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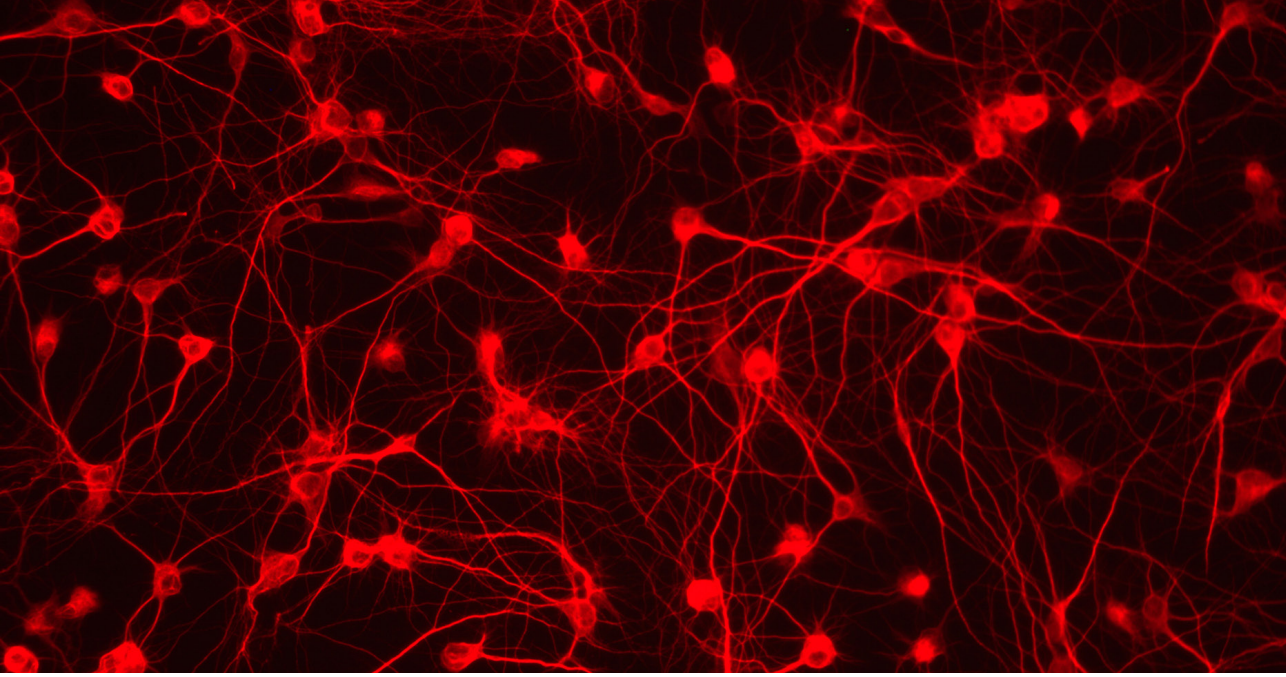

CHRONIC POSTOPERATIVE PAIN AFTER ROBOT-ASSISTED LAPAROSCOPIC HYSTERECTOMY FOR ENDOMETRIAL CANCER

BY
SØREN LUNDE

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AALBORG UNIVERSITY
DENMARK

CHRONIC POSTOPERATIVE PAIN AFTER ROBOT-ASSISTED LAPAROSCOPIC HYSTERECTOMY FOR ENDOMETRIAL CANCER

PhD dissertation by

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Dissertation submitted August 2020

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ENGLISH SUMMARY

Endometrial cancer is a relative common malignant disease among postmenopausal women in Denmark. Early diagnose and advanced robot-assisted laparoscopic surgery contributes to high survival rates. The reported health-related quality of life following surgery for endometrial cancer is high with corresponding low risk of psychosocial and physical long-term effects. Nevertheless, any surgical procedure entails a risk of adverse outcome, like chronic postoperative pain. Chronic postoperative pain decreases the quality of life for the affected patients and poses a significant challenge in the analgesic management for us as clinicians. Chronic postoperative pain is the end product of a complex cascade of interactions between neuronal pathophysiologic processes, comorbidity, psychological traits and socioeconomic factors. Evidence suggest that a range of preoperative risk factors might increase the susceptibility to development of chronic postoperative pain, like pre-existing pain conditions, socioeconomic disadvantage and certain serologic compositions of lipids and lipoproteins. Furthermore, some evidence indicate that preoperative quantitative sensory testing can identify patients at risk of developing chronic postoperative pain.

If we as clinicians had a better understanding of some of these risk factors - or even could identify patients at risk - we could counsel our patients better prior to surgery, and conceivably even reduce the risk of developing chronic postoperative pain through interventions and clinical trials. The overall aim of this PhD dissertation was to investigate some of the many aspects of chronic postoperative pain following surgery for endometrial cancer: What is the prevalence? What are the risk factors? Can the development of chronic postoperative pain be predicted? To answer these questions, we conducted three studies of chronic postoperative pain which are presented in this PhD dissertation.

The first study was a questionnaire-based study among two-hundred-and-seven patients treated for endometrial cancer at Aalborg University Hospital from January 1st, 2010 till July 31st, 2015. The prevalence of chronic postoperative pain was 14.9% (95% CI 10.4-20.6). Preoperative pelvic pain and a high level of acute postoperative pain were shown to be independent risk factors for development of chronic postoperative pain with an OR of 4.99 (95% CI 4.15-5.83) and 1.27 (95% CI 1.09-1.45), respectively.

The second study was a nested, case-control study, where seventy-eight preoperative blood samples from The Danish Cancer Biobank were analyzed by means of nuclear magnetic resonance spectroscopy. Here, we hypothesized that patients who developed chronic postoperative pain had a distinctive preoperative serologic composition of lipids and lipoproteins, compared to patients who did not develop chronic postoperative pain. The results demonstrated that we could not discriminate between these two groups when including all risk assessments groups - nor could we predict the development of chronic postoperative pain.

The third study was a longitudinal, observational cohort study of one-hundred-and-forty patients treated for endometrial cancer from August 1st, 2015 till December 31st, 2018. The prevalence of chronic postoperative pain was 13.6% (95% CI 8.4-20.4) and preoperative pelvic pain again showed to be an independent risk factor with an OR of 6.62 (95% CI 2.26-19.44). In this study, we further hypothesized that preoperative quantitative sensory testing could predict development of chronic postoperative pain, which was rejected.

Through the studies presented in this PhD dissertation we add valuable new insights to the existing knowledge on chronic postoperative pain after robot-assisted laparoscopic hysterectomy for endometrial cancer.

DANSK RESUME

Endometriecancer er en relativ hyppig kræftform blandt danske kvinder efter overgangsalderen. Tidlig diagnosticering og avanceret behandling i form af robot-assisteret laparoskopisk kirurgi bidrager til en høj overlevelsesrate. Den sundhedsrelaterede livskvalitet efter kirurgi for endometriecancer er høj, mens risikoen for psykosociale og somatiske mén er tilsvarende lav. På linje med al anden kirurgi kan robot-assisteret laparoskopisk kirurgi dog medføre uønskede bivirkninger, såsom kronisk postoperativ smerte. Kronisk postoperativ smerte nedsætter livskvaliteten for de ramte patienter, og den smertestillende behandling udgør en betragtelig klinisk udfordring. Kronisk postoperativ smerte er resultatet af en kompleks kaskade af interaktioner mellem neurale patofysiologiske processer, komorbiditet, psykologiske karaktertræk og socioøkonomiske faktorer. Forskningsresultater indikerer, at en række præoperative risikofaktorer måske kan øge modtageligheden for udvikling af kronisk postoperativ smerte, såsom præeksisterende smertetilstande, lav socioøkonomisk status samt visse serologiske sammensætninger af lipider og lipoproteiner. Derudover viser nogle forskningsresultater, at patienter i risiko for udvikling af kroniske postoperative smerter kan identificeres præoperativt ved hjælp af kvantitative sensoriske testmetoder.

Hvis vi som klinikere havde en bedre forståelse for disse risikofaktorer - eller ligefrem kunne identificere risikopatienter - da kunne vi give en bedre præoperativ rådgivning. Endvidere kunne vi muligvis reducere risikoen for udvikling af kroniske postoperative smerter via interventioner og kliniske forsøg. Det overordnede formål med denne PhD afhandling var at belyse nogle af de mange aspekter af kroniske postoperative smerter: Hvad er prævalensen? Hvilke risikofaktorer er der? Kan man forudsige, hvem der udvikler kroniske postoperative smerter? For at besvare disse spørgsmål, gennemførte vi tre studier af kroniske postoperative smerter, som præsenteres i denne PhD afhandling.

Det første studie var et spørgeskema-baseret studie af to-hundrede-og-syv patienter behandlet på Aalborg Universitetshospital i perioden fra 1. januar 2010 til 31. juli 2015. Prævalensen af kronisk postoperativ smerte var 14,9% (95% CI 10,4-20,6). Tilstedeværelsen af præoperative bækkensmerter samt et højt akut postoperativt smerteniveau var begge signifikante risikofaktorer for udvikling af kronisk postoperativ smerte med en OR på henholdsvis 4,99 (95% CI 4,15-5,83) og 1,27 (95% CI 1,09-1,45).

Det andet studie var et case-kontrol studie, hvor otte-og-halvfjerds præ-operative blodprøver fra den Danske Cancer Biobank blev analyseret med nuklear magnetisk resonansspektrografi. Her var vores hypotese, at patienter der udviklede kroniske postoperative smerter, havde en distinkt præoperativ serologisk sammensætning af lipider og lipoproteiner, sammenlignet med patienter, der ikke udviklede kroniske postoperative smerter. Resultaterne viste, at vi ikke kunne skelne disse patientgrupper fra hinanden, når vi inkluderede patienter fra alle risikokategorier - ej heller kunne vi forudsige udvikling af kronisk postoperativ smerte.

Det tredje studie var et longitudinelt observationsstudie af ét-hundrede-og-fyrre patienter behandlet på Aalborg Universitetshospital i perioden fra 1. august 2015 til 31. december 2018. Prævalensen af kronisk postoperativ smerte var 13,6% (95% CI 8,4-20,4) og tilstedeværelsen af præoperative bækkensmerter viste sig atter som en signifikant risikofaktor for udvikling af kronisk postoperativ smerte med en OR på 6,62 (95% CI 2,26-19,44). I dette studie var vores hypotese endvidere, at kvantitative sensoriske testmetoder kunne identificere patienter i risiko for udvikling af kroniske postoperative smerter, hvilket ikke var tilfældet.

Studierne i denne PhD afhandling tilføjer værdifuld ny viden om kronisk postoperativ smerte efter robot-assisteret laparoskopisk kirurgi for endometriecancer.

ACKNOWLEDGEMENTS

This PhD dissertation is the result of my enrolment as a part time PhD student at The Department of Clinical Medicine, Aalborg University from 2015 to 2019. It has truly been an exciting, fulfilling and - at times demanding - journey.

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Søren Lunde
Aalborg, August 2020

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ABBREVIATIONS

AA	Arachidonic acid
AUC	Area under the curve
BMI	Body mass index
CI	Confidence intervals
CPM	Conditioned pain modulation
DAG	Directed acyclic graph
DCB	The Danish Cancer Biobank
DHA	Docosahexaenoic acid
DNIC	Diffuse noxious inhibitory control
EORTC	The European Organization for Research and Treatment of Cancer
EPA	Eicosapentaenoic acid
ESGO	The European Society of Gynecological Oncology
ESMO	The European Society for Medical Oncology
ESTRO	The European Society for Radiotherapy and Oncology
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
HPT	Heat pain threshold
HRQoL	Health-related quality of life
IASP	The International Association for the Study of Pain
IDL	Intermediate density lipoproteins
IDL-L	Total lipids in IDL
IDL-P	Concentration of IDL particles
IDL-TG	Triglycerides in IDL
Ile	Isoleucine
L-LDL-TG	Triglycerides in large LDL
LA	Linoleic acid
LDL	Low density lipoproteins
LDL-TG	Triglycerides in LDL
M-LDL-TG	Triglycerides in medium LDL
NMR	Nuclear magnetic resonance
NRS	Numeric rating scale

OR	Odds ratio
PAG	Periaqueductal gray matter
PCA	Principal component analysis
PDT	Pain detection threshold
PPT	Pressure pain threshold
PTT	Pain tolerance threshold
QLQ	Quality of life questionnaire
QST	Quantitative sensory testing
RASHEC	Robot-assisted surgery for high-risk endometrial cancer
Remnant-C	Remnant cholesterol (non-HDL, non-LDL-cholesterol)
RMIS	Robot-assisted minimally invasive surgery
ROC	Receiver operating characteristic curve
RR	Relative risk
RVM	Rostral ventromedial medulla
S-LDL-TG	Triglycerides in small LDL
S-VLDL-C	Cholesterol in small VLDL
S-VLDL-CE	Cholesteryl esters in small VLDL
SF-36	The medical outcomes study short-form
SLN	Sentinel lymph nodes
sPLA-DA	Sparse partial least squares-discriminant analysis
TSP	Temporal summation of pain
VAS	Visual analogue scale
VLDL	Very low-density lipoproteins
WDT	Warm detection threshold
WHO	World Health Organization
XS-VLDL-C	Cholesterol in very small VLDL
XS-VLDL-CE	Cholesteryl esters in very small VLDL
XS-VLDL-FC	Free cholesterol in very small VLDL
XS-VLDL-L	Total lipids in very small VLDL
XS-VLDL-P	Concentration of very small VLDL particles
XS-VLDL-PL	Phospholipids in very small VLDL
XS-VLDL-TG	Triglycerides in very small VLDL

LIST OF PAPERS

This PhD dissertation is based on three studies presented in the following published, scientific papers:

Paper I

Søren Lunde, Kristian Kjær Petersen, Pirathiv Kugathasan,
Lars Arendt-Nielsen and Erik Søgaard-Andersen.
Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer.
Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146[1].

Paper II

Søren Lunde, Hien Thi Thu Nguyen, Kristian Kjær Petersen,
Lars Arendt-Nielsen, Henrik B. Krarup and Erik Søgaard-Andersen.
Chronic Postoperative Pain After Hysterectomy for Endometrial Cancer:
A Metabolic Profiling Study.
Molecular Pain. Volume 16, May 2020, 1-7[2].

Paper III

Søren Lunde, Kristian Kjær Petersen,
Erik Søgaard-Andersen and Lars Arendt-Nielsen.
Preoperative Quantitative Sensory Testing and Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer: Can Chronic Postoperative Pain be Predicted?
Scandinavian Journal of Pain, E-pub. ahead of print, August 2020, 1-13[3].

CHAPTER 1. BACKGROUND

1.1. ENDOMETRIAL CANCER

1.1.1. EPIDEMIOLOGY

Malignant neoplasm of the endometrium is the fourth most common cancer among women in Western Europe and the United States of America[4]. The incidence in Denmark is approximately 800 cases per year and an age-standardized incidence rate of 13.5 per 100,000 persons / year[5]. Endometrial cancer predominately affects postmenopausal women with an incidence peak at 70 to 75 years of age[5] (fig. 1).

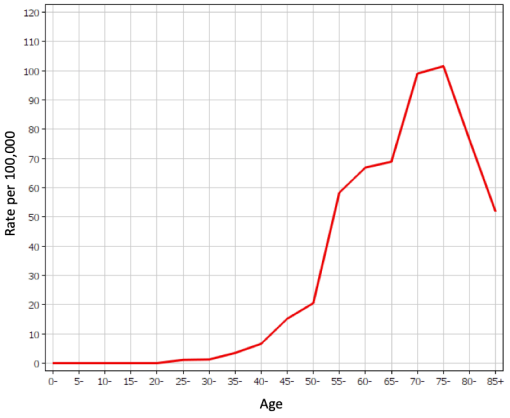

Figure 1: *The age-related incidence of endometrial cancer in Denmark in 2016. Reprint from NORDCAN 2019 - Association of the Nordic Cancer Registries.*

Endometrial cancers can be classified by the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) stage and the clinical and histologic type[6,7] (see section 1.1.2. and 1.1.3.). More than 75% of the Danish cases are diagnosed in FIGO stage I with a 5-year survival of 85.1%[8]. The overall 5-year survival for all FIGO stages is 75.5%[8]. When stratifying mortality rates by the classification in type I and II tumors, Gustafson et al recently found that the mortality rate for type I tumors in Denmark had declined in the time period from 2002-2015 with an annual percent change of -2.3 (95% CI -3.9, -0.7) and a 5-year survival rate of 89.8% (95% CI 89.0-90.5)[9]. In contrast, the authors found that the mortality rate for type II tumors had increased in the same time period with an annual percent change of +5.9 (95% CI 3.0-8.9) and a 5-year survival rate of 57.2% (95% CI 54.0-60.3)[9].

1.1.2. ETIOLOGY

Endometrial cancers are a diverse group of neoplasms which differ in pathophysiology. A classification can either be based on the clinical manifestations in type I and II tumors - or by the histopathologic characteristics; the latter will be described in section 1.1.3.

The estrogen-dependent tumors (type I, endometrioid) account for approximately 90% of the endometrial cancers[10] (fig. 2). Atypical endometrial hyperplasia is considered as a precursor lesion, which over time may progress to endometrial cancer in 5-25% of the cases[11]. Glandular and stromal hyperplasia of the endometrium is stimulated by estrogen[12]. Consequently, unopposed long term estrogen stimulation, obesity, early menarche and late menopause all increase the risk of endometrial cancer[12].

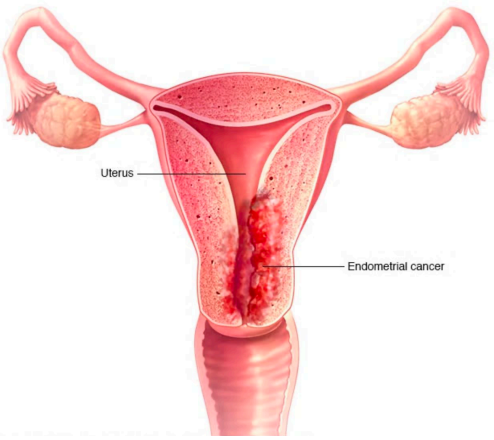

***Figure 2**: Uterus with endometrial cancer. Used with permission of MAYO Foundation for Medical Education and Research, all rights reserved.*

The second group of tumors (type II, non-endometrioid) accounts for less than 10% and mainly consists of the serous, mucinous and clear cell adenocarcinomas, which can arise from an atrophic endometrium and are largely estrogen-independent[13]. Type II tumors are more aggressive in their clinical behavior; even though they comprise only 10% of the endometrial cancers, they account for more than 40% of deaths from the disease[14,15].

1.1.3. CLASSIFICATION AND STAGING

Endometrial cancer is a malignant epithelial tumor which can be classified by histopathological characteristics into endometrioid carcinomas (the vast majority endometrioid adenocarcinomas) and other epithelial carcinomas (serous, mucinous and clear cell adenocarcinomas)[10,16,17]. The endometrioid adenocarcinomas can furthermore be classified based on the degree of glandular differentiation in grade 1 (≤5% solid non-glandular growth), grade 2 (from 6% to 50% solid non-glandular growth) and grade 3 (>50% solid non-glandular growth)[18]. Other rare types of uterine cancer include mesenchymal tumors and mixed epithelial- and mesenchymal tumors[19,20]. Subtypes of the latter group of tumors are carcinosarcomas, which consist of both a malignant carcinomatous and a sarcomatous component - and adenosarcomas, which consist of a benign epithelial component and a sarcomatous component[19,20]. In the clinical setting, carcinosarcomas are classified along with the carcinomas, since they share similar risk factors and are treated alike[21]. The tumors are staged according to the revised FIGO classification from 2009[22] (table 1).

Histopathologic classification	**FIGO stages**
Epithelial tumors	I: Tumor confined to the uterus
Endometrioid carcinomas	IA: <50% myometrial invasion
Endometrioid adenocarcinomas	IB: ≥50% myometrial invasion
Grade 1	II: Tumor invades the cervical stroma but does not extend beyond the uterus.
Grade 2	III: Local or regional spread of tumor
Grade 3	IIIA: Serosal or adnexal invasion
Mucinous adenocarcinomas	IIIB: Vaginal or parametrial involvement
Serous adenocarcinomas	IIIC: Metastasis to pelvic or paraaortic lymph nodes.
Clear cell adenocarcinomas	IIIC1: Pelvic lymph node involvement
Mesenchymal tumors	IIIC2: Paraaortic lymph node involvement
Leiomyosarcoma	IV: Extension to the pelvic wall, lower one-third of the vagina or hydronephrosis or nonfunctioning kidney.
Mixed epithelial and mesenchymal tumors	IVA: Invasion of bladder or bowel mucosa.
Carcinosarcomas	IVB: Distant metastases, including abdominal or involvement of inguinal lymph nodes.
Adenosarcomas	

***Table 1**: Histopathologic classification according to WHO (World Health Organization)[10] and staging according to FIGO (Fédération Internationale de Gynécologie et d'Obstétrique)[18,22].*

1.1.4. DIAGNOSIS AND TREATMENT

The predominant symptoms of endometrial cancer are postmenopausal vaginal bleeding or menometrorrhagia in the premenopausal patients[10]. The diagnosis is based on histologic examination of an endometrial biopsy. The treatment in early stage disease is surgical with hysterectomy and bilateral salpingo-oophorectomy[23]. The removal of pelvic and / or paraaortic lymph nodes does not improve survival, but is solely done for staging purposes[24,25]. In case of stage III or IV disease, the standard adjuvant treatment in Denmark consists of chemotherapy with carboplatin and paclitaxel, while radiotherapy is rarely applied, as studies have shown radiotherapy fails to increase the overall survival, yet increasing the treatment-related morbidity[26–29].

During the last decade, the technological innovation has shifted the procedure from open access surgery and laparoscopic minimally invasive surgery to robot-assisted minimally invasive surgery (RMIS). The introduction of RMIS in gynecology in Denmark began in 2008 at Aalborg University Hospital and nationwide adoption soon followed (fig. 3)[30,31].

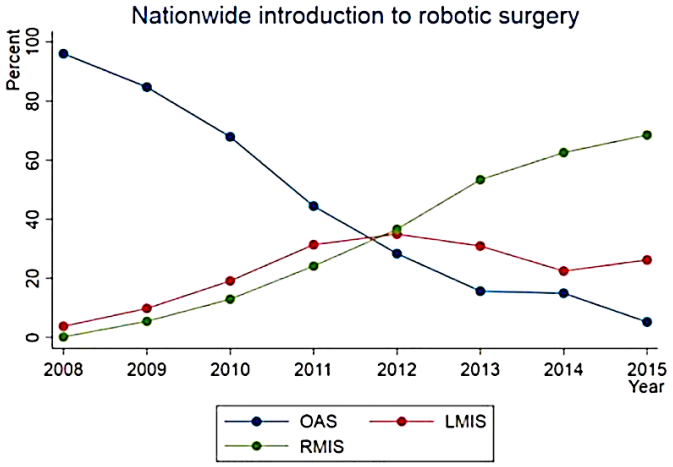

***Figure 3**: The introduction of Robot-assisted Minimally Invasive Surgery (RMIS) in Denmark from 2008 to 2015. Open Access Surgery (OAS), Laparoscopic Minimally Invasive Surgery (LMIS). Reprint from Long term resource consequences of a nationwide introduction of robotic surgery for women with early stage endometrial cancer. Korsholm et al. Gynecol. Oncol. 2019 Aug;154(2):411-419.*

Studies have shown an association between the introduction of RMIS in the surgical treatment of early stage endometrial cancer and improved survival rates and reduced risk of severe complications[30,32,33]. In respect to surgical training, Lim et al found that RMIS had a steeper learning curve for hysterectomy with lymphadenectomy when compared to open access surgery and laparoscopic minimally invasive surgery[34]. Finally, the Robot-Assisted Surgery for High-Risk Endometrial Cancer (RASHEC) trial showed non-inferiority in paraaortic lymphadenectomy, shorter length in hospital stay, and lower total cost for RMIS over open access surgery in high risk cases of endometrial cancer[35].

Different treatment strategies have been applied over the course of time. At the first joint consensus conference of The European Society for Medical Oncology (ESMO), The European Society of Gynecological Oncology (ESGO) and The European Society for Radiotherapy and Oncology (ESTRO) in 2014, a treatment algorithm for lymphadenectomy was agreed upon[36]: The patients were to be preoperatively stratified into risk categories based on histologic type and grade: The low risk cases (endometrioid adeno-carcinoma with grade 1 or 2 and superficial myometrial invasion <50%) should be treated with hysterectomy and bilateral salpingo-oophorectomy; intermediate risk cases (deep myometrial invasion >50% or grade 3 superficial myometrial invasion <50%) with optional, additional lymphadenectomy and in high-risk cases (grade 3 with deep myometrial invasion >50% and all non-endometrioid types) lymphadenectomy was recommended[36].

Comprehensive lymphadenectomy, however, has an inherent risk of perioperative bleeding, nerve damage and postoperative lymphedema[37,38]. In an effort to minimize the risk of these complications, Abu-Rustum and colleagues at Memorial Sloan Kettering Cancer Center introduced a treatment algorithm for removal of sentinel lymph nodes (SLN) during RMIS by intraoperative mapping using near-infrared fluorescence after cervical

injection of indocyanine-green dye[39,40]. The SLN algorithm, which has since been adopted by many centers, has been shown to decrease the incidence of lymphoedema and other major postoperative complications while having a high degree of diagnostic accuracy[41–43].

1.1.5. HEALTH-RELATED QUALITY OF LIFE

As endometrial cancer is a relatively common cancer with high survival rates, the accumulated number of long-term survivors is correspondingly high[44]. Seeing that both endometrial cancer and its treatment can be debilitating, the need to consider the impact on the Health-Related Quality of Life (HRQoL) has become increasingly evident. Consequently, HRQoL has become an integrated part of the evaluation of therapeutic interventions[45]. Several validated questionnaires have been developed for this purpose, e.g. The Medical Outcomes Study Short-Form (SF-36) questionnaire and The Quality of Life Questionnaire (QLQ-C30) from The European Organization for Research and Treatment of Cancer (EORTC)[45,46].

While SF-36 is a general measure of HRQoL, the QLQ-C30 is cancer specific and incorporates functional scales (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, and nausea/vomiting), global health status scale, and finally a number of items assessing cancer related symptoms[45]. Furthermore, a supplementary questionnaire module concerning endometrial cancer has been developed by the EORTC, entitled QLQ-EN24[47].

A literature search of HRQoL studies on endometrial cancer performed over the last two decades found 7 studies using the SF-36 questionnaire[48–54], 4 studies using the QLQ-C30/EN24 questionnaire[44,55–57] and 1 study using the SF36 and the QLQ-EN24 questionnaires in combination[58]. The majority of these studies compare the HRQoL in series of surgery (open access surgery or laparoscopic minimally invasive surgery) versus surgery and adjuvant

radiotherapy[44,52,56–58], while others evaluate the effect on HRQoL of physical activity, lifestyle changes and mental health[49–51]. Overall, endometrial cancer patients report high scores of HRQoL and low risk of psychosocial and physical long-term effects[44,52,58]. The HRQoL of endometrial cancer survivors approximates that of healthy controls within 3-5 years post-treatment[44,51].

Conflicting results have been found when addressing the effect on HRQoL of adjuvant radiotherapy. Here, Becker et al found that radiotherapy did not impact HRQoL or sexual function, while Lonneke et al showed that radiotherapy had a negative effect on HRQoL[52,57]. The latter was moreover the conclusion in a systematic Cochrane review of adjuvant radiotherapy for stage I endometrial cancer[29].

As obesity is a well-known risk factor for endometrial cancer, this could explain the high prevalence of obesity among endometrial cancer survivors[59]. When exploring the impact of physical activity and lifestyle on HRQoL, Basen-Engquist et al and Gruenigen et al both concluded that the high prevalence of obesity and the associated poor lifestyle choices contributed significantly to the reduced quality of life found in these studies among endometrial cancer survivors[49,50].

In regard to surgical approach, Zullo et al examined HRQoL in a prospective randomized trial of open access surgery versus laparoscopic minimally invasive surgery[48]. Here, the authors found that patients treated with laparoscopic minimally invasive surgery scored significantly higher in HRQoL and lower in postoperative pain scores than those treated with open access surgery[48]. Similar conclusions were made by Kornblith et al in a HRQoL study of the Gynecologic Oncology Group Study LAP2 cohort, showing modest support for laparoscopic minimally invasive surgery over open access surgery[54,60].

Of particular interest to the subject of this PhD dissertation, Salehi et al examined the HRQoL in the cohort defined by the RASHEC trial, mentioned above[35,55]. As the only published study of HRQoL among patients treated with robot-assisted minimally invasive surgery, the authors found no significant difference between HRQoL scores 12 months after RMIS compared to open access surgery for high-risk endometrial cancer with comprehensive lymphadenectomy[55].

In a recent study by Klapheke et al, prediagnose HRQoL scores were shown to be associated to the survival rate of elderly women with endometrial cancer, thus implying HRQoL to have a prognostic value in itself[53].

While generic HRQoL questionnaires, like SF-36 and QLQ-C30/EN24, are well-suited for a broad assessment of the quality of life, they are less suited for detailed assessments of chronic postoperative pain as these questionnaires only contain a limited number of items concerning pain[45,46]. Consequently, many studies of chronic postoperative pain utilize questionnaires developed specifically to address this subject[61–65]. Nonetheless, it is important to bear in mind that chronic postoperative pain is merely *one* aspect in the overall quality of life for the patients.

1.2. THE PHYSIOLOGY OF PAIN

Knowledge of the basic principles of pain perception is essential when investigating the phenomenon of chronic postoperative pain. Therefore, a brief introduction to the relevant anatomy and physiology will be given in this section.

1.2.1. THE DEFINITION OF PAIN

The International Association for the Study of Pain (IASP) defines pain as

> *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."* [66]

An unambiguous definition of chronic pain, nevertheless, has not been agreed upon. A widely used definition is persistent pain 3-6 months after the injury[67].

1.2.2. THE ASCENDING PATHWAY

When tissue is exposed to a noxious stimulus, being mechanical, chemical or thermal, afferent sensory neurons are activated once a threshold is reached. The signal is passed along the axon of the neuron, termed the first-order neuron, to the root ganglia of the dorsal horn of the spinal cord[68] (fig. 4).

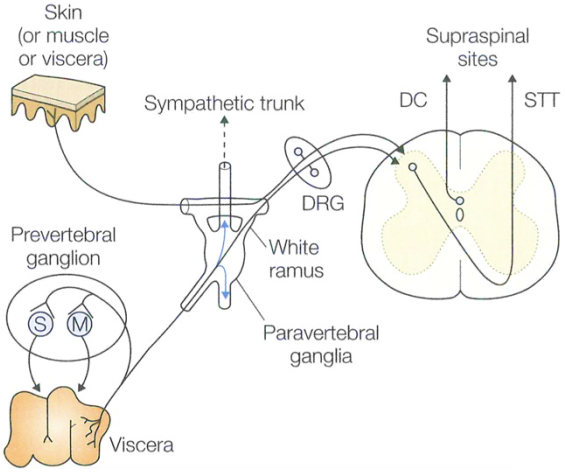

***Figure 4**: Anatomy of the ascending pathway. Dorsal root ganglia (DRG), dorsal column (DC) and spinothalamic tract (STT), Secretory neuron (S), Motor neuron (M).*
Reprint from Wall and Melzack's Textbook of Pain (p706), McMahon et al, 6th Edition, Elsevier, 2013.

Here it synapses with the second-order neuron which decussates to the contralateral side and ascends via the spinothalamic tract to the thalamus and synapses with the third-order neuron[69]. The nociceptive signals are processed in the brain stem, thalamus and the somatosensory cortex, where additional cognitive and emotional context may alter the perception of pain[68].

1.2.3. THE DESCENDING PATHWAY

The existence of a descending modulatory control was proposed more than 50 years ago by Melzack and Wall, when they introduced the gate control theory[70]. The modulatory mechanism, which has since been shown to exist, describes how the dorsal spinal horn modulates neuronal activity by inhibiting or facilitating transmission of the impulses to the upper levels of the central nervous system[71]. Activity in the amygdala of the frontal lobe descends via neurons to the periaqueductal gray matter (PAG) located in the midbrain and then relays via synapses in the rostral ventromedial medulla (RVM). From here it descends further down the spinal cord and terminates in dorsal horn, where the release of neuro transmitters can inhibit or facilitate the transmission of signals from the afferent sensory nerves[72] (fig. 5).

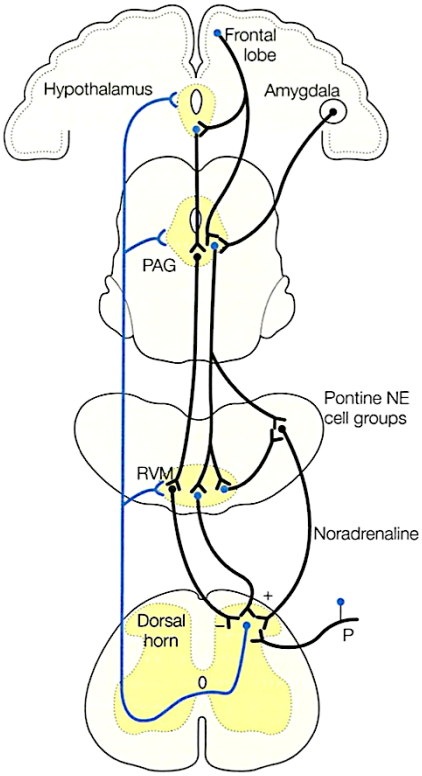

***Figure 5**: Anatomy of the descending pathway. Periaqueductal gray matter (PAG), rostral ventromedial medulla (RVM), noradrenaline (NE), primary afferent nerve (P). Reprint from Wall and Melzack's Textbook of Pain (p131), McMahon et al, 6th Edition, Elsevier, 2013.*

1.2.4. VISCERAL PAIN

While pain arising from superficial somatic structures like skin, fascia or muscle is relatively well-described and studied, much less is known about visceral pain. Visceral structures are, in contrast to somatic structures, innervated by both spinal nerves (including sympathetic nerve fibers) and the parasympathetic vagus nerve and sacral nerves[73]. Furthermore, most visceral nerves synapse in pre- and paravertebral ganglia and give rise to secretory and motor neurons, thereby affecting the function of the organ (fig. 4)[68].

The afferent visceral nerves also synapse in the dorsal horn of the spinal cord, where they converge with nerve endings from other structures from the same spinal segment, i.e. somatic nerves from superficial structures or other visceral afferent nerves[74]. This anatomical relationship is the physiologic substrate for the phenomenon of referred pain between visceral structures and somatic structures (termed viscero-somatic convergence) or between two visceral structures (termed viscero-visceral convergence)[67]. An example of this phenomenon can be seen in cholecystolithiasis patients with cutaneous hyperalgesia in the referred area[75,76]. In contrast to somatic pain, visceral pain is often difficult to pinpoint and diffuse in character[68].

1.2.5. PRIMARY HYPERALGESIA

Tissue injury induces a release of inflammatory mediators which lower the excitatory threshold of the afferent sensory nerves[77]. This sensitization process, termed primary hyperalgesia, increases the peripheral pain sensitivity temporarily and can be categorized as an adequate, physiologic response to trauma[78]. Once the noxious stimulus has stopped and the inflammation has subsided, the excitatory thresholds are - in most cases - restored to normal levels again.

1.2.6. CENTRAL SENSITIZATION

The increase in sensory afferent neuronal activity during primary hyperalgesia causes an equivalent increase in the neuronal activity of the dorsal horn and the rest of the ascending pathway. In some cases, this central sensitization fails to diminish and can furthermore be accentuated by the loss of segmented inhibitory transmission[79,80]. This pathophysiologic phenomenon of widespread sensitization is believed to be a key element in chronic pain conditions with hyperalgesia and allodynia[81].

1.2.7. PRO- AND ANTINOCICEPTIVE MODULATORS

A broad range of hormones and inflammatory mediators act as pro- or antinociceptive modulators, e.g. interleukin-1, interleukin-6 and tumor necrosis factor-α, adrenalin and noradrenalin[77]. Emerging evidence indicates that lipids and lipoproteins may also have a nociceptive modulatory effect via alterations of the cellular membrane microdomain composition[82]. Lipoproteins like the polyunsaturated fatty acids omega-3 and omega-6 demonstrate opposing effects on the serologic environment: The main omega-6 derivatives are linoleic acid (LA) and arachidonic acid (AA), both shown in studies to hold a pronociceptive capacity, while the omega-3 derivatives eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have an antinociceptive capacity[83,84].

The dietary intake of omega-6 and omega-3 fatty acids regulate the circulating levels as de novo synthesis in mammals is not possible[85]. An association between the dietary intake of fatty acids and nociception was shown in a study by Ramsden et al, where a diet induced reduction of circulating LA was shown to lower the frequency and severity of headaches among patients suffering from chronic headaches[86]. Likewise, several rodent studies have shown a high dietary intake of LA induces hyperalgesia and allodynia[84,87,88].

1.3. POSTOPERATIVE PAIN

The terms persistent postsurgical pain, chronic postsurgical pain and chronic postoperative pain are often used interchangeably in the literature. Throughout this dissertation, only the term chronic postoperative pain will be used.

Equivalent to a traumatic tissue injury, a surgical tissue injury triggers the same physiologic cascade of inflammation and neuronal sensitization[77]. Besides establishing a surgical access via the skin and connective tissue, the surgical procedure could moreover transect visceral nerves, e.g. in case of colectomy or hysterectomy, thus further increasing the synaptic activity and neuronal bombardment of the dorsal horn in the given spinal segment.

Chronic postoperative pain is a severe clinical condition with disabling pain for 1 out of 10 affected individuals[89]. Nevertheless, chronic postoperative pain has been largely unrecognized by clinicians[77,90]. In parallel, a review from 2018 by Seers et al found that health care professionals underestimate the pain experienced by their patients and that the extent of underestimation tended to increase with pain severity[91].

The prevalence of chronic postoperative pain varies with the specific surgical procedure, e.g. 12.3% after caesarean section, 30.0% after hernia repair and 52.6% after limb amputation[92–94]. Every year, 40 million patients in Europe and 312 million patients worldwide undergo a surgical procedure[95,96]. Overall, an estimated 10% will develop a state of chronic postoperative pain, equivalent of more than 31 million new cases every year[97]. This alarming figure is gradually being recognized as a global public health problem, not only due to the significantly decreased quality of life of the affected individuals or the major socioeconomic burden it encompasses, but also due to the difficulties we as clinicians face in the analgesic management[98–100].

Many cases of chronic postoperative pain, including chronic postoperative pain following hysterectomy, exhibit the characteristics of neuropathic pain, e.g. burning pain with sensory loss and paradoxical hypersensitivity[77,101]. In these cases, sufficient analgesic effect can rarely be achieved by traditional first line drugs like acetaminophen and non-steroidal anti-inflammatory drugs, but require tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors or gabapentanoids[102].

Opioids have traditionally also been prescribed as an integrated part of the pain management algorithm. The use of opioids for chronic pain conditions in general has increased vastly over the last three decades, especially in the USA, where nearly one-third of the adult population currently use prescription opioids[103]. From 1999 to 2014, death by drug overdose (mainly prescription opioids) tripled in the USA, prompting the US health municipalities to declare an 'Opioid crisis' and initiate programs in order to reduce the use / misuse of opioids[104,105].

1.3.1. FACTORS AFFECTING POSTOPERATIVE PAIN

As described, the perception of pain can be modulated by a range of factors including neuronal sensitization, descending modulatory control and inflammatory mediators. Furthermore, numerous other factors have been shown to alter the perception of pain, including postoperative pain:

Psychological factors

The complex processing in the somatosensory cortex allows for pain perception to be altered by psychological conditions like pain catastrophizing, anxiety, depression, emotional distress and a history of sexual abuse[106–111]. This close relationship between psychological traits and perception of pain has been examined in a range of clinical studies, e.g. by Linton and Vlaeyen showing that the expectation of pain, fear and past memories all had a

negative effect on the perception of pain[112,113]. Conversely, cognitive therapy has been shown to modulate the perception of pain[114].

Socioeconomic factors

Socioeconomic factors like low educational level, undesirable employment status and financial uncertainty have also been shown to have a negative effect on the experienced pain intensity and duration[115–118]. In a review from 2008, Poleshuck and Green found that educational level was a good proxy for socioeconomic disadvantage as it was easy to obtain, unlikely to be changed by impaired health and had a better association with health status than income[119]. Additionally, socioeconomic disadvantage was consistently associated with increased morbidity, decreased life expectancy, higher infant mortality and increased risk for pain[119,120].

Comorbidity

As described above, the central sensitization that occurs in chronic pain conditions may increase the perception of acute pain and the perpetuation to other forms of chronic pain[121–123]. Chronic pain is a common finding in patients with multimorbidity[124,125]. Consequently, this aspect may also affect the development of chronic postoperative pain.

In a large cohort study of more than 200,000 people aged ≥65 years, Guisado-Clavero et al found that multimorbidity clustered in patterns of musculoskeletal disease, endocrine-metabolic disease, digestive / digestive-respiratory disease, neurological disease and cardiovascular disease with a median number of diseases per capita of 7[126].

Barnett et al found that 23.0% of the examined patients in the primary care system had multimorbidity and that 46.0% of those with chronic pain had three or more disorders[127]. Furthermore, the prevalence of multimorbidity increases significantly with age (fig. 6)[127–129].

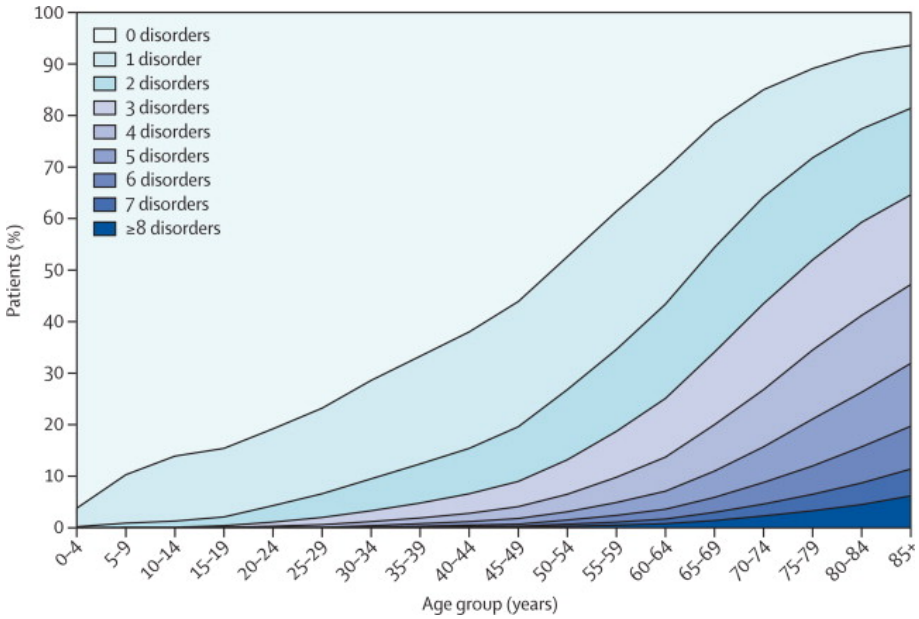

***Figure 6**: Number of chronic disorders by age-group.*
Reprint from Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. Barnett et al.
Lancet. 2012 Jul 7;380(9836):37-43.

Some of the most frequent pain causing comorbidities include arthritis (which affects an estimated 68.7% of all women aged ≥65 years[130]); lower back pain (with a one-year prevalence of 38.0% in the adult population[131]); coronary heart disease (with a lifetime risk of 24.2% for women aged ≥70 years[132]) and diabetes mellitus (which affects 20.0% of all patients ≥65 years of age, while an estimated 51.0% of these patients will develop pain causing peripheral neuropathy[133,134]).

Finally, multimorbidity has been associated with lower socioeconomic status[135]. Due to the association between multimorbidity and chronic pain, we must assume that a significant proportion of patients with endometrial cancer (incidence peak of 70-75 years of age) also have pain causing comorbidity.

Adjuvant treatment

Lastly, we must assume that the development of chronic postoperative pain may be affected by any form of surgical complication or adjuvant treatment. For instance, surgical-site infection has been shown to increase the risk of postoperative pain and adjuvant chemotherapy with carboplatin / paclitaxel have been shown to hold a risk of polyneuropathy[136–141].

The use of analgesic medication pre- and postoperatively is also an important aspect for several reasons. Firstly, consumption of analgesics can serve as a surrogate marker of an underlying chronic pain condition. Secondly, prolonged opioid exposure in some individuals can trigger a paradoxical opioid-induced hyperalgesia with nociceptive sensitization, thus increasing the perception of pain[142,143].

For apparent reasons, any subsequent surgical procedure entails a *de novo* risk of postoperative pain development, thus obscuring if the primary *or* the secondary procedure initiated the postoperative pain - or if it was an additive, synergistic effect of both procedures.

1.4. CHRONIC PAIN IN THE BACKGROUND POPULATION

When studying the prevalence of chronic postoperative pain for a given surgical procedure, the expected prevalence of other underlying chronic pain conditions in the background population is an important aspect to take into consideration. In the case of endometrial cancer, the primary age group of interest is postmenopausal women aged 70 to 75 years. Ayorinde et al performed a cross-sectional study of 5,300 women in Scotland and found a prevalence of chronic pelvic pain of 7.4% in the age group 65-74 years and 6.7% in the age group 75-84 years, while the prevalence was as high as 21.9% in the reproductive age groups[144]. The study further showed

that having multiple somatic symptoms was significantly associated with chronic pelvic pain in older women, thereby confirming the before mentioned association with multimorbidity[144]. An equivalent prevalence of chronic pelvic pain has been found in other studies by Ahangari et al, Zondervan et al and Mathias et al[145–147].

The prevalence of chronic pain (not only confined to pelvic pain) was examined by Dahlhamer et al in a large, population-based cross-sectional study in the USA[148]. Here the authors estimated that 20.4% of all adults had chronic pain and 8.0% had high-impact chronic pain. Additionally, the prevalence of both chronic pain and high-impact chronic pain were significantly higher among women, unemployed, adults living in poverty, and rural residents[148].

1.5. ASSESSMENT OF PAIN

The subjective nature of pain entails an inherent challenge when trying to assess and quantify the painful experience. As a consequence, self-report has shown to be the most valid measure of pain[68]. In the field of pain research, pain is often described by intensity, duration, location, and descriptive characteristics[149].

1.5.1. RATING SCALES

A number of pain rating scales have been developed, where the Visual Analogue Scale (VAS) and the Numerical Rating Scale (NRS) are the most commonly used[150]. Using the VAS, the patient is asked to rate his/her pain on a 10 cm long scale from 0 cm meaning ‘No pain’ to 10 cm meaning ‘Maximum pain’[151]. With some resemblance, the NRS is a verbal or written 11 point scale from 0 meaning ‘No pain’ to 10 meaning ‘Worst possible pain’[151]. Both VAS

and NRS has been shown to have high degrees of sensitivity as well as high degrees of test-retest reliability[152–156].

1.5.2. THE MEMORY OF PAIN

The accuracy of recalled pain has been assessed in several studies. Erskine et al found a high degree of correlation between ratings of pain intensity while experiencing pain and the retrospective recalled rating[157]. Salovey et al studied the accuracy of self-reported pain intensity and found that not only was it accurate but also robust against the influence of transient moods[158]. In a study of recalled postoperative pain, Terry et al found that the intensity of pain was recalled accurately after six weeks - and to a higher degree than the quality of pain[159]. In a prospective study among fifty patients in the emergency room with acute pain, Singer et al examined the recalled pain intensity and correlation between the VAS and the NRS scale after one week and found that the patients accurately recalled the pain and that correlations between the scales ranged from 0.83 to 0.92[160].

In a large prospective study, Bąbel et al examined the accuracy of recalled pain among one hundred-and-forty women six months after gynecologic surgery, vaginal childbirth or caesarean section[161]. The authors concluded that the length of recall delay had no effect on memory of pain[161]. Similar conclusions were made by Cogan et al in a series of studies examining the reliability of a post-partum questionnaire where the patient reported pain measures were stable after one, three and six months[162].

Recently, Halicka et al published a well-designed study of the memory of postoperative pain in older patients undergoing hip surgery[163]. In accordance with the literature mentioned above, the authors found the recall of postoperative pain after three months to be accurate[163].

1.6. QUANTITATIVE SENSORY TESTING

***Figure 7**: Handheld algometer with a 1 cm^2 probe which is placed perpendicular on the skin.*

Quantitative Sensory Testing (QST) has been used over the last 30 years as a non-invasive method to obtain an assessment of the psychophysical response to noxious stimuli, e.g. chemical, electrical, mechanical or thermal modalities[164]. QST has been proposed as a method to predict the outcome of surgery, i.e. predict pain reduction after surgery for chronic pain causing conditions or predict postoperative pain[165,166]. A short introduction will be given in this section, as several QST methods are evaluated in this PhD dissertation.

1.6.1. PAIN THRESHOLDS

Pain thresholds can be assessed by different methods, e.g. handheld algometry, cuff pressure algometry or thermal thresholds (fig. 7). Low pain thresholds suggest primary hyperalgesia when applied to a local painful location. In case of central sensitization, low pain thresholds at distal locations implies widespread hyperalgesia[167].

Pain thresholds have been studied extensively in various pain causing conditions, for instance in total knee replacement due to osteoarthritis, where low preoperative pain thresholds were associated with diminished postoperative pain relief[168]. In the field of gynecology, reduced multifocal pain thresholds were found in patients with persistent pelvic pain[169].

1.6.2. TEMPORAL SUMMATION OF PAIN

Temporal summation of pain (TSP) occurs when repetition of a stimulus causes additive synaptic potentials in the neuron. This triggers a short-term sensitization of the spinal cord, which could lead to increased neuronal activity, thus allowing an otherwise painless stimulus to be perceived as painful[170] (fig. 8). A longer lasting sensitization of the spinal cord - which persists after the stimulus has ceased - has been shown in animal models[171]. This is termed wind-up and is believed to play an important role in human chronic pain conditions as well[172].

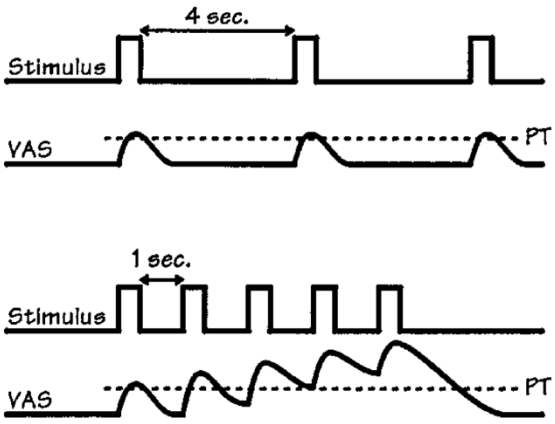

***Figure 8**: Temporal summation of pain. Visual Analogue Scale (VAS), Pain Threshold (PT).*
Reprint from Sensory assessment of regional analgesia in humans: a review of methods and applications. Curatolo et al. Anesthesiology 93(6):1517-30. 2000.

TSP is considered as a surrogate marker of central sensitization[170] and has been utilized as a QST modality in multiple studies, for instance in a study of patients with overactive bladder syndrome where elevated levels of temporal summation were demonstrated. Furthermore, TSP has been shown to predict the level of postoperative pain after hip- and knee arthroplasty[173,174].

1.6.3. CONDITIONED PAIN MODULATION

The phenomenon where a painful, noxious stimulus can alter the perception of another painful stimulus ("pain inhibits pain") was first described by Le Bars et al in 1979[175]. In this study, where the activity of the dorsal horn neurons of rats were recorded during various noxious stimuli, a diffuse noxious inhibitory control (termed DNIC) was shown to inhibit 60-100% of the neuronal response, thereby serving as an endogenous analgesic system[175].

An impaired or less efficient DNIC has since been shown in several idiopathic pain conditions like fibromyalgia and temporo-mandibular disorder[176,177]. In a study published in 2008, Yarnitsky et al examined 62 thoracotomy patients, aiming to determine if QST profiling of their DNIC could predict the degree of susceptibility to development of chronic post-operative pain[166]. The results showed that DNIC efficiency and the intensity of acute postoperative pain were both independent predictors of chronic postoperative pain[166]. Furthermore, a probability plot was constructed to visualize the relationship between the risk of chronic postoperative pain and DNIC efficiency on an arbitrary scale from -30 to 70 (fig. 9). The term conditioned pain modulation (CPM) has been used over the last decade to describe DNIC's inhibitory effects in the descending pathway, especially in the setting of quantitative sensory testing, where it has been defined as the difference in the response to a painful stimulus applied before and during a painful conditioning stimulation[178].

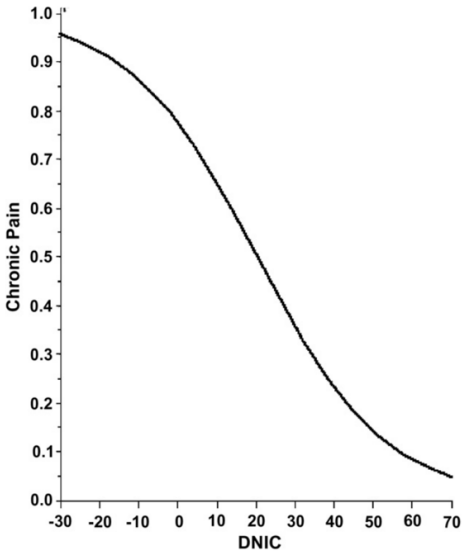

***Figure 9**: Logistic regression probability plot relating diffuse noxious inhibitory control (DNIC) to the probability of development of chronic pain.*
Reprint from Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Yarnitsky et al. Aug. 2008. Pain. 138 (1): 22–8.

Different CPM methods have been suggested over the course of time, many of which were found to have a lack of standardization and inherent observer bias issues[179,180]. As a consequence of these concerns, CPM assessment by cuff pressure algometry was developed as a user-independent method, which has been demonstrated to produce high levels of intraclass correlations in a study by Graven-Nielsen et al[181].

1.7. DEFINING THE KNOWLEDGE GAP

As shown, endometrial cancer is a common malignant disease among postmenopausal women in the developed countries. Still, endometrial cancer has a very high survival rate and a low degree of postoperative sequelae through early diagnose and advanced surgical treatment. Like any other surgical procedure, however, hysterectomy entails a risk of developing chronic postoperative pain as an adverse outcome. Chronic postoperative pain decreases the quality of life for the affected individuals and poses a significant clinical challenge in the analgesic management as well as a major socioeconomic burden for the society. As robot-assisted laparoscopic hysterectomy for endometrial cancer is a fairly new surgical approach, the prevalence of chronic postoperative pain in this group of patients remains to be studied. As part of the evaluation of RMIS as a therapeutic intervention, this would allow for a direct comparison to the prevalences of chronic postoperative pain following hysterectomy by open access surgery or laparoscopic minimally invasive surgery found in previous studies.

Chronic postoperative pain is the product of complex pathophysiologic interactions we do not fully understand. Some evidence suggest that a range of preoperative risk factors might increase the susceptibility to development of chronic postoperative pain, like pre-existing pain conditions or socioeconomic disadvantage. On a molecular level, emerging evidence also indicate that lipids, lipoproteins and other low-molecular metabolites can act as pronociceptive modulators, thus promoting the induction and perpetuation of chronic pain conditions. Therefore, a certain serologic composition could act as an independent risk factor for development of chronic postoperative pain. If we as clinicians knew some of these risk factors, we could counsel our patients better prior to surgery - and more importantly, possibly even find a way to reduce the risk of developing chronic postoperative pain through interventions and clinical trials.

Another approach to identify individuals with an increased susceptibility to development of chronic postoperative pain could be Quantitative Sensory Testing. Several studies have demonstrated the predictive capabilities of preoperative QST profiling, e.g. by identifying patients at risk of developing chronic postoperative pain after total knee replacement. Whether this also can be applied to robot-assisted laparoscopic hysterectomy for endometrial cancer has yet to be evaluated. If preoperative QST profiling could indeed identify patients at risk, we as clinicians could optimize the treatment algorithms in the pre- and postoperative setting through clinical trials, thereby hopefully reducing the prevalence of chronic postoperative pain.

CHAPTER 2. AIMS AND HYPOTHESES

The overall aim of this PhD project was to investigate selected aspects of chronic postoperative pain after robot-assisted laparoscopic hysterectomy for endometrial cancer through three studies:

2.1. STUDY I

- *Aim I*: To determine the prevalence of chronic postoperative pain in a retrospective setting.

- *Aim II*: To assess selected pre- and postoperative risk factors for development of chronic postoperative pain.

- *Hypothesis I*: Development of chronic postoperative pain is associated to the pre- and postoperative risk factors: presence of preoperative pelvic pain, acute postoperative pelvic pain, age, severity of cancer, operating time, blood loss, educational level and employment status.

2.2. STUDY II

- *Aim III*: To investigate the serologic composition of lipids, lipoproteins and other low-molecular metabolites in preoperative blood samples from patients with chronic postoperative pain.

- *Hypothesis II*: Patients who develop chronic postoperative pain have a distinctive preoperative serologic composition of lipids, lipoproteins and other low-molecular metabolites, compared to patients who do not develop chronic postoperative pain.

- *Aim IV*: To explore if serological biomarkers are predictive for development of chronic postoperative pain.

- *Hypothesis III*: Serologic biomarkers of lipids, lipoproteins and other low-molecular metabolites are predictive for development of chronic postoperative pain.

2.3. STUDY III

- *Aim V*: To determine the prevalence of chronic postoperative pain in a prospective setting.

- *Aim VI*: To assess selected preoperative risk factors for development of chronic postoperative pain.

- *Hypothesis IV*: Development of chronic postoperative pain is associated to the preoperative risk factors: presence of preoperative pelvic pain, age, severity of cancer, educational level and employment status.

- *Aim VII*: To evaluate if preoperative profiling by quantitative sensory testing can predict chronic postoperative pain.

- *Hypothesis V*: Quantitative sensory testing by handheld algometry, cuff pressure algometry, temporal summation of pain, conditioned pain modulation and heat evoked pain can predict development of chronic postoperative pain.

CHAPTER 3. MATERIALS AND METHODS

3.1. GENERAL STUDY POPULATION

All three studies were conducted at The Department of Obstetrics and Gynecology, Aalborg University Hospital, Denmark. The general inclusion criteria were women diagnosed with endometrial cancer, scheduled for robot-assisted laparoscopic hysterectomy and bilateral salpingo-oophorectomy, aged 18 to 85 years-of-age. The general exclusion criteria were non-Danish speaking, use of cannabis or opioids, conversion to laparotomy during the surgical procedure or subsequent laparotomy, neurologic-, musculoskeletal- or mental illnesses[1–3].

All participants were given written and verbal information and signed informed consent forms prior to inclusion. The studies were approved by The North Denmark Region Committee on Health Research Ethics (N-20150028), The Danish Data Protection Agency (2008-58-0028) and The Bio- and Genome Bank Denmark[1–3].

3.2. STUDY DESIGNS AND PARTICIPANTS

3.2.1. STUDY I

Study I was a questionnaire survey among patients treated from January 1st, 2010 till July 31st, 2015. To address the aims and hypothesis, the design consisted of two parts where the first part was a cross-sectional assessment of the prevalence of chronic postoperative pain, while the second part was a cohort study with retrospective assessment of risk factors for development of chronic postoperative pain.

3.2.2. STUDY II

A nested, case-control study within the cohort defined by *Study I*.

3.2.3. STUDY III

A longitudinal, observational cohort study of patients treated from August 1st, 2015 till December 31st, 2018.

3.3. MEASURING CHRONIC POSTOPERATIVE PAIN

To determine the outcome measure, the presence of chronic postoperative pain, we decided to use a questionnaire approach. The questionnaire should address the presence, location and intensity of pain in a range of everyday activities and consist of two parts regarding the preoperative- and the postoperative time period, respectively. Preferably, this questionnaire should be thoroughly validated and in Danish language. Finally, the questionnaire should be developed for use in our primary study population of postmenopausal women undergoing a hysterectomy.

Despite a systematic literature search on the topic, we were unable to find a questionnaire meeting all of the above requirements. In the light of these findings, we decided to use a questionnaire concerning chronic postoperative pain following hysterectomy developed by Birgitte Brandsborg and colleagues at The Danish Pain Research Center, Aarhus University. The questionnaire was originally developed as a part of a PhD project concerning chronic postoperative pain after hysterectomy on benign indication[182].

Brandsborg's questionnaire utilized the general terminology and systematics of the validated Brief Pain Inventory questionnaire but also contained more specific items related to hysterectomy[183,184]. The questionnaire consisted of 47 items in Danish language. It was pilot tested on 20 patients who had

previously undergone a hysterectomy, identified via The Danish Hysterectomy Database. Based on the response, the questionnaire was adjusted and a final version of the questionnaire was utilized in the further studies[61,185].

For the present PhD project, the original questionnaire by Brandsborg was slightly modified at Center for Sensory-Motor Interaction, Center for Neuroplasticity and Pain, Aalborg University: The number of items was reduced to 32 as e.g. questions using McGill pain descriptors were removed. This was done to have as few items as possible while still allowing for an assessment of the construct[186,187]. Furthermore, the questions regarding the duration of pain were changed from 'three months' to 'six months' as a consequence of the definition of chronic postoperative pain applied in this PhD project.

The modified questionnaire was then controlled for face validity, which is defined as the degree to which the respondent understands the questions and find them relevant[188]. This was done among 10 patients who had been treated for endometrial cancer 2-3 years prior with robot-assisted hysterectomy at The Department of Obstetrics and Gynecology, Aalborg University Hospital. These patients matched the study population of interest and were subsequently excluded from *Study I*. After returning the filled-out questionnaires, each responder was interviewed by verbal probing technique by telephone regarding each item to ensure that the questions had been perceived as clear and unambiguous[189]. Content validity is defined as the degree to which a panel of experts find the items representative of the theoretical construct[190]. This was controlled by review of the questionnaire by pain researchers from Center for Sensory-Motor Interaction, Center for Neuroplasticity and Pain, Aalborg University as well as clinicians from The Department of Obstetrics and Gynecology, Aalborg University Hospital, thereby allowing for experts on both pain research and endometrial cancer to comment on the questionnaire.

Further theoretical aspects of questionnaire validation are discussed in detail in section '5.6. Methodological Considerations'.

The following variables were collected: presence of preoperative pelvic pain, acute postoperative pelvic pain, chronic postoperative pelvic pain, pain intensity ratings, frequency and location of the pain (marked on an illustration of a woman's torso), and lastly demographic data such as educational level and employment status[1,3].

Throughout *Study I-III,* the definition of chronic postoperative pain was persistent, moderate to severe pain on a daily basis with a mean VAS ≥ 3, six months after the surgical procedure[a], based on the answers of question number 9A, 9B, 9D and 10A. Please refer to the original Danish questionnaire in appendices or the translated questionnaire in Paper III.

3.3.1. STUDY I

Study participants were identified via the database of The Department of Obstetrics and Gynecology, Aalborg University Hospital of patients treated from January 1st, 2010 till July 31st, 2015.

The questionnaire was mailed along with a prepaid return envelope to each participant. Non-responsive participants were contacted by telephone 3 weeks after receiving the mailed questionnaire and again after 2 weeks, if the participant did not respond. The returned questionnaires were gathered for data analysis[1].

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[a] Erratum: Paper I incorrectly states that chronic postoperative pain was defined as "*constant or periodical pain for at least 3 months*", while the definition is specified correctly in Paper II and III.

3.3.2. STUDY II

The questionnaire was indirectly utilized in *Study II*, being a nested, case-control study within the cohort defined by *Study I*.

3.3.3. STUDY III

In this study, the questionnaire was primarily applied to obtain an estimate of postoperative pain as an outcome measure. Furthermore, the questionnaire allowed for profiling of the preoperative pain status of the participants.

Study participants were consecutively included prior to the surgical procedure from August 1st, 2015 till December 31st, 2018. The questionnaire was mailed along with a prepaid return envelope to each participant six months after the surgical procedure and non-responsive participants were contacted by telephone after the same algorithm as in *Study I*. The returned questionnaires were gathered for data analysis[3].

3.4. REVIEW OF THE MEDICAL RECORDS

The medical records of all study participants (*Study I-III*) were reviewed for details concerning Body Mass Index (BMI) at the time of surgery (kg/m^2), duration of surgery (minutes), the blood loss during surgery (mL), intraoperative lesions if any, postoperative complications if any, parity, number of caesarean sections if any, and histopathologic diagnose and stage of cancer.

The review of medical records furthermore disclosed if any exclusion criteria had been met, e.g. subsequent surgery, dementia or prescription of opioids[1–3].

3.5. METABOLIC PROFILING

In *Study II* we performed metabolic profiling of cases with chronic postoperative pain compared with controls without chronic postoperative pain, in order to examine the serologic composition of lipids, lipoproteins and other low-molecular metabolites.

3.5.1. THE DANISH CANCER BIOBANK

Since 2009, all cancer patients in Denmark have been offered to have blood and tissue samples stored in The Danish Cancer Biobank (DCB), part of a national collaboration between public hospitals entitled The Bio- and Genome Bank Denmark. Following an informed consent, the biologic materials are stored according to the Danish Data Protection Agency procedures[2].

The *majority* of the study participants had blood and tissue stored in the DCB, and the fact that the blood samples were drawn preoperatively, allowed us to perform an assessment of the preoperative serologic composition.

The cases with chronic postoperative pain were matched on age and BMI in a 1:2 ratio with controls without chronic postoperative pain from the cohort[2].

3.5.2. THE NMR SPECTROSCOPY

Any type of biochemical com-pound consist of atoms in which the different nuclei have an intrinsic angular momentum or gyromagnetic spin (fig. 10)[191].

The spin is highly dependent on the number of unpaired protons and neutrons in the nucleus as well as the chemical surroundings. In NMR spectroscopy, compounds are placed in a magnetic field and radiated with electromagnetic waves at specific wavelengths for each element and isotope[192]. When the electromagnetic waves are exactly the same as the precessional frequency of the spin (termed the Lamor frequency), the nucleus is excited and briefly transition to a different state of spin[191]. Shortly after, the nucleus will return to the ground spin state and emit an electromagnetic wave at the same resonance frequency. When performing NMR spectroscopy of a biochemical compound, numerous electromagnetic waves are emitted at different frequencies which allows for identification of the various elements as 'molecular finger-prints'. The technology of high-throughput NMR spectroscopy has advanced immensely in the recent years, thus for allowing for detailed metabolic profiling[193].

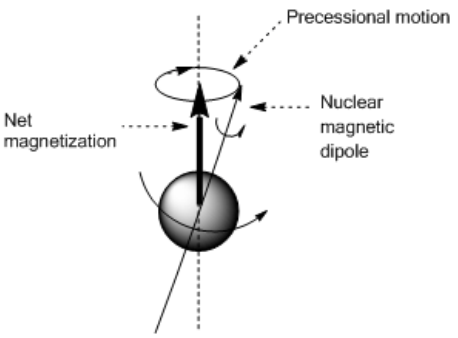

***Figure 10**: Nucleus with precessional spin in a magnetic field.*
Reprint from Libretexts Chemistry. Thomas Wenzel. Open access via Creative Commons license CC BY-NC-SA 3.0

The metabolic profiling in *Study II* was performed by means of serum analysis on a high-throughput NMR metabolomics platform (Nightingale Health Ltd., Helsinki, Finland), which provided quantification of routine lipids and lipoproteins, fatty acids and various low-molecular metabolites, including amino acids, ketone bodies, and gluconeogenesis-related metabolites[2,193].

3.6. QUANTITATIVE SENSORY TESTING

All study participants in *Study III* were included consecutively and subjected to a test platform of selected QST modalities 2-3 days prior to the surgical procedure. All participant information and testing was performed by one examiner (Søren Lunde)[3].

The QST modalities are described in detail in Paper III and will be summarized below.

3.6.1. HANDHELD ALGOMETRY

A handheld algometer (Somedic AB, Hörby, Sweden) (fig. 7) with a 1 cm^2 probe was placed perpendicular on the skin. Pressure was applied and increased gradually until the Pressure Pain Threshold (defined as ‘‘the point at which the pressure sensation becomes painful”) (PPT) was reached. The PPT was assessed at 8 different landmark locations on the body, 4 on each side (lower back, legs and arms)[3].

3.6.2. CUFF PRESSURE ALGOMETRY

Deep-tissue pain sensitivity was assessed by cuff pressure algometry in which a double-chamber tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany) was placed on the right lower leg. The cuff was connected to a computer-controlled compressor and a 10 cm long, electronic Visual Analogue Scale (VAS) from 0 cm to 10 cm (Cortex Technology and Aalborg University, Aalborg, Denmark). The cuff was inflated at 1 kPa/s and the pain intensity during inflation of the cuff was recorded via the electronic VAS. The VAS 0 cm and 10 cm extremes on the VAS were defined as “no pain” and as “maximum pain”, respectively. The patient was instructed to rate the pain intensity continuously on the VAS from the first sensation of pain until the pain intensity was so high, that she wanted to terminate the test (Pain Tolerance Threshold,

PTT). The Pain Detection Threshold (PDT) was defined as the pressure at which VAS had exceeded a score of 2[3].

3.6.3. TEMPORAL SUMMATION OF PAIN

The cuff pressure algometry device was further utilized to assess the TSP. The average of the previously obtained PDT and PTT levels was automatically calculated, and the cuff was now inflated to this pressure in a series of 10 stimuli at 0.5 Hz. During the series of stimuli, the patient was instructed to rate the pain intensity on the electronic VAS. The mean VAS during stimuli number 1-3 (VAS-I) and stimuli number 8-10 (VAS-III) was calculated and TSP was defined as the difference between the first and the last mean values (VAS-III minus VAS-I)[3,168,194].

3.6.4. CONDITIONED PAIN MODULATION

A second, double-chamber tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany) connected to the cuff pressure algometry device was placed on the left lower leg and a painful conditioned stimulus was administered via inflation to the level of 70% of the PTT[181]. Simultaneously, on the right lower leg, the first cuff was inflated by increasing pressure. The patient was instructed to rate the pain intensity via the electronic VAS and exclusively focus on the pain evoked by the cuff on the right leg and disregard the pain evoked by the cuff on the left leg. The Conditioned Pain Modulation (CPM) was defined as the difference between PDT with and without the conditioning stimulus[3].

3.6.5. HEAT EVOKED PAIN

Thermal stimulation was applied by placing a 3×3 cm contact thermode (Medoc Advanced Medical Systems, Ramat Yishai, Israel) on an area of skin on the lower back between the L2 and the L4 vertebra. Each stimulus was started with a thermode temperature of 32°C and tests were performed by

raising the temperature by 0.5°C/s[3,195,196]. The patient was instructed to press a button when she perceived the stimulation as warm (Warm Detection Threshold, WDT) and press the button again once the heat stimulation was perceived as pain (Heat Pain Threshold, HPT)[3].

3.7. THE SURGICAL PROCEDURE

All surgical procedures in *Study I-III* were performed at Aalborg University Hospital using Da Vinci™ Si robotic systems (Intuitive Surgical Inc., Sunnyvale, USA).

During *Study I* (and *II*), lymphadenectomy was performed according to the ESMO-ESGO-ESTRO guideline based on the preoperative histopathologic diagnosis and an intraoperative macroscopic assessment of the tumor's myometrial invasion by a trained pathologist. In the summer of 2015, however, Aalborg University Hospital adopted the Memorial Sloan Kettering Cancer Center Sentinel Lymph Node algorithm (as described in section 1.1.4). Consequently, this approach was applied in *Study III.*

Multi-disciplinary tumor board meetings reviewed and FIGO staged all cases postoperatively[1,3].

3.7.1. PERI- AND POSTOPERATIVE DRUG DOSE REGIMEN

All participants in *Study I-III* were treated with a uniform drug dose regimen:

- 30 minutes prior to the surgical procedure, a dose of Gabapentin (300 mg p.o.) was administered.

- Total intravenous anaesthesia was obtained with a combination of Propofol (10 mg/kg/hour i.v.) and Remifentanil (1 µg/kg/minute i.v.) and non-depolarizing neuromuscular blockade by Mivacurium chloride (0.2 mg/kg/hour i.v.).

- Cefuroxime (1,500 mg i.v.) and Metronidazole (1,000 mg i.v.) were given as prophylactic antibiotics and Tranexamic acid (1,000 mg i.v.) as prophylactic haemostatic.

- In order to reduce the level of postoperative nausea and vomiting, Dexamethasone (8 mg i.v.) and Ondansetron (4 mg i.v.) were administered during the surgical procedure.

- In the postoperative setting, analgesic management consisted of Paracetamol (1,000 mg x 4 p.o.) and Naproxen (500 mg x 2, p.o.) for two weeks while Dalteparin (5,000 IU s.c.) was given as thrombosis prophylactic for four weeks.

3.8. STATISTICAL ANALYSIS

Chronic postoperative pain was defined as persistent, moderate to severe pain on a daily basis with a mean VAS ≥ 3 six months after the surgical procedure. The assumptions behind the statistical tests were assessed prior to analysis, including the distributions of variables. $P \leq 0.05$ was considered statistically significant.

3.8.1. STUDY I

Continuous data were displayed as mean with 95% confidence intervals (CI) and categorical data were displayed as frequency in percentage[1].

To examine potential selection bias among questionnaire responders and non-responders, a Mann-Whitney–U test of the two groups were performed using the independent variables age, BMI, operating time and blood loss[1].

Hypothesis I[b] was tested by a binary logistic regression analysis with backward stepwise selection of risk factors for chronic postoperative pain with the following independent variables: preoperative pelvic pain; acute postoperative pain intensity; preoperative pain elsewhere; age; stage of cancer; operating time; blood loss; education; and employment status[1].

The statistical analyses were performed with IBM SPSS Statistics software for Mac OS, Version 25.0 (IBM Corp., Armonk, NY).

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[b] *Hypothesis I*: Development of chronic postoperative pain is associated to the pre- and postoperative risk factors: presence of preoperative pelvic pain, acute postoperative pelvic pain, age, severity of cancer, operating time, blood loss, educational level and employment status. (Section 2.1.).

3.8.2. STUDY II

In order to investigate any inherent clustering in the data and reduce possible overfitting and noise, the entire dataset was pre-processed by Principal Component Analysis (PCA), thereby reducing the dimensionality and the number of variables of the data, while still maintaining as much variance as possible (fig. 11)[2,197].

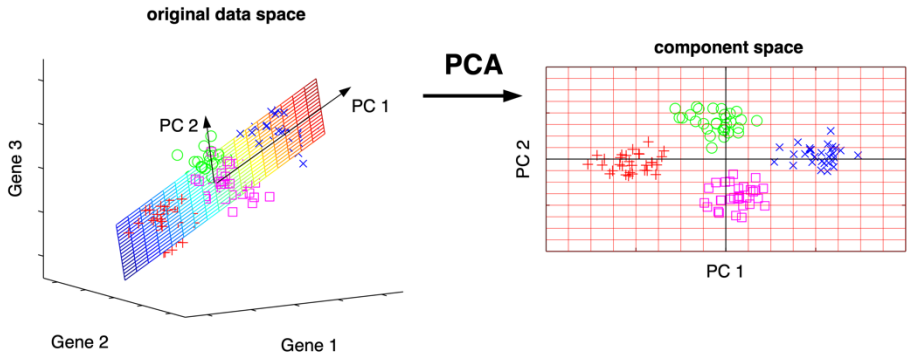

Figure 11*: Principal component analysis (PCA) reduces a large number of variables (in this example gene expression) to a lower number of new variables termed principal components (PCs). Three-dimensional gene expressions are projected onto a two-dimensional component space that maintains the largest variance in the data.*
Reprint from Approaches to analyse and interpret biological profile data, PhD dissertation by Matthias Scholz, Max Planck Institute of Molecular Plant Physiology, Potsdam, 2006.

Hypothesis II[c] was tested by the subsequent supervised modelling by a sparse Partial Least Squares-Discriminant Analysis (sPLS-DA) as described by Lê Cao et al[198], thus effectively reducing the number of variables in high-dimensional metabolomics data further[2].

[c] *Hypothesis II*: Patients who develop chronic postoperative pain have a distinctive preoperative serologic composition of lipids, lipoproteins and other low-molecular metabolites, compared to patients who do not develop chronic postoperative pain. (Section 2.2.).

For evaluation of the classification performance, 5-fold cross-validation together with the receiver operating characteristic curve (ROC) was chosen. Additionally, four machine learning algorithms (random forest, linear support vector machine, PLS-DA and logistic regression) were applied to develop prediction models for chronic postoperative pain based on the identified metabolomic biomarkers, thus testing *hypothesis III*[d]. Finally, a permutation test was used to indicate whether the specific classification model was superior to random classifiers[2].

All multivariate statistics, including unsupervised PCA and supervised sPLS-DA, were performed using MetaboAnalystR 2.0 packages[2,199].

3.8.3. STUDY III

All study parameters were analysed with independent samples t-test between the two sub-groups with and without chronic postoperative pain, thereby testing *hypothesis IV*[e]. Results were displayed as mean and standard deviation (SD) for continuous variables - except results from the Thermal Stimulation which were displayed as Mean, Quartiles and Range - and as proportions with corresponding frequencies for categorical variables[3].

A responder versus non-responder analysis was performed in order to examine potential selection bias, similar to *Study I*. Finally, a binary logistic

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[d] *Hypothesis III*: Serologic biomarkers of lipids, lipoproteins and other low-molecular metabolites are predictive for development of chronic postoperative pain. (Section 2.2.).

[e] *Hypothesis IV*: Development of chronic postoperative pain is associated to the preoperative risk factors: presence of preoperative pelvic pain, age, severity of cancer, educational level and employment status. (Section 2.3.).

regression model was established using the statistically significant *preoperative* parameters, thereby testing *hypothesis V*[f].

The statistical analysis was performed using IBM SPSS Statistics software for Mac OS, Version 26.0 (IBM Corp., Armonk, New York, USA).

[f] *Hypothesis V*: Quantitative sensory testing by handheld algometry, cuff pressure algometry, temporal summation of pain, conditioned pain modulation and heat evoked pain can predict development of chronic postoperative pain. (Section 2.3.).

CHAPTER 4. RESULTS

The main results of *Study I-III* are summarized below, whereas the complete results are described in greater detail in the Paper I-III (see appendices).

4.1. STUDY I

Two-hundred-and-eighty patients were treated for endometrial cancer at Aalborg University Hospital in the time period from January 1st, 2010 till July 31st, 2015. Eight patients were excluded due to dementia, subsequent open surgery or death. The remaining two-hundred-and-seventy-two were included in the study and received the questionnaire via mail. Two-hundred-and-seven patients returned the questionnaire (76.1%) whereas sixty-five patients did not return the questionnaire within 5 weeks (23.9%) (fig. 12)[1].

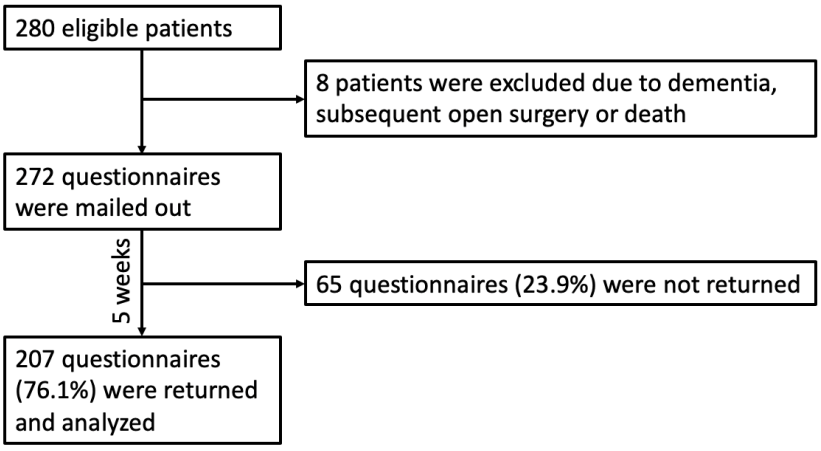

***Figure 12**: Flowchart of Study I.*
Reprint from Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer. Lunde et al. Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146.

4.1.1. NON-RESPONDER ANALYSIS

The mean age of the non-responders was significantly lower compared to the responders (63.4 years, 95% CI 60.6-65.7 versus 67.2 years, 95% CI 65.9-68.5, p = 0.027), no difference was found in BMI (p = 0.869), duration of surgery (p = 0.551) or blood loss (p = 0.126)[1]. See section 4.1.4. for a supplemental sensitivity analysis regarding the non-responders.

4.1.2. BASELINE CHARACTERISTICS

The baseline characteristics of the responders are shown in table 2.

Baseline characteristics (n = 207)	**Mean (CI)[a]**
Age, years	67.2 (65.9-68.5)
BMI[b], kg/m^2	29.4 (28.5-30.3)
Operating time, minutes	70.6 (65.9-75.3)
Blood loss during surgery, mL	75.4 (65.6-85.2)
Follow-up time since surgery, days	1,053.2 (1,009.9-1,096.5)
Education	**n (%)[a]**
Elementary school	70 (33.8)
High school	11 (5.3)
Vocational school	37 (17.9)
Higher education (2-3 years)	31 (15.0)
Bachelor's degree	44 (21.3)
Master's degree	4 (1.9)
Others	5 (2.4)
Missing data	5 (2.4)
Employment status	
Full time	35 (16.9)
Part time	32 (15.5)
Early retired	18 (8.6)
Retired	111 (53.6)
Stay-at-home work	2 (1.0)
Unemployed	2 (1.0)
Others	6 (2.9)
Missing data	1 (0.5)
Parity	
0	27 (13.0)
1-2	117 (56.6)
3-4	53 (25.6)
5 or more	7 (3.4)
Missing data	3 (1.4)

***Table 2**: Baseline characteristics. [a]Data displayed as Mean (95% Confidence Interval, CI) for continuous data and n (%) for categorical data.[b]Body Mass Index.*
Reprint from Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer. Lunde et al. Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146.

4.1.3. TUMOR CHARACTERISTICS

The tumor characteristics of the responders are shown in table 3.

Tumor characteristics (n = 207)	n (%)
Histologic type and grade	
Endometrioid carcinomas	
Endometrioid adenocarcinomas	183 (88.4)
Grade 1	145 (70.0)
Grade 2	32 (15.5)
Grade 3	6 (2.9)
Non-endometrioid carcinomas	23 (11.1)
Serous adenocarcinomas	15 (7.2)
Clear cell adenocarcinomas	2 (1.0)
Carcinosarcomas	6 (2.9)
Sarcomas	1 (0.5)
Adenosarcomas	1 (0.5)
FIGO[a] stage	
IA	136 (65.7)
IB	34 (16.4)
II	18 (8.7)
III	17 (8.2)
IV	2 (1.0)
Risk categories	
Low risk	121 (58.5)
Stage IA (grade 1-2) with endometrioid type	121 (58.5)
Intermediate risk	29 (14.0)
Stage IA (grade 3) with endometrioid type	2 (1.0)
Stage IB (grade 1-2) with endometrioid type	27 (13.0)
High risk	57 (27.5)
Stage IB (grade 3) with endometrioid type	4 (1.9)
Stage II with endometrioid type	17 (8.2)
Stage III with endometrioid type	12 (5.8)
All non-endometrioid types incl. sarcomas	24 (11.6)

***Table 3**: Tumor characteristics. Data displayed as n (%). [a]Fédération Internationale de Gynécologie et d'Obstétrique.*
Reprint from Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer. Lunde et al. Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146.

4.1.4. PAIN CHARACTERISTICS

A total of thirty-one out of the two-hundred-and-seven responders had chronic postoperative pain, equivalent to a prevalence of 14.9% (95% CI 10.4-20.6).

If we were to estimate the true prevalence of chronic postoperative pain in the *entire* study sample of two-hundred-and-seventy-two participants, we could conduct a hypothetical sensitivity analysis. Had the sixty-five non-responders indeed responded, we could calculate two extreme scenarios where these non-responders had a) half the prevalence or b) twice the prevalence of the responder-group[200]. This yielded a prevalence of chronic postoperative pain between a) 13.2% (95% CI 9.4-17.8) to b) 18.8% (95% CI 14.3-23.9) in the entire study sample, respectively.

The pain characteristics of the responders are shown in table 4.

Pain characteristics	**Preoperative pain, n(%)[a]**	**Postoperative chronic pain, n(%)[a]**
Total (n = 207)	35 (16.9)	31 (14.9)
Age		
Age ≤ 67 years (n = 111)[b]	25 (22.5)	24 (21.6)
Age > 67 years (n = 96)	10 (10.8)	7 (7.3)
BMI[c], kg/m^2		
BMI ≤ 29 (n = 109)[d]	18 (16.5)	16 (14.7)
BMI > 29 (n = 98)	17 (17.3)	15 (15.3)
Pain frequency (n = 35/31)		
1-3 days/week	16 (45.7)	16 (51.6)
4-6 days/week	4 (11.4)	2 (6.5)
Every day	15 (42.9)	12 (38.7)
Pain during factors (n = 35/31)		
Running	6 (17.1)	8 (25.8)
Wearing tight clothes	8 (22.9)	6 (19.4)
Having sexual intercourse	13 (37.1)	9 (29.0)
Carrying heavy things	14 (40.0)	15 (48.4)
Other situations	9 (25.7)	15 (48.4)
Affected Sex life (n = 14/10)	7 (50.0)	5 (50.0)
Affected Sleep (n = 35/31)	12 (34.3)	14 (45.2)
Pain elsewhere (n = 35/31)	9 (25.7)	15 (48.4)
Caesarean Section (n = 35/31)	3 (8.6)	4 (12.9)
Pain intensity[e]	**Preoperative pain, mean (CI)[a]**	**Postoperative chronic pain, mean (CI)[a]**
Daily	4.3 (3.2-4.8)	3.6 (2.8-4.4)
At worst	5.6 (4.6-6.5)	5.7 (4.8-6.7)

***Table 4**: Pain characteristics of the preoperative pelvic pain and postoperative pelvic pain. [a]Data displayed as n (%) for categorical data and Mean (95% Confidence Interval, CI) for continuous data. [b]Based on the mean age of the study sample. [c]Body Mass Index. [d]Based on the mean BMI of the study sample. [e]Intensity ratings by Numeric Rating Scale (NRS).*
Reprint from Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer. Lunde et al. Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146.

As supplemental material to Paper I, tables 5 and 6 were constructed to visualize the degree of overlap between patients with pre- and postoperative pain.

		Postoperative pain		Total
		+	-	
Preoperative pain	+	16	19	35
	-	15	157	172
Total		31	176	207

***Table 5**: Cross tabulation of the variables pre- and postoperative pain among patients. Data displayed as n, stratified into the respective groups.*

As shown in table 5, sixteen out of thirty-one patients with postoperative pain indicated an existing preoperative pain condition, equivalent of 51.6% (95% CI 33.1-69.8).

Preoperative pain	Postoperative pain	n	%	95% CI
-	-	157	75.8	69.4-81.5
-	+	15	7.3	4.1-11.7
+	-	19	9.2	5.6-14.0
+	+	16	7.7	4.5-12.2
Total		207	100.0	

***Table 6**: Frequency distribution of the variables pre- and postoperative pain among patients. Data displayed as n, percentage and 95% Confidence Interval, CI.*

As table 6 shows, 75.8% of the responders had neither pre- nor postoperative pain, while the remaining 24.2% were evenly distributed in three diminutive groups with combinations of pre- and postoperative pain, demonstrating no significant difference between groups.

The thirty-one patients with chronic postoperative pain had marked the areas of pain on the illustration of a woman's torso in their questionnaire response. A graphical summation of these areas was constructed on the basis of the questionnaires (fig. 13).

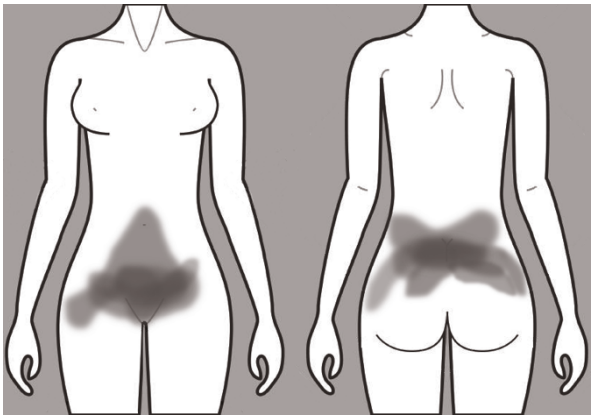

***Figure 13**: Summarized areas of chronic postoperative pain based on thirty-one questionnaire responses.*
Reprint from Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer. Lunde et al. Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146.

4.1.5. THE BINARY LOGISTIC REGRESSION MODEL

A binary logistic regression model was built, initially using nine variables (model 1) with a subsequent backward stepwise selection, reducing the number of variables to four (model 2) (table 7). The unadjusted odds ratio for the variable 'preoperative pelvic pain' was 8.81 (95% CI 3.43-22.38).

Model 1		**Nagelkerke R^2 0.419**
Variable	**OR (CI)[a]**	***p*-value**
Preoperative pelvic pain	4.24 (3.34-5.14)	0.002
Acute postoperative pain	1.20 (1.00-1.40)	0.067
Preoperative pain elsewhere	2.66 (1.52-3.80)	0.092
Age	0.96 (0.88-1.04)	0.351
Severity of Cancer	1.97 (0.97-2.97)	0.182
Operating time	1.00 (0.98-1.02)	0.896
Blood loss	1.01 (0.99-1.03)	0.290
Education	1.41 (1.06-1.76)	0.053
Employment status	0.94 (0.63-1.25)	0.695
Model 2		**Nagelkerke R^2 0.382**
Variable	**OR (CI)**	***p*-value**
Preoperative pelvic pain	4.99 (4.15-5.83)	0.000
Acute postoperative pain	1.27 (1.09-1.45)	0.009
Age	0.94 (0.88-1.00)	0.056
Education	1.34 (1.01-1.67)	0.074

***Table 7**: Binary logistic regression with backward stepwise selection of risk factors for postoperative chronic pain following robot-assisted hysterectomy. [a] Data displayed as Odds Ratio (95% Confidence Interval, CI).*
Reprint from Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer. Lunde et al. Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146.

4.2. STUDY II

In the cohort defined by *Study I*, thirty-one patients with chronic postoperative pain and one-hundred-and-seventy-six patients without chronic postoperative pain were identified (fig. 14).

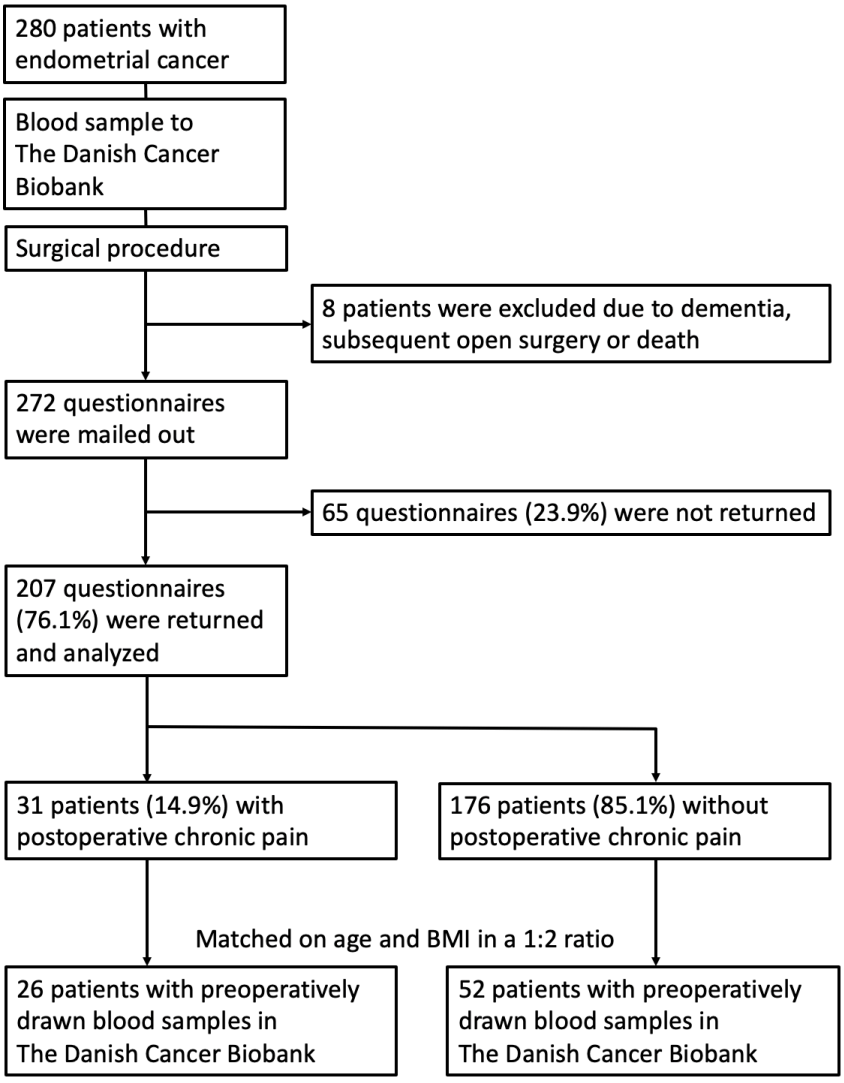

***Figure 14**: Flowchart of Study II.*
Reprint from Chronic Postoperative Pain After Hysterectomy for Endometrial Cancer: A Metabolic Profiling Study. Lunde et al. Molecular Pain. Volume 16, May 2020, 1-7.

Twenty-six of the thirty-one patients with chronic postoperative pain had preoperative blood samples stored in The Danish Cancer Biobank (DCB). These twenty-six cases were matched on age and BMI in a 1:2 ratio with fifty-two controls without chronic postoperative pain, who also had preoperative blood samples stored in the DCB (fig. 14)[2].

4.2.1. TUMOR CHARACTERISTICS

As supplemental material to Paper II, table 8 shows the tumor characteristics of the seventy-eight total cases and controls.

Tumor characteristics (n = 78)	**n (%)**
Histologic type and grade	
Endometrioid carcinomas	
Endometrioid adenocarcinomas	68 (87.2)
Grade 1	54 (69.2)
Grade 2	14 (18.0)
Grade 3	0 (0.0)
Non-endometrioid carcinomas	10 (12.8)
Serous adenocarcinomas	6 (7.7)
Clear cell adenocarcinomas	1 (1.3)
Carcinosarcomas	2 (2.6)
Sarcomas	1 (1.3)
Adenosarcomas	1 (1.3)
FIGO[a] stage	
IA	56 (71.8)
IB	9 (11.5)
II	7 (9.0)
III	5 (6.4)
IV	1 (1.3)
Risk categories	
Low risk	50 (64.1)
Stage IA (grade 1-2) with endometrioid type	50 (64.1)
Intermediate risk	9 (11.5)
Stage IA (grade 3) with endometrioid type	0 (0.0)
Stage IB (grade 1-2) with endometrioid type	9 (11.5)
High risk	19 (24.4)
Stage IB (grade 3) with endometrioid type	0 (0.0)
Stage II with endometrioid type	6 (7.7)
Stage III with endometrioid type	3 (3.8)
All non-endometrioid types incl. sarcomas	10 (12.8)

***Table 8**: Tumor characteristics. Data displayed as n (%). [a]Fédération Internationale de Gynécologie et d'Obstétrique.*

4.2.2. METABOLIC PROFILE VARIANCE

To compare the overall variation of metabolic profiles between the cases and controls, a classification model was built by supervised sPLS-DA. This sPLS-DA model, however, did not show separation between the two groups (fig. 15, a) and the calculated validation parameters had low values (data not shown)[2].

Of the seventy-eight total cases and controls in this study, fifty-nine patients were classified accordingly to the ESMO-ESGO-ESTRO guidelines as low or intermediate-risk and nineteen patients as high-risk (table 8).

As the biological etiology of type II tumors differ to a large extent from type I tumors, the high-risk cases were excluded in a second sPLS-DA model as more than half of the high-risk cases consisted of non-endometrioid carcinomas. Therefore, this second sPLS-DA model was built on the remaining seventeen cases and forty-two controls with a low or intermediate risk assessment, all type I tumors. A discrimination between the two groups could now be seen in the sPLS-DA score plots (fig. 15, b).

This sPLS-DA model explained 38.1% of the variance with the first two components and had a predictive accuracy of 73.1%[2].

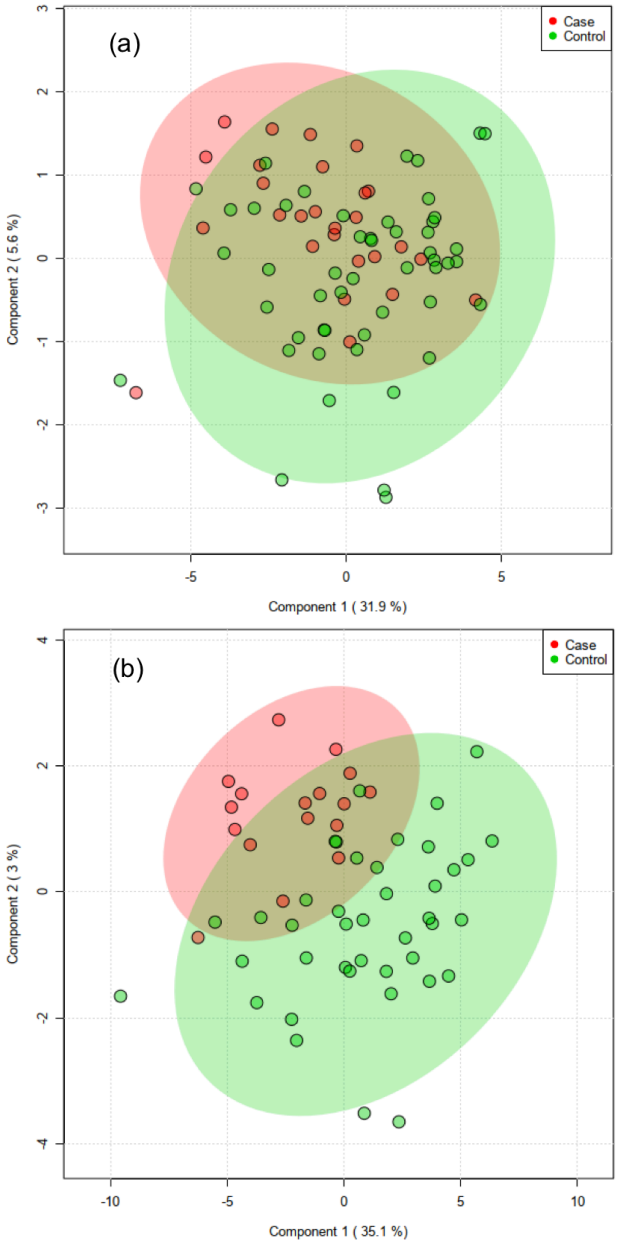

***Figure 15 a and b**: sPLS-DA score plot of the serum metabolome from the cases with chronic postoperative pain (red dots) and controls without chronic postoperative pain (green dots). (a) the sPLS model with twenty-six cases and fifty-two controls. (b) the sPLS-DA model constructed for seventeen cases and forty-two controls after data set was synchronized. Reprint from Chronic Postoperative Pain After Hysterectomy for Endometrial Cancer: A Metabolic Profiling Study. Lunde et al. Molecular Pain. Volume 16, May 2020, 1-7.*

4.2.3. IDENTIFICATION OF DETECTED METABOLITES

A total of one-hundred and forty-seven metabolites were identified and classified into sub-groups of cholesterol; glycerides and phospholipids; apolipoproteins; fatty acids; amino acids; glycolysis related metabolites; ketone bodies; fluid balance; inflammation and lipoproteins[2]. Please refer to the supplemental table in appendices for an overview (Paper II).

Twenty metabolites which belong to fatty acids, amino acids, glycolysis related metabolites and lipoprotein groups were identified as the most influential factors for the difference between case and control groups. Of these, nineteen metabolites, including cholesterol, linoleic acid (LA), phospholipids, lipids and triglycerides, demonstrated statistically significant higher concentrations in the case group than in the control group ($p < 0.05$), while the concentration of glycerol was statistically significant lower in the case group than in the control group ($p < 0.05$) (fig. 16)[2].

Fourteen of these metabolites were found to be the leading contributing metabolites correlated to chronic postoperative pain, based on a combination of high loadings scores and valid AUC values (equal or higher than 0.7). Their detailed information was summarized in table 9[2].

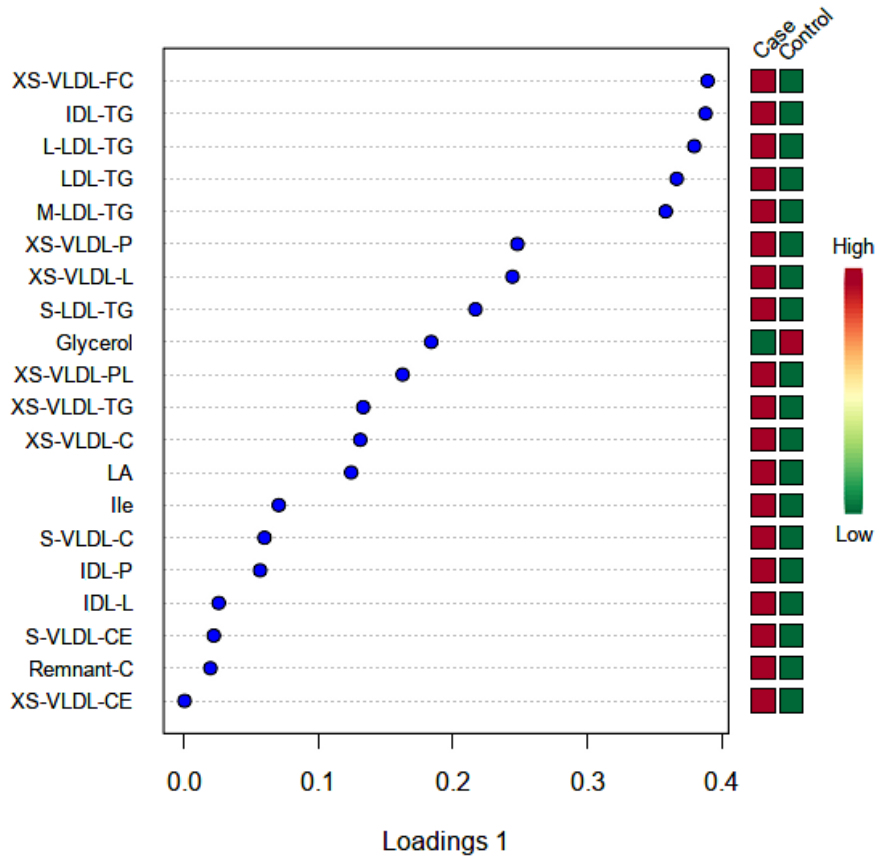

***Figure 16**: Loading plots from the cases with chronic postoperative pain and controls without chronic postoperative pain. High concentrations are depicted as red boxes, while low concentrations are depicted as green boxes.*
Low density lipoproteins (LDL); Intermediate density lipoproteins (IDL); Very low density lipoproteins (VLDL); Free cholesterol in very small VLDL (XS-VLDL-FC); Triglycerides in IDL (IDL-TG); Triglycerides in large LDL (L-LDL-TG); Triglycerides in LDL (LDL-TG); Triglycerides in medium LDL (M-LDL-TG); Concentration of very small VLDL particles (XS-VLDL-P); Total lipids in very small VLDL (XS-VLDL-L); Triglycerides in small LDL (S-LDL-TG); Phospholipids in very small VLDL (XS-VLDL-PL); Triglycerides in very small VLDL (XS-VLDL-TG); Cholesterol in very small VLDL (XS-VLDL-C); Linoleic acid (LA); Isoleucine (Ile); Cholesterol in small VLDL (S-VLDL-C); Concentration of IDL particles (IDL-P); Total lipids in IDL (IDL-L); Cholesteryl esters in small VLDL (S-VLDL-CE); Remnant cholesterol i.e. non-HDL, non-LDL-cholesterol (Remnant-C) and Cholesteryl esters in very small VLDL (XS-VLDL-CE).
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Metabolite	Area under the curve (AUC)	*p*-value	Log2 Fold Change
IDL-TG	0.80	0.01	0.37
LDL-TG	0.80	0.01	0.35
L-LDL-TG	0.80	0.01	0.35
M-LDL-TG	0.79	0.01	0.34
S-LDL-TG	0.79	0.01	0.36
XS-VLDL-FC	0.78	0.01	0.30
XS-VLDL-TG	0.76	0.01	0.40
XS-VLDL-L	0.75	0.01	0.30
XS-VLDL-P	0.75	0.01	0.26
Glycerol	0.74	0.01	-0.48
XS-VLDL-PL	0.73	0.01	0.28
XS-VLDL-C	0.73	0.01	0.28
LA	0.71	0.01	0.18
Ile	0.70	0.02	0.30

***Table 9**: Area under the curve (AUC), p-value and log 2-fold change for a set of 14 metabolites. Low density lipoproteins (LDL); Intermediate density lipoproteins (IDL); Very low density lipoproteins (VLDL); Triglycerides in IDL (IDL-TG); Triglycerides in LDL (LDL-TG); Triglycerides in large LDL (L-LDL-TG); Triglycerides in medium LDL (M-LDL-TG); Triglycerides in small LDL (S-LDL-TG); Free cholesterol in very small VLDL (XS-VLDL-FC); Triglycerides in very small VLDL (XS-VLDL-TG); Total lipids in very small VLDL (XS-VLDL-L); Concentration of very small VLDL particles (XS-VLDL-P); Phospholipids in very small VLDL (XS-VLDL-PL); Cholesterol in very small VLDL (XS-VLDL-C); Linoleic acid (LA) and Isoleucine (Ile).*
Reprint from Chronic Postoperative Pain After Hysterectomy for Endometrial Cancer: A Metabolic Profiling Study. Lunde et al. Molecular Pain. Volume 16, May 2020, 1-7.

4.2.4. PREDICTION MODELS FOR CHRONIC POSTOPERATIVE PAIN

The fourteen metabolites were used to build prediction models for chronic postoperative pain through four machine learning algorithms, all of which exhibited high AUC values (0.79-0.87) and coefficients of variation prediction (0.70-0.77) (table 10)[2].

Algorithm	Area under the curve (AUC)	Coefficient of variation prediction	*p*-value
PLS-DA	0.79 (0.53-0.93)	0.70	0.01
Linear support vector	0.87 (0.69-0.97)	0.77	< 0.001
Logistic regression	0.80 (0.54-0.97)	0.74	0.005
Random forest	0.82 (0.70-0.93)	0.71	< 0.001

***Table 10**: Prediction models based on a set of 14 metabolites distinguishing case from control groups. Data in parenthesis represents the 95% confidence intervals.*
Reprint from Chronic Postoperative Pain After Hysterectomy for Endometrial Cancer: A Metabolic Profiling Study. Lunde et al. Molecular Pain. Volume 16, May 2020, 1-7.

4.3. STUDY III

One-hundred-and-seventy-three patients were diagnosed with endometrial cancer and scheduled for surgery from August 1st, 2015 till December 31st, 2018. Thirteen patients either declined to participate or were excluded. The remaining one-hundred-and-sixty patients were included prior to surgery (fig. 17).

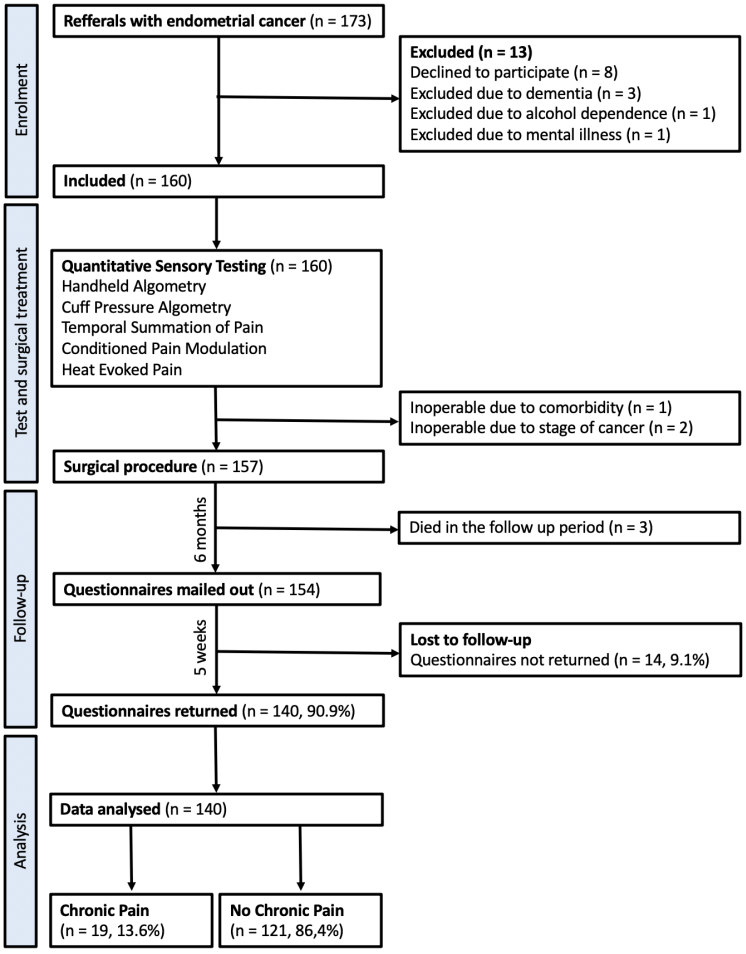

***Figure 17**: Flowchart of Study III.*
Reprint from Preoperative Quantitative Sensory Testing and Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer: Can Chronic Postoperative Pain be Predicted?
Lunde et al. Scandinavian Journal of Pain, E-pub. ahead of print, August 2020, 1-13.

Three included patients were inoperable due to comorbidity or stage of cancer and three other patients died during the six months follow-up. A total of one-hundred-and-fifty-four questionnaires were mailed out and one-hundred-and-forty (90.9%) were returned, while fourteen (9.1%) questionnaires were not returned within 5 weeks[3].

4.3.1. NON-RESPONDER ANALYSIS

No statistically significant difference was found between responders (n = 140) and non-responders (n = 14) in terms of age, BMI, duration of surgery or blood loss[3].

4.3.2. TUMOR CHARACTERISTICS

As supplemental material to Paper III, the tumor characteristics of the responders are shown in table 11.

Tumor characteristics (n = 140)	**n (%)**
Histologic type and grade	
Endometrioid carcinomas	
Endometrioid adenocarcinomas	121 (86.4)
Grade 1	89 (63.6)
Grade 2	22 (15.7)
Grade 3	10 (7.1)
Non-endometrioid carcinomas	
Serous adenocarcinomas	14 (10.0)
Clear cell adenocarcinomas	0 (0.0)
Carcinosarcomas	5 (3.6)
Sarcomas	
Adenosarcomas	0 (0.0)
FIGO[a] stage	
IA	99 (70.7)
IB	19 (13.6)
II	8 (5.7)
III	12 (8.6)
IV	2 (1.4)

***Table 11**: Tumor characteristics. Data displayed as n (%). [a]Fédération Internationale de Gynécologie et d'Obstétrique.*

4.3.3. CHRONIC POSTOPERATIVE PAIN

The prevalence of chronic postoperative pain was 13.6% (95% CI 8.4-20.4) equivalent to 19 patients which were grouped as 'Chronic pain', while the remaining 121 patients were grouped as 'No chronic pain'. An independent samples t-test demonstrated that the patients with chronic pain had a lower BMI ($p = 0.032$), a higher prevalence of preoperative pelvic pain ($p < 0.001$), and a higher level of acute postoperative pain ($p < 0.001$) when compared to patients without chronic pain (table 12). No difference in the distribution of histopathologic diagnose and stage of cancer was found between the 'Chronic pain' and 'No chronic pain' groups (data not shown)[3].

Study parameter	Chronic pain (n = 19)	No chronic pain (n = 121)	*p*-value
Age (years)	64.2 ± 10.0	66.4 ± 8.9	0.321
BMI[a] (kg/m^2)	26.2 ± 7.3	29.9 ± 6.7	0.032*
Preoperative pelvic pain (%)	11/19 (57.9%)	21/121 (17.4%)	0.001*
Blood loss during surgery (mL)	64.7 ± 47.6	76.9 ± 79.7	0.521
Duration of surgery (min)	60.3 ± 22.1	64.7 ± 25.5	0.480
Level of acute postoperative pain (VAS[b])	5.8 ± 2.0	3.1 ± 2.7	0.001*

***Table 12**: The sub-grouped patients with and without chronic postoperative pain. Results are displayed as mean ± SD for continuous variables and as proportions with corresponding frequencies for categorical variables. [a]Body Mass Index (BMI), [b]Visual Analogue Scale (VAS). *Statistically significant difference between groups ($p < 0.05$).*
Reprint from Preoperative Quantitative Sensory Testing and Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer: Can Chronic Postoperative Pain be Predicted?
Lunde et al. Scandinavian Journal of Pain, E-pub. ahead of print, August 2020, 1-13.

4.3.4. QUANTITATIVE SENSORY TESTING

No statistically significant difference was found between the 'Chronic pain' and the 'No chronic pain' group when applying handheld algometry (fig. 18, A), cuff pressure algometry (fig. 18, B), temporal summation of pain (fig. 18, C) or conditioned pain modulation (fig. 18, C). During thermal stimulation, the 'Chronic pain' group demonstrated statistically significant lower HPT compared with the 'No chronic pain' group (40.9°C versus 42.6°C, $p = 0.043$) while no statistically significant difference between groups was found in WDT (fig. 18, D)[3].

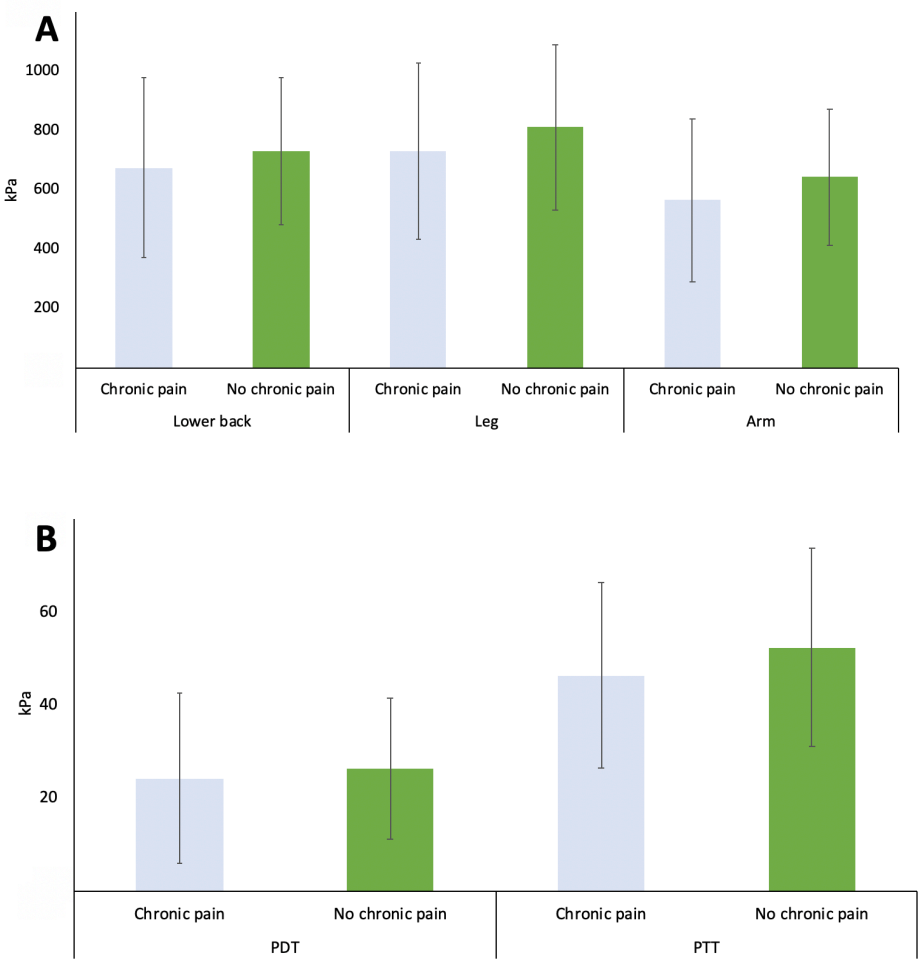

***Figure 18 A and B**: Preoperative Quantitative Sensory Testing of patients with (gray) and without (green) chronic postoperative pain. Results are displayed as mean ± SD.*
(A) Handheld Algometry. Pressure Pain Thresholds (PPT) at three locations.
(B) Cuff Pressure Algometry. Pain Detection Thresholds (PDT) and Pain Tolerance Thresholds (PTT).
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Lunde et al. Scandinavian Journal of Pain, E-pub. ahead of print, August 2020, 1-13.

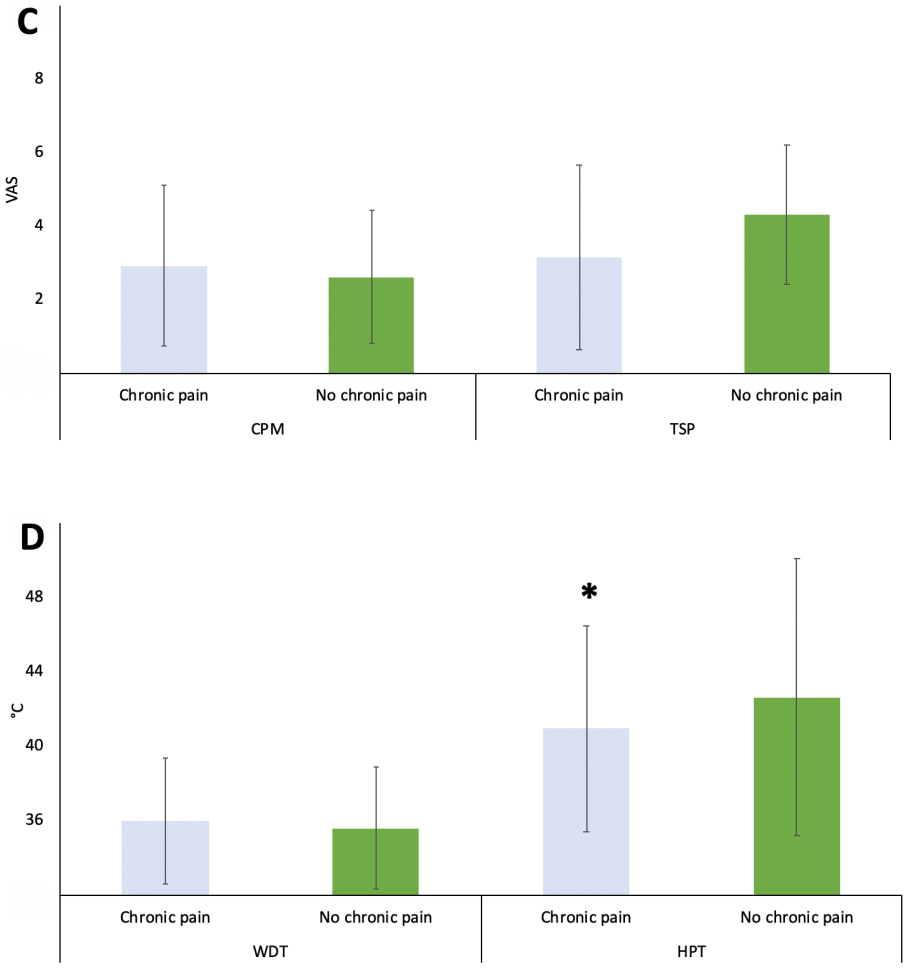

***Figure 18 C and D**: Preoperative Quantitative Sensory Testing of patients with (gray) and without (green) chronic postoperative pain. Results are displayed as mean ± SD, except results from the thermal stimulation which are displayed as mean and range.*
(C) Conditioned Pain Modulation (CPM) and Temporal Summation of Pain (TSP).
(D) Thermal Stimulation. Warm Detection Thresholds (WDT) and Heat Pain Thresholds (HPT).
**Statistically significant difference between groups ($p < 0.05$).*
Reprint from Preoperative Quantitative Sensory Testing and Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer: Can Chronic Postoperative Pain be Predicted?
Lunde et al. Scandinavian Journal of Pain, E-pub. ahead of print, August 2020, 1-13.

4.3.5. THE BINARY LOGISTIC REGRESSION MODEL

A binary logistic regression model was built using only the *preoperative* study parameters HPT, BMI and presence of preoperative pelvic pain. The model had a Nagelkerke R^2 value of 0.251, indicating the model's goodness-of-fit between 0-1, i.e. 25.1% of the difference in one variable can be explained by the difference in a second variable, when predicting chronic postoperative pain[3]. The model showed preoperative pelvic pain as significant, independent predictive risk factor of chronic postoperative pain (OR = 6.62, 95% CI 2.26-19.44) (table 13)[3].

Study parameter	OR	95% CI
Heat Pain Threshold	0.86	0.72 – 1.02
BMI[a]	0.92	0.85 – 1.00
Preoperative pelvic pain	6.62	2.26 – 19.44

***Table 13**: The binary logistic regression model with three predictive factors for development of chronic postoperative pain. Results are displayed as Odds Ratio (OR) and the 95% Confidence Interval. [a]Body Mass Index (BMI).*
Reprint from Preoperative Quantitative Sensory Testing and Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer: Can Chronic Postoperative Pain be Predicted?
Lunde et al. Scandinavian Journal of Pain, E-pub. ahead of print, August 2020, 1-13.

As shown in table 13, the model furthermore indicated a trend towards Heat Pain Thresholds and BMI as independent risk factors, i.e. a high Heat Pain Threshold and a high BMI reduced the risk of chronic postoperative pain[3].

CHAPTER 5. DISCUSSION

This chapter will focus on an overall discussion of the main results in relation to our aims and hypotheses, and the existing literature.

5.1. THE PREVALENCE OF CHRONIC POSTOPERATIVE PAIN

The prevalence of chronic postoperative pain after robot-assisted hysterectomy for endometrial cancer was found to be 14.9% (95% CI 10.4-20.6) in *Study I*, which was supported by an equivalent finding in *Study III* with a prevalence of 13.6% (95% CI 8.4-20.4).

The subsequent, imperative question is: Does the questionnaire in fact measure the prevalence of chronic postoperative pain in our study groups? While this question is simple to ask, an unambiguous answer is harder to give. As shown in section 1.4., studies have found a prevalence of chronic pelvic pain of 7.4% in the background population of the age group in question[144]. This can in part be explained by an accumulated number of comorbidities as discussed in section 1.3.1[127–129]. Whether this prevalence of chronic pain in the background population can be applied to our study group is also difficult to answer. From *Study I*, table 4 we see that 16.9% of the responders indicated a *preoperative* pain condition[1]. From a methodological point of view, one could argue that only the *difference* in the prevalence between preoperative- and postoperative pain reflects the effect of the surgical procedure. Nevertheless, this approach would be too crude, as table 5 shows that only 51.6% (95% CI 33.1-69.8) of the responders with postoperative pain also had preoperative pain. In other words, nearly half of the responders with postoperative pain developed this condition after the surgical procedure had taken place. Still, the expected level of pain in the background population is important to take into consideration when consulting patients prior to surgery.

In a recent, prospective cohort study of patients who underwent abdominal or laparoscopic hysterectomy for benign conditions, Sng et al found a prevalence of chronic postoperative pain (VAS ≥3) of 15.7%, 6 months after surgery[201]. Similar findings were made by Brandsborg et al 4 months after vaginal, abdominal or laparoscopic hysterectomy on benign indication, with a prevalence of chronic postoperative pain (VAS ≥3) of 17.0%[202].

Following abdominal hysterectomy, Stovall et al found a prevalence of chronic postoperative pain of 22.2% and Hillis et al found a prevalence of 26.0%[64,65]. Both studies, however, had chronic pelvic pain of presumed uterine etiology as indication for hysterectomy which is of paramount importance when comparing these studies. As shown in *Study I* and *III*, the presence of preoperative pelvic pain is associated with the risk of developing chronic postoperative pain by a factor 4.99 (95% CI 4.15-5.83) (*Study I*) to 6.62 (95% CI 2.26-19.44) (*Study III*). Therefore, we would *a priori* expect a higher prevalence in these populations, seeing that *all* of the study participants had preoperative pelvic pain. In another study, Brandsborg et al examined the prevalence of chronic postoperative pain following abdominal, vaginal or laparoscopic hysterectomy due to a broader range of benign indications like leiomyomas, dysmenorrhea or endometriosis[61]. The prevalence of chronic postoperative pain in this study was found to be 31.9%. These benign indications are, nevertheless, also associated with an increased prevalence of preoperative pelvic pain, consequently increasing the expected number of patients suffering from chronic postoperative pain[109]. In contrast, the sole indication for hysterectomy in *Study I-III* was endometrial cancer, which rarely causes pain in early stage disease.

The divergence in the indication for hysterectomy was further reflected in the mean age of the study participants, where they in Brandsborg's study had a mean age of 48 years, compared to a mean age of 67 years in *Study I*. This difference in mean age alone could explain some of the discrepancy, seeing

that research has shown high age to be a protective factor of chronic postoperative pain[93,203]. This trend was also indicated in *Study I* by the logistic regression model, where age had an OR of 0.94 (95% CI 0.88-1.00) (table 7). Accordingly, one would assume that the prevalence of chronic postoperative pain was higher in a younger population. The abundant definitions of chronic postoperative pain applied in various studies may also explain some of the variance of the reported findings. In a multicenter cohort study by Theunissen et al they examined three-hundred and seventy-six patients scheduled for abdominal, vaginal or laparoscopic hysterectomy on benign indication. They demonstrated a prevalence of chronic postoperative pain of 9.0% 12 months after the surgical procedure, when defining chronic postoperative pain as persistent pain with a VAS ≥ 4[136]. Other studies of pain following hysterectomy, like our *Study I-III,* defined chronic postoperative pain as persistent pain with a VAS ≥ 3 after 6 months, while Brandsborg et al in a later study from 2009 defined *any* persistent pain (VAS >0) after 4 months as chronic postoperative pain and found a prevalence of 16.7%[185]. Using a parallel definition of chronic postoperative pain (NRS >0), but 6 months after vaginal or laparoscopic hysterectomy on benign indication, Pokkinen et al found a prevalence of 26.0%[62].

As the examples above amply demonstrate, a consensus-based definition of chronic postoperative pain is critically needed. This will in part be achieved in the upcoming, revised version of the WHO's International Classification of Diseases (ICD-11), where the IASP have agreed upon a definition of chronic postoperative pain as persistent pain at least 3 months after the surgical procedure, while no definition of the pain intensity is included[204]. Considering that the indication for hysterectomy is of utmost importance when assessing the risk of chronic postoperative pain and the fact that dissimilar definitions of chronic postoperative pain are being applied, it is necessary to exhibit some degree of caution when comparing studies on chronic postoperative pain following hysterectomy.

5.2. THE CHARACTERISTICS OF POSTOPERATIVE PAIN

Amongst the thirty-one patients with chronic postoperative pain in *Study I*, the pain was most prominent during heavy lifts (48.4%), sexual intercourse (29.0%) and while running (25.8%)[1]. The pain had a daily mean intensity of 3.6 NRS and 5.7 NRS when at worst, which supports the findings of the 2007 study by Brandsborg et al (with a daily mean intensity of 4.0 NRS and 6.0 NRS when at worst)[61].

In a study from 2016, Pokkinen et al characterized persistent pain after hysterectomy by gynecological and sensory examination[101]. Here the authors found that persistent pain in most cases exhibited the characteristics of neuropathic pain and could be categorized as chronic postoperative pain[101].
In *Study I*, the pain was located at the areas corresponding to dermatomes T-12–L-3 and S-2–S-4 (fig. 13)[1]. These are the same spinal segments that receive afferent sensory neurons from the uterus and adnexa, thus supporting the theory of referred visceral pain[205]. This aligns with the findings of experimental pain models, where cervical distension triggered similar visceral pain[206,207].

In our studies, these characteristics and intensities of chronic postoperative pain is the closest approximation to the impact on everyday activities. However, as discussed in section 1.1.5, chronic postoperative pain is merely *one* aspect in the overall Health-Related Quality of Life (HRQoL) for these patients. Therefore, it would have been desirable to have obtained data on the HRQoL using for instance the EORTC QLQ-C30 and QLQ-EN24 questionnaires[45–47]. This would have allowed for a more nuanced and informative characterization of the life following surgery for endometrial cancer.

5.3. SELECTED RISK FACTORS

Aim II and *VI* of this dissertation were to assess selected risk factors for development of chronic postoperative pain. From *Study I* we could conclude that the presence of preoperative pelvic pain was a significant, independent risk factor with an adjusted OR of 4.99 (95% CI 4.15-5.83) (table 7, model 2). This was further substantiated by *Study III*, where the presence of preoperative pelvic pain had an OR of 6.62 (95% CI 2.26-19.44) (table 13). This is fully in agreement with the existing literature, as preoperative pain is a well-known risk factor for chronic postoperative pain after hysterectomy and other types of surgery, e.g. inguinal hernia repair, caesarean section, mastectomy and postamputation phantom pain[61,93,185,201,203,208–212]. As shown in section 4.1.5., the *unadjusted* odds ratio for preoperative pelvic pain as a risk factor for development of chronic postoperative pain was 8.81 (95% CI 3.43-22.38) while the *adjusted* odds ratio as mentioned above was 4.99 (95% CI 4.15-5.83). This discrepancy indicates that the unadjusted odds ratio was confounded. Confounding will be addressed in section '5.6. Methodological Considerations'.

Study I further showed a high level of acute postoperative pain to be a significant, independent risk factor with an OR of 1.27 (95% CI 1.09-1.45) (table 7, model 2), which also concurs with previous findings[203,213]. This risk factor was *not* tested in *Study III* as we only assessed selected *preoperative* risk factors in this study. In *Hypothesis I*[g] we conjectured that the development of chronic postoperative pain was associated with the presence of preoperative pelvic pain and acute postoperative pelvic pain, which was found

[g] *Hypothesis I*: Development of chronic postoperative pain is associated to the pre- and postoperative risk factors: presence of preoperative pelvic pain, acute postoperative pelvic pain, age, severity of cancer, operating time, blood loss, educational level and employment status. (Section 2.1.).

to be true. In *Study III* we tested *Hypothesis IV*[h], where the presence of preoperative pelvic pain was associated to chronic postoperative pain. Neither age, severity of cancer, operating time, blood loss, educational level nor employment status, however, was associated with the development of chronic postoperative pain.

5.4. METABOLIC PROFILING

Aim III of this dissertation was to investigate the serologic composition of lipids, lipoproteins and other low-molecular metabolites in preoperative blood samples from patients with chronic postoperative pain, hypothesizing that these patients had a distinctive metabolic profile compared to patients without chronic postoperative pain (*Hypothesis II*[i]). *Study II* showed that metabolic profiling by NMR could *not* discriminate between these two groups when including patients of all ESMO-ESGO-ESTRO risk assessments[2]. In a large subgroup of patients with low and intermediate risk assessment (75.6% of all patients), nevertheless, a discrimination model could be built[2]. This necessity to differentiate the risk groups could underline the inherent biological heterogenicity between type I and type II tumors, seeing that all type II tumors were excluded in this secondary analysis. Despite the results of this secondary analysis, we must reject our initial *Hypothesis II,* as it included *all* ESMO-ESGO-ESTRO risk assessments groups.

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[h] *Hypothesis IV*: Development of chronic postoperative pain is associated to the preoperative risk factors: presence of preoperative pelvic pain, age, severity of cancer, educational level and employment status. (Section 2.3.).

[i] *Hypothesis II*: Patients who develop chronic postoperative pain have a distinctive preoperative serologic composition of lipids, lipoproteins and other low-molecular metabolites, compared to patients who do not develop chronic postoperative pain. (Section 2.2.).

The concentration of nineteen metabolites were found to be significantly higher in the group of patients, that developed chronic postoperative pain, compared to the control group that did not develop chronic postoperative pain[2]. These metabolites included cholesterol, linoleic acid (LA), phospholipids, lipids and triglycerides. These findings are well in accordance with recent literature, as mentioned in section '1.2.7 Pro- and Antinociceptive Modulators', where LA and other omega-6 derivatives have been shown to form a pronociceptive cellular environment thus promoting the induction and perpetuation of chronic pain[83].

Additionally, studies have shown that cholesterol can act as a modulator of opioid receptors in the cellular membrane, thereby modifying the perception of pain and the intrinsic susceptibility to endogenous and exogenous opioids[214–216]. This association was also shown in both animal and human studies, where individuals with a high serum cholesterol level required a smaller dose of opioid to achieve an equivalent analgesic effect, compared to individuals with a low serum cholesterol level[217,218].

Aim IV was to determine if an array of serological biomarkers were predictive for development of chronic postoperative pain. The sPLS-DA model of *Study II* had a predictive accuracy of 73.1%[2]. Again, despite the noteworthy results of this *explorative* study we must reject *Hypothesis III*[j] as it did not include *all* ESMO-ESGO-ESTRO risk assessments groups. Nonetheless, future metabolic studies are warranted as this novel field of research holds a promising capacity to uncover some of the intricate pathophysiologic pain mechanisms on a molecular level.

[j] *Hypothesis III*: Serologic biomarkers of lipids, lipoproteins and other low-molecular metabolites are predictive for development of chronic postoperative pain. (Section 2.2.).

5.5. QUANTITATIVE SENSORY TESTING

As described in the results section of *Study III*, significant heat pain hyperalgesia (40.9°C versus 42.6°C) was found in the group of patients that would develop chronic postoperative pain at a later stage compared to patients that would not develop chronic postoperative pain[3]. The association between HPT and chronic postoperative pain, however, was non-significant in a binary logistic regression model (OR = 0.86 (95% 0.72-1.02) (table 13)). None of the other QST modalities showed any statistically significant difference between groups. Therefore, we must conclude that none of the tested QST modalities could predict development of chronic postoperative pain - and consequently reject *Hypothesis V*[k].

As demonstrated in fig. 18, the 'Chronic pain' group consistently exhibited lower mean values of PPT, PDT, PTT and TSP than the 'No chronic pain' group. These findings, however, were non-significant due to the broad distributions of data. This could indicate that the study was underpowered, seeing that a larger sample size theoretically would render narrower confidence intervals, thus hypothetically making the differences of the means statistically significant. It is important to note, that this was not the case for the CPM and WDT values, where the 'Chronic pain' group did in fact exhibit higher mean values than the 'No chronic pain' group.

Pan et al found heat pain thresholds to be predictive of postoperative pain in a study of thirty-four patients scheduled for cesarean section[219]. Supra-threshold heat pain was found to be predictive by Granot et al and Werner et

[k] *Hypothesis V*: Quantitative sensory testing by handheld algometry, cuff pressure algometry, temporal summation of pain, conditioned pain modulation and heat evoked pain can predict development of chronic postoperative pain. (Section 2.3.).

al when examining postoperative pain following respectively cesarean section and arthroscopic knee surgery[220,221].

Postoperative pain following hysterectomy on benign indication has only been the subject of fairly few QST studies, one of them being the study by Brandsborg et al from 2011. Here they examined ninety patients with a mean age of 46 years with QST methods for brush-evoked allodynia, pinprick hyperalgesia, wind-up-like pain as well as abdominal and vaginal pressure pain thresholds[202]. The results showed a relatively high frequency of preoperative pelvic pain of 51%, despite the fact that known endometriosis and / or pelvic pain as main indication for hysterectomy were exclusion criteria. In this sub-group of patients with preoperative pelvic pain they found significant brush-evoked allodynia, pinprick hyperalgesia and decreased abdominal and vaginal pressure pain thresholds[202]. Preoperative brush-evoked allodynia, pinprick hyperalgesia, and vaginal pressure pain threshold were all associated with the intensity of acute postoperative pain, while only preoperative brush allodynia was weakly associated to chronic pain after 4 months[202]. The results of Brandsborg's study indicate that patients with preoperative pelvic pain exhibited some degree of central sensibilization with cutaneous hyperalgesia and allodynia as well as the phenomenon of viscero-somatic convergence (as described in section '1.2.4. Visceral Pain')[167,222].

Other QST studies in the field of gynecology have mainly focused on chronic pelvic pain in endometriosis. In a study by Grundström et al they performed QST tests of thirty-seven patients with persistent pelvic pain suspected of endometriosis and found lower thresholds for heat, cold and pressure pain when compared to fifty-five healthy controls, thereby further substantiating the evidence of central sensibilization in agreement with previous studies[169,223].

During the last decades, several studies have shown the predictive capabilities of various QST modalities, while other studies have failed to do so. This inconsistency was further demonstrated in a systematic review of 30 studies on 2,738 subjects by Sangesland et al in 2017[224]. Here the authors concluded:

> *"The majority of the preoperative QST variables showed no consistent association with pain intensity after surgery. Thermal heat pain above the pain threshold and temporal summation of pressure pain were the QST variables, which showed the most consistent association with acute or chronic pain after surgery."* [224]

In another systematic review on the topic published by Petersen et al in July of 2020, the authors also found inconsistent results and heterogeneous methodologies across 25 studies of QST and chronic postoperative pain[225]. As shown by both systematic reviews, one of the major challenges facing QST as a research field is the lack of standardized test paradigms resulting in a considerable variance of the outcome data.

Recently, measures are being taken towards a standardization through guidelines for test algorithms as well as development of novel QST methods to decrease the intra- and interobserver variability[181,196,226]. Finally, for QST to be adopted in a clinical setting, there is a need for unambiguous, large-scale studies demonstrating an ability to distinctly differentiate patients at risk of developing chronic postoperative pain or to facilitate improvements in the postoperative analgesic care.

5.6. METHODOLOGICAL CONSIDERATIONS

Any research methodology holds strengths and limitations which are essential to reflect upon. These methodological considerations are presented in the following section.

5.6.1. STUDY I

The Measure of Association

The probability of a certain event can be represented in different epidemiologic terms. In medical studies, the relative risk (RR) and the Odds Ratio (OR) are frequently used and can be defined as[227]

$$RR = \frac{D_E \,/\, N_E}{D_N \,/\, N_N} \qquad OR = \frac{D_E \,/\, H_E}{D_N \,/\, H_N}$$

when utilising the terminology from table 14, showing the generic outcome groups in a hypothetical study.

	Diseased	**Healthy**	**Total**
Exposed	D_E	H_E	N_E
Not exposed	D_N	H_N	N_N

Table 14: *Tabulated generic outcome groups.*
Adapted and revised from Morris and Gardner. Statistics in Medicine: Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. Br Med J (Clin Res Ed). 1988 May 7; 296(6632): 1313–1316.

From the definitions of RR and OR it is apparent that the OR is an approximation of the corresponding RR in cases of rare diseases, while the OR will be further from 1.0 than the RR in cases of common diseases (approximately >10%)[228]. This is known as 'The rare disease assumption' and is important to take into account[229].

An example of this phenomenon is shown in table 15, where the outcome of 5 different interventions are shown with the corresponding OR and RR calculations.

	Deaths	Survivors	Odds of death	OR	Risk of death	RR
Intervention 1	10	90	10/90 = 0.11	0.11/0.11	10/100 = 0.10	0.10/0.10
Control	10	90	10/90 = 0.11	= 1.0	10/100 = 0.10	= 1.0
Intervention 2	1	99	1/99 = 0.01	0.01/0.11	1/100 = 0.01	0.01/0.1
Control	10	90	10/90 = 0.11	= 0.09	10/100 = 0.10	= 0.10
Intervention 3	3	97	3/97 = 0.0309	0.0309/0.0101	3/100 = 0.03	0.03/0.01
Control	1	99	1/99 = 0.0101	= 3.06	1/100 = 0.01	= 3.0
Intervention 4	30	70	30/70 = 0.43	0.43/0.11	30/100 = 0.30	0.30/0.10
Control	10	90	10/90 = 0.11	= 3.9	10/100 = 0.10	= 3.0
Intervention 5	45	55	45/55 = 0.82	0.82/0.11	45/100 = 0.45	0.45/0.1
Control	10	90	10/90 = 0.11	= 7.45	10/100 = 0.1	= 4.5

Table 15: *Hypothetical example to illustrate the difference between Odds ratio (OR) and Relative Risk (RR) in 5 cases.*
Reprint from Ranganathan et al. Common pitfalls in statistical analysis: Odds versus risk. Perspect Clin Res 2015;6:222-4

Clearly, the OR approximates the RR in intervention 1-3, while the OR is significantly higher than the RR in intervention 4-5[230]. In *Study I* and *III*, this phenomenon is also present as the outcome (chronic postoperative pain) has a prevalence of 13.6-14.9% and thus can be considered as relatively common in respect to 'The rare disease assumption'.

If we use table 5 (section 4.1.4.) as an example:

		Postoperative pain		Total
		+	-	
Preoperative pain	+	16	19	35
	-	15	157	172
Total		31	176	207

Table 5*: Cross tabulation of the variables pre- and postoperative pain among patients. Data displayed as n, stratified into the respective groups.*

The RR and OR can then be calculated

$$RR = \frac{D_E \,/\, N_E}{D_N \,/\, N_N} = \frac{16 \,/\, 35}{15 \,/\, 172} = 5.24 \qquad OR = \frac{D_E \,/\, H_E}{D_N \,/\, H_N} = \frac{16 \,/\, 19}{15 \,/\, 157} = 8.81$$

As this part of *Study I* was designed as a cohort study, the preferred measure of association would be the RR[200]. However, as we use binary logistic regression models to estimate the risk factors for a dichotomous outcome (chronic postoperative pain: yes or no) the measure of association is OR by default. Nevertheless, the distinction between RR and OR is imperative when using the results of studies like our own to counsel patients prior to surgery.

Information Bias

If a measurement instrument does not measure what it was intended to measure, it can generate systematic misclassification, and as such, be classified as information bias[231,232]. As stated in section 5.1., the fundamental question in our studies is: Does the questionnaire in fact measure chronic postoperative pain? To answer this, we must consider the validation of the questionnaire. As described in section 3.3., the questionnaire was validated through pilot testing with verbal probing and face- and content validation. Despite this validation process is similar to other studies of chronic pain following hysterectomy, this must be considered scarce from a methodological point of view[62,186,233,234]. The principal shortcomings are the undetermined construct validity and reliability of the questionnaire.

In our case, the construct validity would describe to which extent the questionnaire did indeed measure chronic postoperative pain. This can be assessed by evaluating the association to other variables, to which the construct should be positively or negatively correlated[190,235]. Often, this is done by comparing the scores from the newly developed questionnaire to the scores of a previously validated questionnaire (from the same individual, at the same point in time)[235]. If the questionnaires were designed to measure the same constructs, we would expect a positive correlation - and if the questionnaires were *not* designed for the same construct, we would expect no correlation (or a negative correlation, if the constructs we inversely related)[235,236]. In our case, scores from the questionnaire could have been compared to scores from the Brief Pain Inventory questionnaire, where we would expect some degree of overlapping constructs[183,184]. Another method for assessing the construct validity would be a confirmatory factor analysis[186]. Here, factors in the questionnaire - which we *a priori* know to be related - are tested via a combination of a multivariate analysis and a principal component analysis (as described in section 3.8.2)[186,237].

The reliability of the questionnaire would describe to which extent the questionnaire measured chronic postoperative pain with consistency and reproducibility[234]. Generally, the reliability is divided into the internal consistency, the test-retest reliability, and the inter-rater reliability[234,237]. The internal consistency describes to which extent the items are consistent in measuring the same construct[190]. Traditionally, this is described in terms of a coefficient ranging from 0 to 1, entitled Cronbach's alpha[234,236]. A Cronbach's alpha value below 0.7 generally indicate low consistency, while a high value above 0.9 could indicate redundancy[238,239]. Another method to test the internal consistency is known as split-half reliability, in which the consistency of half of the items are correlated to the consistency of the other half, expressed by a Spearman-Brown coefficient[239–241].

The test-retest reliability describes to which extent the answers given by a responder remain consistent when the questionnaire is filled out twice or more[234,237]. This is typically described using Pearson's correlation coefficient ranging from -1 to 1, where high positive values indicate a strong test-retest reliability[237]. Finally, the inter-rater reliability describes to which extent answers to the *same* question correlates when given to different data gatherers, and can be expressed using several different correlation coefficients[237,239].

The scarce validation process of our questionnaire is a severe inadequacy, which comprises the generalizability of our results. A systematic and methodical validation of the questionnaire prior to initiating these studies would have been appropriate. Despite this understanding came post festum, it would, nevertheless, be essential to perform a thorough validation of the questionnaire, if it was to be utilized in future studies.

As stated in section '1.5. Assessment of Pain', the subjective nature of pain entails an inherent challenge when trying to assess and quantify pain as an outcome measure. Firstly, the use of questionnaires and other types of self-reported data can - and probably always will - introduce an element of information bias, as responders are asked for a (subjective) assessment of a given variable. The responders might remember details inaccurately (recall bias), unconsciously exaggerate or underestimate - or simply choose to give an answer which is not truthful. Secondly, the need for an operational definition of chronic postoperative pain (in this PhD dissertation, persistent, moderate to severe pain on a daily basis with a mean VAS ≥ 3, six months after the surgical procedure) reduces the complex condition of postoperative pain to a simple, binary outcome. This necessary - yet somewhat oversimplified - definition will irrefutably lead to a risk of misclassification, as some individuals might indeed have a mean VAS ≥ 3 while not being impaired by this level of chronic pain.

As shown by the literature review in section '1.5.2. The Memory of Pain', several studies have shown that pain is recalled accurately after six months. In the studies presented in this PhD dissertation, the risk of recall bias is mainly a concern in *Study I* given its retrospective nature. From table 2 it is seen that the mean follow-up time (i.e. the number of days between the surgical procedure and receiving the questionnaire) was 1,053.2 days equivalent to 2.9 years. Keeping this in mind, it is apparent that the answers related to the preoperative time period could have inherent issues of recall bias in spite of the general accuracy of recalled pain. If all study participants (with or without chronic pain) recalled the level of pain equally poor this would lead to non-differential misclassification, which theoretically would weaken the measure of association (and bias toward the null)[200]. More problematic is the case of differential misclassification, where for instance study participants with chronic postoperative pain falsely recall a higher level of preoperative pain. This would lead to systematic bias and potentially demonstrate an incorrect measure of association between preoperative pain and postoperative pain[200,231]. The risk of differential or non-differential misclassification due to recall bias cannot be disregarded in this study.

Selection Bias

Study I had a responder rate of 76.1% and thereby above the conventional, recommended minimal responder rate of 75.0%, thus minimizing the likelihood of non-response bias[242,243].

The non-responder analysis did not show any statistically significant difference in BMI, duration of surgery or blood loss between responders and non-responders. The mean age, nevertheless, was significantly lower in the non-responder group compared to the responders (63.4 years, 95% CI 60.6-65.7 versus 67.2 years, 95% CI 65.9-68.5), thereby indicating selection bias seeing that the individuals were not equally balanced between the two groups. A hypothetical explanation for this discrepancy could be that the willingness

to participate in a questionnaire study depended on age or whether the individual had retired. As the age of retirement in Denmark was 65 years-of-age at the time of the study, this could potentially explain the difference in responder-rate in the two groups. The positive effect of high age on the willingness to participate in surveys have been demonstrated in other studies[244,245]. Studies have shown high age to be a protective factor of chronic postoperative pain[93,203]. Hence, if all non-responders had indeed responded, this would theoretically have lowered the mean age of the sample, thereby hypothetically increasing the prevalence of chronic postoperative pain in our sample.

If the reason for not responding to the questionnaire is in some way related to the outcome measure, this could generate bias in the measure of association[246]. That is, if the non-responders either had too much pain to fill out the questionnaire *or* it did not seem relevant to fill out the questionnaire since the non-responders did not have any pain at all. Evidently, this can only be considered as hypothetical theories.

From the tumor characteristics in table 3 we can conclude that the distribution of tumor type, grade and FIGO stage of the responders are highly comparable to national- and international reports[8,10], thus indicating that our sample is representative in that respect.

Effect Measure Modification

As stated in section '3.7.1. Peri- and Postoperative Drug Dose Regimen', all study participants received a uniform dose of 300 mg Gabapentin p.o. 30 minutes prior to the surgical procedure as an integrated part of the drug dose regimen at our facility (and not specific to this research protocol). Some studies have shown Gabapentin reduces the risk of acute- and chronic postoperative pain, while other studies have shown it merely decreases the consumption of opioids in the immediate postoperative period[247–250]. As the

pharmacologic effect of Gabapentin is caused by an influx of calcium in the terminals of primary afferent neurons in the dorsal horn of the spinal cord, the potential effect of Gabapentin is most likely derived from a direct alteration in the causative pathway to development of chronic postoperative pain[251,252]. As such, Gabapentin should be considered as potential effect measure modifier (and *not* a confounder). However, since all study participants received the *same* dose of Gabapentin, we would expect this effect measure modification to be equally distributed in both groups (chronic pain and no chronic pain). Nevertheless, the use of Gabapentin in this study should be kept in mind when comparing the results to other studies *not* utilizing Gabapentin in their standard drug dose regimen.

Confounding

Confounding can be described as a confusion of effects[200]. A confounder is associated with both the exposure *and* the outcome but does *not* lie on the causative pathway[200,253,254].

As stated previously, the *unadjusted* OR for preoperative pelvic pain as a risk factor for development of chronic postoperative pain was 8.81 (95% CI 3.43-22.38) while the *adjusted* OR was 4.99 (95% CI 4.15-5.83). In the *unadjusted* OR we merely consider the effect of a single variable (preoperative pelvic pain), which is too simple an approach in the case of a complex outcome like chronic postoperative pain. As shown in section 1.3.1., a multitude of factors affect the development and perpetuation of chronic postoperative pain. For that reason, in addition to preoperative pelvic pain, we also included the variables acute postoperative pain, age and educational level (as a surrogate marker for socioeconomic status[119]) in the binary logistic regression model in table 7, model 2.

Conversely, we *did not* control for other possible confounding variables like comorbidity (including psychological traits like pain catastrophizing), adjuvant

therapy (i.e. chemotherapy in advanced stages of disease), smoking status or use of analgesics and prescription drugs. As a result, some degree of confounding is highly plausible. An example could be comorbidity as a confounder. As stated in section '1.3.1. Factors affecting Postoperative Pain', comorbidity is associated with an increased risk of chronic pain conditions, including chronic postoperative pain as well as an increased risk of cancer[124,125,255]. Consequently, this unadjusted confounding *could* lead to a distortion of the associations in our model, e.g. by overestimating preoperative pelvic pain as a risk factor. Smoking as a confounding variable will be discussed in section '5.6.3. Study III'.

5.6.2. STUDY II

Information Bias

As *Study II* was a nested case-control study within the cohort defined by *Study I*, all elements of information bias described above for *Study I* also applies here.

Selection Bias

The storage of blood and tissue in The Danish Cancer Biobank (DCB) is voluntary - nevertheless, the vast majority of patients chooses to do so, including the study participants of *Study II*, where twenty-six of the thirty-one patients (83.9%) with chronic postoperative pain had samples stored in the DCB (fig. 13). As the samples were obtained *preoperatively*, the choice of having samples stores could not be affected by the outcome (chronic postoperative pain), and in that respect, no sampling bias would occur. Yet, the choice of having biobank samples stored in general might be affected by the 'healthy worker effect', where certain individuals (with a healthy life-style and an interest in health science) are more prone to participating in such research biobanks than others (with a less healthy life-style). Therefore, *Study II* could have an inherent sampling bias[200,256].

Of far greater significance, however, was the fact that we matched the cases with chronic postoperative pain on age and BMI in a 1:2 ratio with controls without chronic postoperative pain. Even though this was done with the best intent to *minimize* the risk of confounding, this could in fact *introduce* sample selection bias. This somewhat counterintuitive effect arises as the matching is done in an effort to ensure that the distributions of the selected variables are identical across outcome groups. By 'homogenizing' the groups you obscure the effect of the variables you matched on, in this case, age and BMI[200,257]. As a result of this overmatching, the external validity is weakened.

The tumor characteristics of the study participants in table 8 demonstrates that the distribution of tumor type, grade and FIGO stage are comparable to the distributions found in national- and international settings, thereby indicating that the sample is representative in that respect[8,10].

5.6.3. STUDY III

As described in section 5.5., *Study III* may suffer from being underpowered and thereby increasing the risk of a type II error. This could have been circumvented by two measures: *either* include study participants over a longer time period *or* include study participants from multiple centers - or do both. The inclusion period of *Study III* was 41 months which was the longest feasible time period in this PhD project. The other option was to enroll study participants from multiple centers, which was abandoned during the design phase of the study due to the costs of having multiple sets of advanced QST equipment at the different centers, as well as reluctance to introduce bias through possible interobserver variance and the dissimilarities of the surgical algorithms at the different centers. Nonetheless, the fact that this study was conducted at a single center could limit the external validity of the results.

Information Bias

Study III also utilized the same questionnaire as *Study I-II*. As a consequence, most of the issues regarding information bias including differential and non-differential misclassification also applies to *Study III*. In one important aspect, however, *Study III* differentiates from *Study I-II*. Being a prospective study, the questionnaire in *Study III* was filled out by the study participants 6 months after the surgical procedure, thereby minimizing the potential issue of recall bias, as compared to the mean follow-up time in *Study I* of 2.9 years. In the planning of *Study III,* we considered asking the study participants to fill out the first part of the questionnaire, concerning the preoperative period, *before* the surgical procedure and thereby minimize the risk of recall bias further. This idea was abandoned as splitting up the questionnaire would require a validation process and could make the comparison of the results to *Study I* problematic.

In *Study III*, all study participants were informed, included and tested by the same examiner (Søren Lunde) according to a standardized algorithm. This ensured that all study participants were given the exact same instructions prior to QST testing and that all tests were performed identically, thus minimizing intraobserver variance and eliminating interobserver variance.

Selection Bias

The inclusion of study participants to *Study III* was consecutive throughout the study period. Of the one-hundred-and-fifty-four questionnaires mailed out, merely fourteen (9.1%) were not returned. The non-responder analysis did not show any statistically significant difference between responders and non-responders in terms of age, BMI, duration of surgery or blood loss. The tumor characteristics of the responders (table 11) furthermore indicated that our samples were representative of the population at interest, as the distribution of histologic type, grade and FIGO stage were equivalent to the distributions found in national and international databases of endometrial cancer[8,10]. Based

on the above, we consider our study sample representative, thereby supporting the overall generalizability of *Study III*.

Effect Measure Modification

As the peri- and postoperative drug dose regimen was similar to *Study I*, the issue regarding potential effect measure modification due to Gabapentin also applies to *Study III.*

Confounding

As described by Hernán et al, identification of potential confounding variables can be achieved by three different strategies: 1) Stepwise selection, 2) Comparing adjusted and unadjusted outcome measures, or 3) By analysing the causal relationship and potential confounders[258]. In the first strategy, all study variables are included in a regression model and a (forward or backward) stepwise selection performed. If the *p* value of the association to the given variable reaches a predetermined significance level, it is included in the final model[200,258]. In the second strategy, the adjusted and unadjusted outcome measures are compared. If the difference exceeds 10%, the variable is considered as a confounder[258,259]. The third and final strategy requires a certain level of knowledge to the causal pathway in question, as the variables are analysed according to the criteria of a confounding variable (associated with both the exposure and the outcome but does not lie on the causative pathway)[200,253,258]. Directed acyclic graphs (DAGs) are often constructed in this analytic process, as it allows for a visual representation of the interrelationship of the variables in question[258,260,261]. Additionally, the DAG approach has been proposed as a visual aid in complex pathways in order to minimize secondary bias introduced by adjusting for covariates[262,263]. Our strategy in *Study I-III* was a combination of stepwise selection in the regression models and a comparison of the adjusted and unadjusted outcome measures.

In the regression model of *Study III*, the variables Heat Pain Threshold, BMI, and preoperative pelvic pain were selected, as we wanted a simple, operational model using only *preoperative* variables and not e.g. the level of acute postoperative pain. In parallel to *Study I*, comorbidity, adjuvant therapy, analgesics / prescription drugs and smoking could potentially all act as confounders in *Study III* as well. Regrettably, the smoking status of the study participants in *Study III* was not obtained. However, if we were to conjecture what smoking as an uncontrolled confounding variable could entail, we must consult the literature. To the best of our knowledge, smoking does *not* lie on the causative pathway to chronic postoperative pain, but interestingly, smoking is associated with a *decreased* risk of endometrial cancer and an *increased* risk of chronic postoperative pain after hysterectomy[62,264]. Furthermore, a large review by Goldenberg et al showed that smoking was a surrogate marker for decreased Health-Related Quality of Life and that this association was directly related to the number of cigarettes smoked[265]. Thereby, smoking could act as an uncontrolled confounding variable in our studies. Additionally, residual confounding from unknown or unmeasured variables in these studies cannot be disregarded.

CHAPTER 6. CONCLUSION

Through the studies of this PhD dissertation, we aimed at investigating selected aspects of chronic postoperative pain. In *Study I* we hypothesized that development of chronic postoperative pain was associated to the pre- and postoperative risk factors: presence of preoperative pelvic pain, acute postoperative pelvic pain, age, severity of cancer, operating time, blood loss, educational level and employment status (*Hypothesis I*). Using a survey approach, the results showed preoperative pelvic pain and a high level of acute postoperative pain to be significant, independent risk factors with an adjusted OR of 4.99 (95% CI 4.15-5.83) and 1.27 (95% CI 1.09-1.45), respectively. Neither age, severity of cancer, operating time, blood loss, educational level nor employment status showed any significant association to chronic postoperative pain. *Study I* further showed a prevalence of chronic postoperative pain of 14.9% (95% CI 10.4-20.6).

From a methodological point of view, *Study I* had several limitations, mainly regarding potential information bias as the validation of the questionnaire was scarce. Moreover, despite adjusting for some confounders, important confounders like comorbidity and smoking were not adjusted for. Finally, it would have been ideal to have obtained HRQoL data for a more nuanced characterization of the life following surgery for endometrial cancer.

In the highly exploratory *Study II,* we hypothesized that patients who developed chronic postoperative pain had a distinctive preoperative serologic composition of lipids, lipoproteins and other low-molecular metabolites, compared to patients who did not develop chronic postoperative pain (*Hypothesis II).* Further, we conjectured that these serologic biomarkers of lipids, lipoproteins and other low-molecular metabolites were predictive for development of chronic postoperative pain (*Hypothesis III*). Through NMR spectroscopy, results showed that we could *not* discriminate between these

two groups when including all ESMO-ESGO-ESTRO risk assessments groups, and as such, *Hypothesis II* and *III* were rejected.

In *Study III* we hypothesized that development of chronic postoperative pain was associated to the preoperative risk factors: presence of preoperative pelvic pain, age, severity of cancer, educational level and employment status (*Hypothesis IV).* A binary logistic regression model established the presence of preoperative pelvic pain as a significant, independent risk factor with an OR of 6.62 (95% CI 2.26-19.44), while none of the other variables showed any association. The prevalence of chronic postoperative pain was found to be 13.6% (95% CI 8.4-20.4). In *Study III*, we also hypothesized that quantitative sensory testing by handheld algometry, cuff pressure algometry, temporal summation of pain, conditioned pain modulation and heat evoked pain could predict development of chronic postoperative pain (*Hypothesis V*). Our results demonstrated significant heat pain hyperalgesia in the group of patients that would develop chronic postoperative pain at a later stage compared to patients that would not develop chronic postoperative pain. However, this association between HPT and chronic postoperative pain was non-significant in a binary logistic regression model (OR = 0.86 (95% CI 0.72-1.02)), hence *Hypothesis V* was rejected.

Through the studies presented in this PhD dissertation we have contributed to the existing body of knowledge concerning chronic postoperative pain following robot-assisted laparoscopic hysterectomy for endometrial cancer.

CHAPTER 7. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

What can we as clinicians learn from these studies - and should the results have implications for the clinical practice? The results suggest that the primary predisposing risk factor for development of chronic postoperative pain is a preexisting pain condition. This strong association has previously been shown in several studies after various types of surgical procedures. The results also showed, that despite using state-of-the-art techniques like NMR spectroscopy and advanced quantitative sensory testing, we were unable to predict the development of chronic postoperative pain. Therefore, we as clinicians should ensure that we ask the patients about their medical history of chronic pain conditions prior to surgery, as this would be the single most important predictor for development of chronic postoperative pain. However, as surgery is essentially mandatory in case of endometrial cancer, it would be highly questionable that *any* patients would decline surgery on the basis of an increased susceptibility to development of chronic postoperative pain. The results of these studies *do not* change the fact, that evidence shows robot-assisted laparoscopic hysterectomy to be a safe and highly effective treatment for endometrial cancer with a low risk of adverse long-term effects.

As stated in section 5.6.1., the methodological issues regarding the questionnaire validation necessitates a thorough and systematic validation if the questionnaire were to be utilized in future studies.

Chronic pain as a research field is both fascinating and frustrating due to the vast number of interrelated pathophysiologic mechanisms of neuronal plasticity and nociceptive modulation. The emerging evidence of lipids and lipoproteins as nociceptive modulators is extremely fascinating. Despite our hypothesis of *Study II* were rejected, the results were still very thought-provoking from an explorative angle. The fact, that metabolic profiling by NMR

could discriminate between patients with and without chronic postoperative pain in a group of patients with low and intermediate risk assessments calls for further investigations. Our results from this subgroup analysis support the theory that LA and other omega-6 derivatives constitute a pronociceptive cellular environment, thus promoting the induction and perpetuation of chronic pain. In the optimal setting of a randomized controlled trial, it would be of great interest to examine if a *preoperative*, diet-induced reduction of omega-6 derivatives in the months prior to the surgical procedure could reduce the prevalence of chronic postoperative pain. However, this is not feasible in the case of endometrial cancer, seeing that patients are treated within a few days from referral. Therefore, this study should focus on chronic postoperative pain following hysterectomy on benign indication. In regard to the sample size of such a study, this would have the further advantage of a reduced number of patients needed to include compared to endometrial cancer patients, as we *a priori* would expect a higher prevalence of chronic postoperative pain in this group of patients with leiomyomas, dysmenorrhea or endometriosis.

Another interesting randomized controlled trial would be a preoperative randomization to either standard care or an additional epidural analgesic algorithm initiated prior to the surgical procedure and maintained for 24 hours postoperatively. This would effectively reduce the level of acute postoperative pain and thereby conceivably minimize the elicited surgical stress response. Consequently, we would hypothesize that the patients treated with the epidural analgesic algorithm would exhibit a lower prevalence of chronic postoperative pain due to a lesser extent of central sensibilization in the immediate postoperative period.

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APPENDICES

Due to copyright issues, Paper I-III are not included in this redacted version of the PhD dissertation. Please refer to the online versions:

Paper I

Søren Lunde, Kristian Kjær Petersen, Pirathiv Kugathasan,
Lars Arendt-Nielsen and Erik Søgaard-Andersen.
Chronic Postoperative Pain after Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer.
Journal of Gynecologic Surgery. Volume 35, Issue 3, June 2019, 140-146.
DOI: https://doi.org/10.1089/gyn.2018.0068

Paper II

Søren Lunde, Hien Thi Thu Nguyen, Kristian Kjær Petersen,
Lars Arendt-Nielsen, Henrik B. Krarup and Erik Søgaard-Andersen.
Chronic Postoperative Pain After Hysterectomy for Endometrial Cancer:
A Metabolic Profiling Study.
Molecular Pain. Volume 16, May 2020, 1-7.
DOI: https://doi.org/10.1177/1744806920923885

Paper III

Søren Lunde, Kristian Kjær Petersen,
Erik Søgaard-Andersen and Lars Arendt-Nielsen.
Preoperative Quantitative Sensory Testing and Robot-Assisted Laparoscopic Hysterectomy for Endometrial Cancer: Can Chronic Postoperative Pain be Predicted?
Scandinavian Journal of Pain, E-pub. ahead of print, August 2020, 1-13.
DOI: https://doi.org/10.1515/sjpain-2020-0030

THE QUESTIONNAIRE (IN DANISH)

Spørgeskema
Smerte efter operation for livmoderkræft

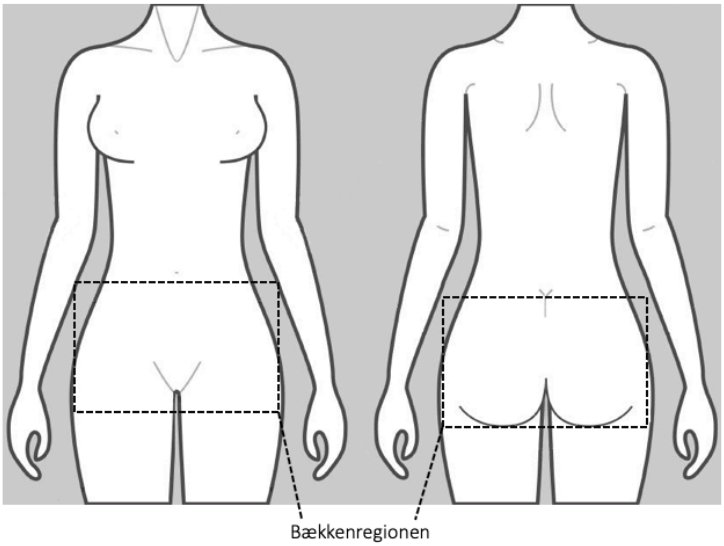
I gode hænder hos
AALBORG UNIVERSITETSHOSPITAL

Bemærk, at disse spørgsmål omhandler tiden **før** operationen.

1) A. Havde du smerter i bækkenregionen (se billedet) før operationen?

Ja ❑
Nej ❑ gå til spørgsmål 7
Husker ikke ❑ gå til spørgsmål 7

B. Skravér området på figuren, hvor du havde smerter før operationen.



2) Hvor ofte havde du smerter i bækkenregionen før operationen?

1-3 dage om ugen ❑
4-6 dage om ugen ❑
Hver dag ❑

3) A. Hvad var dit daglige smerteniveau før operationen? *(0 er ingen smerte og 10 er den værst tænkelige smerte; sæt cirkel om ét nummer)*

0 1 2 3 4 5 6 7 8 9 10

B. Hvor stærk var smerten, når den var værst?

0 1 2 3 4 5 6 7 8 9 10

Deltager nr:

4) Forstyrrede smerten din søvn før operationen?

Ja ❑
Nej ❑
Husker ikke ❑

5) A. Følte du smerte ved nogle af de nedenstående situationer før operationen?

	Ja	Nej	Ved ikke
Løb	❑	❑	❑
Tætsiddende tøj	❑	❑	❑
Under samleje	❑	❑	❑
Ved tunge løft	❑	❑	❑
Andre situationer	❑	❑	❑

B. Hvis ja til "Under samleje", påvirkede det så dit samliv?

Ja ❑
Nej ❑

6) Hvor meget påvirkede smerten din dagligdag før operationen?

Ingen påvirkning ❑
Nogen ❑
Meget ❑
Rigtig meget ❑

7) A. Har du haft smerteproblemer andre steder før operationen? *(F.eks. hovedpine, rygsmerter, brystsmerter, nakkesmerter)*

Ja ❑
Nej ❑ gå til spørgsmål 8

B. Hvor var denne smerte lokaliseret? .....

C. Har en læge stillet en diagnose på disse smerter?

Ja ❑ hvilken: .....
Nej ❑

Bemærk, at de næste spørgsmål omhandler tiden **efter** operationen.

8) Hvad var dit smerteniveau på dagen efter operationen?
(0 er ingen smerte og 10 er den værst tænkelige smerte; sæt cirkel om ét nummer)

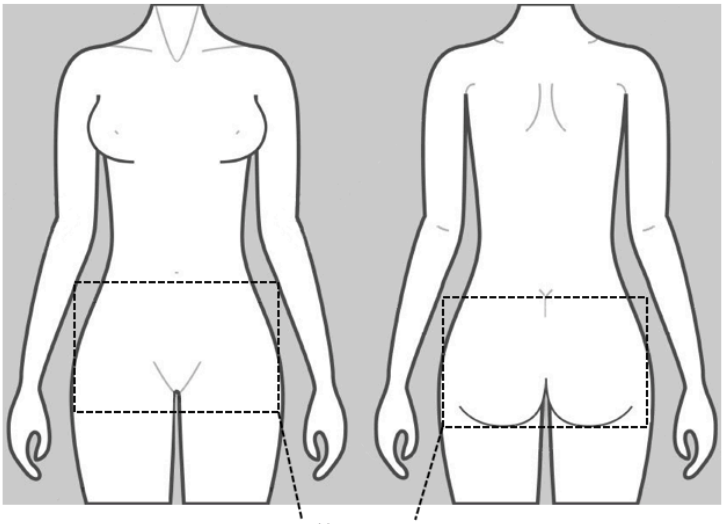
0 1 2 3 4 5 6 7 8 9 10

9) A. Har du oplevet vedvarende eller periodevise smerter indenfor de sidste 6 måneder i bækkenregionen (se billedet)?

Ja ❑
Nej ❑ gå til spørgsmål 14

B. Hvornår begyndte disse smerter efter operationen: _____ måneder *(0 måneder betyder at smerterne har været til stede lige siden operationen)*

C. Skravér området på figuren, hvor dine smerter er lokaliseret.



D. Hvor ofte har du smerter?

1-3 dage om ugen ❑
4-6 dage om ugen ❑
Hver dag ❑

10) A. Hvad er dit daglige smerteniveau?

(0 er ingen smerte og 10 er den værst tænkelige smerte; sæt cirkel om ét nummer)

0 1 2 3 4 5 6 7 8 9 10

B. Hvor stærk er smerten, når den er værst?

0 1 2 3 4 5 6 7 8 9 10

11) A. Føler du øget smerte ved en eller flere af følgende situationer?

	Ja	Nej	Ved ikke
Løb	❑	❑	❑
Tætsiddende tøj	❑	❑	❑
Under samleje	❑	❑	❑
Ved tunge løft	❑	❑	❑
Andre situationer	❑	❑	❑

B. Hvis ja til "Under samleje", påvirker det så dit samliv?

Ja ..... ❑
Nej ..... ❑

12) Har smerten forstyrret din søvn indenfor de sidste 6 måneder?

Ja ..... ❑
Nej ..... ❑

13) A. Har du haft smerteproblemer andre steder indenfor de sidste 6 måneder? *(f.eks. hovedpine, rygsmerter, brystsmerter, nakkesmerter)*

Ja ..... ❑
Nej ..... ❑ gå til spørgsmål 15

B. Hvor er smerten lokaliseret? .....

C. Har en læge stillet en diagnose på disse smerter?

Ja ..... ❑ hvilken: .....
Nej ..... ❑

14) A. Hvordan er din arbejdssituation?

Fuldtidsjob	❑	Førtidspensioneret	❑	Hjemmearbejdende	❑
Deltidsjob	❑	Pensioneret	❑	Andre:	
Uden arbejde	❑	Studerende	❑		

B. Hvad er dit uddannelsesniveau?

Folkeskole / Mellemskole	❑	Mellemlang videregående udd.	❑
Gymnasial (HF, STX, HTX, HHX)	❑	Lang videregående udd.	❑
Erhvervsfaglig uddannelse (HG)	❑	Forskeruddannelse (Ph.D.)	❑
Kort videregående uddannelse	❑	Andre:	

C. Hvilken alder har du? ..... år

D. Hvor høj er du? ..... cm

E. Hvor meget vejer du? ..... kg

F. Hvor mange børn har du født? .....
Heraf antal fødsler gennem skeden? .....
Heraf antal fødsler ved kejsersnit? .....

Mange tak, fordi du tog dig tid til at besvare dette spørgeskema.

Send venligst skemaet retur i medfølgende frankerede svarkuvert. Når du gør dette, giver du samtidig samtykke til vi må benytte spørgeskemaets informationer i vores studie.

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