain (CPSP), a lot is unknown. Therefore, protocols are often missing and thus optimal treatment is not performed. Nevertheless, the problem of CPSP is significant, as literature has already demonstrated that 10-50% of patients suffer from CPSP, and in 2-10% of the cases CPSP is severe.^{9, 10} Surgeons and anesthesiologists need to be aware of this serious problem and methods of identifying patients at risk will be the first step towards prevention and treatment of CPSP.

This thesis aims to contribute to the knowledge regarding prevalence and risk factors of CPSP after several types of surgery. In the first part of this thesis we aim to identify demographic, clinical and psychological risk factors for the development of CPSP (Chapters II and III). These risk factors can be easily identified with use of questionnaires, and without invasive testing of patients. Furthermore, since clinical and psychological risk factors have only been able to explain part of the observed variance in prevalence and severity of CPSP, genetic factors have become of interest. It is therefore that in the second part of this thesis, we aim to identify genetic risk factors for the development of CPSP (Chapters V and VI). Moreover, the additional value of using genetic risk factors in clinical and psychological prediction models was determined (Chapter VI). In this general discussion the research questions as described in the general introduction (Chapter I) are answered and recommendations for future research are suggested.

RQ 1: What is the prevalence of CPSP after relatively minor procedures in an outpatient setting?

In order to answer this question we performed a large prospective cohort study of 908 patients undergoing a wide variety of outpatient procedures. Data were gathered by using three questionnaires. The first questionnaire was filled out a week before the surgery and included questions about demographic risk factors, present pain intensity and analgesic use, and three validated psychological questionnaires (i.e. Pain Catastrophizing Scale, Surgical Fear Questionnaire, Life Orientation Test).¹¹⁻¹³ Four days after the surgery the second questionnaire was filled out to measure acute postoperative pain intensity and analgesic use. The main outcome parameter, CPSP, was measured one year after the outpatient surgery. Pain was measured by an 11-point numeric rating scale (NRS), and moderate to severe pain was defined as an NRS > 3.^{14, 15} Patients were specifically asked to only rate the pain related to the surgical procedure.

The main outcome of this study was as follows: the prevalence of moderate to severe CPSP one year after outpatient surgery was 15.3%, and in 3.2% of the cases the pain was rated as severe (NRS >7). A procedure-specific variation in the prevalence of CPSP was noted. In case of ophthalmologic surgery the prevalence of CPSP was only 2.9%, but in case of orthopedic surgery 34.5% of patients reported moderate to severe CPSP.

Since we demonstrated that the prevalence of CPSP was extremely high after orthopedic surgery, and because arthroscopic knee surgery was one of the most commonly performed outpatient procedures in the Netherlands,¹⁶ a subgroup analyses was performed in 104 patients after outpatient knee arthroscopy. Partial meniscectomy was achieved in 77.9% of patients, in the remaining cases only debridement and lavage was performed. The prevalence of CPSP one year after arthroscopic knee surgery was 32.7%. In 94.2% of the patients pain was the indication for the surgery, and fortunately 71.1% of the patients reported less pain after one year as compared to preoperatively, but 16.4% of patients reported more pain.

In conclusion, outpatient surgery was associated with a significant chance of developing CPSP in our cohort, but a procedure-specific variance was observed (Chapter II). Especially orthopedic surgery was associated with a high prevalence of CPSP (Chapter II & III). In order to better understand the reasons behind this, we aimed to further the risk factors for the development of CPSP.

RQ 2: Which demographic, clinical and psychological factors are associated with the development of CPSP after outpatient surgery?

The same cohort of 908 patients undergoing outpatient surgery was used to answer the second research question. Studied demographic factors were age, gender, work status, and educational level. None of the demographic factors was associated with the

presence of CPSP. Of the studied clinical variables preoperative pain, preoperative analgesic use, and acute postoperative pain (APSP) proved to be important predictors for the presence of moderate to severe CPSP. The predictive value of preoperative pain was the highest. An explanation can lie in the peripheral and central sensitization caused by pre-existing pain.^{9, 10} Preoperative pain has often been present during a longer period of time, while APSP is of a shorter nature. Preoperative pain might therefore be more likely to cause sensitization of the nervous system, and thus be a stronger predictor for CPSP. Other studies have confirmed the importance of both preoperative and acute postoperative pain as risk factors for the development of CPSP.^{10, 17-20} The preoperative use of analgesics was also associated with CPSP in our cohort. In this case, the efficacy of analgesic use might be more important, as we also demonstrated that patients with preoperative analgesics but without preoperative pain experienced less CPSP than patients with inadequately treated preoperative pain.

Tested psychological factors were surgical fear, optimism and pain catastrophizing. Both surgical fear and lack of optimism were associated with the development of CPSP in our cohort. Other studies have confirmed the importance of psychological factors with regard to the development of CPSP.²⁰⁻²² Furthermore, poor preoperative quality of life also proved to be associated with CPSP in our cohort.

In conclusion, we were able to define preoperative pain, preoperative analgesic use, acute postoperative pain, surgical fear, lack of optimism and poor preoperative quality of life as risk factors for the development of CPSP (Chapter II). The association between preoperative pain and the presence of CPSP one year after outpatient surgery was the strongest.

RQ 3: Is moderate to severe preoperative pain associated with an increase in postoperative hospital costs and health care utilization after outpatient surgery?

A few small studies have shown that CPSP is associated with increased health care utilization.^{23, 24} With regard to this economic burden, it would be interesting to know if it is possible to identify patients at risk for increased postoperative health care costs. Since we have already demonstrated that preoperative pain is one of the most important predictors for CPSP (Chapter II),^{25, 26} it is very important to know whether preoperative pain is also associated with increased postoperative health care costs.

In order to answer this question, we performed a large prospective cohort study in 1353 patients undergoing various types of outpatient surgery. Questionnaires were used to determine the severity of preoperative pain one week before the surgery. The amount of hospital-based health care costs during the first postoperative year was gathered from the hospital's data management system. Another questionnaire was filled out one year after the surgery, in which patients provided the number of visits to their general practitioner, medical specialist, emergency department or other health

care professional. Patients were also asked about the number of days of absenteeism from their work or other social activities.

The main findings of this study were as follows: the average of hospital-based health care costs one year after outpatient surgery was €1.520. The average costs in patients with moderate to severe preoperative pain (€1.662) were statistically significantly higher than in patients without preoperative pain (€1.431). There was also a procedure-specific variance in postoperative costs. The highest costs were associated with ENT-surgery, dental surgery and orthopaedic surgery.

Patients with moderate to severe preoperative pain visited their general practitioner, medical specialist or other health care professional more often during first postoperative year than patients without preoperative pain. Patients with preoperative pain were more often absent from paid work during the first postoperative year as well.

In conclusion, in our cohort moderate to severe preoperative pain was associated with higher hospital-based health care costs during the first postoperative year, as well as an increased number of visits to the general practitioner, medical specialist or other health care professional and an increased amount of absenteeism from paid work (Chapter IV).

RQ 4: Which genetic polymorphisms are associated with the prevalence and severity of CPSP?

In order to answer this question we performed a systematic review of the available literature. We included 14 studies, describing a total of 5269 patients in 17 cohorts. The most commonly included surgical procedures were breast surgery²⁷⁻³² and inguinal hernia repair.³³⁻³⁵ CPSP was measured at 3 months or more in all studies. The relatively small sample size and the large number of polymorphisms studied, resulted in low statistical power for most studies. Correction for multiple testing was reported by only one study.³³ Furthermore, six of the included cohorts were of retrospective design.²⁹⁻³² Both the heterogeneity in study design and the fact that only a few polymorphisms were reported by more than one study, precluded the performance of a meta-analysis.

Our systematic review demonstrated associations between the prevalence or severity of CPSP and polymorphisms within the following genes: the COMT (catechol-O-methyl transferase) gene, the OPRM1 (opioid receptor mu 1) gene, potassium channel genes, GCH1 (GTP cyclohydrolase 1) gene, CACNG2 (calcium channel voltage gate dependent gamma subunit 2) gene, CHRNA6 (cholinergic receptor nicotinic alpha 6) gene, P2X7R (P2X purinoceptor 7) gene, cytokine-associated genes, human leukocyte antigens, DRD2 (dopamine receptor D2) gene and ATXN1 (ataxin 1). It should be taken into account that only polymorphisms within COMT, OPRM1, GCH1 and KCNS1 were researched by more than one study.

Associations between CPSP and polymorphisms within the COMT gene were explored in several of the included studies, and two of them reported a significant

association.^{36, 37} The minor alleles of rs4818 and rs4633 and the major alleles of rs6269 and rs4680 were correlated with an increased severity of CPSP.³⁶ The importance of the COMT gene in pain processing mechanisms is confirmed by others studies, that have described associations between the COMT gene and experimental pain, non-surgical chronic pain and acute postoperative pain.³⁸⁻⁴² Polymorphisms within the OPRM1 were investigated by three studies, but only one of these studies was able to confirm an association between the rs1799971 polymorphism and the severity of CPSP.⁴³ Multiple studies have linked have previously linked the OPRM1 gene to morphine consumption in the acute postoperative phase.^{44, 45} Of the potassium channel genes, the KCNS1 gene has been most extensively studied. The minor allele of rs734784 has been linked to the severity of CPSP in several cohorts.^{27, 31} Other polymorphisms within potassium channel genes have been described by only study, but without the correction for multiple testing.²⁷ Polymorphisms of the GCH1 gene were researched in by studies, but only one found an association with the prevalence of CPSP, but only before multiple testing correction.³³ Even though an association between GCH1 and both experimental pain and non-surgical chronic pain has been reported,⁴⁶ more research is necessary to determine its role in the development of CPSP.

In conclusion, several studies have investigated the association between CPSP and genetic polymorphism, but the heterogeneity in methodology of these studies does not enable us to draw accurate conclusions. Nevertheless, promising genes can be selected and include the COMT gene, opioid receptor genes, potassium channel genes, GCH1, CACNG, CHRNA6, P2X7R, cytokine-associated genes, human leukocyte antigens, DRD2 and ATXN1.

RQ 5 Does the addition of genetic risk factors to an existing clinical and demographic prediction model for CPSP after hysterectomy increase the accuracy of this model?

Our systematic review (Chapter V) demonstrates that several genetic polymorphisms are probably associated with the prevalence and severity of CPSP.⁴⁷ However, none of the included studies researched the additional value of incorporating genetic polymorphisms into existing clinical and psychological prediction models for CPSP. Since determination of genetic polymorphisms requires a blood draw and is still relatively expensive on a per-patient basis, the additional value has to be demonstrated before it should be commonly deployed in a clinical setting.

In order to answer this research question we performed a large multicenter prospective cohort study in 345 patients undergoing hysterectomy for benign indication. Patients were asked to fill out several questionnaires.²² The baseline questionnaire before the hysterectomy included questions about demographics, general health status, preoperative pain and several psychological predictors. Surgery-related and anesthesia-related variables were collected at the time of the procedure.

Acute postoperative pain was assessed by questionnaire each day during the first four postoperative days. At three and twelve months after hysterectomy patients were asked to fill out questionnaires with regard to CPSP. Peripheral blood samples for genotyping were obtained at the time of the surgery. Polymorphisms selected for genotyping were within the COMT gene, GCH1, KCNS1 gene, OPRM1 gene and CACNG2 gene. These genes were selected because they have been previously linked to CPSP (Chapter V).⁴⁷

Clinical and psychological risk factors for CPSP in this cohort were shown to be hysterectomy-related and nonhysterectomy-related preoperative pain, number of pregnancies, surgery-related worries, neuropathic pain at day 4, and self-reported surgery-related infection at 3 months.²² In our analysis for genetic risk factors in the very same patient population, only rs4818 was associated with the prevalence of CPSP three months after hysterectomy, and no polymorphisms were associated with CPSP after twelve months. The area under the curve (AUC) of the prediction model improved from 0.78 to 0.82 with the addition of the rs4818 polymorphism, but this was however not statistically significant. A possible explanation could be the relatively small size of the study population. This research should be repeated in larger patient cohorts.

In conclusion, the rs4818 polymorphisms within the COMT-gene was associated with the prevalence of CPSP three months after hysterectomy, but the implementation of rs4818 into the clinical and psychological prediction model, did not significantly improve the chance of identifying hysterectomy patients at risk for CPSP.

Recommendations for future research

In order to further clarify the prevalence and risk factors of CPSP, future research should not only focus on the intensity of the reported pain (e.g. NRS or VAS), but also on the characteristics (e.g. neuropathic, inflammatory, etc.) and the location of the reported pain. Not only is this necessary in order to discriminate between the continuation of a pre-existing problem and newly formed postoperative pain,⁴⁸ as it is known that various types of pain do have a different origin and are therefore associated with different risk profiles. Moreover, pain should not be the only outcome measure studied. Other Patient Reported Outcome Measures (PROMs, e.g. postoperative quality of life, quality of recovery, etc.) could give a more general impression of the success of the procedure from the patient's point of view.⁴⁹⁻⁵¹ This is especially true for procedures that are performed in order to improve the patient's quality of life.

The identification of genetic risk factors for the development of CPSP is still in its infancy. Most studies have so far focused on genetic polymorphisms that have been associated with other types of pain (hypotheses-driven research). A different approach, in the form of genome-wide association studies (GWAS) is necessary in order to identify promising polymorphisms in CPSP. With GWAS, an extremely large amount (millions) of polymorphisms spread over the entire genome is studied simultaneously.⁵² This method

can help formulate hypotheses as to which polymorphisms are likely to be correlated with CPSP (hypotheses-generating research).⁵³ Once GWAS have identified promising polymorphisms in multiple large patient cohorts, these polymorphisms can be tested in smaller procedure-specific cohorts and incorporated into clinical and psychological prediction models.

All together, prediction and prevention of CPSP needs further research. Future studies will have to focus on interventions to reduce the prevalence and severity of CPSP. Small studies have already shown that the prevalence of CPSP is decreased with treatment of acute postoperative wound pain and neuropathic pain.^{54, 55} However, since our studies demonstrate that preoperative pain appears to be the strongest predictor for the development of CPSP, it would be interesting to know if optimal treatment of preoperative pain would be able to reduce the prevalence and severity of CPSP. Furthermore, the role of targeting preoperative anxiety, pain catastrophizing and pessimism in the prevention of CPSP, should also be clarified. More research in the field of genetics and CPSP will further improve prediction models, but might also lead to new targets for prevention and treatment of CPSP.

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Chapter 8

Summary
Samenvatting

Summary

Chronic postsurgical pain (CPSP) remains a frequent problem with serious consequences, such as a reduced quality of life, absenteeism from work and social activities and an increase in health care consumption. The aim of this thesis was improve our insight into the complex interaction of clinical, psychological and genetic risk factors for the development of CPSP after a wide variety of surgical procedures.

The results of a large prospective cohort study, describing the prevalence and predictors of CPSP in patients undergoing a wide variety of outpatient procedures is described in **Chapter II**. The prevalence of CPSP one year after outpatient surgery was 15.3%. Severe CPSP was reported by 3.2% of patients. The prevalence of CPSP was strongly dependent on the procedure performed. Orthopedic surgery was most often associated with the presence of CPSP. The most important risk factor for the development of CPSP was the presence of preoperative pain. Other risk factors were preoperative analgesic use, surgical fear, lack of optimism, low preoperative quality of life and the presence of acute postsurgical pain.

Chapter III describes the prevalence and predictive factors of CPSP after arthroscopic knee surgery. The prevalence of moderate to severe CPSP was 32.7%. Both the presence of preoperative pain and the preoperative use of analgesics were strongly predictive for the development of CPSP.

The results of a large prospective cohort study, describing hospital-based health care costs during the first year after outpatient surgery, are presented in **Chapter IV**. Hospital-based health care costs during the first postoperative year were significantly higher in patients with moderate to severe preoperative pain, than in patients without preoperative pain. Furthermore, patients with preoperative pain visited their general practitioner, medical specialist or other health care professional more often with questions about pain and were more often absent from their paid job.

Chapter V describes the results of a systematic review regarding the genetic risk factors for the development of CPSP after a variety of surgical procedures. Associations with the prevalence or severity of CPSP was reported for polymorphisms in the COMT gene, OPRM1 gene, potassium channel genes, GCH1 gene, CACNG gene, CHRNA6 gene, P2X7R gene, cytokine-associated genes, human leukocyte antigen genes, DRD2 gene and ATXN1 gene. Unfortunately, most studies were small and of retrospective design, and most polymorphisms were described by only one study.

The results of our own clinical study with regard to genetic risk factors for the development of CPSP are presented in **Chapter VI**. The rs4818 polymorphism within the COMT gene was associated with the prevalence of CPSP three months after

hysterectomy. No associations were found between the included polymorphisms and CPSP twelve months after hysterectomy. Addition of genetic polymorphisms to the clinical and psychological prediction model for CPSP in this cohort, did not significantly improve the accuracy of the model.

Samenvatting

Chronisch postoperatieve pijn (CPOP) is een frequent probleem met potentieel ernstige gevolgen, zoals een verminderde kwaliteit van leven, verzuim van werk en sociale activiteiten, en een toegenomen behoefte aan zorg. Het doel van dit proefschrift was het verbeteren van de kennis ten aanzien van de complexe interactie van klinische, psychologische en genetische risicofactoren voor het ontwikkelen van CPOP na verschillende chirurgische ingrepen.

De resultaten van een grote prospectieve cohort studie, waarin werd gezocht naar de prevalentie en predictoren voor CPOP na verschillende procedures in dagbehandeling, worden beschreven in **Hoofdstuk II**. De prevalentie van CPOP een jaar na chirurgie in dagbehandeling was 15,3%. Ernstige CPOP werd gerapporteerd door 3,2% van de patiënten. De prevalentie van CPOP was sterk afhankelijk van de uitgevoerde ingreep. Orthopedische ingrepen werden het vaakste geassocieerd met de aanwezigheid van CPOP. De belangrijkste risicofactor voor het ontwikkelen van CPOP was de aanwezigheid van preoperatieve pijn. Andere risicofactoren waren analgeticagebruik, angst voor de operatie, een gebrek aan optimisme, lage preoperatieve kwaliteit van leven, en de aanwezigheid van acute postoperatieve pijn.

Hoofdstuk III beschrijft de prevalentie en predictoren voor CPOP na arthroscopie van de knie. De prevalentie van matige tot ernstige CPOP was 32,7%. De aanwezigheid van preoperatieve pijn en het gebruik van analgetica in de preoperatieve fase, waren beide sterke predictoren voor de ontwikkeling van CPOP.

De resultaten van een grote prospectieve cohort studie, waarin werd gekeken naar de ziekenhuiskosten in het eerste jaar na chirurgie in dagbehandeling, worden beschreven in **Hoofdstuk IV**. De ziekenhuiskosten in het eerste postoperatieve jaar van patiënten met matige tot ernstige preoperatieve pijn waren significant hoger dan van patiënten zonder preoperatieve pijn. Patiënten met preoperatieve pijn brachten vaker een bezoek aan hun huisarts, medisch specialist of andere zorgverlener met vragen over pijn, en tevens was het ziekteverzuim hoger.

Hoofdstuk V beschrijft de resultaten van een systematische review omtrent de genetische factoren voor het ontwikkelen van CPOP na verschillende chirurgische ingrepen. Een relatie met de prevalentie of ernst van de CPOP werd gerapporteerd voor het COMT gen, OPRM1 gen, kaliumkanaalgenen, GCH1 gen, CACNG gen, CHRNA6 gen, P2X7R gen, cytokine-geassocieerde genen, HAL-genen, DRD2 gen en het ATXN1 gen. Helaas waren de meeste studies klein of retrospectief en werden de meeste polymorfismen maar door een enkele studie beschreven.

De resultaten van onze eigen klinische studie met betrekking tot de genetische risicofactoren voor het ontwikkelen van CPOP worden beschreven in **Hoofdstuk VI**. Het rs4818 polymorfisme in het COMT gen was geassocieerd met de prevalentie van CPOP drie maanden na een hysterectomie. Er werd geen relatie gevonden tussen de onderzochte polymorfismen en CPOP twaalf maanden na een hysterectomie. Het toevoegen van genetische polymorfismen aan het bestaande klinische en psychologische predictiemodel voor CPOP in dit cohort, verbeterde de nauwkeurigheid van het model niet significant.

Chapter 9

Valorisation addendum

Valorisation addendum

The goal of this thesis is to contribute to the scientific knowledge and understanding of the pathologic processes involved in the human body with regard to pain; but also to find approaches to improve and optimize healthcare in the perioperative setting in order to decrease the prevalence and severity of chronic postsurgical pain (CPSP). The goal of this paragraph is to highlight the societal and economic importance of the research aims in this thesis; both on the voluminous group of surgical patients, as well as on society in general.

We will start by explaining the impact of pain on the individual patient and on society. Second, we will explain the importance of developing prediction models for CPSP. We will end this paragraph by highlighting the future research directions that are necessary to develop methods for preventing CPSP as adequately as possible.

Personal and societal impact of pain

Pain is an important and widely prevalent health problem, especially in the developed world. Pain causes discomfort and suffering, and research has demonstrated that pain severity is an important determinant of quality of life.¹⁻³ Aiming to prevent and treat pain as adequately as possible therefore has a substantial moral ground, and is considered an essential part of optimal patient care.⁴ In addition to this, research has also demonstrated that pain, especially acute postsurgical pain (APSP), is associated with increased morbidity and mortality. Patients who suffer from APSP are prone to cardiac morbidity (e.g. myocardial infarction), pulmonary morbidity (e.g. pulmonary infections), stroke and postoperative delirium.⁵⁻⁷ It has also been demonstrated that pain has a negative impact on other organ systems, such as the gastrointestinal system, the renal system, blood coagulation and the immune system.⁸

In addition to the negative consequences of pain for the individual patient, research has shown that pain can have an important negative impact on society in general. Multiple studies have shown that chronic pain is associated with increased consumption of health care resources, absenteeism from work and a substantial associated economic burden.⁹⁻¹³ More specifically, moderate to severe acute postsurgical pain has been clearly demonstrated to be associated with delayed hospital discharge and, in case of ambulatory surgery, with unanticipated hospital admission and contact with the general practitioner or other health care professionals.^{5, 14} Since it is estimated that over 80% of all surgical patients experience inadequately managed pain during the acute postoperative phase, it is easy to imagine that APSP leads to a substantial increase in health care costs and a negative impact on society.⁵ This is especially true for societies which are based on a system of solidarity, and in which health care costs are thus considered a shared individual and governmental responsibility.

The societal consequences of CPSP have been less extensively studied. A small study has demonstrated that patients with severe neuropathic CPSP or neuropathic post-trauma pain visit physicians more frequently and use more prescription medication than patients with less severe pain.¹⁵ Another study demonstrated an increase in health care utilization of patients with CPSP after kidney transplantation.¹⁶

The described negative consequences of acute and chronic postsurgical pain on the individual patient (e.g. discomfort and suffering, increased morbidity and mortality) and on society in general (e.g. increased health care costs, absenteeism from work and increased economic burden) are important reasons to make every attempt to reduce the prevalence and severity of APSP and CPSP. As mentioned before, adequate treatment of APSP and CPSP is very important in order to reduce the prevalence and severity of these pain problems, and should be part of optimal patient care. However, prevention will be far more effective in reducing the negative consequences for the individual patient and society. In order to prevent the development of CPSP in postsurgical patients, it is of paramount importance that we first understand the risk factors for the development of CPSP. Only then will we be able to focus research on identifying strategies to prevent the development of moderate to severe CPSP.

Importance of prediction of CPSP

During the last decade many researchers have attempted to develop tools to identify patients at risk for the development of moderate to severe CPSP. Until recently, the focus has been on demographic, clinical and psychological risk factors. These risk factors can be easily identified with the use of questionnaires and do not require invasive testing. One of the most important risk factors seems to be the presence of moderate to severe preoperative pain.¹⁷⁻²⁰ Other risk factors are the presence of moderate to severe acute postoperative pain, preoperative analgesic use, surgical fear, lack of optimism and pain catastrophizing.^{2, 17, 21, 22} However, clinical and psychological risk factors have only been able to explain part of the observed variance in the prevalence and severity of CPSP. For this reason, genetic factors have recently become of interest. Our own studies, as well as several others, have been able to identify genetic polymorphisms as possible predictors for CPSP.^{23, 24} Especially polymorphisms within the COMT gene, opioid receptor genes, potassium channel genes, GCH1, CACNG, CHRNA6, P2X7R, cytokine-associated genes, human leukocyte antigens, DRD2 and ATXN1 seem to be promising predictors for CPSP.

Defining the risk factors for CPSP is the first step towards reduction and prevention of CPSP. It will create possibilities for an individual approach, which is paramount in the time of personalized medicine. It could help identify the predictors for CPSP on an individual level during the preoperative phase, after which a personalized plan can be made. It will allow patients to be informed of their individual risk at CPSP, which might lead to an informed decision of the treatment plan. In some cases patients might decide

not to undergo the planned surgery at all. This could be the case for patients with a high risk at developing CPSP, who are about to undergo surgery that is not strictly necessary (e.g. cosmetic procedures), or procedures for which non-surgical alternatives exist. In other cases, a preoperative tailor-made treatment plan might be offered to the patient, in order to try to influence the present risk factors (e.g. treatment of preoperative pain or psychological factors).

Future research will hopefully make us gain even more insight into the predictors for the development of CPSP. In order to further clarify this, future research should not only focus on the intensity of the reported pain (e.g. NRS or VAS), but also on the characteristics of the pain (e.g. neuropathic, inflammatory, etc.), as well as the location of the reported pain. This is important because various types of pain can have a different origin and can therefore be associated with various risk profiles. Future research should also try to further reveal the genetic risk factors for the development of CPSP. Most studies have so far focused on genetic polymorphisms that have been associated with other types of pain, as well as psychiatric diseases. This type of genetic research is also known as hypothesis-driven research. A different approach, in the form of genome-wide associated studies (GWAS) will hopefully lead to the identification of other promising polymorphisms associated with CPSP.^{25, 26} Once GWAS have identified promising polymorphisms, and these data have been validated in large patient cohorts, these polymorphisms can be tested in smaller procedure-specific cohorts, and can be incorporated into clinical and psychological prediction models.

Towards prevention of CPSP

Our research has demonstrated that the prevalence of CPSP is at least 10-15% after several types of surgical procedures.^{17, 24, 27} Several studies have demonstrated that the presence of CPSP is associated with an increase in health care costs and societal economic burden.^{15, 16} Our own research found an association between preoperative pain, one of the most important predictors of CPSP, and the amount of hospital-based health care costs as well as absenteeism from paid work.²⁸ All these data suggest that adequate prevention of moderate to severe CPSP will be able to reduce health care costs and societal economic burden significantly.

Even though the research in this thesis does not describe preventative methods with regards to CPSP, the importance of adequate prevention in society does warrant a short summary of possible methods for prevention. Future research will have to demonstrate whether these methods will actually be able to reduce the prevalence and severity of CPSP.

Small studies have already suggested that the prevalence of CPSP can be reduced by treating acute postoperative wound pain and neuropathic pain.^{29, 30} However, our own studies, as well as several others, have demonstrated that preoperative pain appears to be an even stronger predictor for the development of CPSP.^{17, 18, 20} It would therefore be

interesting to know if treatment of preoperative pain is able to reduce the prevalence and severity of CPSP even further. In order to be successful, treatment of preoperative pain will probably have to be as timely and as effective as possible, in order to limit preoperative sensitization of the peripheral and central nervous system.

Furthermore, research has also demonstrated that preoperative anxiety, pain catastrophizing and pessimism are important risk factors in the development of CPSP.^{2, 17, 21, 22} The role of targeting these psychological risk factors should also be clarified by future research. More research in the field of genetics and CPSP might lead to new perioperative pharmacologic targets for the prevention and treatment of CPSP.

Summary

Defining the predictive factors for the development of CPSP after several types of surgery is the first step towards the prevention of CPSP. A decreased prevalence and severity of CPSP will in turn lead to a reduction of health care costs, work absenteeism and societal economic burden.

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Chapter 10

Acknowledgements
Dankwoord

Dankwoord

Bijna negen jaar geleden begon ik, destijds als semi-arts, met het verzamelen van data voor de studie die uiteindelijk een belangrijk onderdeel zou worden van mijn proefschrift. Nu, zoveel jaren later, kan ik eindelijk zeggen dat het proefschrift af is en dat ik met veel plezier terugkijk op deze periode. Het was niet altijd makkelijk naast mijn opleiding tot anesthesioloog en later mijn klinische werkzaamheden als stafid. Er zijn meerdere momenten geweest waarop ik mij afvroeg of ik nog de energie had en of het überhaupt zou gaan lukken om het promotietraject tot een goed einde te brengen, maar dit proefschrift is het bewijs dat de aanhouder wint.

Als ik iets heb geleerd, is het dat het verrichten van goed en waardevol wetenschappelijk onderzoek iets is wat geen enkele onderzoeker of promovendus alleen kan. De steun en kritische blik van de mede-onderzoekers en het promotieteam zijn hierbij onmisbaar, maar ook het begrip en de waardering van de collega's op de werkvloer zijn niet te onderschatten. Last, but not least, zonder de steun en het geduld van mijn familie en vrienden zou dit zeker allemaal niet gelukt zijn!

Het promotieteam

Prof. Dr. Buhre, beste Wolfgang, in 2013 heb je zonder aarzelen de taken van Marco Marcus overgenomen. Je hebt je verdiept in mijn onderzoek, waardoor het voor mij mogelijk was door te gaan met mijn promotietraject. Je bent zeer nauw betrokken geweest bij de vier manuscripten die nog moesten worden geschreven en je wist mij in contact te brengen met deskundigen van andere vakgebieden. Ik wil je bedanken voor je vertrouwen en je onmisbare hulp om dit promotie-traject tot een goed einde te brengen.

Prof. Dr. Joosten, beste Bert, zonder jouw hulp had ik dit proefschrift nooit tot een goed einde kunnen brengen. Ondanks al het extra werk en tijd, had je er vertrouwen in dat ik in staat was het project 'genetica en pijn' op te pakken en ben je me hierin blijven steunen. Hierdoor heb ik veel ervaring kunnen opdoen als onderzoeker en dit heeft mijn proefschrift vele malen interessanter gemaakt. Je kritische blik en je snelle reacties op mijn vragen waren onmisbaar voor dit proefschrift!

Dr. Gramke, beste Hans, jouw werk was de basis waaruit al mijn onderzoek is voortgekomen. Als geen ander had je inzicht in de stof en ontelbare keren heb ik jouw proefschrift gelezen om inspiratie op te doen voor mijn eigen manuscripten. Ondanks al je andere verplichtingen en drukke bestaan wist je tijd te maken om mijn manuscripten te lezen en te verbeteren door je kritische blik.

Dr. Fiddelaers, beste Audrey. Vanaf het begin was jij mijn steun en toeverlaat. Als geen ander wist jij hoe de database in elkaar stak en heb je mij de beginselen van het

verrichten van wetenschappelijk onderzoek bijgebracht. Je hebt me geleerd een database op te bouwen en de data te analyseren. Bij elke vraag die ik had, was jij bereid om mij te helpen, ongeacht hoe veel tijd je dit zelf kostte. Zelfs nadat je ging werken voor een andere afdeling ben jij betrokken gebleven en was je altijd bereid met een kritische blik naar mijn manuscripten te kijken. Jij was de rode draad in dit promotie-traject!

De co-auteurs

Prof. Dr. Marcus, beste Marco, jij was de eerste die wetenschappelijke potentie in mij zag. Je hebt mij, al heel vroeg in mijn carrière, het vertrouwen geschonken om met deze database aan de slag te gaan en dit onderzoek uit te bouwen tot een mooi project. De eerste jaren van mijn promotie hebben we dan ook samen gewerkt aan een aantal mooie publicaties. Deze jaren hebben mij gevormd!

Dr. Maurice Theunissen, al vanaf het begin was jij, samen met Audrey, betrokken bij mijn onderzoek en was je altijd bereid methodologische vragen te beantwoorden, ook als je zelf druk bezig was. Veel dank ben ik je verschuldigd voor het beschikbaar stellen van de perfect uitgebouwde database met hysterectomiepatiënten, en voor je bereidheid om bij herhaling toe te lichten waar bepaalde informatie te vinden was.

Drs. Roel van Reij, zonder jou was het nooit gelukt om de genetische database uit te bouwen. Samen met *Dr. Nynke van den Hoogen* heb je me geholpen met het klaarmaken van alle samples voor genetische analyse. Je heb je, met behulp van collega's in Bonn, weten te bekwamen in de ontzettend moeilijk stof van de statische analyse van GWAS-data. Je was onmisbaar bij het klaarmaken van de database en hulp bij de analyses. Ik wens je heel veel succes bij het schrijven van je eigen proefschrift!

Dr. Bjorn Stessel, jarenlang hebben we in hetzelfde schuitje gezeten. We zijn min of meer samen aan ons promotietraject begonnen en deelden interesse in hetzelfde onderwerp. Ik heb veel gehad aan je goede ideeën en aan je kritische blik. Jij hebt je verdediging er inmiddels al opzitten en ik hoop dat ik je snel mag volgen!

Prof. Dr. Bart Rutten en *Dr. Gunter Kenis*, jullie hebben me wegwijs weten te maken in de beginselen van het genetisch onderzoek. Jullie ervaring en geduld heeft ertoe geleid dat ik wist waar ik moest beginnen!

Prof. Dr. Carmen Dirksen, bedankt voor je tips en adviezen met betrekking tot de ingewikkelde stof van de economische analyses.

Dr. Pieter Emans, dankzij jouw hulp was ik in staat de resultaten met betrekking tot chronisch postchirurgische pijn in een cohort van orthopedische patiënten op de juiste manier te interpreteren.

Dr. Sander van Kuijk, bedankt voor jouw hulp, vaak op zeer korte termijn, met methodologische en statistische vraagstukken en voor je kritische blik op de geschreven manuscripten.

Overige collegae

Hermine Gielen, jou ben ik speciale dank verschuldigd dat je altijd bereid was een plekje te zoeken in de drukke agenda van Wolfgang, zodat mijn proefschrift geen vertraging zou oplopen. Ook bedank ik je voor de praktische hulp in de afrondende fase en de tips en informatie die ik nodig had om alles tijdig af te hebben.

Mijn dank gaat uit naar de leden van de beoordelingscommissie; *Prof. Dr. Karin Faber* als voorzitter, *Prof. Dr. Ide Heyligers*, *Prof. Dr. Roy Kruitwagen*, *Prof. Dr. Gert Jan Scheffer* en *Dr. Marc Buise*. Bedankt voor jullie beoordeling en goedkeuring van mijn proefschrift.

Alle *AIOS en semi-artsen* die hebben meegeholpen met het verzamelen van de data voor mijn onderzoek mogen natuurlijk niet vergeten worden. Zonder de vele uren die jullie hebben besteed aan het includeren van patiënten en het bijhouden van data in de database, was mijn onderzoek nooit mogelijk geweest.

Beste *maten, vakgroepleden uit het Zuyderland*, bedankt voor het vertrouwen dat jullie me hebben gegeven door mij in jullie vakgroep op te nemen! Jullie hebben geen idee hoeveel ik jullie steun heb gewaardeerd en hoe blij ik ben met jullie voorbereidingen om massaal aanwezig te kunnen zijn bij de verdediging van mijn proefschrift.

Mijn paranimfen *Fleur Franssen* en *Markus Janssen*, jullie wil ik bedanken voor jullie onmisbare hulp om deze dag tot een goed einde te brengen!

Mijn familie

Pap, jij was de eerste die tegen me zei dat ik deze kans niet moest laten schieten, de eerste die me ervan wist te overtuigen dat ik dit kon. Zonder jouw steun was ik nooit aan dit promotietraject begonnen. *Marijke*, jij hebt er altijd voor gezorgd dat álle kinderen konden rekening op een veilige plek en de nodige steun!

Jos en Philomène, bedankt voor alle keren, gepland en ongepland, dat jullie op Lexie hebben willen passen. Hierdoor heb ik de tijd gekregen om in alle rust aan mijn onderzoek te werken én hebben Robbie en ik de tijd gekregen om regelmatig samen lekker te gaan eten.

Lieve *Robbie*, toen we elkaar leerden kennen was ik al druk bezig met mijn promotietraject, waardoor ik ook regelmatig thuis in mijn eigen tijd bezig was. Dit heeft je er niet van weerhouden om me jarenlang te steunen. Meerdere keren heb ik eraan

gedacht de moed op te geven, maar jij wist me er steeds van te overtuigen dat ik in staat was dit tot een goed einde te brengen, waardoor ik weer voldoende moed kreeg om door te zetten. Inmiddels zijn we ruim zes jaar verder, zijn we getrouwd, hebben we een prachtige dochter, *Lexie*, en is ons tweede meisje onderweg. Ik hou ontzettend veel van jullie en kijk ernaar uit om nog meer tijd met jullie door te brengen!

Chapter 11

Curriculum Vitae and list of publications

Curriculum vitae

Daisy Hoofwijk was born on July 31st, 1985 in Sittard, The Netherlands. After graduating cum laude from high school at the Trevianum in Sittard in 2004, she started medical training at the University of Maastricht, where she obtained her bachelor degree cum laude in 2007 and her master degree in 2010. She finished her scientific internship at the department of Anesthesiology and Pain Treatment of the Maastricht University Medical Center, during which she started gathering the data for her thesis. After receiving her medical degree in 2010 she started her residency in Anesthesiology at the Maastricht University Medical Center. She finished her residency in 2016, after which she started working as a staff anesthesiologist and followed a fellowship in Pain Treatment in the same hospital. In 2017 she started working as an anesthesiologist and pain practitioner in Zuyderland Medical Center, Heerlen and Sittard. Daisy is married to Robbie, and together they have a daughter, Lexie.

List of publications

Publications

- Hoofwijk DMN, Fiddelers AAA, Peters ML, Stessel B, Kessels AG, Joosten EA, Gramke HF, Marcus MAE. Prevalence and predictive factors of chronic postsurgical pain and poor global recovery one year after outpatient surgery. *Clin J Pain*, 2015 Dec;31(12):1017-25
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- Hoofwijk DMN, van Reij RRI, Rutten BPF, Kenis G, Theunissen M, Joosten EA, Buhre WF, van den Hoogen NJ. Genetic polymorphisms and prediction of chronic postsurgical pain 3 and 12 months after hysterectomy. *Submitted*

Book Chapters

- Chronische pijn na een lumpectomie; Hoofwijk DMN, Fiddelers AAA, Bouman EA. Probleemgeoriënteerd denken in de pijngeneeskunde, De Tijdstroom, 2017

Posters and presentations

- Hoofwijk DMN, Fiddelaers AAA, Klein Ovink J, Gramke HF, Marcus MAE. Postoperative analgesic use increases by providing a preoperative prescription. Euroanesthesia 2010, Helsinki, Finland
- Fiddelaers AAA, Hoofwijk DMN, Klein Ovink J, Gramke HF, Marcus MAE. Preoperative analgesic use is a predictor of postoperative pain in ambulatory surgery. Euroanesthesia 2010, Helsinki, Finland
- Hoofwijk DMN. Does preoperative analgesic use and quality of life predict postoperative pain after outpatient surgery? Presentation NVA dagen, Maastricht, The Netherlands.
- Hoofwijk DMN, Fiddelaers AAA, Gramke HF, Marcus MAE. Does preoperative quality of life predict pain after outpatient surgery? Euroanesthesia 2011, Amsterdam, The Netherlands
- Hoofwijk DMN, Fiddelaers AAA, Kropman L, Gramke HF, Marcus MAE. Health care consumption during the first four days after outpatient surgery. Euroanesthesia 2012, Paris, France.
- Fiddelaers AAA, Hoofwijk DMN, Gramke HF, Marcus MAE. The correlation between preoperative, acute postoperative and persistent postoperative pain. Euroanesthesia 2012, Paris, France
- Hoofwijk DMN, Fiddelaers AAA, Gramke HF, Marcus MAE. Health care consumption and chronic postsurgical pain one year after outpatient surgery. Anesthesiology (ASA meeting) 2012, Washington DC, United States
- Hoofwijk DMN, Fiddelaers AAA, Gramke HF, Marcus MAE. Does acute postoperative pain truly predict chronic postsurgical pain (CPSP)? 7th World Congress World Institute of Pain, Maastricht, The Netherlands
- Hoofwijk DMN, Fiddelaers AAA, Emans PJ, Joosten EA, Gramke HF, Marcus MAE, Buhre WFFA. Prevalence and predictive factors of chronic postsurgical pain and global recovery one year after outpatient knee arthroscopy. Anesthesiology (ASA meeting) 2015, San Diego, United States
- Van Reij RRI, Hoofwijk DMN, Rutten BP, Kenis G, van den Hoogen NJ, Buhre WFFA, Joosten EA. Genetic polymorphisms and their association with the prevalence and severity of chronic postsurgical pain. NVA Wetenschapsdag 2016, Ede, The Netherlands