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Real-world outcomes in spinal cord stimulation: predictors of reported effect and explantation using a comprehensive registry-based approach

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Abstract

Introduction: Despite advancements in implanted hardware and development of novel stimulation paradigms in Spinal Cord Stimulation (SCS), real world evidence suggests a large variation in patient reported outcomes and a proportion of patients are later explanted due to loss of analgesia. Possible predictors for outcome have been explored in smaller short-term evaluations, but few clinically applicable robust measures for long term outcome have emerged.

Methods: We performed a comprehensive retrospective study based on an assembled patient-level aggregated database from multiple local and national registries in Sweden. Variables associated with risk of explantation (due to insufficient analgesia) and analgesic effect was analyzed using a Cox regression analysis and an ordered logit regression model, respectively.

Results: We found the accumulated risk of explantation due to loss of analgesia to be 10% and 21% at two and ten years follow up, respectively. The use of 10 kHz spinal cord stimulation (compared with Tonic waveform; $p = 0.003$), and being 60 years or older (reference 18-40 years; $p = 0.003$) were associated with an increased risk of explantation.

At a mean follow up at 1 year, 48% of patients reported a pain intensity reduction from baseline of at least 30%. Secondary ($p = 0.030$) and post-secondary ($p = 0.001$) education (compared with primary education) was associated with an increased probability of successful patient reported outcomes.

Conclusion: This study suggests that a higher educational level and being employed are associated with successful treatment outcome in patients with chronic pain treated with SCS in Sweden.

Keywords: Neuromodulation, Administrative register, Chronic pain, Effectiveness, Education, Real-world evidence

1. Introduction

Pain is the most commonly perceived symptom in surveyed adult populations and the primary reason for seeking medical attention in Europe and in the United States of America.[31,46] Chronic pain is defined by the International Association for the Study of Pain (IASP) as a pain condition lasting or recurring for more than 3 to 6 months,[35] and several chronic pain conditions are among the diagnoses resulting in the most years lived with disability.[13]

"Real-world data" (RWD) and "real-world evidence" (RWE) are terms increasingly used and discussed in the medical literature, referring to analysis of data collected in routine health care.[3] Although analyses of complex unstructured linked data have limitations, they may offer unique possibilities over traditional trials. First, RWD may further clarify treatment outcome in populations or time frames beyond those assessed in most investigational studies. Moreover, RWD could help in the design of future clinical trials, as well as monitor dissemination, effectiveness, and safety of novel technologies and treatments.

Implanted neurostimulation devices, such as spinal cord stimulation (SCS) systems, have been used for decades to alleviate pain from refractory primarily neuropathic pain states.[48] The most well-

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established indication is chronic back and leg pain following spine surgery, known as persistent spinal pain syndrome (PSPS) and formerly as failed back surgery syndrome (FBSS).[12] Seminal randomized clinical trials have documented the efficacy of SCS on this indication for both traditional tonic stimulation patterns[28,38] and the more novel higher-frequency subsensory stimulation patterns, such as burst stimulation[15] and 10 kHz stimulation.[24] However, because of their nature, such trials frequently include a selected patient group and a limited follow-up time. Publications on RWD with longer follow-up indicate that exit of therapy is common, and patient benefit varies among individuals over time.[22,30,49,56] Several studies have tried to appraise the frequency and cause of explantations and found loss of analgesic effect to be the most common cause for exit from therapy.[9,23,40] A number of studies have investigated the association between psychometric variables and SCS treatment outcome, sometimes with conflicting results.[41,44,52] Considering the heterogenous RWE for invasive neurostimulation treatments, there is a need for evidence beyond expert opinion to better guide patient selection and inform design of future clinical trials.

To investigate factors associated with SCS outcome and to better understand the population treated with implanted neurostimulation devices, we conducted a study on RWD available in Sweden. The overarching aim of this project was to identify the association of key clinical, patient-reported, and economic outcomes of SCS treatment and potential predictive factors for each outcome. The health economic assessment of this project is published elsewhere.[50]

The specific study objectives for this publication were (1) to analyze the rate of explantation of SCS systems because of insufficient analgesic effect, (2) to identify possible predictors for explantation of SCS systems because of insufficient analgesic effect, (3) to assess patient-reported analgesic and global effect of therapy, and (4) to identify possible predictors of efficacy in patients treated with SCS.

2. Methods

This is an observational, retrospective, cohort study on patients treated with SCS for chronic pain in Sweden. This study was conducted on data from an extensive research database designed and assembled to manage linked pseudoanonymized data from local and national quality registries and administrative registries.

2.1. Data sources and data collection

Data were collected from 8 Swedish local or national registries. **Table 1** provides an overview of data sources.

RAY is a local cohort registry of prospectively collected outcome and procedural data on consenting patients implanted with a permanent neurostimulation system at the Multidisciplinary Pain Centre at Uppsala University Hospital, Sweden. All patients included had completed a successful 7-day or 14-day trial of stimulation before permanent implantation. Data on adverse events, reoperations, and explantations were entered into the database prospectively during the study. Baseline Patient-Reported Outcome Measures (PROMs), including Brief Pain Inventory (BPI)[53] and a 11-graded numerical rating scale (NRS) for pain intensity, were collected before implantation of a permanent stimulation device. Follow-up PROMs, including a 6-level categorical global assessment of effect of stimulation (EoS), were collected annually at a fixed time point (in January) for up to 5 years by questionnaires mailed to study participants. Returned data were transferred from paper to a structured query language (SQL) database. Before the end of data collection and data lock, procedural data were verified against medical records and PROMs against questionnaires to assure completeness of data.

From the *National Patient Register*, a second SCS population covering all implants in Sweden was identified, based on surgical procedural codes according to the NOMESCO classification. From this register, the Elixhauser comorbidity index, indicating the degree of comorbidities in an individual, was calculated based on diagnostic codes for admissions and outpatient visits.[19] Detailed patient-level demographic data were collected from the *Register of the Total Population*. Data from the *Cause of Death Register*, comprising all deaths in Sweden were added to account for deaths in the study population. Information on medication was supplied by the *Prescribed Drug Register*, which covers all pharmaceutical products dispensed at any pharmacy in Sweden since 2005. Data were extracted as defined daily doses (DDD), which is the assumed average maintenance dose for a certain drug on its main indication in adults.[57] Further data on education, income, work status, and sick leave were extracted from the *Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA)* and the *Swedish Social Insurance Agency*, covering all individuals who work and live in Sweden. Data from *SWESPINE*, the National Swedish Spine Register, containing data on 95% of all back surgery performed in Sweden were added.

The research unit at Statistics Sweden, a governmental agency, collected data sets from all sources and linked data on a patient level using the unique social security number of individuals, a variable present in all registers in the study. The final data set was then pseudoanonymized and made available to the study group.

Table 1

Overview of data sources.

Name of register	Type of data	National/Local	Holder of register
RAY	Indications, outcome, and therapy-specific data on invasive neurostimulation treatments	Local	Uppsala University Hospital
The national patient register (NPR)	Diagnoses and procedures in inpatient and outpatient care in Sweden	National	The Swedish Board of Health and Welfare
The register of the total population (RTP)	Demographic and socioeconomic data	National	Statistics Sweden
The cause of death register	Cause of all deaths	National	The Swedish Board of Health and Welfare
Prescribed drug register (PDR)	Prescribed pharmaceutical products	National	The Swedish Board of Health and Welfare
The LISA Register	Labor market and educational level data	National	Statistics Sweden
Data from the Swedish Social insurance Agency	Work status and sick leave	National	The Swedish Social insurance Agency
SWESPINE	Outcome and procedural data on spine surgery	National	The Swedish Association of Spine surgeons

See supplemental data, available at http://links.lww.com/PR9/A210 for a further description of individual data sources.
LISA, national register on labor market and educational level data; RAY, a local registry on invasive neurostimulation treatments for pain; SWESPINE, the national register on spine surgery.

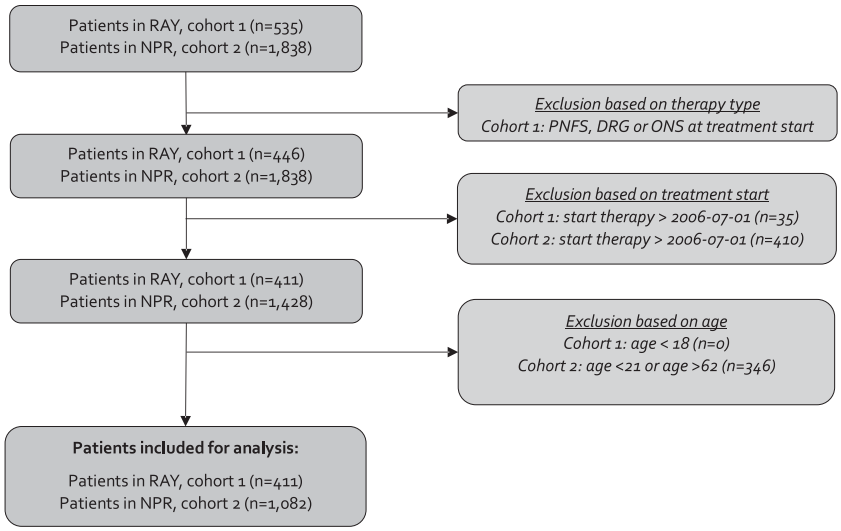

Figure 1. Patient attrition from raw data to study population (cohort 1) and reference (cohort 2). DRG, dorsal root ganglion stimulation; NPR, National Patient Registry in Sweden; ONS, occipital nerve stimulation; PNFS, peripheral nerve field stimulation; RAY, a local registry on invasive neurostimulation treatments for pain.

Table 2

Demographics, comorbidities, and pharmacotherapy in the study and reference populations.

	Study population (n = 411) Cohort 1		All SCS implants (n = 1082) Cohort 2		SWESPINE (n = 83,786) Cohort 3		Healthy controls (n = 2055) Cohort 4		Data source(s)
	Mean or percent	SE or count	Mean or percent	SE or count	Mean or percent	SE or count	Mean or percent	SE or count	
Age at index (y)	52.3	0.6	47.1	0.3	57.7	16.1	52.3	0.2	NPR
Follow-up time (y)	4.7	0.7	4.4	0.4	5.1	2.9	N/A	N/A	RAY & SWESPINE
Sex									NPR & RTP
Male	45%	186	44%	480	49%	40,738	45%	925	
Female	55%	225	56%	602	52%	43,048	55%	1130	
Income (000, €)	21.1	0.6	21.6	0.6	24.8	0.2	29.4	1.2	LISA
Birth country									LISA
Sweden	87%	356	86%	931	85%	71,428	81%	1665	
Europe, except Sweden	7%	31	9%	99	10%	8,172	8%	164	
Other	6%	24	5%	52	5%	4,186	11%	226	
Education level									LISA
Primary education	21%	85	19%	201	23%	19,538	13%	267	
Secondary education	55%	227	58%	629	48%	39,911	43%	884	
Post-secondary/postgraduate education	22%	91	22%	242	28%	4,186	44%	904	
Employment status									LISA
Employed	42%	174	47%	508	53%	44,311	70%	1438	
Not employed	58%	237	53%	574	47%	39,475	30%	617	
Elixhauser comorbidity index	1	0.1	0.8	0	0.9	1.4	0.3	0.1	NPR
Prior spine surgery	47%	191	40%	443	N/A	N/A	<1%	N/A	SWESPINE & NPR
Pharmacotherapy									PDR
Nonopioid pain medication usage*	51%	211	45%	484	47%	39,077	5%	102	
Antidepressant medication usage*	42%	173	46%	494	17%	13,972	9%	185	
Any opioid usage*	60%	245	55%	594	45%	37,788	4%	82	
Strong opioid usage*	27%	110	27%	288	19%	15,695	1%	13	
Weak opioid usage	40%	164	36%	394	35%	29,091	3%	66	

* At least 1 drug dispensation in the prior 3 months before index date.

LISA, national register on labor market and educational level data; NPR, the national patient register; PDR, the prescribed drug register; RAY, a local therapy specific register on invasive neurostimulation; RTP, the register of the total population; SE, standard error; SWESPINE, the national register on spine surgery.

Table 3

Treatment indications, implanted hardware and waveforms in cohort 1 (N = 411).

	Mean or percent	SE or count
Mean pain duration in y before implantation	9.3	0.4
Main indications for spinal cord stimulation		
Persistent spinal pain syndrome, type 1 or 2	50%	207
Persistent postsurgical pain	11%	47
Neuropathic pain in extremity	7%	30
Primary waveform		
Tonic waveform	55%	225
Burst waveform	28%	114
10-kHz waveform	18%	72
Impulse generator type		
Rechargeable	26%	107
Nonrechargeable	74%	304
Lead type		
Percutaneous lead	95%	392
Surgical lead	5%	19

Burst, a 5-pulse train paresthesia-free waveform with internal frequency of 500 Hz delivered at 40 Hz using a passive recharge pattern. 10 kHz, a paresthesia-free, 10-kHz, continuous, spinal cord stimulation waveform. Tonic, refers to a 30- to 80-Hz continuous spinal cord stimulation waveform producing paresthesia.
SE, standard error.

The study period was defined as the start of data availability to the end of data availability (January 1, 2000 to December 31, 2018). The index date was defined as the date of implantation of a permanent SCS system. Follow-up period was from the index date until the occurrence of an outcome event that ends the follow-up, death, or end of data availability (December 31, 2018). For further details and specifics on data sources, see appendix (available at http://links.lww.com/PR9/A210).

2.2. Study population

Variables relevant for the objectives in this study were limited to data from RAY, thus the study population was defined by patients in RAY (cohort 1). For descriptive purposes, 3 reference cohorts were identified: cohort 2 was identified from the National Patient Register, using procedural codes to identify patients implanted with an SCS system. Thus, all patients in cohort 1 exist in cohort 2. Cohort 3 was identified using SWESPINE, detailing baseline characteristics of patients scheduled for spine surgery. In addition, a cohort of matched healthy controls (cohort 4) was identified in the Register of the Total Population. Controls were matched in a 5:1 ratio to cohort 1 using exact matching without replacement. Cases and controls were matched based on age in years, sex, and region of residence. **Figure 1** provides details on how the final study population was defined.

2.3. Outcome measures

The risk of explantation because of insufficient analgesic effect was measured as the cumulative probability of explantation. To assess the patient global effect of treatment, the variable effect of stimulation (EoS) was used. This is a 6-level categorical patient-reported outcome measurement used at follow-up in RAY as a response to the question "What is the effect of the stimulation?" without any specified recall period. The response possibilities given were as follows: freedom from pain/considerable pain relief/

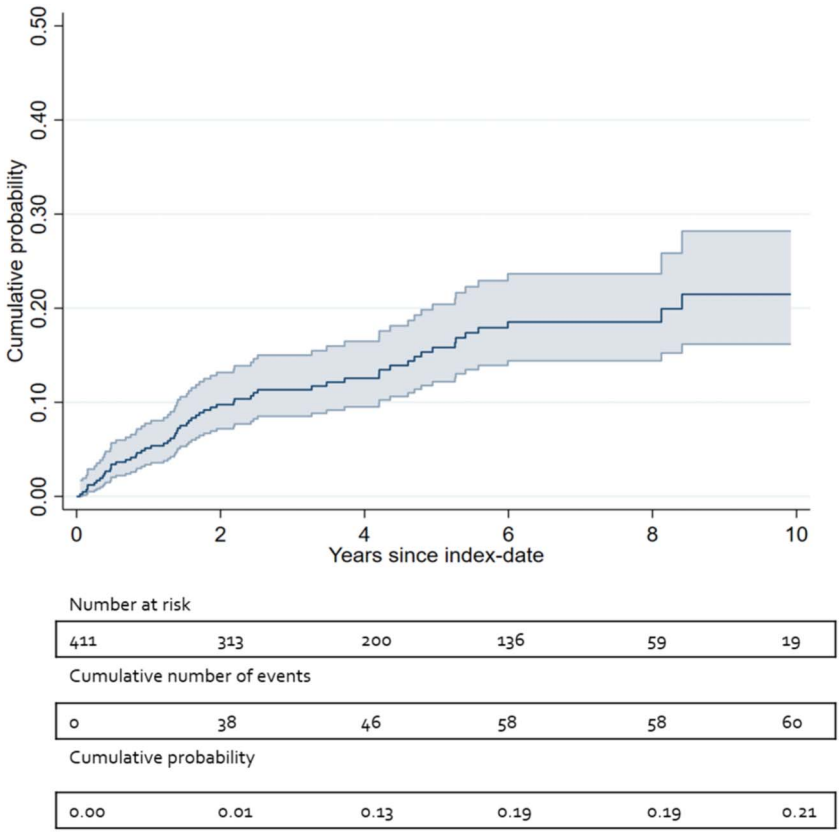

Figure 2. Kaplan–Meier curve: cumulative number of events and probability of explantation because of insufficient analgesic effect, with 95% confidence intervals.

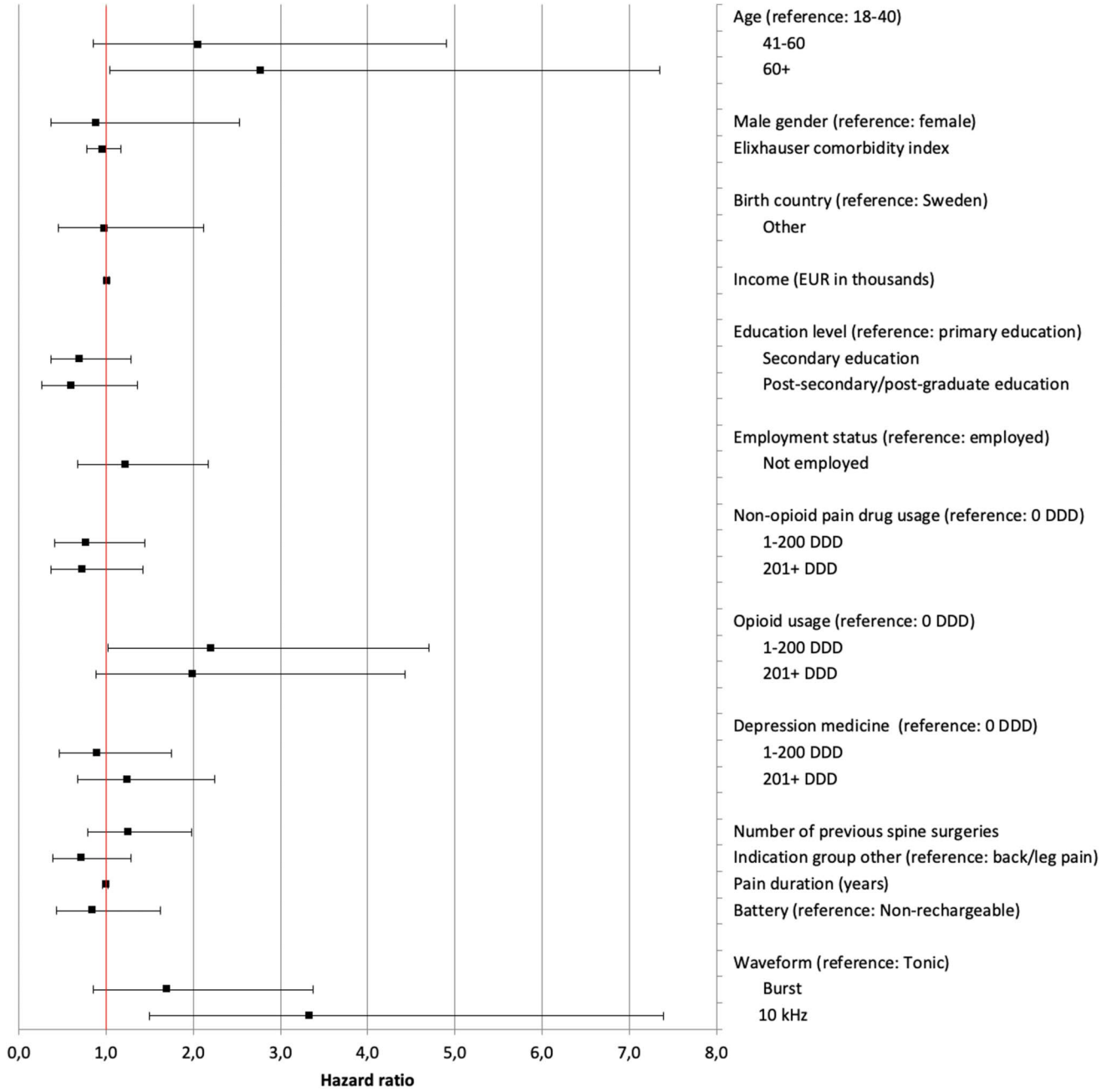

Figure 3. Variables analyzed for association with explants because of insufficient analgesic effect. Each point is the hazard ratio, and lines indicate 95% confidence intervals. Higher hazard ratio indicates a stronger association to the risk of explantation. DDD, the total number of defined daily doses dispensed to a patient in the 12 months before implantation. Indication group "Other" refers to a group of indications made up of all treatment indications except "persistent spinal pain syndrome, type 1 or 2" as defined by indication groups in RAY, a local quality registry for implantable neurostimulation therapies for pain at the Uppsala University Hospital, Sweden. Burst: A 5-pulse train paresthesia-free waveform with internal frequency of 500 Hz delivered at 40 Hz using a passive recharge pattern. 10 kHz, a paresthesia-free, 10-kHz, continuous, spinal cord stimulation waveform. Tonic: refers to a 30- to 80-Hz continuous spinal cord stimulation waveform producing paresthesia. See appendix for data in table format, available at http://links.lww.com/PR9/A210.

acceptable pain relief/some pain relief/no pain relief/worsened pain. Change in reported pain intensity was measured using the 11-point NRS for global pain (NRS) or BPI item 5 at baseline and follow-up. Pain interference was measured using BPI.

2.4. Statistical methods

All statistical tests are based on two-sided *P* values. A *P*-value threshold of 0.05 was used for statistical significance. Data management and statistical analyses were performed using MySQL (Uppsala, Sweden) and Stata16 (StataCorp LLC, College Station, TX).

2.4.1. Objective 1: analysis of risk of explantation because of insufficient analgesic effect

Risk of explantation was analyzed from index date, and continuously over time, until death or end of data availability, using a time-to-event analysis with the first explantation as the failure event. Explantation was a binary variable measured during follow-up for every patient in

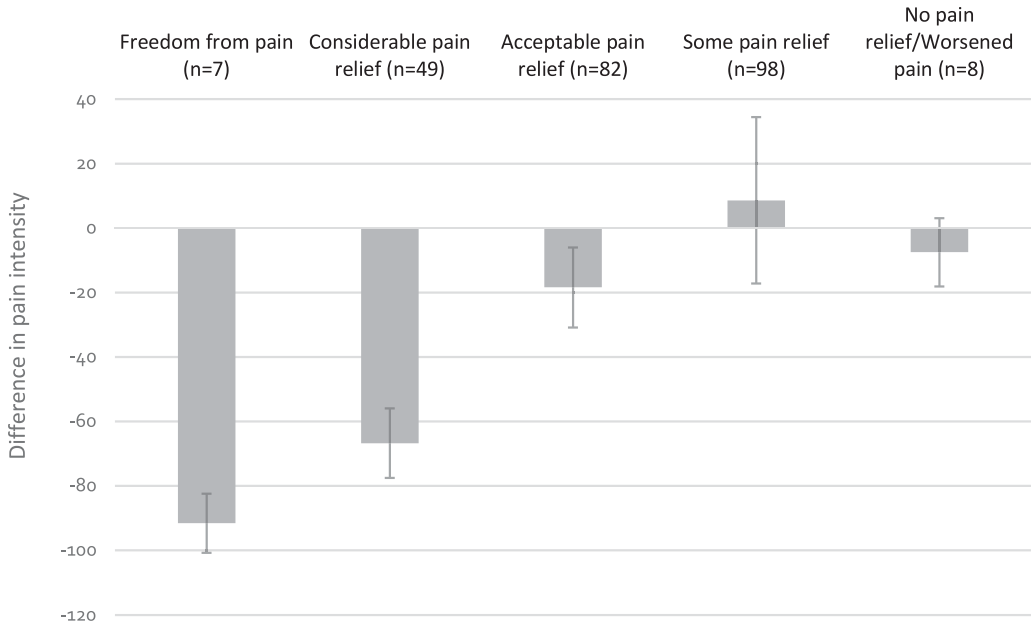

Figure 4. Mean difference in pain intensity between baseline and follow-up, by category of effect of stimulation. Error bars represent 95% confidence interval.

the RAY register (cohort 1). Patients were censored at death, at the end of data availability, or at replacement of SCS with another neuromodulation therapy (eg, dorsal root ganglion stimulation). No censoring was done for implantable pulse generator (IPG) replacements due to depleted battery. The model used is a single failure model, and thus, multiple explantations for an individual patient will not be accounted for.

2.4.2. Objective 2: analysis of potential risk factors for explantation

The strength of the association of the potential predictors was analyzed using Cox proportional hazard regression. Time-to-event data were presented and visualized by Kaplan–Meier curves.

2.4.3. Objective 3: patient-reported analgesic and global effect

In RAY, depending on the time of patient inclusion, 2 different 11-point NRS scales of pain intensity were used at baseline and follow-up: BPI or NRS for global pain. We hypothesized that the difference from baseline to follow-up could be merged into one outcome variable for pain intensity. A *t* test for equal means of change in BPI and NRS revealed no significant difference and supported the merger into one outcome variable (see appendix for full analysis, available at http://links.lww.com/PR9/A210).

The EoS levels were categorized into successful or unsuccessful outcome based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations on

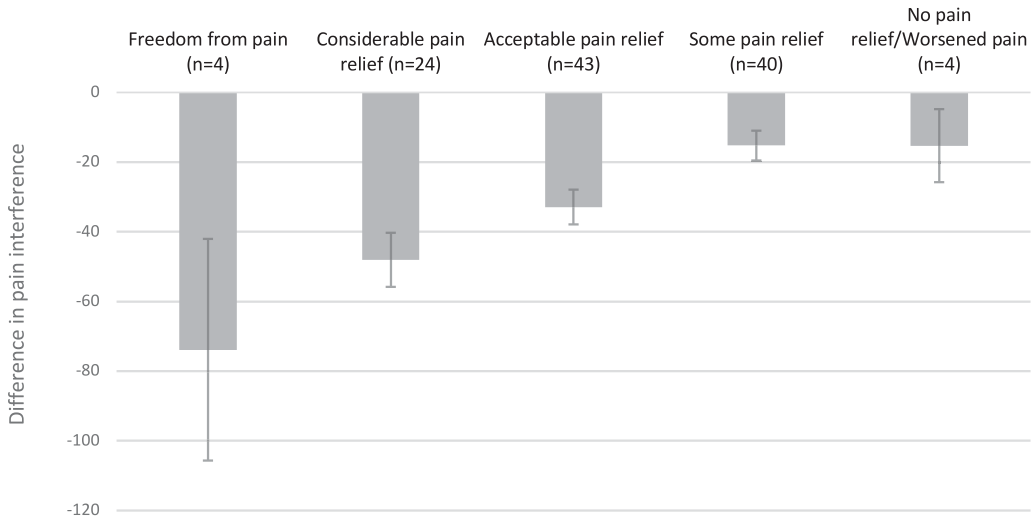

Figure 5. Mean difference in pain interference between baseline and follow-up, by category of effect of stimulation. Error bars represent 95% confidence interval.

Table 4

Mean pain intensity and pain interference at baseline and follow-up.

	Baseline (BL)		Follow-up (FU)		Mean percent difference from BL to FU (CI)	Proportion of patients reporting > −30% change from BL to FU	Proportion of patients reporting > −50% change from BL to FU
	Mean	SD	Mean	SD			
Pain intensity (N = 244)	8.0	1.8	5.4	2.2	−30.6 (−27.2 to −34.0)	48.3%	20.1%
Pain interference (N = 115)	6.5	2.0	4.7	2.8	−21.4 (−9.7 to −33.2)	43.9%	31.6%

Pain intensity and pain interference measured using the Brief Pain Inventory.
CI, 95% confidence interval; SD, standard deviation.

interpreting the clinical importance of treatment outcomes in clinical pain trials, proposing that a clinically meaningful change in pain intensity measures should be >30% decrease in the reported pain intensity from baseline.[17] The following EoS levels were thus categorized as successful outcome: freedom of pain, considerable pain relief, and acceptable pain relief; the rest of the EoS levels were categorized as unsuccessful outcome. The EoS levels "no pain relief" and "worsened pain" were merged together due to insufficient number of observations.

Missing data in PROMs increased by time from baseline. Thus, the time point for follow-up was the first available follow-up data after baseline. Mean follow-up time was 384 and 217 days for pain intensity and pain interference, respectively.

2.4.4. Objective 4: potential predictors of analgesic and global effect of therapy

A logistic regression using a binary transformation of EoS as the dependent variable was conducted. The strength of association of potential predictors and EoS levels were analyzed by an ordered logit regression model.

2.5. Ethics

This research project was vetted and approved by the Regional Ethical Board in Stockholm, project number ID 2017/5:3.

3. Results

3.1. Description of study population

Table 2 describes the study population (cohort 1) and 3 reference populations (cohort 2–4) available in the study database. In general, patients included in the RAY cohort (cohort 1) and patients identified in the National Patient Register (cohort 2) were similar in sociodemographic variables and comorbidities. On average, the healthy controls had a higher educational level and employment rates compared with the study population. Comorbidities were on average less frequent in the control group compared with the treatment groups (mean 0.3 vs 1.0 in cohort 1 and 0.8 in cohort 2).

The average use of opioids, nonopioid pain medications, and antidepressant medications were substantially higher in the treatment groups compared with healthy controls and patients scheduled for spine surgery. Drug usage (opioids, nonopioids, and depression) was fairly similar in cohort 1 and cohort 2.

Patients treated with SCS reported a mean pain duration of 9.3 years before implantation of a permanent system. In 50% of patients, chronic back and leg pain was the main indication for SCS therapy. Conventional tonic simulation was the most commonly used waveform, followed by burst stimulation and 10 kHz stimulation. Nonrechargeable batteries were more commonly used than rechargeable ones. **Table 3** provides further details.

3.2. Risk of explantation because of insufficient analgesic effect (objective 1)

The cumulative risk of explantation of SCS system because of insufficient analgesic effect was found to be 9.8%, 15.8%, and 21.3% at 2, 5, and 10 years, respectively. **Figure 2** provides a visual representation of the time to explantation (Kaplan–Meier plot).

3.3. Predictors for explantation because of insufficient analgesia (objective 2)

Higher age was associated with higher risk of ExIA (41–60 year old; $P = 0.108$ and 60+ years old; $P = 0.041$). Higher opioid consumption was associated with a higher risk of ExIA (1–200 DDD; $P = 0.044$ and 200+ DDD; $P = 0.095$). A 10 kHz stimulation was significantly associated with a higher risk of ExIA ($P = 0.003$). Having a postsecondary/postgraduate education was associated, although insignificantly ($P = 0.213$), with a lower risk of explantation because of insufficient analgesic effect (ExIA). **Figure 3** provides further details.

In a subanalysis (N = 99), having a normal body mass index (BMI) was associated with a lower risk of ExIA compared with overweight patients (HR 0.193; $P = 0.019$) (see appendix for details, available at http://links.lww.com/PR9/A210).

3.4. Patient-reported analgesic and global effect (objective 3)

As can be observed in **Figures 4,5**, the difference in pain perception between baseline and follow-up is greater among patients answering "freedom from pain," with decreasing amount towards "no pain relief," demonstrating a strong consistency between global perceived effect of stimulation and reduction in pain relief and pain interference. Mean difference in pain intensity across all EoS categories was −21.3% (95% CI −32.9% to −9.6%) and for pain interference, it was −29.4% (95% CI −33.0 to −25.9). **Tables 4–6** provide further details.

3.5. Predictors for patient-reported effect of stimulation (objective 4)

Figure 6 details the results of the ordered logit regression model. Increased probability of successful SCS treatment was significantly associated with secondary education (95% CI −1.10 to −0,06; $P = 0.030$) and postsecondary/postgraduate education (95% CI −1.68 to −0.43; $P = 0.001$). Older than 60 years (95% CI 0.02–1.33; $P = 0.044$) and unemployment (95% CI 0.13–1.02; $P = 0.001$) were significantly associated with decreased probability of successful outcome. Higher opioid consumption was

Table 5

Mean difference in pain intensity between baseline and follow-up, by category of the effect of stimulation.

Pain intensity				
EoS category	**N**	**Mean difference (%)**	**95% CI lower (%)**	**95% CI upper (%)**
Freedom from pain	7	−91.5	−100.7	−82.4
Considerable pain relief	49	−66.7	−77.5	−55.9
Acceptable pain relief	82	−18.4	−30.8	−6.0
Some pain relief	98	8.6	−17.2	34.4
No pain relief/ Worsened pain	8	−7.5	−18.1	3.1
All groups	244	−21.3	−32.9	−9.6

Data available for analysis in 244 of 411 patients.
CI, confidence interval; Eos, effect of stimulation, a 6-level, categorical, patient-reported, outcome measurement to assess the global effect of the implanted neurostimulation system at follow-up.

Table 6

Mean difference in pain interference between baseline and follow-up, by category of the effect of stimulation.

Pain interference				
EoS category	**N**	**Mean difference**	**95% CI lower**	**95% CI upper**
Freedom from pain	4	−73.8	−105.7	−42.0
Considerable pain relief	24	−48.0	−55.8	−40.3
Acceptable pain relief	43	−32.9	−37.9	−27.9
Some pain relief	40	−15.3	−19.5	−11.0
No pain relief/worsened pain	4	−15.3	−25.8	−4.8
All groups	115	−29.4	−33.0	−25.9

Data available for analysis in 115 of 411 patients.
CI, confidence interval; Eos, effect of stimulation, a 6-level, categorical, patient-reported, outcome measurement to assess the global effect of the implanted neurostimulation system at follow-up.

insignificantly associated with decreased probability of successful outcome ($P = 0.078$–0.164).

4. Discussion

In this study, we chose study objectives we judged as the most relevant to evaluate the clinical effectiveness of implanted neurostimulation devices for chronic pain: patient-reported global assessment of the treatment and explantation and termination of stimulation systems due to inadequate pain relief.

4.1. Patient population

The demographics and indications for SCS of the study population are largely similar to comparable reports previously published.[20,34,45,55] Baseline low-dose (1–200 DDD) opioid consumption for implanted patients was 5 times more common and high-dose (>200 DDD) was 20 times more common, compared with the matched healthy control group; 43% of patients in cohort 2 did not consume opioids in the 3 months before implant, which is considerably lower compared with published US national claims data.[47]

4.2. Socioeconomic status and outcomes of spinal cord stimulation treatment

The main novel findings in this study are that higher education level and employment are associated with better outcome in patients treated with invasive neurostimulation. These associations are in the expected direction and fits well into the extensive literature on the relationship between socioeconomic factors and perceived health, impact, and prevalence of chronic pain and outcome of treatments aimed at treating pain.[8,11,25,36,39]

The biopsychosocial model, introduced by Engel 1977, has been widely adopted and is implemented clinically in the management of pain through the development and practice of multidisciplinary pain management clinics and programs.[21] In research aimed at improving our understanding of factors predicting the outcome of implanted neurostimulation devices, the focus has been mainly directed towards biological[10,18,27] and psychological predictors.[2,4,6,7,51] To the best of our knowledge, the impact of social aspects on outcome, such as income, education level, or employment status, have not been investigated previously. This study is important because it adds information on the "social" aspects to previous "bio" and "psycho" research on SCS.

4.3. Explantations of spinal cord stimulation systems because of insufficient analgesia and potential predictors

The first objective of this study was to calculate the incidence of explantation due to insufficient analgesic effect (ExIA), which we found to be at 2% per year in the first 10 years after implantation of a permanent SCS system. This is lower compared with other studies.[23,40,49] In comparison, a retrospective chart review of 955 SCS implants in 4 European centers found ExIA to be 4.2% per year of follow-up.[9] The therapeutic armamentarium in the neuromodulation field has grown over the past years, and the option to switch from one neurostimulation therapy to another has increased.[42] Patient switching from spinal cord stimulation to another invasive neurostimulation therapy (eg, dorsal root ganglion stimulation) was censored in our study and not counted as failure of therapy, which may have contributed to the relatively low rate of explants.

The second objective was to investigate potential predictors of ExIA. In contrast to Van Buyten et al.,[9] we found higher age, but not sex, to be associated with a higher risk of ExIA. The aforementioned study found rechargeable systems, both high-frequency (10 kHz) and tonic low-frequency systems, to be associated with a higher frequency of ExIA compared with nonrechargeable systems, speculating that the burden of frequent recharging might affect patient experience and risk of explantation. In our study, waveform and type of IPG were treated as separate variables, and 10 kHz was significantly associated with ExIA, whereas type of IPG (rechargeable or nonrechargeable) was not. Moreover, we found opioid consumption in the 12 months before a permanent implant to be significantly associated with a higher risk of ExIA, which is in line with work by Sharan et al.[47]

4.4. Patient-reported global effect, analgesia, and potential predictors

Objective 3 was to assess the patient-reported global effect and analgesia in SCS-treated patients. We dichotomized outcome as successful or unsuccessful using a 6-level categorical scale constructed to reflect the effect of stimulation (EoS), representing the patient-reported global assessment of invasive neurostimulation. The reasons for this were several. First, pain

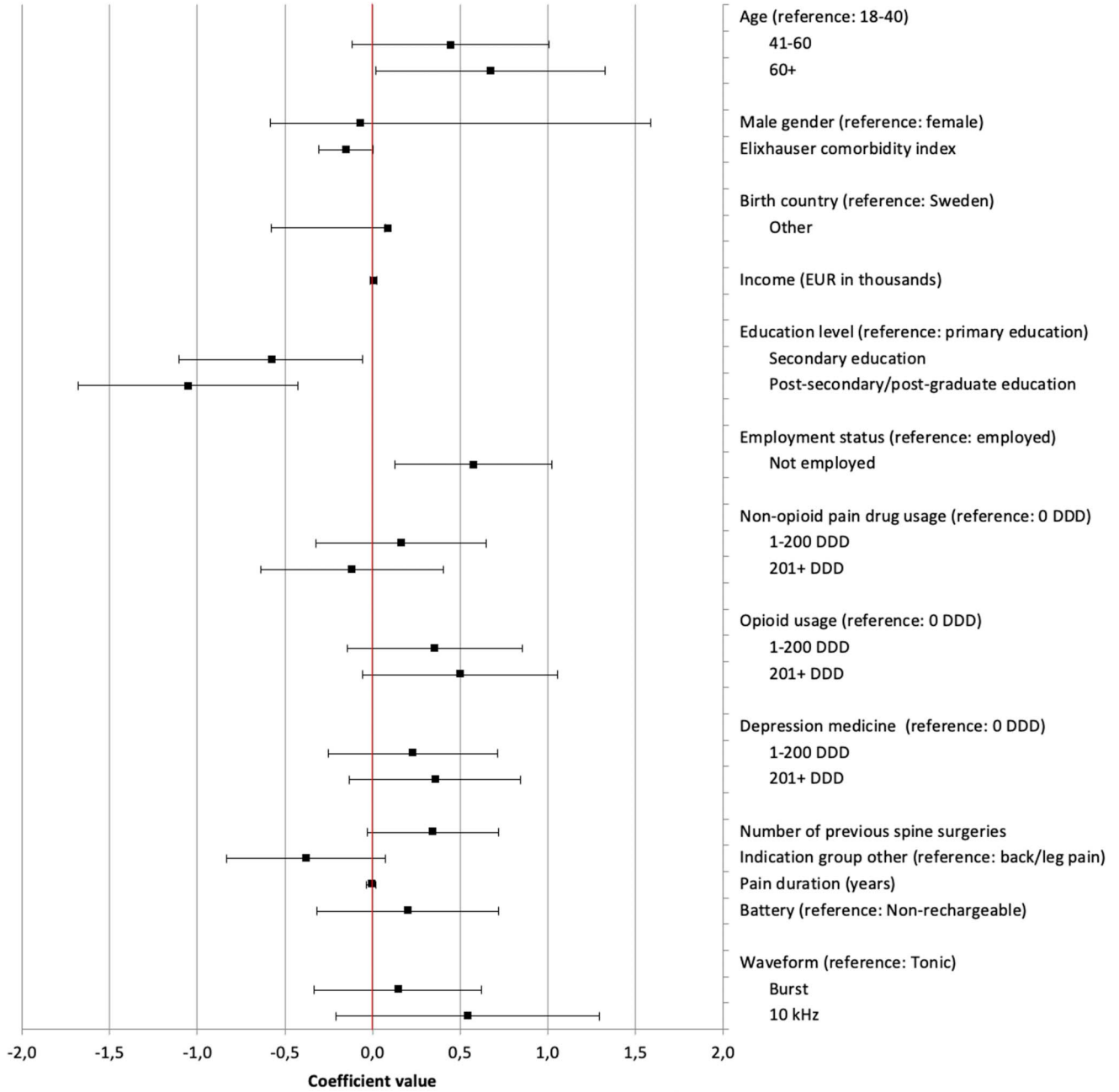

Figure 6. Variables analyzed for association with successful or unsuccessful outcome of SCS treatment, based on a binary transformation of EoS levels. Each point is the coefficient value from ordered logit regression; lines indicate 95% confidence intervals. Positive coefficient values indicate a stronger association to an unsuccessful outcome. DDD, the total number of defined daily doses dispensed to a patient in the 12 months before implantation. Group "Other" refers to a group of indications made up of all treatment indications except "persistent spinal pain syndrome, type 1 or 2" as defined by indication groups in RAY, a local quality registry for implantable neurostimulation therapies for pain at the Uppsala University Hospital, Sweden. Burst, a 5-pulse train paresthesia-free waveform with internal frequency of 500 Hz delivered at 40 Hz using a passive recharge pattern. 10 kHz, a paresthesia-free, 10-kHz, continuous, spinal cord stimulation waveform. Tonic refers to a 30- to 80-Hz, continuous, spinal cord stimulation waveform producing paresthesia. See appendix for data in table format, available at http://links.lww.com/PR9/A210. SCS, spinal cord stimulation.

intensity was reported on an 11-grade NRS scale or using the BPI in the RAY cohort, whereas all patients with available outcome data reported EoS. Second, this approach gives the opportunity to define responders and nonresponders and dichotomize outcome as successful or not successful, which again allows for regression analysis and exploring the association between EoS and other variables. Third, using a categorical primary outcome parameter rather than a continuous variable (eg, VAS pain intensity) is repeatedly emphasized in methodological articles and recommendation on research standards on treatments of pain.[16,26] In the studied population, close to half of the patients reported a successful outcome, meaning "acceptable pain relief" or better, with a corresponding mean 30.6% pain intensity reduction. A strong close to linear correlation was found between EoS and mean reduction in pain intensity and pain interference.

Objective 4 was to investigate whether potential predictors of reported EoS could be identified. Of all variables examined, the

strongest association was found between Eos and education level, where both secondary and post/secondary education were associated with a higher chance of successful reported outcome. Inversely, unemployment was associated with lower risk of successful outcome, compared with being employed. However, the possible covariance between employment and education level cannot be assessed with the analysis used in this study. Nonetheless, income level, a variable often associated with both education level and degree of employment, was not predictive of reported outcome.

The mean pain duration before implantation of a permanent stimulation system is longer in our study population than reported in most other real-world cohorts studied.[14] The relationship between pain duration and outcome of SCS is conflicting, and different reports vary in their definition of a successful outcome and are difficult to compare. A systematic review and meta-analysis using multivariate analysis could not confirm the prior finding that long-term outcome is better in patients with a shorter pain duration.[54] Our findings support the fact that pain duration alone does not predict long-term pain relief in the study population.[43]

Pharmacotherapy data were provided in the DDD format. The DDD concept makes comparison of our findings regarding the effect of opioid dose on outcome difficult, and our study were not able to contribute to the current ongoing discussion on the importance of preimplant opioid tapering and to whether there is a maximum daily average morphine equivalent dose important for long-term outcome.[1,20,37] We could not identify any significant association of the level of opioid consumption on reported outcome, which mirrors the findings of Maher et al.[29]

Two studies in the United States have explored the relationship of body mass index (BMI) and outcome of SCS.[32,33] Our data were limited by the fact that only individuals with data from the SWESPINE registry had data on BMI (N = 99). The association between BMI and the risk of ExIA was explored in a separate Cox regression analysis, and normal BMI was associated with a lower risk of ExIA compared with overweight patients, indicating that obesity may be related to a higher risk of explantation (see appendix, available at http://links.lww.com/PR9/A210).

4.5. Limitations

The limitations to this study are multiple and important to consider. The reported outcome should not be interpreted as a measure of efficacy of implanted neurostimulation devices because no control group (ie, sham stimulation) other than healthy controls was used. Moreover, in a retrospective association study with a limited study population, it is difficult to rule out possible covariance between potential explanatory variables in the regression models, eg, between the variables employment and education levels. Our findings would be enhanced by future similar studies in different settings, preferably in a larger, prospective, multicenter trial.

Cohort 1, which provides patient-reported outcome data in this database, is from a tertiary care, high-volume, single center and may reflect practices and patient selection criteria not representative for other populations. The time to follow-up, at which patient-reported outcome criteria were collected, varied, as these data were collected on a fixed time point annually. This fact is not relevant in the time-to event analysis of risk of explants, but should be taken into account when assessing the patient-reported effect of therapy.

A real-world study length of 7 years leads inevitably to the introduction of new technologies and emerging scientific evidence during the study period, adding risk of period effects at different times in the study.

To limit this risk of bias because of data mining, study protocol, and statistical analysis, plan was agreed upon by the study group before analysis. However, retrospective trials with large data sets may be vulnerable to this phenomenon. Recently, Benjamin et al.[5] has proposed using a more conservative threshold for statistical significance ($P < 0.005$ for "statistically significant evidence" and <0.05 for "suggestive evidence") to lower the risk of false-positive findings. We used the more conventional significance threshold at $P < 0.05$ but note that several of our findings even hold for thresholds at $P < 0.005$.

4.6. Conclusion

Socioeconomic factors, especially education and employment, may be associated with outcome in spinal cord stimulation and should be considered both when designing future trials in the area, as well as when interpreting outcome data, both for the individual patient and on an aggregate level.

Disclosures

T.K. has received consulting fees from Abbott Laboratories. E.S. and T.J. was employees of Quantify Research during the study period. F.B. owns stocks in Quantify Research. Other coauthors have no declared conflict of interest. This study was not preregistered.

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Data availability statement: Data from this study will not be made available to anyone outside the study group.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A210.

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