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SPINAL CORD STIMULATION IN CHRONIC PAIN
A study of health outcomes and costs

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SPINAL CORD STIMULATION IN CHRONIC PAIN: A STUDY OF HEALTH OUTCOMES AND COSTS

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By

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ABSTRACT

Background: The aetiology of chronic pain is complex and encompasses many different causes. Chronic pain commonly arises due to spinal disorders causing pain in the back and legs. Chronic pain is a substantial global public health problem, with a high prevalence, detrimental effects on health and health-related quality of life (HRQoL), ability to work and associated societal costs. Results from clinical studies indicate that spinal cord stimulation (SCS) decreases pain, improves HRQoL and disability, in patients with chronic pain of predominantly neuropathic origin, and has long been used in clinical practice. SCS, a minimal-invasive type of neuromodulation device (implant of electrodes in the epidural space), is commonly indicated for patients with intractable pain, who do not respond to prior treatments such as spine surgery. However, there is little known about the characteristics of patients receiving SCS in clinical practice, the long-term effects, and the potential influence of patient characteristics on treatment effects. The broader aim of the thesis is to investigate health outcomes and societal costs in patients with chronic pain treated with SCS.

Methods: The studies were based on Swedish national register data. Study I investigated pre- and post-lumbar spine surgery costs, HRQoL, disability, and pain, in patients who received SCS treatment following lumbar spine surgery. The study was exploratory and included several health and cost outcomes in relation to initial lumbar spine surgery and subsequent SCS. HRQoL, pain, and disability were measured up to five years after spine surgery, and costs were measured three years before and after spine surgery and SCS, respectively. Study II analysed the impact of SCS on short-term sick leave and long-term disability pension and what explored potential predictors are associated with the impact. A matched reference group was used to control for societal changes that may impact usage of sickness benefits.

Conclusions: Spine surgery preceding SCS did not have any effect on pain, HRQoL, and costs at one, two and five years in patients who were subsequently treated with SCS. Patients who subsequently received SCS after spine surgery were statistically significantly worse off in terms of disability and HRQoL already at the initial spine surgery. SCS, in patients with or without prior spine surgery, is associated with statistically significant decrease in sick leave days, but not disability pension which increased. SCS decreased the overall net disability days and consequently indirect cost in working age patients. Large productivity losses prior to SCS were demonstrated, indicating a significant burden on the employers, the patient, and the society at large. Usage of anti-depressants was significantly associated with poorer effect on disability days. Other socioeconomic and clinical factors had no association with the effect of SCS on sick leave and disability pension.

LIST OF SCIENTIFIC PAPERS

I. Jonsson E, Hansson-Hedblom A, Kirketeig T, Fritzell P, Hägg O, Borgström F. Cost and Health Outcomes Patterns in Patients Treated With Spinal Cord Stimulation Following Spine Surgery-A Register Based Study. Neuromodulation: journal of the International Neuromodulation Society. 2020;23(5):626-33

II. Söreskog E, Jacobson T, Kirketeig T, Fritzell F, Karlsten R, Zethraeus N, Borgström F. Spinal Cord Stimulation Reduces Sick Leave in Patients with Chronic Neuropathic Pain: A Real-world Evidence Study in Sweden. *Manuscript*

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LIST OF ABBREVIATIONS

CI	Confidence Interval
CMM	Conventional Medical Management
CRPS	Complex Regional Pain Syndrome
EQ-5D	EuroQoL Five Dimensions Questionnaire
FBSS	Failed Back Surgery Syndrome
HF-10	High Frequency 10 kHz
HRQoL	Health Related Quality of Life
IASP	International Association for the Study of Pain
ICD-10	International Classification of Diseases version 10
ICER	Incremental Cost-Effectiveness Ratio
IMMPACT	The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IPG	Implantable Pulse Generator
NCSP	NOMESCO Classification of Surgical Procedures
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
ODI	Oswestry Disability Index
PROM	Patient-Reported Outcome Measure
QALY	Quality-Adjusted Life-Year
RCT	Randomised Controlled Trial
RMDQ	Roland-Morris Disability Questionnaire
SCS	Spinal Cord Stimulation
SD	Standard Deviation
SE	Standard Error
VAS	Visual Analogue Scale
WTP	Willingness-To-Pay

1 INTRODUCTION

Chronic pain, a condition lasting for more than three months, affects one in five adult Europeans (1). The condition has significant impact on patients' quality of life and health. The aggregated costs of chronic pain are high due to high prevalence and high indirect costs associated with productivity losses (2). In patients with degenerative spinal diseases with associated chronic back and leg pain, pharmacotherapy such as opioids and other analgesics is common amend the pain. The underlying cause of the pain may be treated surgically, when a specific cause can be found, such as disc herniation and spinal stenosis. Patients who do not find cure in common non-surgical and surgical treatments—or where in fact the treatment has caused further problems—may benefit from neuromodulation therapies. Spinal cord stimulation (SCS) is the most common treatment in this area (3). SCS is a minimal-invasive treatment for patients with chronic pain of predominantly neuropathic origin that does not respond to other treatments. Results from randomised controlled trials (RCTs) indicate that SCS decreases pain and disability and improves health-related quality of life (HRQoL). SCS has been used in clinical practice for over 50 years.

RCTs generally include highly selected patient cohorts that may not be representative of patients in real-world clinical practice. There is currently little known about characteristics of patients receiving SCS in clinical practice, real-world long-term clinical and economic effects, and the potential influence of patient clinical and sociodemographic characteristics on effects. Resources in healthcare are limited, and it is important to efficiently allocate those resources to maximise health outcomes. To improve efficient allocation of resources and ultimately improve health and quality of life of individuals affected by chronic pain, it is important to increase the knowledge about real-world and long-term costs, effects, what potential factors predicts successful outcome, and which patients may benefit from other interventions.

Drawing causal inference on the effect of one healthcare intervention versus another can be more difficult in retrospective observational studies compared with RCTs due to lack of natural randomisation and control group. RCTs generally have higher internal validity than observational studies since randomisation increases the likelihood of treatment being allocated independently of observable and unobservable patient characteristics (4). An RCT generally identify internally valid sample average causal effect where the sample is the trial population. However, the target population (where the treatment is intended in the real-world practice) may differ systematically from the trial population and the target population is often the population in which we want to evaluate societal health economic aspects of an intervention. Retrospective observational studies can answer questions regarding effects in a population reflecting the patient population in clinical practice (4). Such studies also have the benefits of study participants and caregivers not knowing they are being studied and behaviours therefore reflect real-world patterns to a greater extent—RCTs may evaluate treatments delivered more rigorously compared with those delivered in clinical practice (5).

Sweden has a taxpayer funded universal healthcare system with several mandatory national registers, such as patient register, prescribed drug register, social insurance register, and several have been in use for over 20 years. Everyone that lives in Sweden has a personal identification number which is used every time they visit healthcare or utilise social insurance benefits, making it possible to link individuals across registers. Therefore, Swedish registers enable population-based research representative of the patient population in clinical practice and enable long-term follow-up. The broader aim of the thesis is to investigate health outcomes and societal costs in patients with chronic pain treated with SCS.

2 BACKGROUND

2.1 AETIOLOGY OF PAIN

The International Association for the Study of Pain (IASP) defines pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (6). This definition emphasises the subjectivity of pain. Individuals learn about pain through life experiences influenced to varying degrees by biological, psychological, and social factors. Those affected may adapt to the pain although it may still have adverse effects on function and social and psychological well-being.

The aetiology of chronic pain is complex and encompasses many different causes. Pain can be caused by cancer/tumours, trauma, nerve damage, degenerative conditions such as arthritis and spinal stenosis, and inflammations, but the pathology is commonly unknown (for example non-specific low back pain and fibromyalgia). Chronic pain is defined as pain lasting for more than three months. Most people experience pain problem at some point in life but not all develop into chronic disability. There is a strong link between chronic pain and depression, and it has been shown that only a small portion of patients seeking care for low back pain have a "serious" physiological pathology (7, 8). Although advances in physiological and psychological explanation models have been made, why some individuals develop into chronic pain remain largely unanswered (9).

This thesis will focus on pain conditions of predominantly neuropathic origin that are commonly indicated for SCS treatment, and degenerative spinal diseases commonly indicated for lumbar spine surgery. The reason for this dual, albeit overlapping, focus is because it is common to undergo spine surgery prior to SCS and both aetiologic groups are associated with back and/or leg pain. Degenerative spinal diseases cause back and/or leg pain, while not all treated with SCS have the indication back and leg pain. The majority, however, of patients treated with SCS have the main indication chronic back and leg pain with or without prior surgery (>60%), and less than 10% are indicated for neuropathic pain in extremity after injury (10). Most common diagnoses indicated for lumbar spine surgery are disc herniation, spinal stenosis, spondylolisthesis and degenerative disc disease, together around 90% of all indications for performed lumbar spine surgeries performed in Sweden (11). The diagnoses are described in brief below.

Disc herniation is formed when a disc in the spine changes and displaced which may cause pressure on nerves. Many times, disc herniation does not cause any symptoms or very moderate symptoms, but sometimes it causes severe low back pain and/or leg pain. The most common disc herniations occur in the two lowest discs in the lower back (L4–L5 or L5–S1) and cause pressure on the ischia nerve. Spinal stenosis is a degenerative disease caused by narrowing of the spinal canal which eventually results in pressure on the spinal cord or nerves. Spinal stenosis may cause pain in the lower back and legs. Spondylolisthesis occurs when a vertebra slips out of position and is most common in the lower back. It can be caused by degeneration, trauma, and fracture. Degenerative disc disease is degeneration of motion segments (two vertebras, disc and two facet joints). Symptoms include pain in the lower back and is often depending on motion and position of the body.

Neuropathic pain is defined as "*pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system*" according to the IASP (12). Conditions associated with neuropathic pain include for example radiculopathy (pinching of a nerve root in the spinal column), diabetic neuropathy, peripheral nerve injury, and trigeminal neuralgia (disruption of the trigeminal nerve causing pain in the face) (13). Neuropathic pain is usually chronic and difficult to treat (14).

The Neuropathic Pain Special Interest Group ("NeuPSIG") of IASP has defined a grading system to determine if the pain is neuropathic (12). Definite neuropathic pain is present if the following criteria are fulfilled: 1) pain with a distinct neuroanatomical distribution, 2) a medical history that suggests a lesion or disease of the nervous system, 3) a confirmatory test to demonstrate neuroanatomical distribution, and 4) a confirmatory test to demonstrate a lesion or disease of the nervous system. Probable neuropathic pain is categorised as fulfilling only criteria 1 and 2, and possible neuropathic pain as only criteria 1.

SCS is commonly indicated for patients with severe chronic pain in the leg and back of predominantly neuropathic origin where other treatments do not provide satisfactory pain relief (15). This has been called failed back surgery syndrome (FBSS) because it usually comprised of lingering pain after spine surgery, however, similar pain conditions can present without prior spine surgery. Other indications are Complex Regional Pain Syndrome (CPRS), angina pectoris, and painful diabetic neuropathy.

2.2 BURDEN OF PAIN

There is a consensus in the literature that pain is a substantial global public health problem. Low back pain alone affects almost everyone at some point in life and 4–33% depending on age group at any given time point (16). Pain with neuropathic origin (disease or damage on the somatosensory system) affects 7–8% of Europeans (17, 18). The prevalence of chronic pain has been estimated to 19% in adult Europeans but is also common in children and adolescents with a prevalence as high as 25% estimated in a Dutch population (1, 19). Back and leg pain constituted 60% of chronic pain locations in the European study (1). Estimates of the prevalence of chronic pain in United States adults range between 11–40%, with

considerable variation across subgroups, particularly socioeconomic statuses (20). The prevalence of "high-impact" chronic pain (defined as chronic pain that frequently limits life or work activities) has been estimated to 8% in United States adults (20).

The impact of pain on individual well-being and health varies, for some it may be a brief acute sensation, but for others it becomes a permanent feature of their lives affecting quality of life, sleep, social relationships, leading to depression and fatigue, and decrements in physical and cognitive functioning. Individuals with chronic pain have significantly lower HRQoL compared with the general population (21). Neuropathic chronic pain is associated with lower HRQoL and worse pain than non-neuropathic chronic pain (22). In the PROCESS trial of SCS for the treatment of chronic neuropathic pain, the average baseline HRQoL was found to be considerably lower than HRQoL estimated in patients hospitalised due to ischemic stroke (23, 24).

In addition to detrimental effects on individuals' health and well-being, chronic pain is associated with high societal costs, chiefly due to reduced productivity and increased risk of leaving the labour force. The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) estimated the societal cost of chronic pain to be €9.6 billion per year in 2003 in Sweden, where more than 90% (€8.8 billion) were related to indirect costs due to absence from work (2). Chronic pain has been estimated to be the most common reason of visiting primary care in Sweden (25). Together with mental disorders, often co-existing with chronic pain, it is the most common reason for sick leave and disability pension (26). The total cost of chronic pain, including both indirect costs due to absence from work, medical, and other costs, has been estimated at €200 billion in Europe and between $560 and $635 in the United States (21, 27).

2.3 HEALTH OUTCOME MEASURES OF CHRONIC PAIN

2.3.1 Pain Intensity

Visual Analogue Scale (VAS) is frequently used in pain research. VAS was introduced in the 1960s and is used in many other research areas such as psychiatry. The respondent expresses their average pain intensity by indicating their position on a 10 cm long vertical or horizontal line using a marker, where one end of the line represents "no pain" and the other "worst pain imaginable". The marked point is then measured, yielding a number between 0 and 100. VAS is in general considered to have a high test-retest reliability (high consistency when repeating the same test in the same sample) (28, 29).

Other methods to measure pain is the Numerical Rating Scale (NRS), where the respondent is asked to give a number, e.g., between 0 and 10 that corresponds to pain intensity, or Verbal Rating Scale (VRS), where the respondent chooses between several words that describes hers/his pain. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), consisting of representants from research, patient organisations and industry, has developed recommendations for outcome measures in clinical studies of chronic pain (30). IMMPACT recommendations declares that there are no important differences

between VAS, NRS, or VRS regarding responsiveness (sensitivity to clinical change), but NRS is preferable over VAS due to potentially larger data loss using VAS, possibly because VAS is more abstract than NRS and therefore more difficult to answer (30).

2.3.2 Back Pain Specific Functional Measures

The Oswestry Disability Index (ODI) is a measure of back pain-related functional limitation (31). It consists of ten questions regarding pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and travelling. Six response options are possible ranging from "no problem" to "worst problem imaginable". An overall score is calculated based on the answers, ranging from 0 to 100 where 0–20 indicates "minimal disability," 21–40 "moderate disability," 41–60 "severe disability," 61–80 "crippling back pain," and 81–100 ("bed bound", or "exaggeration of symptoms"). ODI is commonly included in studies of spinal disorders and surgery (32). ODI has shown high reliability, validity, responsiveness, and sensitivity to change in patients with chronic back pain (33). Another common measure in back pain research is the Roland-Morris Disability Questionnaire (RMDQ). ODI and RMDQ have been shown to be equally valid in non-specific back pain, but ODI may be better at detecting change in more severe spinal disorders (34, 35).

2.3.3 Health-Related Quality of Life

Common generic HRQoL instruments are the EuroQoL Five Dimensions Questionnaire (EQ-5D), Short-Form 36 Health Survey (SF-36), and Health Utilities Index (HUI). The EQ-5D questionnaire consists of five questions regarding mobility, hygiene, activity level, pain/discomfort, and anxiety/depression. EQ-5D is available in two versions: EQ-5D-3L with three levels of severity, and EQ-5D-5L containing five levels of severity. The answers to the questions are compiled into an overall index, where a score closer to 1 implies highest levels of HRQoL and 0 implies a HRQoL equivalent to being dead. Country-specific value sets can be used to assign the index score and value sets can be experience-based (based on valuations of individuals with the described health condition) or reference-based/hypothetical (based on a population which the health conditions have been described to). The EQ-5D index can be used to calculate quality-adjusted life years (QALYs) used in health economic evaluations. Currently existing Swedish value set is experience-based (36), while the United Kingdom value set is reference-based (37). SF-36 questionnaire can also be used to calculate QALYs, transformed using the SF-6D, while EQ-5D is more commonly used and the preferred measure of HRQoL by for example the National Institute for Health and Care Excellence (NICE) in the United Kingdom (38). High reliability, validity and responsiveness of EQ-5D have been shown in low back surgery (39).

2.4 ECONOMIC EVALUATION AND COSTS

An economic evaluation is "*the comparative analysis of alternative courses of action in terms of both their costs and consequences*" according to Drummond et al. (40). In other words, it is the analysis of costs (resource use) and consequences (health outcomes, effects) of two or

more alternatives such as healthcare interventions. The purpose of economic evaluation is to inform decision-making to improve the efficiency in the allocation of limited resources (money, time, people). Economic evaluations play an important role in healthcare since choosing one intervention over another will have effects not only for those who will receive the intervention and their health, but will take resources from other parts of healthcare, and may also have effects outside healthcare. An economic evaluation needs evidence on all relevant effects of the intervention. One source is results from clinical studies, such as RCTs, but often complemented with evidence representing the effects in the everyday clinical practice.

Because resources are scarce and can be used for different purposes, we must make choices on how to use resources. If we decide to use resources for one alternative, another alternative must be rejected, which results in opportunity cost, which is the value of the next best alternative that is foregone. Costs in economic evaluation can be divided into direct and indirect costs. Direct costs can be further divided into medical (hospital care, outpatient care, diagnostics, procedures, drugs) and non-medical (transportation, social assistance) costs. Indirect costs are costs of lost productivity due to the disease and leisure time cost. Economic evaluations can be conducted from different perspectives which determines what type of costs to include. Taking a healthcare sector, or payer, perspective, only costs that arise in the healthcare sector are included i.e., direct medical costs. Taking a societal perspective, all costs should be included irrespective of where they arise, and irrespective of whom pays the costs, implying that both direct and indirect costs should be included. A societal perspective has for example been recommended when applying for reimbursement to the Dental and Pharmaceutical Benefits Agency in Sweden while National Institute for Health and Care Excellence in the United Kingdom requires a healthcare perspective.

2.5 TREATMENT OPTIONS FOR CHRONIC PAIN

2.5.1 Non-Surgical Treatments

Optimal treatment varies, and when a specific cause of the pain, such as disc herniation or spinal stenosis, then the underlying cause may be treated. Even if a specific cause is identified, it is common to start with non-surgical treatments before considering spine surgery or other invasive methods. Treating the pain itself typically require several methods. The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) concluded in a large evidence review of pain treatments that multimodal rehabilitation (usually a combination of psychological therapy and physical activity/exercise or physical therapy) has stronger evidence compared with separate interventions such as exercise (2). Patients with pain from muscles and skeleton who receive both measures to improve the physical function and psychological therapy have less days of sick leave than patients with solitary treatments or passive control. Active and professionally-led exercise provided a 20–30% better pain relief in patients with chronic pain compared with treatments where the patient was not physically active (2). Pharmacotherapy with antidepressants and analgesics

such as opioids is common in patients with neuropathic pain but the evidence on pain relief has been shown to be poor and adverse effects are common (41, 42).

2.5.2 Spine Surgery

About 10,000 in Sweden and 900,000 in the United States undergo spine surgery annually and the numbers are increasing (11, 43). The most common diagnoses leading to surgery in Sweden are disc herniation and spinal stenosis (11). Other common diagnoses are spondylolisthesis and degenerative disc disorder. Main indication for surgery of disc herniation is substantial chronic leg pain, i.e., pain with substantial effect on quality of life. Surgery (discectomy) entails that a part of the disc causing the pressure on the nerve root is removed. Main indication for surgery of spinal stenosis is when pain or functional impairment is deemed unacceptable, and magnetic resonance imaging or computed tomography show clear changes that could be consistent with the patient's discomfort. A decompression is performed entailing a widening of the spinal canal and thereby making space for the nerve structures. Sometimes, decompression is combined with spinal fusion.

2.5.3 Spinal Cord Stimulation

2.5.3.1 Mechanism of Action

The "gate-control theory", developed in the 1960s by Melzack and Wall (44), claims that activation of nerves that do not cause pain signals (non-nociceptive nerves) can inhibit nociceptive nerve signals causing pain. Neuromodulation therapies, originally based on this theory, have since then been developed and are increasingly used to treat intractable pain with neuropathic origin.

SCS, a minimal-invasive type of neuromodulation (implant of electrodes in the epidural space), was the first clinically used electric neuromodulator to target chronic pain with a neuropathic component. Between 300 and 600 SCS have been implanted annually in Sweden since 2008, based on publicly available data on registered procedure codes (NOMESCO Classification of Surgical Procedures, NCSP) for SCS (code ABD30) from the Swedish National Board of Health and Welfare (45). Treatment with SCS entails that an implantable pulse generator (IPG) is implanted under the skin, typically in the low back area (Figure 1). The IPG sends low currents into the leads implanted in the dorsal column. The current creates a tingling sensation that inhibits pain signals as they travel to the brain. Traditional SCS produces tonic waveforms where pulses are delivered at a consistent frequency, pulse width, and amplitude. Newer waveforms include burst stimulation (introduced in 2010) which delivers high-frequency group pulses and amplitudes lower than tonic stimulation. High-frequency 10 kHz (HF-10) delivers consistently high frequency.

Figure 1. Illustration of spinal cord stimulation (SCS) system with implantable pulse generator (IPG) and electrodes placed between the spinal cord and vertebrae (epidural space)

Neuropathic pain is typically a result from peripheral sensitisation (increased responsiveness for nociceptive stimuli in peripheral neurons) which in turn leads to central sensitisation of neurons in the spinal cord. Abnormal pain sensitivity occurs in the central nervous system as pain thresholds are lowered due to activation of N-methyl-D-aspartate receptors and size of receptive fields increase. The molecular mechanism behind central sensitisation is complex and involves several neuroactive substances. It is perceived that stimuli increases inflow of neurotransmitters and neuromodulators including the excitatory amino acid glutamate, calcitonin, and substance P to the dorsal horn of the spinal cord. A reduction in the release of gamma-aminobutyric acid may also be involved in sensitisation. Animal models have shown that high frequency SCS decreases spinal glutamate concentration in rats with spared nerve injury (46). Additional rat model of neuropathy showed that SCS decreased glutamate as well as increased gamma-aminobutyric acid release (47). It is perceived that changes in for example glutamate and gamma-aminobutyric acid may have important roles in the neuropathic pain relief of SCS, however, experts in the field believe more research is required and it is uncertain how the results from experimental studies can be translated to a clinical setting (48, 49).

2.5.3.2 Effect of SCS

The effect of SCS is primarily measured as patient-reported percentage pain relief using VAS or NRS. Response to treatment is commonly defined as ≥50% pain relief. The IMMPACT recommendations of minimal clinical important difference in chronic pain and identified that ≥50% pain relief is considered substantial improvements while ≥30% pain relief is considered a moderately important improvement (50).

A search in PubMed/MEDLINE was conducted from 2016 to 2021 to identify systematic literature reviews of the effectiveness of SCS on pain, HRQoL, disability, and function, and health economic evaluations. Details of search methods are presented in Appendix A. The search provided 95 hits and 15 reviews were deemed relevant, whereof 12 studied effectiveness on pain, HRQoL, and other clinical measures, two studied cost-effectiveness of SCS compared with conventional medical management (CMM) or reoperation for FBSS, and one focused on the effect of SCS on return to work. Results from selected systematic literature reviews are summarised in brief below and in Table 1. Summary of additional reviews can be found in Appendix B.

2.5.3.2.1 Study Designs

Most systematic literature reviews focused on within-group comparisons, i.e., comparisons in outcomes after SCS treatment initiation made with baseline and not with active comparator outcomes. Common comparators were CMM, typically including analgesics, antidepressants, steroid injections, and physical therapy, repeated spine surgery (FBSS patients), and different waveform (for example burst/HF-10 SCS vs. tonic SCS). The two most cited RCTs were the studies by North et al. and Kumar et al., comparing SCS with repeated spine surgery and CMM, respectively, which precluded patient and clinician blinding (51, 52). One double-blinded study (n=33) comparing SCS with sham (stimulator off) was identified (53). Several RCTs comparing different waveforms were double-blinded (54). In the clinical studies, the SCS treatment protocol often started with a trial stimulation to eliminate non-responders. Trial stimulation often entails that leads are implanted and connected via temporary extension to an external battery that the patient can wear for around two weeks. If sufficient response is achieved, the patient may receive a permanent implant. Test stimulation was successful 80% in a study by Rigoard et al. and 67% in a study by Kemler et al. (55, 56).

2.5.3.2.2 Change in Pain, Disability, Function, HRQoL, and Medication Use Compared with Baseline

Most studies showed that SCS has an effect on pain, and studies generally report response rates (defined as at least 50% pain relief) between 46–90%. Baranidharan et al. conducted a systematic literature review of retrospective studies investigating the effect of HF-10 SCS (57). At follow-up of 12 months or less, average pain relief ranged from 46–77% and response rate (at least 50% pain relief) varied between 48–64%. At follow-up longer than 12 months, average pain relief ranged from 48–64% and response rate from 46–76%. Improvements in ODI and RMDQ ranged from 72–84%. An additional review and meta-analysis by Baranidharan et al. of the effect of HF-10 SCS on pain reduction and opioid consumption in patients with neck and upper extremity pain included 15 studies (58). The pooled response rate (≥50% pain relief) was 83% (95% confidence interval [CI] 77–89%). The proportion who reduced or ceased opioid consumption was 39% (95% CI 31–46%) in a fixed-effect model and 39% (95% CI 31–48%) in a random-effects model.

A systematic literature review by Eckermann et al. of clinical studies investigating the effect of SCS in patients without prior spine surgery was conducted in 2021 (15). Response rate (≥50% pain relief) at 12 months varied between 52–90% in the SCS-treated patients. One study reported an 80% response rate at 36 months (59, 60). Results on disability, function and HRQoL relative to baseline varied between studies. Al-Kaisy et al. and Baranidharan et al. reported statistically significant improvement on HRQoL measured by SF-36 and EQ-5D at 6 and 12 months ($p<0.05$) (60, 61). No statistically significant difference in HRQoL measured by SF-36 ($p>0.05$) were seen in the study by Lucia et al. (62). Significant improvement in disability measured by ODI at 6 months and 12 months were reported (60-63). Eckermann et al. found in the review that opioid consumption declined, on average, after SCS. The proportion who ceased opioid use at 12 months ranged from 17–67% (15).

2.5.3.2.3 Effects of SCS Compared with CMM and Repeated Spine Surgery

Results from randomised controlled trials that compared SCS with CMM, physical therapy, or repeated spine surgery indicate that SCS is associated with significantly higher response rate up to 5-years follow-up. Deer et al. conducted a systematic literature review of RCTs of SCS in patients with chronic and intractable back pain, back and limb pain, and CRPS (54). Five RCTs of SCS in back and radicular pain were identified. Primary outcome was the proportion achieving at least 50% pain reduction in VAS in three studies. Compared with repeated spine surgery, patients with FBSS treated with SCS achieved higher response rate (52% vs. 19% with at least 50% pain reduction, $p<0.05$) with an average follow-up time of 2.9 years in a study by North et al. (51). Patients randomised to repeated operation required an increase in opioids significantly more often ($p=0.025$) than those randomised to SCS. Compared with medical management alone (Kumar et al.), patients with FBSS treated with SCS achieved higher response rate (47% vs. 7%) at 24-months follow-up (52). Crossover was from CMM to SCS was significant (30 of 41 randomised to CMM had crossed over to SCS at 24 months). A study by Kemler et al. included in the review investigated the effect of SCS combined with physical therapy versus physical therapy alone in CRPS. SCS combined with physical therapy was superior to physical therapy alone until month 36 whereafter the difference was no longer statistically significant (56). At two years follow-up, there was a statistically significant improvement in HRQoL (Nottingham Health Profile pain dimension) for SCS combined with physical therapy versus physical therapy alone ($p<0.05$) (64). However, no statistically significant difference with regards to HRQoL at five-years follow-up (56). In an RCT by Rigoard et al., SCS combined with "optimal medical management" was compared with optimal medical management alone (n=218) in patients with FBSS (55). SCS was associated with higher improvement in HRQoL (SF-36), disability (ODI), low back pain and leg pain at 6 months follow-up in the intention-to-treat group (both trial-only and implanted patients) ($p<0.001$). the as-treated analysis also showed results for HRQoL, pain, and disability, favourable to SCS ($p<0.001$), Patients were allowed to switch treatment group beyond month 6 and 55 of 108 in the optimal medical management group (51%) switched to SCS. At 12- and 24-months follow-up, there was no significant difference in pain between groups.

2.5.3.2.4 Comparisons of Waveforms

Results from studies comparing tonic SCS with the newer waveforms burst or HF-10 generally indicate that the newer waveforms are associated with better effect than traditional tonic waveform. Three studies included in the review by Deer et al. in back and radicular pain compared different SCS waveforms showing that both tonic SCS, burst and HF-10 are effective in terms of pain relief, and burst may be superior to tonic (54, 65-67). HF-10 was superior to tonic SCS in a study by Kapural et al. but no difference was found in the study by De Andres et al. (65, 67). In a review by the Ontario Health Technology Assessment, including RCTs and randomised crossover studies, concluded that HF-10 was associated with significant improvement in disability, and HRQoL compared with tonic SCS (68). Pollard et al. identified no statistically significant difference between tonic SCS and high frequency SCS with regards to reduction in opioid and pain medication (69). Karri et al. performed a meta-analysis of five RCTs and prospective observational studies and found that burst SCS was statistically significantly associated with higher pain score reduction compared with tonic SCS (70).

2.5.3.3 Health Economic Studies

A review by Moens et al. was the only literature review that focused on evidence of return to work or productivity loss following SCS (71). Studies that measured return to work following SCS were retrospective case series, RCTs or prospective cohort studies with sample sizes between 20 and 410 patients and follow-up up to five years. Seven studies were included in the meta-analysis with a total sample size of 924. Data on work status before and after SCS were patient-reported. The pooled analysis showed a statistically significant increase in the odds of working following SCS compared with the same population before SCS (odds ratio 2.15, 95% CI 1.44–3.21). The effect appeared to be similar in patients treated with SCS for back and leg pain and other indications. A medical chart study of sick leave and disability pension in FBSS patients treated with SCS in Finland was published in 2019 and not included in the systematic review (72). This showed that permanent SCS was associated with reduced sick leave and disability pension compared with baseline.

Results from health economic evaluations of SCS indicate that SCS may be a cost-effective option compared with several other treatment options. However, most studies on health economic evaluations of SCS were conducted within-trial, with small sample sizes, short time horizons, and do not adopt societal perspective, which may not fully capture all effects and costs of the pain condition. Although within-trial evaluations have their merits, they may not fully reflect the patient population in clinical practice, or the most relevant comparator in clinical practice. Niyomsri et al. conducted a systematic review of cost-effectiveness of SCS (73). The authors included trial-, model-, and case series based economic evaluations. Fourteen studies were included for evidence synthesis, of which two evaluated SCS for the indication angina pectoris, eight for FBSS, and four for CRPS and other indications. For studies evaluating SCS for FBSS, four studies were conducted from a United Kingdom healthcare perspective, one United States healthcare, one United States labour/industries, and

two from a Canadian healthcare perspective. Studies evaluating SCS for CRPS were conducted from a United Kingdom healthcare and Netherlandic health insurance/societal perspective, respectively. Time horizon of the economic evaluations varied from one year to lifetime, and most (11 of 14) studies had time horizon of 15 years or shorter. Ten studies were based on RCT data. Choice of comparator varied, six studies compared SCS with CMM, two compared with repeated spine surgery. The incremental cost-effectiveness ratios varied widely from cost-saving to more than £100,000 per quality-adjusted life year depending on the indication, time horizon, and comparator. SCS was estimated to be cost-saving and cost-effective over long-time periods, from 15 years to lifetime, for most chronic pain conditions considered.

Table 1. Systematic literature reviews on the effect of SCS and eligibility criteria of the reviews

Author	Population/ condition	Intervention and comparator	Outcomes	Study designs	Findings
Baranidharan, 2021 (58)	Neck and extremity pain	Cervical HF-10 SCS Comparisons with baseline	• Change in pain levels • Response rate (achieving ≥50% pain reduction) • QoL • Disability • Function • Sleep • Medication use • Safety	Single-armed prospective, retrospective observational, case reports	• 15 studies included • Pooled response rate at 12 months: 88% (95%CI 81–95%) for upper limb pain, and 86% (78–93%) for neck pain
Baranidharan, 2021 (57)	Chronic pain	HF-10 SCS Comparisons with baseline	• Change in pain levels • Response rate (achieving ≥50% pain reduction) • Medication change • Function • QoL • Adverse events	Retrospective studies	• 16 studies included • Response rates ranged 67–100% at ≤12 months follow-up • Response rate ranged 46–76% at >12 months follow-up • 32–71% of patients decreased opioid or non-opioid intake at 9–30 months follow-up • Functional capacity (ODI/RMDQ) improved with 72–84%
Deer, 2020 (54)	Chronic and intractable back pain, back and limb pain, CRPS	SCS vs. CMM/re-operation (FBSS)/other SCS modalities	• Change in pain levels • Response rate (achieving ≥50% pain reduction) • QoL • Disability • Function • Sleep • Pain medication use	RCTs	• 6 studies included • Response rates ranged 67–100% at ≤12 months follow-up • SCS vs. CMM: Response rate 47% (SCS) vs. 7% (CMM) at 24 months • SCS+PT vs. PT: SCS+PT superior vs. PT at follow-up <36 months; no significant difference beyond 36 months

					• SCS vs. reoperation: Response rate 52% (SCS) vs. 19% (reoperation)
Eckermann, 2021 (15)	Chronic back pain without prior spine surgery	SCS Comparisons with baseline	• Change in pain • Response rate (achieving ≥50% pain reduction) • Adverse events • QoL • Disability • Function • Medication use	Retrospective cohort, retrospective database, RCT subgroup data	• 16 studies included • Response rates ranged 52–90% at 12 months follow-up • Proportion who ceased opioid use at 12 months ranged 16.7–66.7%
Moens, 2019 (71)	Chronic pain	SCS Comparisons with baseline	• Return to work	RCTs, retrospective case series, prospective cohort	• 15 studies included • Pooled odds of returning to work after SCS vs. before SCS: OR 29.06 (95%CI 9.73–86.75)
Niyomsri, 2020 (73)	Chronic pain	SCS/DRG, several comparators including CMM and reoperation in FBSS	• Costs • Utility • Incremental cost-effectiveness ratio (cost per QALY)	Economic evaluations model or trial based	• 14 studies included • Cost-effectiveness ranged widely from dominant (SCS cost-saving and more effective) to incremental cost-effectiveness ratio of £100,000 per QALY • Cost-effectiveness appeared to depend on the time horizon, choice of comparator, and indication. 10 of the studies indicated SCS as cost-saving or cost-effective compared with the alternative strategies

Abbreviations: CI: Confidence Interval; CMM: Conventional Medical Management; CRPS: Complex Regional Pain Syndrome; FBSS: Failed Back Surgery Syndrome; HF-10: High Frequency 10 kHz; ODI: Oswestry Disability Index; OR: Odds Ratio; PT: Physical Therapy; RCT: Randomised controlled trial; RMDQ: Roland-Morris Disability Questionnaire; SCS: Spinal Cord Stimulation; QALY: Quality-Adjusted Life-Year; QoL: Quality of Life

2.5.4 National Treatment Guidelines

The National Institute of Health and Care Excellence (NICE) in the United Kingdom has published guidelines for assessment of chronic primary and secondary pain and management of primary pain (74). The guidelines recommend exercise programmes and physical activity, psychological therapy, acupuncture, and pharmacotherapy in patients where no clear underlying condition or impact of pain is out of proportion to any observable injury or disease. NICE publishes separate treatment guidelines for management where a specific cause for the condition is found. For neuropathic pain, NICE has published recommendations for pharmacological management in non-specialist settings (75).

There is currently no national care guideline in Sweden for chronic pain but was suggested by in a report published in 2016 by the Swedish Association of Local Authorities and Regions in collaboration with several patient organisations, researchers, clinical experts (76). The report

pointed out that regional or local primary and secondary care guidelines were lacking, and that overarching care programmes was missing in half of Sweden’s regions.

3 RESEARCH AIMS

It is important to efficiently allocate the limited resources in healthcare to maximise health outcomes. Clinical studies have shown that SCS improves pain, HRQoL and disability, in patients with chronic pain of neuropathic origin, and has long been used in clinical practice. However, there is currently little known about characteristics of patients receiving SCS in clinical practice, the long-term effects, and the potential influence of patient characteristics on effects. To improve efficient allocation of resources and ultimately improve health and quality of life of individuals affected by chronic pain, it is important to increase the knowledge about real-world and long-term costs, effects, what factors predicts successful outcome, and which patients may benefit from other interventions.

The broader aim of the thesis is to investigate health outcomes and societal costs in patients with chronic pain treated with SCS. Two sub-studies with the following aims were conducted to achieve the overarching aim:

Study I: To describe the use of SCS, costs, and pre-spine surgery and post-spine surgery HRQoL, disability, and pain, in patients who have received SCS treatment following spine surgery.

Study II: To analyse the impact of SCS on sick leave and disability pension and to explore what potential predictors are associated with the impact.

4 MATERIALS AND METHODS

4.1 DATA SOURCES STUDY I AND II

4.1.1 The National Patient Register

The National Patient Register held by the Swedish National Board of Health and Welfare contains patient data, geographical data, administrative data, and medical data for both inpatient and outpatient hospital care (i.e., patient visits in non-primary outpatient care) in Sweden. The register contains main and secondary diagnosis codes for each admission and outpatient visit as well as procedure codes. Complete in- and outpatient data between 2001–2012 were available from the register for all patients included in the study population in Study I. For Study II, data between 2001–2019 were available.

4.1.2 Swespine

Swespine is administered by a steering group appointed by the Swedish Spine Surgery Association. About 95% of Sweden's clinics currently report to Swespine (11). Swespine includes clinical information at baseline spine surgery and follow-up conducted at one, two, five, and ten years after surgery. Swespine also includes patient-reported outcome measures (PROMs), as well as with patient-reported experience measures. Swespine data from 2000–2012 were used in Study I. Swespine data were not used in Study II.

4.1.3 The Register of the Total Population

The Register of the Total Population, held by Statistics Sweden, was used to construct a reference group for Study II. The register covers the entire Swedish population and contains basic demographic and socioeconomic information on individual level. A random sample of individuals from the register was used to construct the reference group. Cases and reference individuals were matched on age, gender and region of residence based on data from the register of the total population.

4.1.4 Micro Data for Analysis of the Social Insurance (MiDAS)

Individuals at least 16 years old living in Sweden, with income from work, unemployment, or parental-leave benefits can get disability benefits if they have a disease or condition leading to reduced work capacity (26). Data from the Swedish Social Insurance Agency are available on all sick leaves (episodes longer than 14 days, dates of start and end of episode and cause of sick leave) covered by the social insurance at individual level. Moreover, individual data is available on episodes of disability pension. The National Social Insurance Agency is the sole administrator of sick leave and disability pension benefits in Sweden and holds the MiDAS register. This allows for complete coverage of productivity loss of the study population. Extracted data included start and end of sick episodes and proportion of a patient’s working time covered by a benefit and more. Data from MiDAS was extracted for the period 2000–2012 for the study population in Study I and for the period 2000–2019 in Study II.

4.1.5 Longitudinal Integration Database for Insurance and Labour Market Studies (LISA)

The LISA register held by Statistics Sweden integrates existing data from the labour market, educational, and social sectors and is updated every year with a new annual register. Extracted data included disposable income, country of birth, immigration, place of residence, and highest level of education. Data for the period 2000–2012 were extracted for Study I and 2000–2019 for Study II.

4.1.6 The Cause of Death Register

Date of death was obtained from The Cause of Death Register held by the National Board of Health and Welfare. The statistics on causes of death comprise all deaths, covering Swedish residents, whether the person in question was a Swedish citizen or not and irrespective of whether the deaths occurred in Sweden or not. The quality of the statistics varies, depending on the examinations made to define the underlying cause of death and due to changes in the classification system and processing methods. Complete data from the register between 2000–2012 were available for analysis for all patients included in the study population of Study I and between 2000–2019 for Study II.

4.1.7 The Prescribed Drug Register

The Prescribed Drug Register held by the National Board of Health and Welfare covers all medicines and consumables (such as stoma products and special diet foods) dispensed on prescription at pharmacies in Sweden. The register started in July 2005, and data were available for the study populations from July 2005–2012 in Study I and from July 2005–2019 in Study II.

4.1.8 Linking of Data Files

When all patients (and individuals in the reference group were identified in Study II) were identified, personal identification numbers were sent to Statistics Sweden. Statistics Sweden created study keys that enabled linking between the registers described above.

4.2 STUDY I

4.2.1 Study Design

This study was an exploratory, retrospective observational study of the effects of spine surgery in patients subsequently treated with SCS and cost trajectories before and after spine surgery and subsequent SCS. All patients who underwent spine surgery in Sweden served as a reference cohort.

4.2.2 Study Participants

Two cohorts with separate inclusion criteria were included in this study, which were partially overlapping.

Cohort 1 ("*All spine surgery patients*"): All patients who underwent lumbar spine surgery according to relevant diagnosis (International Classification of Diseases version 10, ICD-10) and procedure (NCSP) codes.

Cohort 2 ("*To-be SCS patients*"): All patients who had undergone lumbar spine surgery and subsequent SCS treatment. Patients were required to have two registered codes within 100 days registered in the National Patient Register with NCSP code ABD30, that is, permanent SCS implantation. The procedure code ABD30 is frequently used for test stimulation as well as for the subsequent permanent implant (also confirmed by a mapping of all SCS-related procedure codes recorded in the database). Therefore, two consecutive ABD30 codes were required to differentiate patients only undergoing the test stimulation from those receiving permanent SCS implants.

Two separate index time points were defined. The index time point was the start of observation for each participant. Index time point 1 was the date of the first identified lumbar spine surgery. Index time point 2 was at the date of the first identified SCS implantation. Patients with an index time point 2 also had an index time point 1, but patients with an index time point 1 did not necessarily have an index time point 2.

4.2.3 Outcomes

The study was exploratory in nature and included several health and cost outcomes in relation to initial lumbar spine surgery and subsequent SCS. Health outcomes of SCS were not assessed due to unavailability of data collected specifically at baseline and after SCS. The following pain, functional, and HRQoL outcomes of initial lumbar spine surgery were assessed in this study:

- Patient reported back pain intensity on a 100mm VAS at year 1, 2, and 5 after lumbar spine surgery
- Patient reported leg pain intensity on a 100mm VAS at year 1, 2, and 5 after lumbar spine surgery
- Patient reported disability due to back pain measured using ODI at year 1, 2, and 5 after lumbar spine surgery
- Patient reported HRQoL measured using EQ-5D-3L at year 1, 2, and 5 after lumbar spine surgery

The following cost outcomes of initial lumbar spine surgery and SCS, respectively, were assessed:

- Indirect costs of sick leave and disability pension year 1, 2, and 3 after lumbar spine surgery/SCS and 1, 2 and 3 years before lumbar spine surgery/SCS
- Direct healthcare costs (outpatient, inpatient care, and pharmaceuticals dispensed at pharmacy) year 1, 2, and 3 after lumbar spine surgery/SCS and 1, 2 and 3 years before lumbar spine surgery/SCS

- Total costs (indirect + direct costs) year 1, 2, and 3 after lumbar spine surgery/SCS and 1, 2 and 3 years before lumbar spine surgery/SCS

The United Kingdom value set by Dolan was used to convert EQ-5D health states to HRQoL index scores (37). Costs were calculated by multiplying the number of each resource used with its corresponding unit cost. Unit costs for outpatient visits and inpatient hospitalisations were collected from the regional price list of an administrative region of Sweden (Södra Regionvårdsnämnden) (77). Costs of spine surgery were collected from diagnosis-related groups price lists and the reimbursement system of spine surgery in Region Stockholm because of sufficiently detailed prices for different interventions (78). For drug prescriptions, the total cost registered in the Prescribed Drug Register, including fees paid by the patient and by the county council, was used.

The Swedish sick insurance system can broadly be divided into sick leave (absences longer than >14 days) and disability pension that are generally approved for persons with such disability making it unlikely for her/him to return to work within foreseeable future. Indirect costs consisted of productivity loss related to sick leave and disability pension. The most commonly used approach to value the indirect cost of reduced work productivity is the human capital approach (79). This approach was used to value days of sick leave/disability pension in monetary terms. According to this approach one day of work absence was assumed to be equal to the average gross daily wage (€147 in Sweden at the time of the study based on data from Statistics Sweden).

4.2.4 Data Analysis

Descriptive statistics, including mean values and frequencies were used to describe the two cohorts. Independent sample t-tests were conducted to test the difference between "All spine surgery patients" and "To-be SCS patients" in continuous variables. Statistical tests were two-sided and based on a significance threshold level of 0.05. PROMs (VAS, ODI, and EQ-5D) were analysed by calculating the mean values at baseline and up to five years after spine surgery. Direct, indirect costs, and total costs (indirect and direct) were summarised for each patient and presented as mean costs per month three years before and after spine surgery (index date 1), and three years before and after SCS implantation (index date 2). Formal significance testing of outcomes were not conducted due to the exploratory nature of the study. Costs are presented in EUR (€) 2016 (€1=9.47SEK).

4.3 STUDY II

4.3.1 Study Design

This study was a population-based retrospective observational study using data from Swedish nation-wide registers of the impact of SCS on sick leave and disability pension and what potential predictors are associated with the impact. This study included a reference group matched on sex, age, and region of residence.

4.3.2 Study Participants

The study population consisted of patients who initiated SCS treatment identified using the NCSP code ABD30 during 2006–2017. The inclusion criteria were:

- In working age (defined as 19–64 years) during the follow-up period, i.e., aged 21–62 years at first implantation
- Had permanent SCS, defined as permanent implantation within 100 days of the test period

A matched reference group was drawn from the Swedish general population to rule out potential effect of societal changes that may impact the use of sick or disability benefits (e.g., unemployment, changes to the social security system). The reference group consisted of five individuals matched without replacement with respect to age, sex, and region of residence to each SCS patient.

4.3.3 Outcomes

Main outcome of the study was the change in net disability days from two years (month 24 to 12) before SCS to two years after SCS (month 12 to 24). Net disability days were defined as the degree of compensation (the percentage of the patient's working time which is covered by sick leave benefits and/or disability pension) multiplied with the gross number of days with granted sick leave or disability pension. Given the differences between the two types of sick benefits (sick leave and disability pension), potential differences in treatment effect for sick leave and disability pension were tested in a sensitivity analysis.

Additional outcome was the indirect cost of sick leave and disability pension. Indirect cost was measured by assigning a monetary value to net disability days according to the human capital approach (79). As in Study I, one day of work absence was assumed to be equal to the average gross daily wage which in Study II was differentiated based on sex and education level. Data on wages were based on publicly available data from Statistics Sweden.

4.3.4 Data Analysis

A difference-in-difference approach was used to create a model in which the change in net disability days in SCS patients before and after treatment-start was compared with the change during the same calendar time-period of matched reference individuals. The change in net disability days was measured as the difference in total days month 12–24 after index date ("*after period*") compared with month 24–12 before index date ("*before period*"). The difference-in-difference model subtracts the average change over time in the reference group from the average change over time in the treated group (80). The period of 12–24 months before and after index date was chosen to wash-out the initial increase in disability days in the months before and after SCS implantation that could be related to preparing or recovering from the procedure, rather than long-term effect on sick leave/disability pension. Data on education level and employment status were missing in 1–2% of the study groups. These data were imputed using Multiple Imputation by Chained Equations (81). Five complete datasets

were simulated based on regressions using data available for all predictors. The average of the simulated values (that were originally missing) were then used in the analysis. Independent sample t-tests were conducted to test the difference between SCS patients and matched individuals in continuous variables. Chi square test was used to test differences in categorical variables. Statistical tests were two-sided and based on a significance threshold level of 0.05. Costs are presented in EUR (€) 2020 (€1=10.49SEK).

4.4 RESEARCH ETHICS AND FUNDING

The sub-studies were approved by the Swedish national ethical review board (registration numbers 2013/2225-31/5 [Study I], 2017/812-32 and 2017/297-31 [Study II]) and were conducted in accordance with legal and regulatory requirements, followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and with the ethical principles laid down in the Declaration of Helsinki (82-84). The sub-studies were conducted in accordance with the EU General Data Protection Regulation 2016/679 (GDPR). The sub-studies were based on already collected electronic registry sources and used pseudo-anonymised data that contain no direct identifiable patient information. Patient consent is not required for registry-based studies. Study individuals were not contacted. Only researchers in the study group had access to the data to perform statistical calculations and analyses. All study reports and publications contained aggregate data only and identification of individual patients is not possible.

Study I was financially supported by Medtronic Inc. and Study II was financially supported by Abbott Inc., both companies manufacturing and marketing SCS products. The research group had full authority over the different parts of the doctoral thesis: collection, management, data analysis, interpretation of results, writing of the scientific papers in the thesis, and the decision to submit the scientific papers for publication.

5 RESULTS

Below is a summary of results from each sub-study included in the thesis.

5.1 STUDY I: COST AND HEALTH OUTCOME PATTERNS IN PATIENTS TREATED WITH SCS FOLLOWING SPINE SURGERY

Study I describes health outcomes and costs in 73,765 *All spine surgery patients* (the reference cohort) and 239 *To-be SCS patients* (patients who received SCS treatment after spine surgery). Mean age at index spine surgery and index SCS were 55 and 47 years, respectively, and around 50% of the two cohorts were women. Spinal stenosis was the most common primary diagnosis at index spine surgery in *All spine surgery patients* (45%; 30% had disc herniation), while the most common diagnosis in the SCS cohort at index spine surgery was disc herniation (38%; 27% had spinal stenosis). The two cohorts were similar in terms of education level, ethnicity, and comorbidities. *To-be SCS patients* had in general higher number of reoperations compared with *All spine surgery patients* (48% vs. 16% had ≥2 spine surgeries). Mean time to SCS after spine surgery was 4.3 years.

Comparing follow-up values after lumbar spine surgery with baseline, there were statistically significant improvements in back and leg pain intensity, HRQoL, and disability (ODI) in *All spine surgery patients* (Table 2). Mean EQ-5D score increased from 0.34 at baseline to 0.70 after five years, ODI decreased from 43 to 22, VAS back pain decreased from 53 to 29 and VAS leg pain decreased from 61 to 26 ($p<0.001$).

HRQoL, disability, and back and leg pain intensity did not change during follow-up compared with baseline in *To-be SCS patients*. The *To-be SCS patients* had statistically significantly worse HRQoL and higher disability (ODI) at baseline compared with *All spine surgery patients*. Back and leg pain intensity were numerically higher at baseline compared with *All spine surgery patients*, but the difference was not statistically significant.

Table 2. Overview of changes in PROMs over five years after spine surgery (n=73,765)

PROMs	**To-be SCS patients (Cohort 2): patients receiving SCS after spine surgery**	**All spine surgery patients (Cohort 1): reference cohort**
	Mean value (95% CI)	Mean value (95% CI)
EQ-5D		
Baseline	0.22 (0.15–0.29)	0.34 (0.34–0.34)
12 months	0.21 (0.13–0.30)	0.68 (0.68–0.68)
24 months	0.20 (0.10–0.30)	0.69 (0.68–0.70)
60 months	0.20 (0.10–0.31)	0.70 (0.68–0.72)
ODI		
Baseline	47.65 (44.44–51.05)	43.48 (43.35–43.61)
12 months	49.59 (44.90–53.79)	21.85 (21.70–22.00)
24 months	50.25 (45.01–55.16)	21.49 (21.30–21.68)
60 months	49.67 (44.33–55.27)	21.51 (21.25–21.77)
VAS Back Pain		
Baseline	56.08 (50.71–61.49)	52.65 (52.46–52.84)
12 months	52.31 (45.75–59.11)	28.61 (28.38–28.84)
24 months	60.96 (53.15–68.32)	29.50 (29.23–29.77)

60 months	57.40 (47.97–67.61)	28.70 (28.31–29.09)
VAS Leg Pain		
Baseline	61.83 (55.63–67.49)	61.43 (61.24–61.62)
12 months	58.05 (50.30–65.70)	26.08 (25.85–26.31)
24 months	66.78 (58.77–75.12)	27.02 (26.75–27.29)
60 months	63.15 (53.70–72.46)	25.80 (25.41–26.19)

Abbreviations: CI: Confidence Interval; EQ-5D: EuroQoL Five-Dimensions; ODI: Oswestry Disability Index; PROMs: Patient Reported Outcome Measures; SCS: Spinal Cord Stimulation; VAS: Visual Analogue Scale

In *All spine surgery patients*, mean direct costs gradually increased during the three years up until spine surgery, peaked during the month of surgery, and then decreased three years after surgery (mean cost year -3: €110, year -2: €131, year -1: €198, year 1: €616, year 2: €197, year 3: €176). For *To-be SCS patients*, direct costs were slightly lower three and two years prior to spine surgery compared with *All spine surgery patients*, whereas direct costs were higher in the three years after spine surgery (year -3: 82, year −2: €105, year −1: €203, year 1: €797, year 2: €435, year 3: €442). Over the period of three years before and three years after spine surgery, costs related to surgery and other inpatient care constituted the majority of direct costs (68%). Drug costs and costs related to outpatient visits accounted for similar shares (16%, respectively) of direct costs. These shares were similar in the two groups *All spine surgery patients* and *To-be SCS patients*.

Similarly to direct costs, indirect costs in *All spine surgery patients* increased in the three years leading up to surgery, peaked at the first month after surgery and then gradually decreased. In *To-be SCS patients*, indirect costs increased leading up the initial lumbar spine surgery. Costs due to sick leave peaked at the first month after surgery and then gradually decreased, whereas costs due to disability pension continued to increase during the first month after spine surgery. In total, indirect costs remained on a rather stable level more than three years following spine surgery. After SCS treatment initiation, indirect costs decreased. The decrease in sick leave is more pronounced, whereas the disability pension rate initially slightly increased for one year after the implant, after which it slightly decreased (Figure 2).

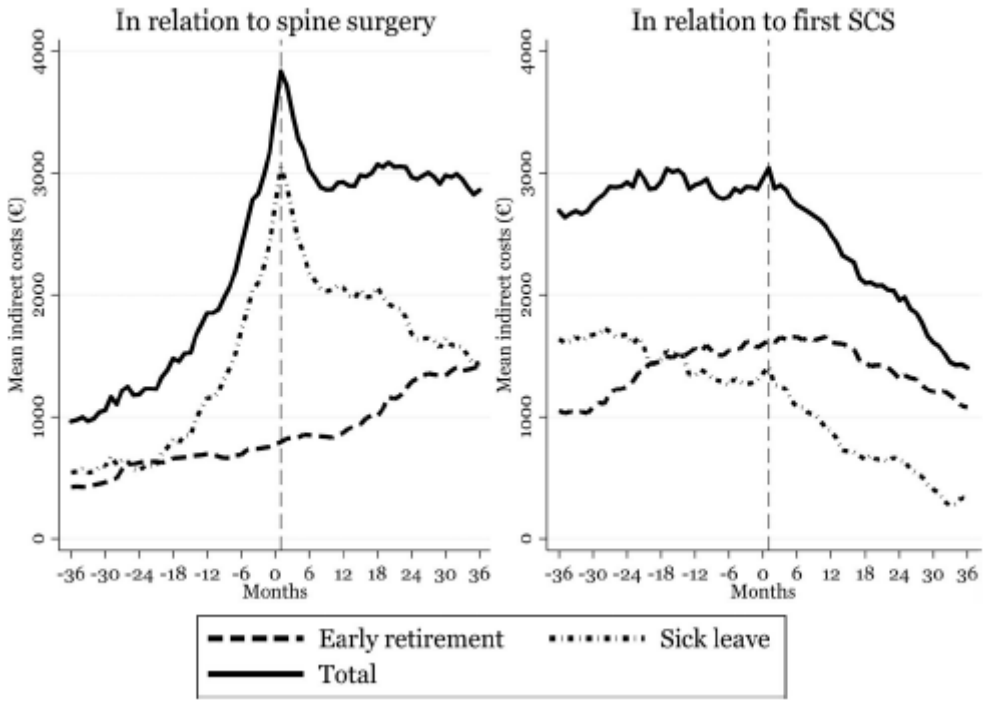

Figure 2. Mean indirect costs per month in To-be SCS patients by sickness benefit before and after initial spine surgery and SCS implantation (early retirement=disability pension)

Regarding total costs, *To-be SCS patients* had higher costs both before and after spine surgery compared with *All spine surgery patients*. The difference in total cost between these two cohorts increased after spine surgery. For *To-be SCS patients*, from the third year before spine surgery to the third year after surgery, total monthly costs increased with on average €2,193, whereas during the corresponding period before and after SCS, costs decreased with €1,133. In *All spine surgery patients*, total costs increased slightly after the spine surgery. Excluding the cost of the initial SCS procedure and assuming the costs would have remained at the same level as in the six months prior to surgery, the estimated total cost reduction three years post-SCS compared with three years pre-SCS was estimated at €32,036/patient (including the cost per SCS: €19,814). On average, over the study period and across cohorts, the share of total costs that were indirect cost was 87% when excluding cost per SCS and 71% including cost per SCS.

5.2 STUDY II: IMPACT OF SCS ON SICK LEAVE AND DISABILITY PENSION

Results from Study II show that the majority treated with SCS in Sweden are women (56%), most were born in Sweden (86%), and the average age at initiation is 47 years. In total, 6,492 individuals were included in the study: 1,082 SCS patients and 5,410 matched reference individuals. Compared with the age-, sex- and region matched reference group, SCS patients were statistically significantly less likely to have post-secondary/post-graduate education, being employed, and had lower income. Twenty-three percent had a prior spine surgery (last five years). The use of anti-depressants, opioids and other analgesics was substantially higher than the general population. Around half of the SCS patients had at least one prescription of an opioid or anti-depressant in the last three months.

The crude number of net disability days in the SCS group in the "before period" (24–12 months before index date) was 214 (95% CI: 206–222), and in the "after period" (12–24 months after index date) 194 days (95% CI: 185–203), yielding a crude difference of 20 days. In the reference group, net disability days slightly increased by 1.2 days: mean days was 33 (95% CI: 31–35) and 34 (95% CI: 32–36) in the before and after period, respectively.

The difference-in-difference analysis showed that SCS reduced the net number of disability days ($p<0.001$) when taking into account the change in net disability days in the reference group (Table 3). The adjusted change in net disability days was slightly higher than in the crude analysis (21 vs. 20 days). Higher age, more comorbidities, use of either strong or weak opioids, and more extensive usage of non-opioids and anti-depressives were associated with an overall (disregarding group or time period) larger number of disability days ($p<0.001$). Men and individuals with higher education level had fewer such days ($p<0.001$).

Interactions of potential predictors, group (SCS patients or reference individuals) and time period (before or after index date) were used to identify the difference in treatment effect (change in net disability days) by predictor. Males, and being born outside Europe were numerically associated with better treatment effect compared with other treated patients although not statistically significant ($p=0.228$). Higher age was numerically associated with poorer treatment effect (net disability days increased), although not statistically significant ($p=0.154$). Similarly, use of non-opioid pain medicine and any opioids were associated with a poorer, but not statistically significant, treatment effect. Use of anti-depression medicine was significantly associated with poorer treatment effect (coefficient 21.9, $p<0.001$).

Table 3. Difference-in-difference estimates of net disability days (n=6,492)

Variable	**Coefficient (SE)**	**Interaction effect of potential predictors & treatment effect (predictor*τ_{DiD}), coefficient (SE)**
SCS group effect, β_2	112.0 (5.8)***	
Period effect, β_1(1 if after index date, 0 if before index date)	1.2 (0.7)	
Treatment effect, τ_{DiD}	**-21.2 (4.1)*** **	
Calendar year	-4.4 (0.4)***	
Predictors		
Age	1.9 (0.1)***	0.6 (0.4)
Male	-11.0 (2.1)***	-8.4 (8.2)
Comorbidities	14.2 (1.7)***	5.0 (3.9)
Any opioid use 3 months before index date	44.9 (15.0)***	8.0 (11.1)
Use of strong opioid 3 months before index date	-6.7 (13.2)	-15.1 (26.7)
Use of weak opioid 3 months before index date	-23.9 (13.6)*	12.8 (11.3)
Any non-opioid pain medicine use 3 months before index date	27.6 (5.4)***	6.0 (9.9)
Any anti-depression medicine use 3 months before index date	40.8 (4.6)***	21.9 (9.4)***
Previous spine surgery	-3.8 (8.1)	16.0 (82.5)
Country of birth: Europe, not Sweden (RC: Sweden)	-5.2 (4.2)	-27.6 (15.6)*
Country of birth: Other (RC: Sweden)	-37.0 (4.4)***	-24.9 (20.7)
Education level: Secondary school (RC: primary school)	-20.4 (4.0)***	11.8 (11.6)
Education level: Post-secondary/post-graduate (RC: primary school)	-35.8 (4.0)***	7.6 (12.9)
Yearly income (€)	-1.4 (1.9)	8.9 (20.0)

Unemployed	73.5 (3.1)***	13.0 (8.2)

***Significant on 1% level, ** Significant on 5% level, *Significant on 10% level. Abbreviations: SE: Standard Error; RC: Reference Category. Negative coefficient indicates decreased net disability days

The indirect cost associated with sick leave and disability pension were estimated by group and period using a two-part regression model. Mean indirect cost decreased in the SCS groups from the before to the after period and slightly increased in the reference group. Mean saving of indirect costs during year two after index date compared with year two before index date on the treated SCS group was €3,372.

Sensitivity analyses were conducted to test whether the impact of SCS was different depending on sick/disability benefit type. SCS was associated with a reduction in sick leave (decreases net sick leave days, coefficient -39.0, $p<0.01$), and with an increase in disability pension (increases net disability days coefficient 17.8, $p<0.01$). In an additional sensitivity analysis, net disability days in month 25–36 after index date was compared with month 25–36 before index before in each group. This sensitivity analysis showed that SCS treatment had no impact on net disability days, indicating that in the third year after SCS, net disability days decreased to a similar level as three years before index date (coefficient 1.2, $p=0.796$).

6 DISCUSSION

Chronic pain is complex, with many different causes often associated with psychological aspects that may increase the difficulty to find optimal treatments. At the same time, chronic pain is common and the losses in quality of life and productivity on a population basis are substantial. To address these challenges, the importance of selecting both effective and cost-effective interventions is crucial. Significant efforts have been made to elucidate the burden of chronic pain on the individual and the society, while less efforts have been made to evaluating long-term effect of treatments on populations in clinical practice what factors influence treatment effect. Optimising patient selection is important to designing effective therapy.

This thesis aimed at investigating societal costs and health outcomes in patients with chronic pain treated with SCS and to explore what potential factors may impact the effect of treatment. Both sub-studies (Study I and II) used Swedish register data to address this research aim. Study I and II were based on two different data extractions that were similar in terms of registers included, although the inclusion criteria for data extraction in Study I was individuals who underwent spine surgery and for Study II individuals who underwent either spine surgery or SCS. Study I was an exploratory study with the aim of describing the characteristics of patients receiving SCS, costs, and pre-spine surgery and post-spine surgery HRQoL, disability, and pain, in patients who have received SCS treatment following spine surgery in clinical practice. All patients who underwent spine surgery, with or without subsequent SCS, served as a reference group so that the effect of spine surgery in SCS treated patients could be compared with. Study II aimed at analysing the impact of SCS on sick leave and disability pension and explore what potential predictors are associated with the impact. Study II compared the change in net disability days in patients treated with SCS (with or without prior spine surgery) with a reference group from the general population.

Study I showed that the initial spine surgery did not have any effect on HRQoL, disability, pain, work ability, and healthcare resource use in patients subsequently treated with SCS. Patients with subsequent SCS (*To-be SCS patients*, n=239) had statistically significantly higher disability and lower HRQoL already at baseline spine surgery compared with *All spine surgery patients* (n=73,765). *To-be SCS patients* also had numerically higher pain at baseline spine surgery compared with *All spine surgery patients*, but this difference was not statistically significant. Follow-up data on health outcomes specifically in relation to SCS were not available, but a numerical decrease in direct healthcare and indirect costs following SCS was noted (difference was not formally tested). Study II showed that SCS (with or without prior spine surgery, n=1,082) was associated with a statistically significant decrease in sick leave days, but not disability pension days which increased. The overall net disability days and consequently indirect cost in working age patients decreased followed SCS when compared with the change in a reference group from the general population. Large productivity loss in SCS patients was demonstrated, indicating a significant burden on the patients, the employers, and the society at large. Usage of anti-depressants was statistically

significantly associated with poorer effect of SCS on disability days. Other socioeconomic and clinical factors had no statistically significant association with the effect of SCS on disability days.

6.1 THE USE OF SCS IN SWEDISH CLINICAL PRACTICE

This thesis showed that the mean age of SCS treated individuals was 47 years and the proportion women was 56%. This is similar to characteristics of patients with FBSS treated with SCS seen in a Finnish study where mean age was 45.5 and the share women was 50–47% (72). Study I included individuals treated with SCS and prior spine surgery while Study II included individuals treated with SCS disregarding prior treatments. These two populations were similar in terms of age, sex, ethnicity, and education level. Patients treated with SCS had substantially higher usage of opioids, other analgesics, and anti-depressants compared with the matched reference group from the general population. About 50% of patients treated with SCS used opioids or anti-depressants in the three months before treatment start, as compared with 4% and 8% in the matched reference group, respectively. Surprisingly, Study II showed that only 23% of the patients had a prior spine surgery, which has historically been the most common indication (FBSS) for SCS and the most evidence from clinical studies. However, this figure may not be representative of any historical spine surgeries, since there were only five years of look-back data in the National Patient Register for patients who received SCS early in the study period. In a retrospective study of HF-10 SCS, 61% had FBSS, however this study was small (31 patients) and was restricted to patients who had failed on tonic SCS (85).

6.2 HRQOL, DISABILITY AND PAIN

Results from Study I show that there are differences in HRQoL, disability, and pain between patients who eventually underwent SCS treatment after lumbar spine surgery (*To-be SCS patients)* and all patients who underwent spine surgery. The *To-be SCS patients* experienced on average an increase in pain intensity and disability, although not statistically significant, and a lowering of HRQoL two and five years after spine surgery compared with baseline. Although worse outcomes of spine surgery in the to-be SCS patient group is expected, given that they received further treatment for persistent pain, the data contributes to the knowledge of that these patients experience no effect to worsening of spine surgery and this can be observed already one year after surgery. Also, the *To-be SCS patients* had statistically significantly lower reported HRQoL and worse disability already at the time of the spine surgery compared with *All spine surgery patients*. *To-be SCS patients* also had numerically worse pain at baseline, but this difference was not statistically significant. These findings may warrant for investigating the possibility of identifying these patients for SCS or other treatments even before spine surgery or earlier after the spine surgery. There might be a proportion of patients who could benefit from SCS treatment, but who in fact were not treated with SCS, potentially due to restricted access. In this thesis, it was not possible to identify these patients as data on, for example, patient history and clinical examinations were not available. Future research may investigate whether there are potential improvements in health

outcomes if more patients with persistent pain following spine surgery could be identified and treated with SCS, and also whether initial spine surgery could in some cases be avoided. Cost-effectiveness analysis of spine surgery compared with SCS instead of spine surgery may also be warranted, if sufficiently detailed data allowing to predict outcomes of spine surgery versus SCS becomes available.

6.3 IMPACT OF SPINE SURGERY AND SCS ON COSTS

Patients who received SCS following spine surgery (*To-be SCS patients*) had higher costs before the initial spine surgery and remained at a higher cost level after spine surgery compared with *All spine surgery patients*. The spine surgery appeared not to have any impact on costs in *To-be SCS patients*, in contrast to *All spine surgery patients* who, on average, experienced a cost decrease after spine surgery. Future studies may investigate whether the observed decline in costs following SCS treatment corresponded to an improved HRQoL and decreased pain for these patients. Results from clinical studies indicate that SCS is associated with improved HRQoL compared with before SCS (55, 64). However, studies for larger samples from real-world clinical practice is needed.

Large loss of work ability in patients treated with SCS, with or without prior spine surgery, was identified in Study II, as patients had on average 214 net disability days during a single year prior to treatment start. The difference in work loss between patients with chronic pain treated with SCS and the age- and gender matched reference group was also substantial and statistically significant after adjusting for comorbidities, usage of opioids, non-opioid analgesics and antidepressants, and sociodemographic variables such as education level. This adds details to the existing literature about the impact that chronic pain has on the patient and the society at large. The main analysis of Study II compared the outcome of net disability days two years after SCS with two years before SCS, subtracting the change in the reference group. The results showed that SCS had a statistically significant effect on net disability days (decrease in net disability days of 21 days per patient). The reduction in net disability days corresponded to a decrease in indirect costs of €3,372 per patient comparing year two after SCS with year two before SCS.

In Study II, SCS was statistically significantly associated with a decrease in sick leave but an increase in disability pension. Although it was expected that disability pension would not substantially decrease (as such benefits are approved for long time periods), it was unexpected that disability pension would significantly increase. A decrease in disability pension following SCS was observed in Finland, but because of potential differences in social insurance system and rules for different types of benefits, it is difficult to compare the results with other settings (72). In Study I, indirect costs related to disability pension decreased numerically (from about €1,500/month 1 year before SCS to €1,200/month year 3 after SCS), which may indicate that patients with FBSS experienced better effect on disability pension compared with other indications. Study II identified that prior spine surgery (as opposed to no prior spine surgery) was associated with statistically significantly lower disability pension use overall, disregarding treatment and time period. However, there was no statistically

significant difference in treatment effect depending on prior spine surgery. Further analyses may be needed to investigate these somewhat conflicting results, and particularly if there are any potential differences in systematic differences in FBSS population and non-FBSS populations that could explain this result. It would also be of interest to investigate in future studies if patients where disability pension days increased are patients with insufficient treatment response and what additional treatments potentially are or could be offered to those patients.

The compared time periods in Study II were changed in a sensitivity analysis where the outcome three years after SCS was compared with three years before and the results from this analysis indicated no effect of SCS. This illustrates the importance of choice of time periods when analysing the changes. The sensitivity analysis showed that the number of disability days reverted to a similar level as three years before, however, it may be possible that the disability days further decreased beyond this point entailing higher cost-savings. An underlying assumption in the difference-in-difference analysis is the parallel trend assumption, which entails that in absence of treatment, the two groups (treatment and reference group) would follow the same trend. It is not possible to observe what would have happened in the SCS patients without treatment, but it is reasonable to assume that there would not be a steep increase in disability days right before treatment which is more likely to be related to the treatment rather than the underlying condition. A remedy to the issue of not having a randomised sample was that the reference group was matched and adjusted for predictors with the purpose of making the two groups more similar. Since such detailed clinical data were not available, it cannot be certain that the two groups are similar in all respects except treatment status.

Independent of treatment (SCS patient or reference group) and time period in relation to index date, higher age, more comorbidities, more use of opioids, non-opioid pain medicines, and anti-depression medicine were statistically significantly associated with higher net disability days. Male sex was associated with statistically significantly less net disability days compared with females, and higher education level was also associated with less net disability days. No statistically significant difference in treatment effect (comparing the change in group and period) on net disability days was detected for most of the potential predictors included in this study. However, use of anti-depression medicines were significantly associated with poorer treatment effect ($p<0.001$) even though comorbidity index, which includes depression, did not have significant impact. It would be of interest to repeat this analysis in other settings to investigate whether this relationship holds, but also to investigate the cause of this relationship in further detail. No prior studies, as we are aware, have evaluated the impact of such predictors on outcomes of SCS which makes it difficult to compare our results with others.

Study I as well as previous studies using register data in Finland indicated that sick leave decreased after SCS in patients with prior spine surgery (i.e., FBSS) (72). Calendar year of index date was significantly associated with decreasing number of disability days (overall,

disregarding treatment status and time period). There are two potential reasons for this finding: firstly, there may have been societal changes during the study period, in for example the social security system or unemployment rates affecting the overall use of disability benefits; secondly, there was a shift in the SCS treatment regimen around year 2010, where burst waveform was introduced which in trials has been shown to have better effect on pain relief compared with the traditional tonic waveform (54). Although Study II indicate that net disability days decreased after SCS overall, having prior spine surgery compared with no prior spine surgery was not associated with treatment effect. This might be a somewhat surprising result, given that SCS has been extensively evaluated for FBSS, and which is the main indication for SCS. However, this result could potentially indicate that SCS for other indications may have a similar treatment effect as for FBSS, in this data material.

6.4 OTHER METHODOLOGICAL CONSIDERATIONS

Study I and II included only patients with "permanent" SCS (and excluded those with only test stimulation), but the number of patients is associated with uncertainty. Both Study I and II included only patients based on having two consecutive codes for implantation registered within 100 days. There is no example from the literature that have defined permanent SCS based on NCSP coding, therefore it was decided to assume maximum 100 days based on expert experiences in time to permanent implant. Some clinics may perform the SCS procedure without a test simulation. Further, some clinics may have a longer waiting time than 100 days. Therefore, it is possible that some patients who indeed had permanent implant were excluded, and sample sizes might be underestimated.

The sub-studies relied to a large extent on Swedish register-based data which are known to have a high degree of completeness. Reporting of certain variables used in this study is mandatory so for healthcare visits and drug dispensations all the necessary information can be expected to be present. This entails that virtually all SCS procedures, all diagnoses, prescribed drugs, and socioeconomic variables can be captured. In 2006, the proportion of stays with missing personal registration number was 0.6% in the National Patient Register, whereas the main diagnosis was missing in 1.0% of cases (86). All dispensed medications are collected centrally and registered in the Prescribed Drug Register (87). Missing information is rare and has been estimated to range from 0.02% to 0.6% depending on sex, age, and region. Missing information about the cause of death is less than 0.5% in the Causes of Death Register (88). Swespine covers around 80% of all spine surgeries performed in Sweden (89). The Swedish social security number allows following patients over time and allows data to be linked to other registers. Not all data on sick leave were available for analysis which to some extent may underestimate sick leave days. Episodes of 14 days or less were during the study period the responsibility of the employer in Sweden and were therefore not recorded in the Social Insurance Register. Thus, such episodes could not be included in the analyses. However, the first 14 days for all recorded sick leave episodes are recorded in the register. The findings of this study are based on Swedish data and are as such directly not transferable to other countries. In particular, differences in social insurance system between countries may

entail different propensity to utilise such benefits, possibly entailing different impact of SCS on return to work.

7 CONCLUSIONS

- Spine surgery did not have any statistically significant effect on pain, disability. HRQoL at one, two, and five years in patients who were subsequently treated with SCS. These patients, *To-be SCS patients*, remained with impaired HRQoL, disability and pain up to five years after spine surgery. A reference group, consisting of all patients who underwent spine surgery, statistically significantly improved in terms of HRQoL, and pain and disability significantly decreased at one, two, and five years after spine surgery.
- The *To-be SCS patients*—patients who were treated with SCS after spine surgery—were statistically significantly worse off in terms of disability and HRQoL already at the initial spine surgery compared with all spine surgery patients. *To-be SCS patients* also had numerically higher pain intensity at baseline spine surgery, but this difference was not statistically significant.
- A numerical decrease in direct healthcare costs and indirect costs related to sick leave and disability pension following SCS in patients treated with SCS after spine surgery was observed. Further long-term data from real-world clinical practice are needed to measure HRQoL, pain, and disability following SCS. Further studies are also needed to investigate if it is possible to predict health outcomes and costs in patients considered for spine surgery, and whether SCS or other interventions would be a cost-effective alternative over spine surgery for specific patient populations.
- Of patients treated with SCS, with or without prior spine surgery, slightly over half were female and average age was around 50 years. Most patients initiating SCS treatments used opioids, weak or strong, and/or anti-depressants prior to SCS.
- Large work loss in patients with chronic pain and treated with SCS was demonstrated. The difference in work loss between patients with chronic pain treated with SCS and an age- and gender matched reference group was also substantial and statistically significant after adjusting for comorbidities, usage of opioids, non-opioid analgesics and antidepressants, and sociodemographic variables such as education level. This adds to the literature on the significant burden of chronic pain on the patient, the employers, and the society at large.
- SCS (with or without prior spine surgery) is associated with a statistically significant decrease in sick leave days, but not disability pension which significantly increased. SCS decreased the overall net disability days and consequently indirect cost in working age patients. Further studies are needed to investigate why disability pension increased in some patients and whether those patients need additional treatments.
- Higher age, more comorbidities, females, opioid usage, lower education, being unemployed, were significantly associated with higher number of net disability days overall but were not significantly associated with difference in effect of SCS on net disability days. In other words, this study did not provide any evidence that SCS is

unequally effective on disability days depending on sociodemographic factors, comorbidities, and medication use. Usage of anti-depressants was statistically significantly associated with poorer effect of SCS on disability days, but further studies are needed to confirm this association.

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9 REFERENCES

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287-333.

2. The Swedish Council on Technology Assessment in Health Care (Statens beredning för medicinsk utvärdering). Metoder för behandling av långvarig smärta: En systematisk litteraturöversikt. 2006.

3. Knotkova H, Hamani C, Sivanesan E, Le Beuffe MFE, Moon JY, Cohen SP, Huntoon MA. Neuromodulation for chronic pain. Lancet. 2021;397(10289):2111-24.

4. Sharma M, Nazareth I, Petersen I. Observational studies of treatment effectiveness: worthwhile or worthless? Clin Epidemiol. 2019;11:35-42.

5. Rothman JK. Epidemiology: an introduction 2nd edition. 198 Madison Avenue, New York, New York 10016, United States: Oxford University Press; 2012.

6. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-82.

7. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plast. 2017;2017:9724371.

8. Henschke N, Maher CG, Refshauge KM, Herbert RD, Cumming RG, Bleasel J, York J, Das A, McAuley JH. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. Arthritis Rheum. 2009;60(10):3072-80.

9. Linton SJ, Flink IK, Vlaeyen JWS. Understanding the Etiology of Chronic Pain From a Psychological Perspective. Phys Ther. 2018;98(5):315-24.

10. Kirketeig T, Wåhlstedt A, Leljevahl E, Gordh T, Söderdahl FA, Karlsten R. Device Survival and Explant Patterns in 449 Patients Treated with Spinal Cord Stimulation: A Pragmatic Observational Study. SASP (The Scandinavian Association for the Study of Pain); 2019; Oslo.

11. Swespine. Årsrapport 2020 Uppföljning av ryggkirurgi utförd i Sverige år 2019 (Annual report 2020 Follow-up of spine surgery performed in Sweden year 2019). 2020.

12. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, Raja SN, Rice ASC, Serra J, Smith BH, Treede RD, Jensen TS. Neuropathic pain: an updated grading system for research and clinical practice. Pain. 2016;157(8):1599-606.

13. Scholz J, Finnerup NB, Attal N, Aziz Q, Baron R, Bennett MI, Benoliel R, Cohen M, Cruccu G, Davis KD, Evers S, First M, Giamberardino MA, Hansson P, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Nurmikko T, Perrot S, Raja SN, Rice ASC, Rowbotham MC, Schug S, Simpson DM, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ, Barke A, Rief W, Treede RD, Classification Committee of the Neuropathic Pain Special Interest G. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019;160(1):53-9.

14. Pasero C. Pathophysiology of neuropathic pain. Pain Manag Nurs. 2004;5(4 Suppl 1):3-8.

15. Eckermann JM, Pilitsis JG, Vannaboutathong C, Wagner BJ, Province-Azalde R, Bendel MA. Systematic Literature Review of Spinal Cord Stimulation in Patients With Chronic Back Pain Without Prior Spine Surgery. Neuromodulation : journal of the International Neuromodulation Society. 2021.

16. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646-56.

17. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. The journal of pain : official journal of the American Pain Society. 2006;7(4):281-9.

18. Bouhassira D, Lanteri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain. 2008;136(3):380-7.

19. Perquin CW, Hazebroek-Kampschreur A, Hunfeld JAM, Bohnen AM, van Suijlekom-Smit LWA, Passchier J, van der Wouden JC. Pain in children and adolescents: a common experience. Pain. 2000;87(1):51-8.

20. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(36):1001-6.

21. Hadi MA, McHugh GA, Closs SJ. Impact of Chronic Pain on Patients' Quality of Life: A Comparative Mixed-Methods Study. J Patient Exp. 2019;6(2):133-41.

22. O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics. 2009;27(2):95-112.

23. Manca A, Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, Taylor RJ, Goeree R, Sculpher MJ. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). Eur J Pain. 2008;12(8):1047-58.

24. Calvert MJ, Freemantle N, Cleland JG. The impact of chronic heart failure on health-related quality of life data acquired in the baseline phase of the CARE-HF study. Eur J Heart Fail. 2005;7(2):243-51.

25. Hasselstrom J, Liu-Palmgren J, Rasjo-Wraak G. Prevalence of pain in general practice. Eur J Pain. 2002;6(5):375-85.

26. Försäkringskassan (Social Insurance in Sweden). Socialförsäkringen i siffror 2021 (Social Insurance in numbers 2021). 2021.

27. Gaskin DJ, Richard P. The economic costs of pain in the United States. The journal of pain : official journal of the American Pain Society. 2012;13(8):715-24.

28. Roach KE, Brown MD, Dunigan KM, Kusek CL, Walas M. Test-retest reliability of patient reports of low back pain. J Orthop Sports Phys Ther. 1997;26(5):253-9.

29. Jensen MP. The validity and reliability of pain measures in adults with cancer. The journal of pain : official journal of the American Pain Society. 2003;4(1):2-21.

30. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal

MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J, Immpact. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.

31. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy. 1980;66(8):271-3.

32. Chapman JR, Norvell DC, Hermsmeyer JT, Bransford RJ, DeVine J, McGirt MJ, Lee MJ. Evaluating common outcomes for measuring treatment success for chronic low back pain. Spine. 2011;36(21 Suppl):S54-68.

33. Vianin M. Psychometric properties and clinical usefulness of the Oswestry Disability Index. J Chiropr Med. 2008;7(4):161-3.

34. Chiarotto A, Maxwell LJ, Terwee CB, Wells GA, Tugwell P, Ostelo RW. Roland-Morris Disability Questionnaire and Oswestry Disability Index: Which Has Better Measurement Properties for Measuring Physical Functioning in Nonspecific Low Back Pain? Systematic Review and Meta-Analysis. Phys Ther. 2016;96(10):1620-37.

35. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine. 2000;25(22):2940-52; discussion 52.

36. Burstrom K, Sun S, Gerdtham UG, Henriksson M, Johannesson M, Levin LA, Zethraeus N. Swedish experience-based value sets for EQ-5D health states. Qual Life Res. 2014;23(2):431-42.

37. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.

38. National Institute of Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013.

39. Solberg TK, Olsen JA, Ingebrigtsen T, Hofoss D, Nygaard OP. Health-related quality of life assessment by the EuroQol-5D can provide cost-utility data in the field of low-back surgery. Eur Spine J. 2005;14(10):1000-7.

40. Drummond F, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes: Oxford University Press; 2015.

41. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice ASC, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237-51.

42. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73.

43. Cram P, Landon BE, Matelski J, Ling V, Perruccio AV, Paterson JM, Rampersaud YR. Utilization and Outcomes for Spine Surgery in the United States and Canada. Spine. 2019;44(19):1371-80.

44. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971-9.

45. Database for procedures in inpatient and specialised outpatient care (Statistikdatabas för operationer i sluten och specialiserad öppen vård) [Internet]. 2021 [cited 2021-10-24]. Available from: https://sdb.socialstyrelsen.se/if_ope/val.aspx.

46. Liao WT, Tseng CC, Chia WT, Lin CR. High-frequency spinal cord stimulation treatment attenuates the increase in spinal glutamate release and spinal miniature excitatory postsynaptic currents in rats with spared nerve injury-induced neuropathic pain. Brain Res Bull. 2020;164:307-13.

47. Cui JG, O'Connor WT, Ungerstedt U, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates augmented dorsal horn release of excitatory amino acids in mononeuropathy via a GABAergic mechanism. Pain. 1997;73(1):87-95.

48. Deer T, Pope J, Hayek S, Narouze S, Patil P, Foreman R, Sharan A, Levy R. Neurostimulation for the treatment of axial back pain: a review of mechanisms, techniques, outcomes, and future advances. Neuromodulation : journal of the International Neuromodulation Society. 2014;17 Suppl 2:52-68.

49. Linderoth B, Meyerson BA. Spinal cord stimulation: exploration of the physiological basis of a widely used therapy. Anesthesiology. 2010;113(6):1265-7.

50. Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, Farrar JT, Hertz S, Raja SN, Rappaport BA, Rauschkolb C, Sampaio C. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009;146(3):238-44.

51. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery. 2005;56(1):98-106; discussion -7.

52. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery. 2008;63(4):762-70; discussion 70.

53. Bicket MC, Dunn RY, Ahmed SU. High-Frequency Spinal Cord Stimulation for Chronic Pain: Pre-Clinical Overview and Systematic Review of Controlled Trials. Pain medicine. 2016;17(12):2326-36.

54. Deer TR, Grider JS, Lamer TJ, Pope JE, Falowski S, Hunter CW, Provenzano DA, Slavin KV, Russo M, Carayannopoulos A, Shah JM, Harned ME, Hagedorn JM, Bolash RB, Arle JE, Kapural L, Amirdelfan K, Jain S, Liem L, Carlson JD, Malinowski MN, Bendel M, Yang A, Aiyer R, Valimahomed A, Antony A, Craig J, Fishman MA, Al-Kaisy AA, Christelis N, Rosenquist RW, Levy RM, Mekhail N. A Systematic Literature Review of Spine Neurostimulation Therapies for the Treatment of Pain. Pain medicine. 2020;21(7):1421-32.

55. Rigoard P, Basu S, Desai M, Taylor R, Annemans L, Tan Y, Johnson MJ, Van den Abeele C, North R, Group PS. Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial. Pain. 2019;160(6):1410-20.

56. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg. 2008;108(2):292-8.

57. Baranidharan G, Edgar D, Bretherton B, Crowther T, Lalkhen AG, Fritz AK, Vajramani G. Efficacy and Safety of 10 kHz Spinal Cord Stimulation for the Treatment of Chronic Pain: A Systematic Review and Narrative Synthesis of Real-World Retrospective Studies. Biomedicines. 2021;9(2).

58. Baranidharan G, Bretherton B, Montgomery C, Titterington J, Crowther T, Vannabouathong C, Inzana JA, Rotte A. Pain Relief and Safety Outcomes with Cervical 10 kHz Spinal Cord Stimulation: Systematic Literature Review and Meta-analysis. Pain Ther. 2021.

59. Al-Kaisy A, Van Buyten JP, Carganillo R, Caraway D, Gliner B, Subbaroyan J, Panwar C, Rotte A, Amirdelfan K, Kapural L. 10 kHz SCS therapy for chronic pain, effects on opioid usage: Post hoc analysis of data from two prospective studies. Sci Rep. 2019;9(1):11441.

60. Al-Kaisy A, Palmisani S, Smith TE, Carganillo R, Houghton R, Pang D, Burgoyne W, Lam K, Lucas J. Long-Term Improvements in Chronic Axial Low Back Pain Patients Without Previous Spinal Surgery: A Cohort Analysis of 10-kHz High-Frequency Spinal Cord Stimulation over 36 Months. Pain medicine. 2018;19(6):1219-26.

61. Baranidharan G, Feltbower R, Bretherton B, Crowther T, Cooper L, Castino P, Radford H. One-Year Results of Prospective Research Study Using 10 kHz Spinal Cord Stimulation in Persistent Nonoperated Low Back Pain of Neuropathic Origin: Maiden Back Study. Neuromodulation : journal of the International Neuromodulation Society. 2021;24(3):479-87.

62. Lucia K, Nulis S, Tkatschenko D, Kuckuck A, Vajkoczy P, Bayerl S. Spinal Cord Stimulation: A Reasonable Alternative Treatment in Patients With Symptomatic Adult Scoliosis for Whom Surgical Therapy Is Not Suitable? A Pilot Study. Neuromodulation : journal of the International Neuromodulation Society. 2021.

63. Campwala Z, Datta P, DiMarzio M, Sukul V, Feustel PJ, Pilitsis JG. Spinal Cord Stimulation to Treat Low Back Pain in Patients With and Without Previous Spine Surgery. Neuromodulation : journal of the International Neuromodulation Society. 2020.

64. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. Ann Neurol. 2004;55(1):13-8.

65. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Yearwood TL, Bundschu R, Yang T, Benyamin R, Burgher AH. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. Neurosurgery. 2016;79(5):667-77.

66. Deer T, Slavin KV, Amirdelfan K, North RB, Burton AW, Yearwood TL, Tavel E, Staats P, Falowski S, Pope J, Justiz R, Fabi AY, Taghva A, Paicius R, Houden T, Wilson D. Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation : journal of the International Neuromodulation Society. 2018;21(1):56-66.

67. De Andres J, Monsalve-Dolz V, Fabregat-Cid G, Villanueva-Perez V, Harutyunyan A, Asensio-Samper JM, Sanchis-Lopez N. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain medicine. 2017;18(12):2401-21.

68. Ontario Health (Quality). 10-kHz High-Frequency Spinal Cord Stimulation for Adults With Chronic Noncancer Pain: A Health Technology Assessment. Ont Health Technol Assess Ser. 2020;20(6):1-109.

69. Pollard EM, Lamer TJ, Moeschler SM, Gazelka HM, Hooten WM, Bendel MA, Warner NS, Murad MH. The effect of spinal cord stimulation on pain medication reduction in intractable spine and limb pain: a systematic review of randomized controlled trials and meta-analysis. J Pain Res. 2019;12:1311-24.

70. Karri J, Orhurhu V, Wahezi S, Tang T, Deer T, Abd-Elsayed A. Comparison of Spinal Cord Stimulation Waveforms for Treating Chronic Low Back Pain: Systematic Review and Meta-Analysis. Pain physician. 2020;23(5):451-60.

71. Moens M, Goudman L, Brouns R, Valenzuela Espinoza A, De Jaeger M, Huysmans E, Putman K, Verlooy J. Return to Work of Patients Treated With Spinal Cord Stimulation for Chronic Pain: A Systematic Review and Meta-Analysis. Neuromodulation : journal of the International Neuromodulation Society. 2019;22(3):253-61.

72. Kaijankoski H, Nissen M, Ikaheimo TM, von Und Zu Fraunberg M, Airaksinen O, Huttunen J. Effect of Spinal Cord Stimulation on Early Disability Pension in 198 Failed Back Surgery Syndrome Patients: Case-Control Study. Neurosurgery. 2019;84(6):1225-32.

73. Niyomsri S, Duarte RV, Eldabe S, Fiore G, Kopell BH, McNicol E, Taylor RS. A Systematic Review of Economic Evaluations Reporting the Cost-Effectiveness of Spinal Cord Stimulation. Value Health. 2020;23(5):656-65.

74. National Institute of Health and Care Excellence (NICE). Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain NICE guideline 193 2021.

75. National Institute of Health and Care Excellence (NICE). Neuropathic pain – pharmacological management NICE clinical guideline 173. Manchester, UK2013.

76. Swedish Association of Local Authorities and Regions (Sveriges Kommuner och Regioner). Nationellt uppdrag: Smärta. På uppdrag av nationell samverkansgrupp för kunskapsstyrning (NSK). 2016.

77. Southern Healthcare region (Södra Sjukvårdsregionen). Regional price list, Regionala priser och ersättningar för södra sjukvårdsregionen. Lund, Sweden; 2016.

78. Karolinska University Hospital. Regional price list (Prislista för utomlänsvård samt för utlandspatienter inom EU 2016) Stockholm, Sweden2016 [

79. van den Hout WB. The value of productivity: human-capital versus friction-cost method. Ann Rheum Dis. 2010;69 Suppl 1:i89-91.

80. Imbens GW, Wooldridge JM. Recent developments in the econometrics of program evaluations. 2008.

81. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? Int J Methods Psychiatr Res. 2011;20(1):40-9.

82. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

83. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, Initiative S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology. 2007;18(6):805-35.

84. Public Policy Committee ISoP. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016;25(1):2-10.

85. Ghosh PE, Gill JS, Simopoulos T. The Evolving Role of High-Frequency Spinal Cord Stimulation as Salvage Therapy in Neurostimulation. Pain Pract. 2020;20(7):706-13.

86. National Board of Health and Welfare (Socialstyrelsen). The National Patient Register (Patientregistret). 2018.

87. National Board of Health and Welfare (Socialstyrelsen). The Prescribed Drug Register (Läkemedelsregistret). 2018.

88. National Board of Health and Welfare (Socialstyrelsen). Cause of Death Register (Dödsorsaksregistret). 2018.

89. National Board of Health and Welfare (Socialstyrelsen). The Swedish Spine Surgery Register Swespine (Svenska ryggregistret - Swespine). 2018.

90. Chakravarthy K, Malayil R, Kirketeig T, Deer T. Burst Spinal Cord Stimulation: A Systematic Review and Pooled Analysis of Real-World Evidence and Outcomes Data. Pain medicine. 2019;20(Suppl 1):S47-S57.

91. Conger A, Sperry BP, Cheney CW, Burnham TM, Mahan MA, Onofrei LV, Cushman DM, Wagner GE, Shipman H, Teramoto M, McCormick ZL. The Effectiveness of Spinal Cord Stimulation for the Treatment of Axial Low Back Pain: A Systematic Review with Narrative Synthesis. Pain medicine. 2020;21(11):2699-712.

92. Texakalidis P, Tora MS, Boulis NM. Neurosurgeons' Armamentarium for the Management of Refractory Postherpetic Neuralgia: A Systematic Literature Review. Stereotact Funct Neurosurg. 2019;97(1):55-65.

93. Visnjevac O, Lee K, Bulatovic R, Pourafkari L, Porhomayon J, Nader ND. Outcomes-based systematic review for management of massive intra-cardiac or pulmonary thrombotic emboli during surgery. Heart Lung Vessel. 2014;6(1):24-32.

10 APPENDIX A: LITERATURE SEARCH PROTOCOL

Table 4. Literature search protocol

1. Review question	
What is the current evidence base on the effect of SCS on pain, disability, function, HRQoL, return to work, costs and cost-effectiveness in patients with chronic pain compared with other treatments or no treatment?	
2. Criteria for including studies in the review	
Participants and conditions of interest	Chronic neuropathic pain, complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS)
Interventions	Spinal cord stimulation (tonic, burst, HF-10, low or high frequency)
Comparisons/control groups	Sham, conventional medical management (CMM), pharmacological treatments, other invasive or non-invasive treatments, comparisons with baseline
Outcomes	Pain Disability Function HRQoL Costs Incremental cost-effectiveness ratio
Setting	Any setting
Study designs	Systematic literature reviews or meta-analysis
Publication date	18 November 2016–18 November 2021
3. Criteria for excluding studies in the review	
Studies written in non-English language, non-Scandinavian language. Studies published only in abstract/poster form (not full-length article). Reviews based on animal studies. Non-systematic reviews and reviews not reporting study eligibility criteria, search methods and search results.	
4. Search strategy	
Electronic databases	PubMed/MEDLINE
Other methods used for identifying relevant research	Reference checking and hand searching of these
Search string PubMed/MEDLINE	**1.** "spinal cord stimulation"[Title/Abstract] (3,816 hits) **2.** systematic[Title/Abstract] (440,441 hits) **3.** review[Title/Abstract] (1,858,529 hits) **4.** "2016/11/17"[Date - Publication] : "2021/11/17"[Date - Publication] (6,591,844 hits) #1 AND #2 AND #3 AND #4 (95 hits)
5. Review methods	
Details of methods	ES conducted all searches and data extraction
Quality assessment	No formal quality assessment was conducted
Data extraction	EndNote was used to keep track of references. The following information was extracted from the studies and tabulated: Study design, Study duration, Intervention, Comparison/Control, Primary outcome, Secondary outcome(s), Study Eligibility Criteria, Main Findings

11 APPENDIX B: SUMMARY OF SYSTEMATIC LITERATURE REVIEWS ON THE EFFECT OF SCS

Table 5. Systematic literature reviews on the effect of SCS and eligibility criteria of the reviews

Author	Population/ condition	Intervention and comparator	Outcomes	Study designs	Findings
Bicket, 2016 (53)	Chronic pain	HF-10 SCS vs. sham (stimulator off)/T-SCS	• Pain improvement • Response rate (achieving ≥50% pain reduction) • Satisfaction • Function • QoL • Return to work • Adverse events	Randomised trials and prospective non-randomised	• 8 studies included • 1 double-blind RCT of 33 patients with showed no significant difference in response rate of HF-SCS vs. sham (42.2% vs. 30.3%, p=0.30), VAS pain (4.26 vs. 4.35, p=0.82) or EQ-5D (0.48 vs. 0.463, p=0.78) • 1 open-label RCT of 198 patients showed higher response rate for HF-SCS vs. T-SCS (75.0% vs. 37.7%, p<0.001)
Chakravarthy, 2019 (90)	Chronic pain	B-SCS vs. T-SCS	• Pain ratings • Function • QoL	RCTs, single-arm prospective cohort, retrospective case reports	• 15 studies included • Baseline weighted pooled mean pain score 76.7 (±27.4). With T-SCS, this was reduced to 49.2 (±12.9), and with B-SCS it was further reduced to 36.7 (±11.6). B-SCS was shown to have a clinically important incremental benefit over T-SCS
Conger, 2020 (91)	Axial low back pain	B-SCS, LF-SCS, HF-SCS vs. sham/ placebo/active treatment/no treatment	• Response rate (achieving ≥50% pain reduction) • Function • Medication use • QoL • Disability	Randomised and non-randomised, cohort, case series	• 17 studies included • HF-SCS response rate ranged 79% (95% CI 70–87%) • Meta-analysis not performed due to study heterogeneity
Karri, 2020 (70)	Chronic low back pain secondary to failed back surgery syndrome, axial LBP, lumbar radiculopathy, and spinal stenosis	B-SCS vs. T-SCS	• Pain relief	RCTs, prospective observational	• 11 studies included • B-SCS vs. T-SCS: Pooled estimate MD pain scores -1.64 (95%CI -2.43 to -0.84, p<0.001) favouring B-SCS over T-SCS

McClure, 2021	FBSS, persistent low back pain	SCS vs. CMM/ repeated spine surgery	• Incremental cost-effectiveness ratio		Cost-effectiveness studies, retrospective, prospective and model-derived retrospective	• 6 studies included • SCS is cost-effective compared with CMM and/or reoperation assuming a WTP of $25,000
Ontario health (68)	Chronic noncancer pain	HF-10 SCS vs. any other SCS modality	• Pain intensity • Response rate (achieving ≥50% back/leg pain reduction) • Remitter rate (VAS pain score ≤2.5) • Functional disability • Medication use • Patient satisfaction • Global impression • Sleep quality • QoL • Adverse events		RCTs, randomised crossover studies	• 5 studies included • Higher response rates reported in included studies for HF-10 vs. T-SCS • Very large difference in back pain response rate for the control groups across trials (44% in SENZA-RCT vs. 82% in SURF trial) • All RCTs showed significant improvement in disability, HRQoL for HF-10 vs T-SCS
Pollard, 2019 (69)	Intractable back or limb pain	T-SCS vs. medical therapy, T-SCS vs. HF-SCS	• Reduction in opioid and pain medication		RCTs	• 5 studies included • Odds ratio of reducing opioid use T-SCS vs. medical therapy 8.60 (95%CI 1.93–38.30. • No statistically significant difference between T-SCS and HF-SCS
Texakalidis, 2019 (92)	Refractory postherpetic neuralgia	SCS, DREZ, DRG, and other	• Pain reduction		RCTs, prospective and retrospective observational	• 39 studies included (10 SCS) • SCS: Pain reduction >50% was documented in 41.1% of patients
Visnjevac, 2016 (93)	CPRS	SCS several comparators	• Pain relief • Pain score • Resolution of CRPS signs • Function • QoL • Psychological impact • Sleep • Analgesic medication use • Patient satisfaction		RCTs, prospective, retrospective, case-control, case reports, cohort studies	• 19 studies included • Pain relief, pain score improvement, QoL, and treatment satisfaction were rated 1B+ evidence grade, high-level evidence favouring SCS for the use in CRPS • Evidence for functional status and psychological effects of SCS was inconclusive

Abbreviations: B-SCS: Burst SCS; CI: Confidence Interval; CMM: Conventional Medical Management; CRPS: Complex Regional Pain Syndrome; DREZ: Dorsal Root Entry Zone; DRG: Dorsal Root Ganglion; HF-SCS: High-Frequency SCS; HF-10: High Frequency 10 kHz; LF-SCS: Low-Frequency SCS; MD: Mean Difference; RCT: Randomised Controlled Trial; SCS: Spinal Cord Stimulation; T-SCS: tonic SCS; QoL: Quality of Life; WTP: Willingness-To-Pay