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How does the number of previous operations affect patient-rated outcome after surgery for lumbar spinal stenosis or lumbar disc herniation?

A population-based cohort study from the Norwegian Registry for Spine Surgery

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Preface

Throughout the first years of medical school I had no idea what kind of doctor I wanted to become. I have always been curious, and almost every topic taught to us at school appealed to me. There are simply so many intriguing medical disciplines, and I wanted to immerse myself in them all. Although I did not know exactly what I was going to do after finishing medical school, one thing was certain; I was never going to be a researcher. Maybe it was the preconceived notion of many lonely hours of working in a dimly lit room, the gnawing insecurity provoked by the thought of doing something I had never done before or the acute lack of imagination that announced its arrival when asked to come up with a research question. I don`t know. All I know is that I had to write a research paper to get myself through medical school.  The next thing I know I found myself in Tor Ingebrigtsen`s office asking for guidance. Tor Ingebrigtsen is a neurosurgeon and professor at the Department of Clinical Medicine, University of Tromsø. Together with Tore K. Solberg, neurosurgeon, professor and scientific leader of the Norwegian Registry for Spine Surgery, Tor presented the idea of writing a paper about lumbar back surgery to me. By a stroke of luck Tor and Tore ended up being my supervisor and co-supervisor, respectively. I could not have asked for better supervisors. Thank you, Tor, for including me in the whole research process from filling out applications to putting the finishing touches, for your invaluable advice on how to write a good research paper, and for breaking down information into pieces small enough for a duckling to swallow. Thank you, Tore, for sharing your expertise in statistical analysis, for all your good ideas and for your unwarranted faith in this project and in me. Tom Wilsgaard contributed with much appreciated advice on statistical methods. After finishing this thesis and hopefully soon the fifth year of medical school, I still don`t know exactly where the road leads. But one thing is certain; research is added to the list of possible future job alternatives.

Anniken S. Riksaasen, Tromsø 14.05.21

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Abstract

Background Several small, mainly single centre studies have linked repeated operations to inferior outcomes compared to primary operations after lumbar spine surgery. Few studies have specifically quantified the influence of previous operations on the outcome.

Objectives The aim of the study was to examine whether, and if so, to which extent the number of previous operations is associated with the outcome after surgery for lumbar spinal stenosis or lumbar disc herniation.

Methods This is a population-based study from the Norwegian Registry for Spine surgery (NORspine). The study included 26 723 cases operated for lumbar spinal stenosis or lumbar disc herniation in public or private Norwegian hospitals during the period 01.01.07 to 31.12.18. The primary outcome measure was Oswestry Disability Index (ODI). Secondary outcome measures were Numeric Rating Scale (NRS) score for back pain and leg pain, EuroQoL 5 Dimensions (EQ-5D), the Global Perceived Effect Scale (GPE) score, occurrence of perioperative complications and wound infections, and working capability. Binary logistic regression analysis was conducted to examine how the number of previous operations influenced the odds for not reaching a Patient Acceptable Symptom State (PASS).

Results The proportion achieving PASS (ODI raw score ≤ 22) decreased stepwise from 66.0 % in cases with no previous operation to 22.0 % in cases with four or more previous operations. The odds for not reaching PASS was doubled in cases with one previous operation, nearly tripled in cases with two previous operations and four to nearly seven times increased in cases with three or more previous operations. The ODI raw score and change score, the GPE and all the other secondary outcome measures showed trends with increasingly inferior outcomes with increasing number of previous operations.

Conclusion We found a dose-response relationship between increasing number of previous operations and inferior outcomes among patients operated for lumbar spinal stenosis or lumbar disc herniation. This information should be taken into consideration, along with other known predictors for favourable and unfavourable outcomes, in the shared decision-making process prior to surgery.

Abbreviations

ASA – American Society of Anaesthesiologists

BMI – Body Mass Index

COMI – Core Outcome Measurement Index

DALY – Disability-Adjusted Life Years

DPO – Data Protection Officer

EQ-5D – EuroQoL 5-Dimensions

GBD - The Global Burden of Diseases, Injuries and Risk Factors Study

GPE – Global Perceived Effect

HRQoL – Health-related Quality of Life

MCIC – Minimally Clinically Important Change

NORspine – Norwegian Registry for Spine Surgery

NRS – Numeric Rating Scale

ODI – Oswestry Disability Index

PASS – Patient Acceptable Symptom State

PROM – Patient Rated Outcome Measure

VAS – Visual Analogue Scale

WHO – World Health Organization

YLD – Years Lived with Disability

YLL – Years of Life Lost

1 Introduction

1.1 Background

Musculoskeletal complaints are among the most common reasons for contact with primary health care in Norway (1). A population survey showed that 75 – 81 % of the Norwegian working population experience some sort of musculoskeletal complaints during a month. The prevalence of musculoskeletal complaints has been stable since the late 1990s. (2). Even though symptoms often are self-limiting, these conditions remain a considerable challenge to the public health. Two consecutive studies from Nord-Trøndelag (The HUNT studies) found that 51 % of the population had musculoskeletal complaints lasting three months or more during the past year (3). Moreover, the largest payments from the Social Security Services in Norway are attributable to musculoskeletal complaints; in 2019, musculoskeletal complaints accounted for 37.3 % of missed work days and 32. 7 % of sickness absence (4)

Back pain is one of the most common pain syndromes. Approximately 80 % experience back pain during a lifetime, and 50 % during a year (5). At the individual level, back pain can be very disabling. At the community level, back pain results in large economic costs. In fact, no other single diagnosis category causes larger social security benefit pay-outs (5). Expenses for diagnostics and treatment come in addition.

When assessing burden of disease, both fatal and non-fatal health loss must be taken into consideration. The Global Burden of Diseases, Injuries and Risk Factors Study (GBD) has defined the term Disability-Adjusted Life Years (DALYs), which is the sum of years of life lost (YLL) and years lived with disability (YLD), representing a summary measure of disease burden. Pain in the lower back and neck was the second most important cause of DALYs in Norway in 2016. The share of disease burden attributable to non-fatal health loss increased from 48 % in 2006 to 52 % in 2016. Low back pain was responsible for the largest proportion of YLD (6).

Among people suffering from axial back pain, there is only a small fraction of patients who will benefit from surgery. More than 80 % of low back pain is non-specific, which means that there is no specific treatment (7). According to Norwegian National Clinical Guidelines, surgery on patients with non-specific back pain is reserved for those who have had severe pain lasting one to two years, without relief of knowledge-based interdisciplinary treatment, and where degenerative changes are limited to one or two levels in the lumbar spine, considered to be the origin of the pain. There is weak evidence for the usefulness of surgery with fusion, disc prothesis or discectomy in this group (5).

However, the vast majority of patients undergoing surgery in the lumbar spine has both back pain and leg pain, and a more specific diagnosis, mainly lumbar spinal stenosis or lumbar disc herniation (8). In this group, there is good scientific evidence that surgery has a favourable effect on selected patients (5).

The etiology of lumbar spinal stenosis and lumbar disc herniation is multifactorial. Spondylosis plays an important role in the pathophysiology. Spondylosis constitutes a combination of joint hypertrophy, loss of intervertebral disc height, disc bulging, osteophyte formation and hypertrophy of the ligamentum flavum. This leads to a gradual narrowing of the spaces around the neurovascular structures of the spinal canal and its foramina, described as spinal stenosis (9). There are two types of lumbar spinal stenosis: Central stenosis causing anatomic narrowing of the spinal canal and lateral stenosis causing anatomic narrowing of the intervertebral nerve root foramen. The former leads to mechanical compression of the cauda equina and the latter leads to compression of one or more nerve roots, with subsequent impairment of the nerve root function. This usually causes radiating pain, numbness, tingling, and/or muscle weakness that corresponds to the specific nerve root(s), i.e. radiculopathy.

Depending on the location of the stenosis, patients with lumbar spinal stenosis may experience neurogenic claudication and/or radicular pain. Neurogenic claudication is discomfort in the low back which radiates to the buttocks and frequently to the thighs and lower legs. It is exacerbated by lumbar extension and alleviated by lumbar flexion (10). The natural course of lumbar spinal stenosis is largely unknown, but research suggests that in most patients the condition remains unchanged for years (9).

The degenerative process of spondylosis starts in the intervertebral disc and may cause a disc herniation. This occurs when the nucleus pulposus penetrates a degenerated annulus fibrosus and protrudes into the spinal canal or intervertebral foramen. One or more nerve roots may be affected mechanically, depending on the specific location and size of the disc herniation.

In patients with radiculopathy due to spinal stenosis or lumbar disc herniation, a prerequisite for having surgery is a close correspondence between clinical features and radiological findings. In patients with lumbar disc herniation, there is a recommended observation period of six to eight weeks after onset of symptoms before surgery is considered because most patients experience symptom relief spontaneously. Patients with persistent symptoms are at risk for chronic back pain and/or radiculopathy. The consequences are disability, reduced health-related quality of life (HRQoL) and reduced working capacity (11).

The use of spinal surgery has increased considerably the last couple of decades. The annual surgical rate in Norway increased from 77.8 per 100 000 in 1999 to 119.9 per 100 000 in 2013. During the same period, repeated operations accounted for 14.8 % of lumbar spine surgery (12). From 2014 to 2018 the surgical rates have remained stable with an average of 120 operations per 100 000 per year (13). In 2019, a total of 7 707 operations for degenerative disorders of the lumbar spine were performed in Norway. The outcome of surgical interventions is variable. A Norwegian study has shown an association between increasing treatment rates and lower health gains (14). The key to a favourable result is to ensure correct indications for surgery (11), i.e. careful patient selection based on knowledge about predictors for favourable and unfavourable outcomes.

Repeated operations have been linked to inferior outcomes compared to primary operations in several small, mainly single centre studies. A retrospective study conducted at St. Olavs

Hospital in 1988-1989 showed worse outcome in previously operated patients compared to patients who only underwent primary operations for lumbar disc herniation and unilateral sciatica (15). There are also a few larger international studies aimed at investigating the effect of repeated operations on the outcome of surgery, based on data from the EUROSPINE Spine Tango registry. Sobottke et al. found that fewer previous surgeries was a significant predictor increasing the likelihood of improvement in quality of life and improvement in back and leg pain among patients operated for lumbar spinal stenosis (16). Zehnder et al. analysed 4 940 patients with degenerative disorders of the lumbar spine, and found a dose-response effect for previous surgery: The risk of worse outcome 12 months after surgery increased modestly with the number of previous operations (17). The Spine Tango registry includes patients operated in different countries. The reporting to the registry is voluntary, implying that both completeness and follow up rates are low. Thus, Spine Tango does not have access to population-based data, contrary to the Norwegian Registry for Spine Surgery (NORspine). The risk of introducing selection bias is therefore much higher in studies based on data from Spine Tango. Furthermore, the proportion of patients being operated with lumbar fusion surgery is lower in the Nordic countries compared to the rest of Europe. New knowledge about the impact of repeated operations on surgical outcome is highly warranted by both patients and professionals within the field (17).

1.2 Objectives

The aim of the study was to examine whether, and if so, to which extent the number of previous operations is associated with the outcome after surgery for lumbar spinal stenosis or lumbar disc herniation.

2 Methods

2.1 Study design

This is a prospective population-based cohort study based on data from the NORspine registry. Patients were allocated into groups based on the number of previous operations. This enabled comparison of baseline scores and outcome measures after first time operation and one or more previous operations, respectively.

2.2 Setting

NORspine was established in 2006 to provide an overview of treatment outcomes and to improve the quality of surgery for degenerative disorders of the spine, conducted in public and private Norwegian hospitals (specialists` health care). The surgical procedures are performed by orthopaedic surgeons or neurosurgeons, or residents in training in one of these specialties.

In 2017, the national coverage of the NORspine was 100 % at the institutional level and 70.2 % at the individual level for lumbar spine surgery. Several scientific articles published by NORspine in international medical journals show that the response rate at one year follow up is 70-80 % for patients operated for lumbar spinal stenosis and 65-70 % for patients operated for lumbar disc herniation. The completeness of gathered data is high (96.6 % for the main outcome measure Oswestry Disability Index (ODI)) (8).

The data in the registry are mainly based on Patient Reported Outcome Measures (PROMs) and the information is gathered from questionnaires filled out by the patients before, 3 and 12 months after surgery. In addition, the surgeon responsible fills out a form containing information about diagnosis, comorbidity and treatment (8). At follow-up, the questionnaires are distributed by, and return to, the central NORspine registry unit, without involvement of the treating hospitals.

2.3 Participants

All patients being operated for degenerative disorders in the lumbar spine in Norway are eligible for registration in NORspine. Exceptions are patients younger than 16 years of age, those with cognitive failure, severe mental disorders, substance abuse, and patients operated for fractures, primary infections or tumors in the spine (8).

All cases operated for lumbar spinal stenosis or lumbar disc herniation and registered in NORspine from 01.01.07 to 31.12.18 were eligible for inclusion in this study. The operations were decompression for disc herniation (discectomy) and decompression with or without fusion for lumbar spinal stenosis. NORspine registers reoperations within three months as a treatment for complications and does not register such events as a separate operation. Operations conducted three months or more apart were considered separate treatments and registered as such.

The following were excluded:

- Cases operated for other main conditions in the lumbar spine.
- Cases with missing outcome data at 12 months after surgery.
- Cases with missing data on whether they were previously operated.

2.4 Variables

The main outcome measure is pain related disability assessed with the ODI. Secondary outcome measures are back pain and leg pain assessed by the Numeric Rating Scale (NRS), health assessed by EuroQoL 5 Dimensions (EQ-5D-3L), the Global Perceived Effect Scale (GPE) score, occurrence of perioperative complications and wound infections, and working capability.

2.5 Data sources

All data were retrieved from NORspine.

Outcome measures

PROMs are widely used to assess the outcome of treatment. ODI is the most commonly recommended condition specific PROM for spinal disorders (18). The questionnaire comprises 10 sections with questions concerning pain related disability in 10 activities of daily living, i.e. personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and travelling. Within each section, the patient is asked to check the box for the statement which best applies to him/her. The score from each section ranging from 0-5 is summed, and the total score is divided by the total possible score. Multiplied by 100, this yields a percentage score ranging from 0 to 100, where 0 indicates no disability and 100 indicates most severe disability (19). Two discussion groups have concluded that the ODI is confined to disability according to the World Health Organization (WHO) definition, which is widely accepted. ODI has proven to be a versatile and robust questionnaire applicable for both patients with severe and less severe symptoms. Several studies have confirmed the validity and reliability of the questionnaire (19). ODI results are presented as the proportion of cases who reached a Patient Acceptable Symptom State (PASS), ODI raw score and ODI change score.

Van Hooff et al. states that there are two ways to conceptualize success: relevant change or improvement, and achievement of a patient acceptable symptom state (PASS). The limitations of using change scores to assess success is, among other things, that change does not indicate whether a “normal” or “healthy” symptom state has been reached. Therefore, values beyond which patients consider themselves well or consider their health states to be acceptable, has been defined on commonly used PROMs. Van Hooff et al. found that an ODI raw score ≤ 22 was the most accurate cut off for defining PASS in patients operated for degenerative disorders in the lumbar spine (20).

NRS is widely used for pain intensity assessment and has shown good psychometric properties in patients with degenerative disorders of the spine. The scale is unidimensional, ranging from 0 to 10, with 0 representing no and 10 representing worst conceivable pain. The NRS is a segmented numeric version of the Visual Analogue Scale (VAS), which makes it very versatile because it can be administered both verbally and in writing (21). NRS results are presented as NRS raw score and NRS change score for back pain and leg pain.

EQ-5D is a generic measure of health related quality of life, developed by the EuroQoL Group (22). Unlike ODI, which is condition specific, EQ-5D is applicable across various health conditions and interventions. It has been widely used in clinical trials and population studies the last 25 years. The EQ-5D has proven to be valid, reliable and responsive across numerous conditions and populations, including patients operated for degenerative disorders of the spine (22, 23). The questionnaire comprises five dimensions, each describing a different aspect of health, with questions concerning mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In EQ-5D-3L, which is the version used in this study, the patient is presented with three response levels of severity: no, some and severe problems. The patient is then asked to select the most appropriate response level in each of the five dimensions. Depending on the response level in each of the dimensions, a five-digit code is derived. A summary index value for health status can be derived from the code by using a value set which weights the health state descriptions according to the preferences of the general population of a country/region. In this way, a total of 243 possible health states are defined. Health state index scores range from -0.594 to 1, where 1 corresponds to perfect health and 0 to death. Negative values are considered to be worse than death (22). EQ-5D-3L results are presented as EQ-5D index score and change score.

Patient-rated benefit of the operation was assessed by using GPE. The GPE is a balanced 7-point Likert scale in which the patient is asked to answer the question: “To what degree did you benefit from the operation?”. The answer options are “completely recovered”, “much improved”, slightly improved”, “unchanged”, “slightly worsened”, “much worsened” and “worse than ever”. A study has found that the test-retest reliability of GPE is excellent in people with musculoskeletal disorders (24).

Occurrence of perioperative complications including dural tear was registered by the surgeons shortly after the operation. Occurrence of wound infections was reported by the participants in the questionnaire at 3 months follow-up. To assess working capability, we calculated the proportion of cases who received sickness or disability benefits preoperatively who still received sickness- or disability benefits 12 months postoperatively. Use of sickness- or disability benefits was repeatedly reported by the participants in all questionnaires completed.

Possible prognostic factors

In addition to the abovementioned primary and secondary outcome measures and the exposition variable (number of previous operations), we analysed the following known sociodemographic, anthropometric and medical predictors (25-30): age, gender, smoking status, level of education, marital status, native language, body mass index (BMI), working status, whether the participant was a disability pension applicant, duration of back pain, duration of radiating pain, use of painkillers, level of operation in participants previously operated, comorbidity, American Society of Anaesthesiologists' (ASA) classification and anxiety/depression reported by the patient (EQ 5D, 5th item). Among those operated for lumbar spinal stenosis, a variable stating whether the operation included lumbar fusion or not was also analysed.

2.6 Bias

Comparative analysis of baseline characteristics of respondents and those lost to 12 months follow-up was done to identify possible selection bias. Confounding bias was assessed as described below.

2.7 Statististical analysis

Descriptive data are presented as means with 95 % confidence intervals (CI`s) for continuous variables and counts with percentages for proportions. Differences between samples were examined with one-way Analysis of Variance (ANOVA) for continuous variables and Pearson`s Chi-squared test for categorical variables. The level of significance was set to 0.05.

To assess whether the exposition variable (number of previous operations) was independently associated with the primary outcome (dependent variable: reaching PASS (no or yes)), a binary logistic regression analysis was conducted. To identify possible confounders, a range of known prognostic factors from table 1 were checked in bivariate analyses with the exposition variable. The continuous variables were: BMI and baseline PROM scores; i.e. the ODI (0-100), EQ-5D-3L (-0.594 - 1) and NRS for leg and back pain (0-10). Among the categorical variables, some were dichotomized to improve data to model fit and the interpretability of the results. The following categorical variables were included: age (5 year categories:15-19, 20-24 etc.), female gender (yes or no), smoking (yes or no), level of education: college or university education (yes or no), marital status: living alone (yes or no), native language: Norwegian (yes or no), working status: sickness or disability benefit recipient (full or partial sick leave or work assessment allowance or disability pension: yes or no), applied for disability pension: have applied or planning to apply (yes or no), duration of back pain: more than 12 months (yes or no), duration of radiating pain: more than 12 months (yes or no), use of painkillers (yes or no), any comorbidity (yes or no), ASA classification: ASA score > 2 (yes or no) and anxiety and/or depression: moderate to severe problems (yes or no). Among those operated for lumbar spinal stenosis, the use of lumbar fusion surgery (yes or no) was also evaluated as a possible confounder. Confounding was defined to be present if a covariate altered the strength of the association between the exposition variable and outcome by more than 10 percent, meaning that the Beta of the exposition variable was changed by ± 10 %, in bivariate analyses. Finally, the exposition would be entered as a categorical variable (no (reference), one, two, three and four or more previous operations) along with any covariates found to be significant confounders. To assess robustness, we included all possible confounders and the exposition variable in a separate multivariate analysis (backward logistic regression), as sensitivity analysis.

2.8 Ethical considerations

The project is defined as quality improvement and approved by the Data Protection Officer (DPO) at the University Hospital of North Norway (UNN) (case processing number: 02388). According to the resolution passed by DPO, data from NORspine was handed out without retrievable personal identifiers and age was stratified into 5-year categories to avoid indirect identification. Mean age presented in the baseline characteristics tables was calculated by the registry. All participants have signed a written consent form, granting the registry permission to collect, retain and use their information for research and quality improvement purposes.

3 Results

3.1 Participants

The flowchart in figure 1 defines the study population. In total, 37 698 cases of operations for lumbar spinal stenosis or lumbar disc herniation were registered in NORspine during the study period. We excluded 10 975 (29.1 %), most because of loss to follow-up at 12 months (n = 10 717 (28.4 %)).

We included 26 723 (70.9 %) cases in the study. 20 412 (76.4 %) cases had no previous operation, 4 107 (15.4 %) one previous operation, 1 137 (4.3 %) two previous operations, 336 (1.3 %) three previous operations and 128 (0.4 %) four or more previous operations.

3.2 Descriptive data

Table 1 shows baseline characteristics for the included cases and for cases excluded because of missing outcome data at 12 months (lost to follow-up). The cases lost to follow up were younger, healthier, and more likely to be male, smoke and to live alone. The difference in the proportion previously operated and the distribution of the number of previous operations between the groups were small.

Table 2 shows the baseline characteristics for the 26 723 included cases. The baseline ODI score increased stepwise from mean 42.1 (95 % CI 41.8 – 42.4) in cases with no previous operation to 48.6 (95 % CI 46.5 – 50.7) in cases with three previous operations. The proportion of cases who reported that they were working prior to the operation decreased from 19.1 % among cases with no previous operations to 8.9 % among those with three previous operations. In concordance, the proportion receiving disability pension increased. Also, the proportion reporting comorbidity increased with the number of previous operations.

Table 3 shows the distribution of operations for lumbar disc herniation and lumbar spinal stenosis. In the group operated for lumbar spinal stenosis, the proportion of cases operated with fusion surgery increased from 12.2 % in cases with no previous operation to 42.0 % in cases with four or more previous operations.

3.3 Main results

Figure 2 shows the proportion of cases with 95 % CI`s who reached PASS 12 months after the operation, stratified by the number of previous operations. The proportion decreased stepwise and significantly ($p < 0.001$) from 66.0 % in the group with no previous operations to 22.0 % in the group with four or more previous operations. The differences between groups were statistically significant ($p < 0.001$) at each step from no to three previous operations, but not ($p = 0.062$) for the last step from three to four or more previous operations.

Figure 3 shows mean ODI raw score and mean ODI change score with 95 % CI's 12 months after surgery, stratified by the number of previous operations. The mean ODI raw score at 12 months increased successively and significantly ($p < 0.001$) with the number of operations, from 18.6 (95 % CI 18.4 – 18.8) for cases with no previous operation to 36.4 (95 % CI 33.2 – 39.5) for cases with four or more previous operations, demonstrating that the level of disability 12 months after surgery increased with the number of operations. The between groups differences were statistically significant ($p < 0.001$) at each step from no to three previous operations, but not ($p = 0.234$) for the last step from three to four or more previous operations. There was a mean increase in mean ODI raw score at 12 months by 4.5 points for each additional previous operation. The mean ODI change score decreased significantly ($p < 0.001$), from 23.5 (95 CI 23.3 – 23.8) for cases with no previous operation to 13.1 (95 % CI 9.8 – 16.2) for cases with four or more previous operations, indicating that with increasing number of previous operations, there was less improvement in ODI from baseline to 12 months after surgery. There were statistically significant differences between cases with no and one ($p < 0.001$), and two and three previous operations ($p = 0.009$), but not between cases with one and two ($p = 0.704$), and three and four or more previous operations ($p = 0.263$).

Figure 4-9 shows the secondary outcome measures EQ-5D, NRS back pain, NRS leg pain, peroperative complications, wound infections and working capability. The secondary outcome measures all exhibited increasingly inferior results with increasing number of previous operations. The trends were statistically significant ($p < 0.001$) for all the measures.

Table 4 shows the results from the secondary outcome measure GPE. The proportion of cases reporting to be completely recovered or much improved decreased with the number of previous operations. The proportion of cases reporting to be slightly improved, unchanged or slightly worsened increased with the number of previous operations. The proportion of cases reporting to be much worsened or worse than ever was small across all groups, but increased from 1.1 % in cases with no, to 2.4 % in cases with four or more previous operations.

Binary logistic regression analysis of predictors for outcome

Table 5 shows the results from the bivariate analysis. None of the tested variables changed the beta value with 10 % or more. Thus, we did not identify confounders. Fusion surgery, among cases operated for lumbar spinal stenosis, was the covariate which changed the Beta value of the exposition variable most. Table 6 shows the results from the univariate analysis. There was a dose-response relationship between number of previous operations and the odds for not reaching PASS, as the odds increased from 2.1 (95 % CI 1.9 – 2.2) in cases with one, 2.6 (95 % CI 2.3 – 3.0) in cases with two, 4.4 (95 % CI 3.4 – 5.5) in cases with three and 6.9 (4.5 – 10.5) in cases with four or more previous operations. The increase was statistically significant ($p < 0.001$) from the reference (no previous operation) for all categories. The 95 % CI`s did not overlap between the steps except for the last step from three to four or more previous operations.

The sensitivity analysis showed that the increasing number of previous operations, adjusted for the other covariates (shown in table 5), remained an independent predictor (OR 1.6 (95 % CI 1.5 - 1.7)) for not reaching PASS.

4 Discussion

4.1 Key results

The main finding in this study is a dose-response relationship between the number of previous operations and the proportion of cases reaching PASS at 12 months follow-up after surgery for lumbar spinal stenosis or lumbar disc herniation. The proportion achieving PASS decreased stepwise from 66 % in cases with no previous operation to only 22 % in cases with four or more previous operations. The odds for not reaching PASS was doubled in cases with one previous operation, nearly tripled in cases with two previous operations and four to nearly seven times increased in cases with three or more previous operations. The ODI raw score and change score, the GPE and all the other secondary outcome measures showed trends with increasingly inferior outcomes with increasing number of previous operations.

4.2 Interpretation

The main findings are supported by the secondary outcome measures. The association between previous operations and inferior outcomes are in concordance with previous studies (15, 16, 31). Zehnder et al. published the only previous study aimed at investigating the possible dose-response effect of the number of previous operations (17). They used data from the Spine Tango-registry, and reported less improvement in the Core Outcome Measurement Index (COMI) by 0.4 points for each additional operation. The authors found that this trend was statistically significant, but they did not consider it large, as the cut-off for Minimally Clinically Important Change (MCIC) is 2-3 points (32). In the present study, we observed a mean stepwise increase in the ODI raw score at 12 months by 4.5 ODI points for each additional operation. This change is more than twice as large as the effect size found by Zehnder et al., as the MCIC cut-off for ODI is considered to be approximately 10 points (33).

Importantly, the MCIC is not recommended to be used for comparisons of mean outcome scores between groups, since these thresholds are developed to determine clinically relevant outcome at the individual level. Therefore, we compared the proportion of patients reaching a validated threshold for the PASS in each subgroup (number of previous operations). This strategy allows for comparison of effect sizes across groups and has been highly recommended (34-37).

In the analyses of the dose-response effects, there was a consistent lack of statistically significant differences between the groups with three, and four or more previous operations, despite a nearly consistent trend towards worse results also at this step. This is most likely a power-problem (type 2 error), given that the number of cases with four or more previous operations was low (n = 128), as indicated by the wide CI`s. Accordingly, we consider it likely that the dose-response effect is present from one to four or more previous operations. Overall, the effect sizes indicate an almost linear trend.

None of covariates evaluated met the predefined criteria for confounding. Importantly, this was also the case for the baseline ODI raw score, even though its mean score increased with the number of previous operations. The variable which changed the beta value of the exposition variable the most, was additional fusion surgery among cases operated with decompression for lumbar spinal stenosis. However, its modifying effect was weak, only reducing the odds ratio for an unfavourable outcome from 1.74 to 1.66. Consequently, fusion surgery does not seem to compensate much for the negative impact of previous operations.

When specifically quantified, the influence of the number of previous operations on the outcome after lumbar spine surgery is a convenient aid for both clinicians and patients. Therapeutic decisions concerning invasive procedures should be based on shared and informed decision-making. Surgeons and patients should acknowledge the increased risk of inferior outcomes linked to repeated operations, along with other known predictors when discussing possible risks and benefits of the treatment. Other causes of chronic axial back pain, e.g. neuropathic pain, should be thoroughly considered since many patients are unlikely to respond to repeated surgery. In settings with restrained resources, the results can also be applied in matters of prioritization, as health gains ensuing operation are higher in patients with fewer previous operations.

4.3 Generalisability

Strengths and Limitations

The large study population is a major strength which allowed us to allocate the participants into five groups based on the number of previous operations. NORspine is a population-based registry which registers data from all public and private hospitals in Norway, with relatively high individual-level coverage and high data completeness. This yields low risk for selection bias at inclusion and high external validity. The applicability of the results is high, as the data were retrieved from routine clinical practice at a large number of hospitals. All the PROMs are valid, reliable, and widely used.

Even though we consider the individual-level coverage sufficient, loss to follow up introduces a risk for selection bias in the reporting of outcomes. To address this, drop-out analysis was done. It showed no notable difference in pre-scores for the primary and secondary outcome measures, and the differences in the distribution of the number of previous operations were small. However, the cases lost to follow-up were younger, and the proportions of males, smokers, unmarried and less comorbid participants were higher. We consider these differences less important, as the effect of these factors on the outcome are likely to counterweigh each other. Additionally, in a previous study in which we interviewed non-respondents to the questionnaire by telephone, we found no statistically significant differences in outcomes between responders and non-respondents of the questionnaire after two years (38). This renders selection bias unlikely.

Some of the minor differences in outcomes may have been statistically significant by incident (type 1-error). The study may also be subject to unmeasured confounding. For instance, we had no exact information about the indications for the previous operations, only that they were performed for degenerative changes. This could imply a risk for overestimation of the effect of the number of previous operations on the outcome measures. Information about working status has not been verified against data from the Norwegian Welfare and Labour Administration (NAV). This could be a possible source of information bias.

Although valid and reliable, there are shortcomings of the PROMs used in this study. The disease specific ODI could fail to address issues that are important to patients. Furthermore, the different sections of the ODI are not preference-weighted. This suggests that all the 10 aspects of daily living are equally important in relation to disability, even though individuals may weight the importance of each item differently according to preferences. However, we also used the generic and preference-weighted EQ-5D, which revealed exactly similar trends as we found for the ODI. We used a GPE scale based on one question; "To what degree did you benefit from the operation?". An answer can reflect both preferences and expectations, and may be strongly influenced by the current health status at 12 months follow-up (24). The accuracy may also decrease as transition time increases (recall bias) (36). Some authors argue that the criteria for measurement of global effects should be defined more objectively. However, no such alternative scale exists. Therefore, we consider the GPE scale most suitable for assessing a global perceived effect (34). A limitation of the NRS is that it only evaluates one component of the pain experience, pain intensity, and therefore does not capture the complexity and idiosyncratic nature of the pain experience (21).

5 Conclusion

We found a dose-response relationship between increasing number of previous operations and inferior outcomes among patients operated for lumbar spinal stenosis or lumbar disc herniation. The odds for not reaching PASS was doubled in cases with one previous operation, nearly tripled in cases with two previous operations and four to nearly seven times increased in cases with three or more previous operations. This information should be taken into consideration, along with other known predictors for favourable and unfavourable outcomes, in the shared decision-making process prior to surgery.

6 Figure and table

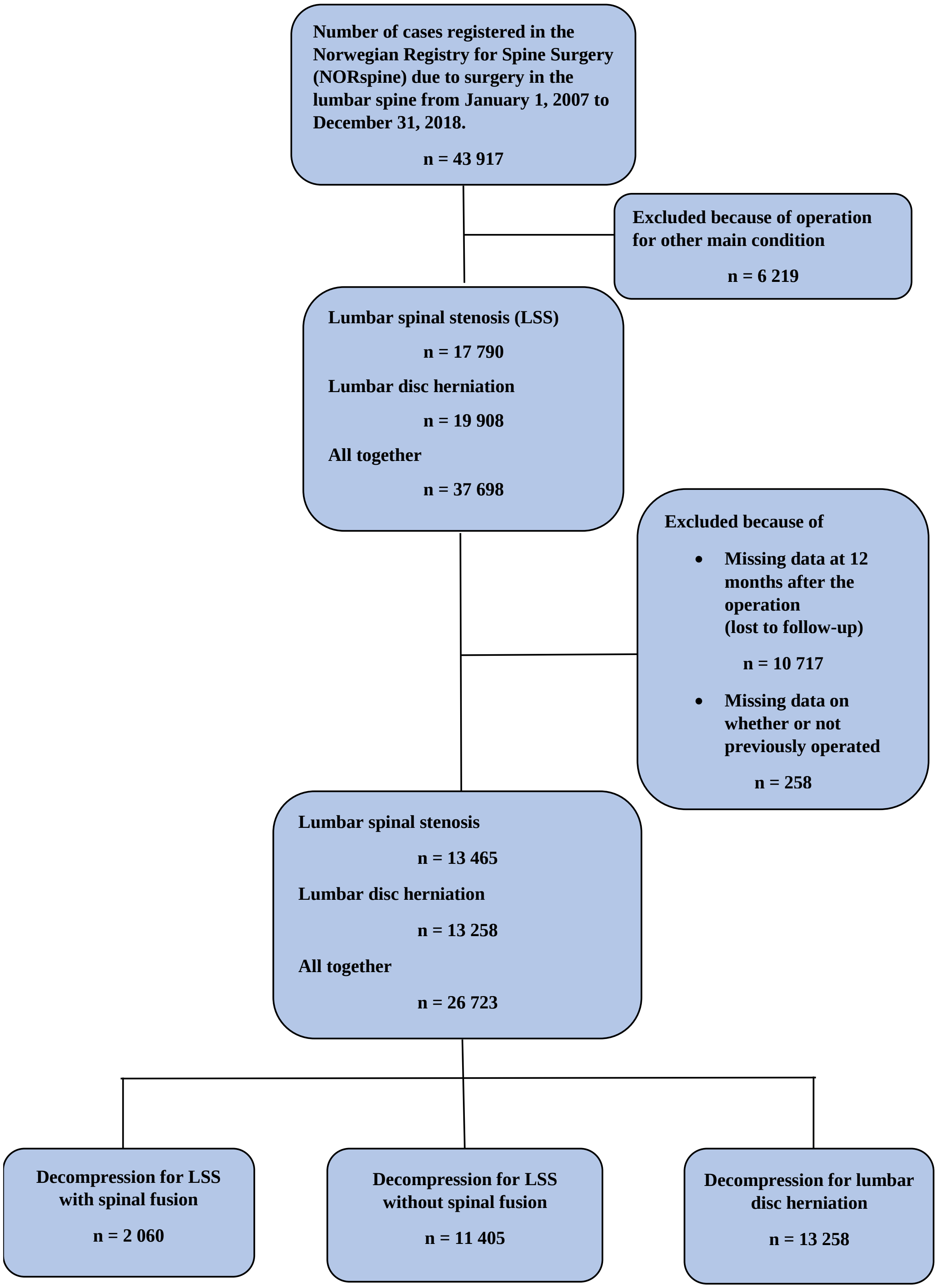

Figure 1- Flowchart showing the recruitment process to the study.

	Included cases n = 26 723	Cases excluded because of loss to follow-up n = 10 717
Age, mean (95 % Confidence Interval (CI)) Missing, n (%)	56.5 (56.3 – 56.7) 74 (0.3 %)	48.9 (48.6 – 49.2) 65 (0.6 %)
Gender, n (%)		
Male	14 047 (52.6 %)	6 040 (56.4 %)
Female	12 676 (47.4 %)	4 677 (43.6 %)
Missing	0	0
Smoking status, n (%)		
Smoker	5 624 (21.0 %)	3 350 (31.3 %)
Non-smoker	20 864 (78.1 %)	7 267 (67.8 %)
Missing	235 (0.9 %)	100 (0.9 %)
Level of education, n (%)		
Primary school or equivalent	5 302 (19.8 %)	2 053 (19.2 %)
High school	11 766 (44.0 %)	5 081 (47.4 %)
College/University	9 339 (34.9 %)	3 431 (32.0 %)
Missing	316 (1.2 %)	152 (1.4 %)
Marital status, n (%)		
Married	16 084 (60.2 %)	5 154 (48.1 %)
Cohabitant	4 068 (15.2 %)	2 319 (21.6 %)
Single	6 415 (24.0 %)	3 169 (29.6 %)
Missing	156 (0.6 %)	75 (0.7 %)
Native language, n (%)		
Norwegian	25 270 (94.6 %)	9 926 (92.6 %)
Sami	28 (0.1 %)	18 (0.2 %)
Other	1 324 (5.0 %)	734 (6.8 %)
Missing	101 (0.4 %)	39 (0.4 %)
Body Mass Index (BMI), mean (95 % CI) Missing	27.2 (27.1 – 27.2) 1 533 (5.7 %)	27.4 (27.3 – 27.5) 631 (5.9 %)
Working status, n (%)		
Working	4 820 (18.0 %)	2 018 (18.8 %)
Homemaker	408 (1.5 %)	140 (1.3 %)
Student	315 (1.2 %)	234 (2.2 %)
Pensioner	8 149 (30.5 %)	1 779 (16.6 %)
Unemployed	241 (0.9 %)	190 (1.8 %)
Sick leave (full or partial)	8 117 (30.5 %)	969 (31.4 %)
Work assessment allowance	972 (3.6 %)	595 (5.6 %)
Disability pension	2 993 (11.2 %)	1 236 (11.5 %)
Missing	708 (2.6 %)	342 (.21 %)
Applied for disability pension, n %		
Yes	554 (2.1 %)	254 (2.4 %)
No	20 122 (75.3 %)	8 358 (78.0 %)
Planning to apply	465 (1.7 %)	211 (2.0)
Already granted	3 197 (12.0 %)	1 206 (11.3 %)
Missing	2 385 (8.9 %)	688 (6.4 %)
Numeric Rating Scale (NRS) score for back pain, mean (95 % CI) Missing, n (%)	6.4 (6.3 – 6.4) 1 190 (4.1 %)	6.5 (6.4 – 6.5) 451 (4.2 %)
NRS score for leg pain, mean (95 % CI) Missing, n (%)	6.7 (6.7 – 6.8) 1 183 (4.4 %)	6.8 (6.8 – 6.9) 479 (4.5 %)
Oswestry Disability Index (ODI), mean (95 % CI) Missing, n (%)	42.9 (42.7 – 43.2) 126 (0,5 %)	44.5 (44.1 – 44.9) 73 (0.7 %)
EuroQoL 5 Dimensions (EQ-5D), mean (95 % CI) Missing, n (%)	0.32 (0.32 – 0.33) 1 501 (5.6 %)	0.28 (0.27 – 0.29) 654 (6.1 %)
Duration of back pain, n (%)		
No symptoms	702 (2.6 %)	220 (2.1 %)

Less than 3 months	2 566 (9.6 %)	1 053 (9.8 %)
3 – 12 months	8 167 (30.6 %)	3 542 (33.1 %)
12 – 24 months	4 478 (16.8 %)	1 775 (16.6 %)
More than 24 months	9 520 (35.6 %)	3 583 (33.4 %)
Missing	1 290 (4.8 %)	544 (5.1 %)
Duration of radiating pain, n (%)		
No symptoms	666 (2.5 %)	196 (1.8 %)
Less than 3 months	3 696 (13.8 %)	1 520 (14.2 %)
3 – 12 months	9 675 (36.2)	4 098 (38.2 %)
12 – 24 months	4 750 (17.8 %)	1 817 (17.0 %)
More than 24 months	6 342 (23.7 %)	2 418 (22.6 %)
Missing	1 594 (6.0 %)	668 (6.2 %)
Use of painkillers, n (%)		
Yes	2 2034 (82.5 %)	8 949 (83.5 %)
No	4 401 (16.5 %)	1 629 (15.2 %)
Missing	288 (1.1 %)	139 (1.3 %)
Previous operation, n (%)		
Yes, same level	3 522 (13.2 %)	1 751 (16.3 %)
Yes, different level	2 396 (9.0 %)	882 (8.2 %)
Yes, same and different level	393 (1.5 %)	171 (1.6 %)
No	2 0412 (76.4 %)	7 800 (72.8 %)
Missing	0 (0 %)	113 (1.1 %)
Number of previous operations, n (%)		
0	20 412 (76.4 %)	7 805 (72.8 %)
1	4 107 (15.4 %)	1 822 (17.0 %)
2	1 137 (4.3 %)	507 (4.7 %)
3	336 (1.3 %)	153 (1.4 %)
4-10	128 (0.4 %)	68 (0.6 %)
Missing	603 (2.3 %)	362 (3.4 %)
Any comorbidity, n (%)		
Yes	12 419 (46.5 %)	4 278 (39.9 %)
No	11 930 (44.6 %)	5 404 (50.4 %)
Missing	2 374 (8.9 %)	1 035 (9.7 %)
American Society of Anaesthesiologists` (ASA) classification, n (%)		
I	8 228 (30.8 %)	3 924 (36.6 %)
II	14 553 (54.4 %)	5 557 (51.9 %)
III	3 599 (13.5 %)	1 106 (10.3 %)
IV	58 (0.2 %)	14 (0.1 %)
Missing	285 (1.1 %)	116 (1.1 %)
Anxiety/depression, n (%)		
No	15 573 (58.3 %)	5 603 (52.3 %)
Moderate	9 608 (36.0 %)	4 240 (39.6 %)
Severe	790 (3.0 %)	530 (4.9 %)
Missing	752 (2.8 %)	344 (3.2 %)
Paresis, n (%)		
Yes	3 660 (13.7 %)	1 489 (13.9 %)
No	23 063 (86.3 %)	9 228 (86.1 %)
Missing	0	0

Table 1 - Baseline characteristics of included cases and cases lost to follow-up

	All included cases	No previous operation	One previous operation	Two previous operations	Three previous operations	Four or more previous operations
Age, mean (95 % Confidence Interval (CI)) Missing, n (%)	56.5 (56.3 – 56.7) 74 (0.3 %)	56.0 (55.7-56.2)	58.0 (57.6-58.5)	58.3 (57.5-59.2)	61.2 (59.9-62.6)	61.4 (59.2-63.6)
Gender, n (%)						
Male	14 047 (52.6 %)	10 577 (51.8 %)	2 250 (54.8 %)	625 (55.0 %)	191 (56.8 %)	67 (52.3 %)
Female	12 676 (47.4 %)	9 838 (48.2 %)	1 857 (45.2 %)	512 (45.0 %)	145 (43.2 %)	61 (47.7 %)
Missing	0					
Smoking status, n (%)						
Smoker	5 624 (21.0 %)	4 160 (20.4 %)	939 (22.9 %)	259 (22.8 %)	85 (25.3 %)	26 (20.3 %)
Non-smoker	2 0864 (78.1 %)	16 068 (78.7 %)	3 132 (76.3 %)	869 (76.4 %)	249 (74.1 %)	101 (78.9 %)
Missing	235 (0.9 %)					
Level of education, n (%)						
Primary school or equivalent	5 302 (19.8 %)	3 977 (19.5 %)	853 (20.8 %)	245 (21.5 %)	76 (22.6 %)	29 (22.7 %)
High school	11 766 (44.0 %)	8 908 (43.6 %)	1 851 (45.1 %)	529 (46.5 %)	145 (43.1 %)	55 (42.9 %)
College/University	9 339 (34.9 %)	7 284 (35.7 %)	1 356 (33.0 %)	356 (31.3 %)	110 (32.7 %)	39 (30.5 %)
Missing	316 (1.2 %)					
Marital status, n (%)						
Married	16 084 (60.2 %)	12 187 (59.7 %)	2551 (62.1 %)	704 (61.9 %)	210 (62.5 %)	75 (58.6 %)
Cohabitant	4 068 (15.2 %)	3 127 (15.3 %)	596 (14.5 %)	186 (16.4 %)	41 (12.2 %)	17 (13.3 %)
Single	6 415 (24.0 %)	4 970 (24.3 %)	937 (22.8 %)	245 (21.5 %)	84 (25.0 %)	36 (28.1 %)
Missing	156 (0.6 %)					
Native language, n (%)						
Norwegian	25 270 (94.6 %)	19 241 (94.3 %)	3 911 (95.2 %)	1 095 (96.3 %)	321 (95.5 %)	126 (98.4 %)
Sami	28 (0.1 %)	24 (0.1 %)	4 (0.1 %)	0	0	0
Other	1 324 (5.0 %)	1 065 (5.2 %)	181 (4.4 %)	37 (3.3 %)	14 (4.2 %)	2 (1.6 %)
Missing	101 (0.4 %)					
Body Mass Index (BMI), mean (95 % CI) Missing	27.2 (27.1 – 27.2) 1533 (5.7 %)	27.1 (27.0-27.1)	27.5 (27.4-27.6)	27.7 (27.4-28.0)	27.4 (26.9-27.9)	27.6 (26.7-28.5)
Working status, n (%)						
Working	4 820 (18.0 %)	3 892 (19.1 %)	646 (15.7 %)	137 (12.0 %)	30 (8.9 %)	19 (14.8 %)
Homemaker	408 (1.5 %)	312 (1.5 %)	65 (1.6 %)	19 (1.7 %)	4 (1.2 %)	1 (0.8 %)
Student	315 (1.2 %)	280 (1.4 %)	24 (0.6 %)	6 (0.5 %)	1 (0.3 %)	0
Pensioner	8 149 (30.5 %)	6 164 (30.2 %)	1 295 (31.5 %)	366 (32.2 %)	113 (33.6 %)	39 (30.5 %)

Unemployed	241 (0.9 %)	181 (0.9 %)	43 (1.0 %)	11 (1.0 %)	2 (0.6 %)	1 (0.8 %)
Sick leave (full or partial)	8 117 (30.5 %)	6 453 (31.6 %)	1 128 (27.5 %)	283 (24.9 %)	56 (16.7 %)	12 (9.3 %)
Work assessment allowance	972 (3.6 %)	618 (3.0 %)	228 (5.6 %)	76 (6.7 %)	25 (7.4 %)	7 (5.5 %)
Disability pension	2 993 (11.2 %)	1 973 (9.7 %)	562 (13.7 %)	225 (19.8 %)	96 (28.6 %	47 (36.7 %)
Missing	708 (2.6 %)					
Applied for disability pension, n %						
Yes	554 (2.1 %)	378 (1.9 %)	114 (2.8 %)	27 (2.4 %)	16 (4.8 %)	7 (5.5 %)
No	20 122 (75.3 %)	15 878 (77.8 %)	2 886 (70.0 %)	719 (63.2 %)	177 (52.7 %)	49 (38.3 %)
Planning to apply	465 (1.7 %)	312 (1.5 %)	101 (2.5 %)	29 (2.6 %)	6 (1.8 %)	4 (3.1 %)
Already granted	3 197 (12.0 %)	2 117 (10.4 %)	590 (14.4 %)	239 (21.0 %)	99 (29.5 %)	51 (39.8 %)
Missing	2 385 (8.9 %)					
Numeric Rating Scale (NRS) score for back pain, mean (95 % CI)	6.4 (6.3 – 6.4)	6.3 (6.2-6.3)	6.60 (6.5-67)	7.0 (6.9-7.2)	7.1 (6.9-7.4)	7.2 (6.7-7.6)
Missing, n (%)	1 190 (4.1 %)					
NRS score for leg pain, mean (95 % CI)	6.7 (6.7 – 6.7)	6.7 (6.6-6.7)	6.9 (6.8-7.0)	7.0 (6.9-7.2)	7.2 (6.9-7.4)	7.1 (6.7-7.5)
Missing, n (%)	1 183 (4.4 %)					
Oswestry Disability Index (ODI), mean (95 % CI)	42.9 (42.7 – 43.2)	42.1 (41.8-42.4)	44.7 (44.1-45.3)	46.9 (45.8-48.0)	48.6 (46.5-50.7)	47.8 (44.6-50.9)
Missing, n (%)	126 (0.5 %)					
EuroQoL 5 Dimensions (Eq5D), mean (95 % CI)	0.32 (0.32 – 0.33)	0.34 (0.33-0.34)	0.29 (0.28-0.30)	0.25 (0.23-0.28)	0.20 (0.16-0.24)	0.22 (0.16-0.28)
Missing, n (%)	1501 (5.6 %)					
Duration of back pain, n (%)						
No symptoms	702 (2.6 %)	571 (2.8 %)	93 (2.3 %)	23 (2.0 %)	7 (2.1 %)	1 (0.8 %)
Less than 3 months	2 566 (9.6 %)	1 986 (9.7 %)	392 (9.5 %)	128 (11.3 %)	20 (6.0 %)	10 (7.8 %)
3 – 12 months	8 167 (30.6 %)	6 276 (30.7 %)	1 262 (30.7 %)	394 (34.7 %)	76 (22.6 %)	29 (22.7 %)
12 – 24 months	4 478 (16.8 %)	3 337 (17.5 %)	759 (18.5 %)	213 (18.7 %)	60 (17.9 %)	23 (18.0 %)
More than 24 months	9 520 (35.6 %)	7 277 (35.7 %)	1 402 (34.1 %)	324 (28.5 %)	154 (45.8 %)	54 (42.2 %)
Missing	1 290 (4.8 %)					
Duration of radiating pain, n (%)						
No symptoms	666 (2.5 %)	498 (2.4 %)	120 (2.9 %)	26 (2.3 %)	8 (2.4 %)	3 (2.3 %)
Less than 3 months	3 696 (13.8 %)	2 902 (14.2 %)	530 (12.9 %)	128 (11.3 %)	34 (10.1 %)	10 (7.8 %)
3 – 12 months	9 675 (36.2)	7 541 (36.9 %)	1 415 (34.5 %)	394 (34.7 %)	88 (26.2 %)	29 (22.7 %)
12 – 24 months	4 750 (17.8 %)	3 569 (17.5 %)	775 (18.9 %)	213 (18.7 %)	70 (20.8 %)	23 (18.0 %)
More than 24 months	6 342 (23.7 %)	4 677 (22.9 %)	1 033 (25.2 %)	324 (28.5 %)	108 (32.1 %)	54 (42.2 %)
Missing	1 594 (6.0 %)					
Use of painkillers, n (%)						
Yes	22 034 (82.5 %)	1 6561 (81.1 %)	3 511 (85.5 %)	1 017 (89.4 %)	308 (91.7 %)	117 (91.4 %)

No Missing	4 401 (16.5 %) 288 (1.1 %)	3 621 (17.7 %)	556 (13.5 %)	114 (10.0 %)	27 (8.0 %)	11 (8.6 %)
Previous operation, n (%)						
Yes, same level	3 522 (13.2 %)	0	2 361 (57.5 %)	601 (52.9 %)	161 (47.9 %)	50 (39.1 %)
Yes, different level	2 396 (9.0 %)	0	1 625 (39.6 %)	373 (32.8 %)	114 (33.9 %)	47 (36.7 %)
Yes, same and different level	393 (1.5 %)	0	121 (2.9 %)	163 (14.3 %)	61 (18.2 %)	31 (24.2 %)
No	20 412 (76.4 %)	20 412	0	0	0	0
Missing	0 (0 %)					
Number of previous operations, n (%)						
0	20 412 (76.4 %)	20 412 (100 %)				
1	4 107 (15.4 %)		4 107 (100 %)			
2	1 137 (4.3 %)			1 137 (100 %)		
3	336 (1.3 %)				336 (100 %)	
4-9	128 (0.4 %)					128 (100 %)
Missing	603 (2.3 %)					
Any comorbidity, n (%)						
Yes	12 419 (46.5 %)	9 138 (44.8 %)	2 119 (51.6 %)	626 (55.1 %)	204 (60.7 %)	90 (70.3 %)
No	11 930 (44.6 %)	9 539 (46.7 %)	1 627 (39.6 %)	402 (35.4 %)	103 (30.7 %)	34 (26.6 %)
Missing	2 374 (8.9 %)					
American Society of Anaesthesiologists` (ASA) classification, n (%)						
I	8 228 (30.8 %)	6 717 (32.9 %)	1 045 (25.4 %)	233 (20.7 %)	46 (13.7 %)	10 (7.8 %)
II	14 553 (54. 4 %)	10 843 (53.1 %)	2 386 (58.1 %)	701 (61.7 %)	205 (61.0 %)	78 (60.9 %)
III	3 599 (13.5 %)	2 584 (12.7 %)	626 (15.2 %)	192 (16.9 %)	79 (23.9 %)	39 (30.5 %)
IV	58 (0.2 %)	42 (0.2 %)	10 (0.2 %)	2 (0.2 %)	1 (0.3 %)	0
Missing	285 (1.1 %)					
Anxiety/depression, n (%)						
No	15 573 (58.3 %)	12 023 (58.9 %)	2 308 (56.2 %)	647 (56.9 %)	182 (54.2 %)	73 (57.0 %)
Moderate	9 608 (36.0 %)	7 224 (35.4 %)	1 540 (37.5 %)	433 (38.1 %)	134 (39.9 %)	49 (38.3 %)
Severe	790 (3.0 %)	575 (2.8 %)	146 (3.6 %)	36 (3.2 %)	13 (3.9 %)	2 (1.6 %)
Missing	752 (2.8 %)					
Paresis, n (%)						
Yes	3 660 (13.7 %)	2 783 (13.6 %)	556 (13.5 %)	167 (14.7 %)	48 (14.3 %)	16 (12.5 %)
No	23 063 (86.3 %)	17 629 (86.4 %)	3 551 (86.5 %)	970 (85.3 %)	288 (85.7 %)	112 (87.5 %)
Missing	0					

Table 2 - Baseline characteristics for all included patients, stratified by the number of previous operations.

Operation	All included cases	No previous operations	One previous operation	Two previous operations	Three previous operations	Four or more previous operations
Lumbar disc herniation						
Microdiscectomy	12 199 (92.0 %)	9 632 (92.1 %)	1 751 (92.1 %)	424 (93.6 %)	104 (89.7 %)	24 (85.7 %)
Open decompression	1 059 (8.0 %)	822 (7.9 %)	150 (7.9 %)	29 (6.4 %)	12 (10.3 %)	4 (14.3 %)
Total	13 258 (100 %)	10 454 (100 %)	1 901 (100 %)	453 (100 %)	116 (100 %)	28 (100 %)
Lumbar spinal stenosis						
Midline preserving decompression	9 559 (71.0 %)	7 450 (74.8 %)	1 365 (61.9 %)	382 (55.8 %)	113 (51.4 %)	46 (46.0 %)
Laminectomy	1 846 (13.7 %)	1 296 (13.0 %)	361 (16.4 %)	100 (14.6 %)	30 (13.6 %)	12 (12.0 %)
Fusion	2 060 (15.3 %)	1 212 (12.2 %)	480 (21.8 %)	202 (29.5 %)	77 (35.0 %)	42 (42.0 %)
Posterior Lumbar Fusion	1 206 (58.5 %)	737 (60.8 %)	264 (55.0 %)	102 (50.4 %)	39 (50.6 %)	30 (71.4 %)
Posterior Lumbar Interbody Fusion	79 (3.8 %)	51 (4.2 %)	16 (3.3 %)	6 (3.0 %)	3 (3.9 %)	1 (2.4%)
Transforaminal Lumbar Interbody Fusion	760 (36.9 %)	418 (34.5 %)	196 (40.8 %)	93 (46.0 %)	33 (42.9 %)	9 (21.4 %)
Anterior Lumbar Interbody Fusion	7 (0.3 %)	4 (0.3 %)	1 (0.2 %)	0 (0.0 %)	1 (1.3 %)	1 (2.4 %)
eXtreme Lateral Interbody Fusion	3 (0.1 %)	0 (0.0 %)	1 (0.2 %)	0 (0.0 %)	1 (1.3 %)	1 (2.4 %)
Undefined fusion	5 (0.2 %)	2 (0.2 %)	2 (0.4 %)	1 (0.5 %)	0 (0.0 %)	0 (0.0 %)
Total	13 465 (100 %)	9 958 (100 %)	2 206 (100 %)	684 (100 %)	220 (100 %)	100 (100 %)

Table 3 – Distribution of the operations for all included cases, stratified by the number of previous operations.

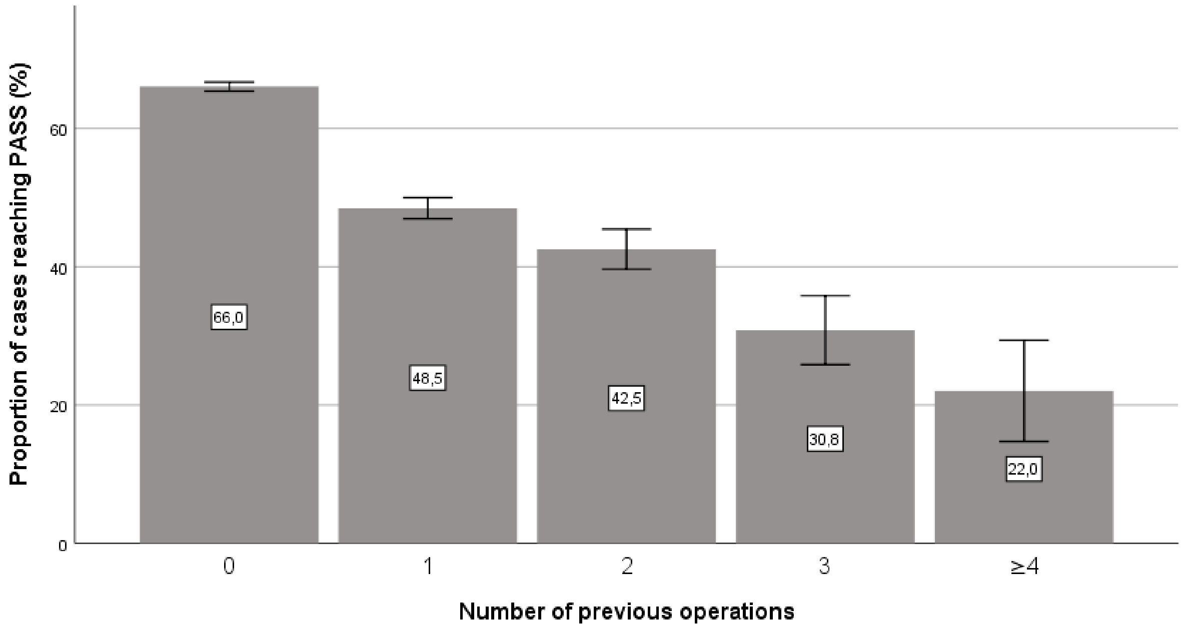

Figure 2 - Proportion of cases reaching a Patient Acceptable Symptom State (ODI raw score ≤ 22) at 12 months follow-up, stratified by the number of previous operations. Error bars represent 95 % CI`s.

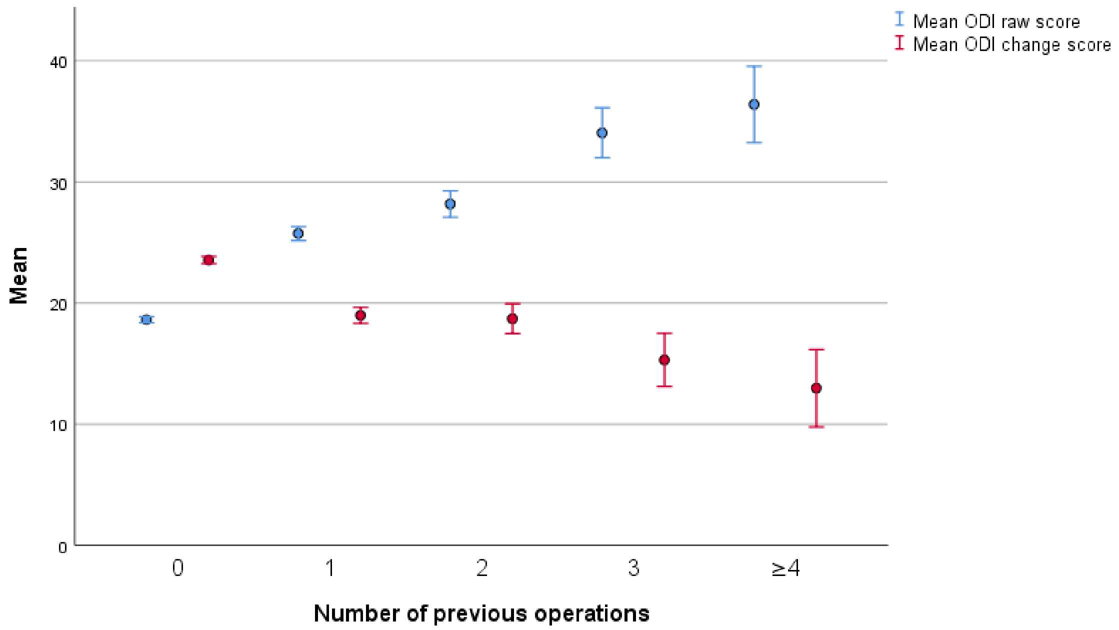

Figure 3 – Mean ODI raw score and mean ODI change score at 12 months follow-up, stratified by the number of previous operations. Error bars represent 95 % CI`s.

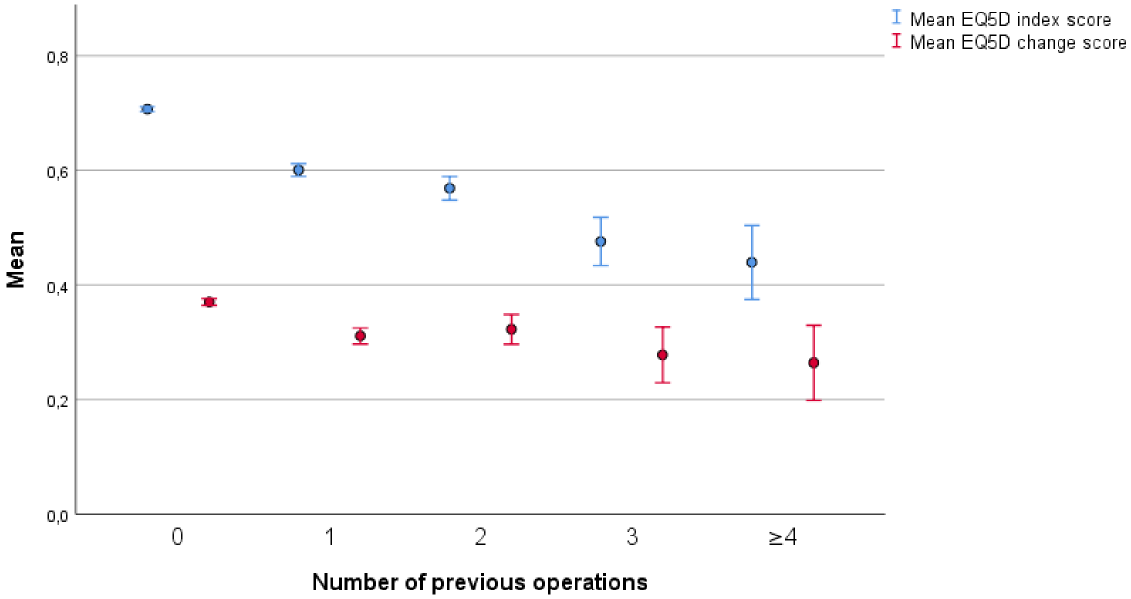

Figure 4 – Mean EQ5D index score and mean EQ5D change score at 12 months follow-up, stratified by the number of previous operations. Error bars represent 95 % CI`s.

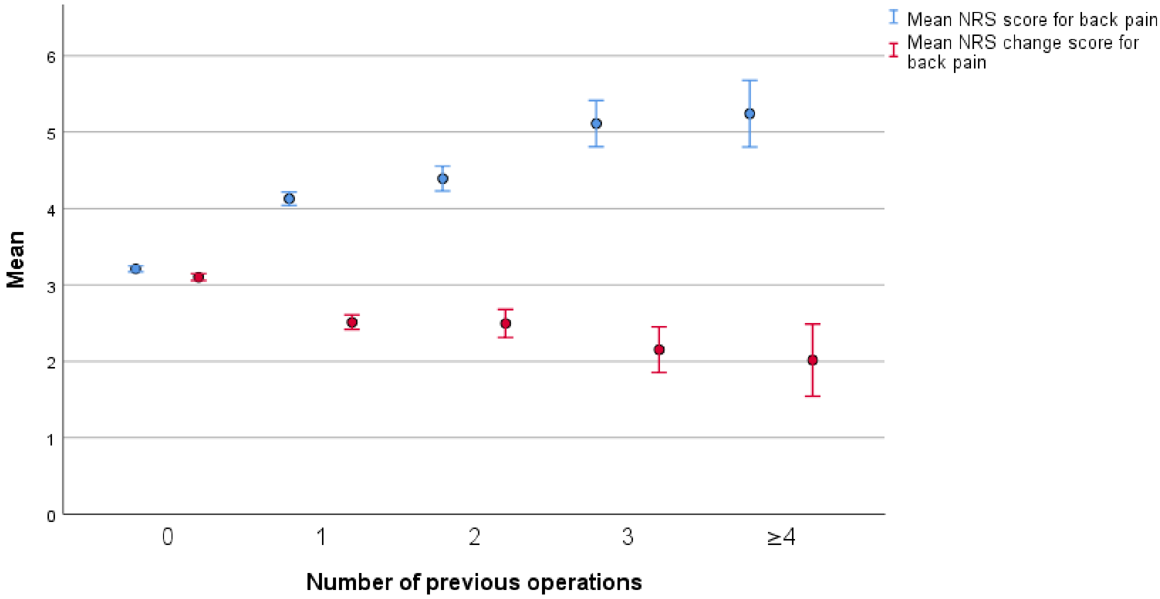

Figure 5 – Mean NRS score and mean NRS change score for back pain at 12 months follow-up, stratified by the number of previous operations. Error bars represent 95 % CI`s.

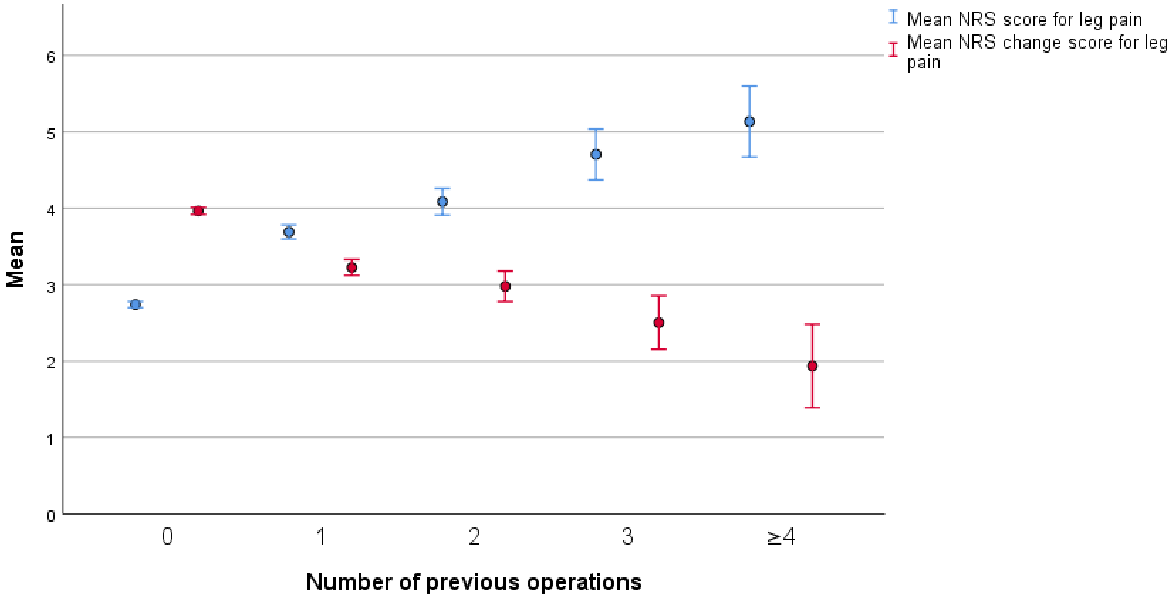

Figure 6 – Mean NRS score and mean NRS change score for leg pain at 12 months follow-up, stratified by the number of previous operations. Error bars represent 95 % CI`s.

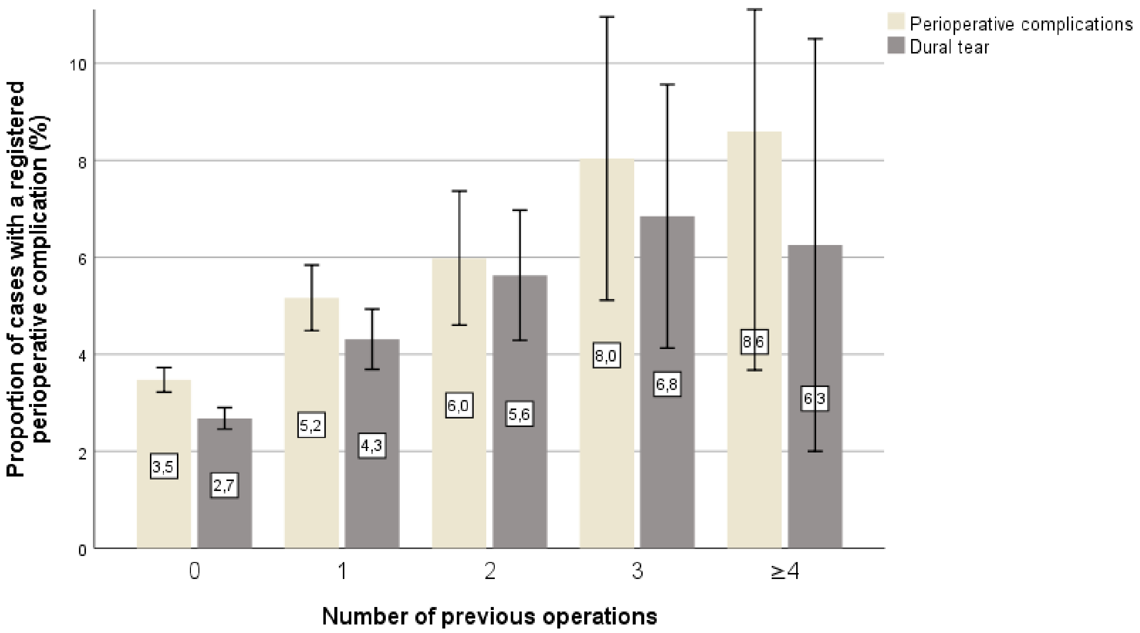

Figure 7 – Proportion of cases with a registered perioperative complication, including dural tear, stratified by the number of previous operations. Error bars represent 95 % CI`s.

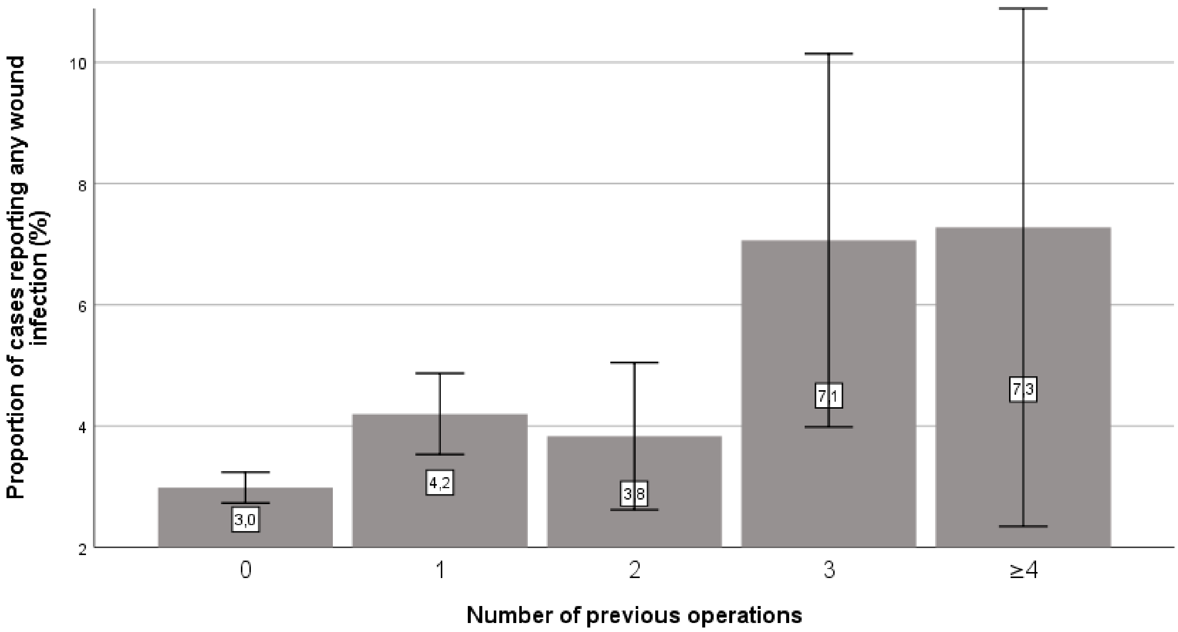

Figure 8 - Proportion of cases reporting any wound infection at 3 months follow-up, stratified by the number of previous operations. Error bars represent 95 % CI`s.

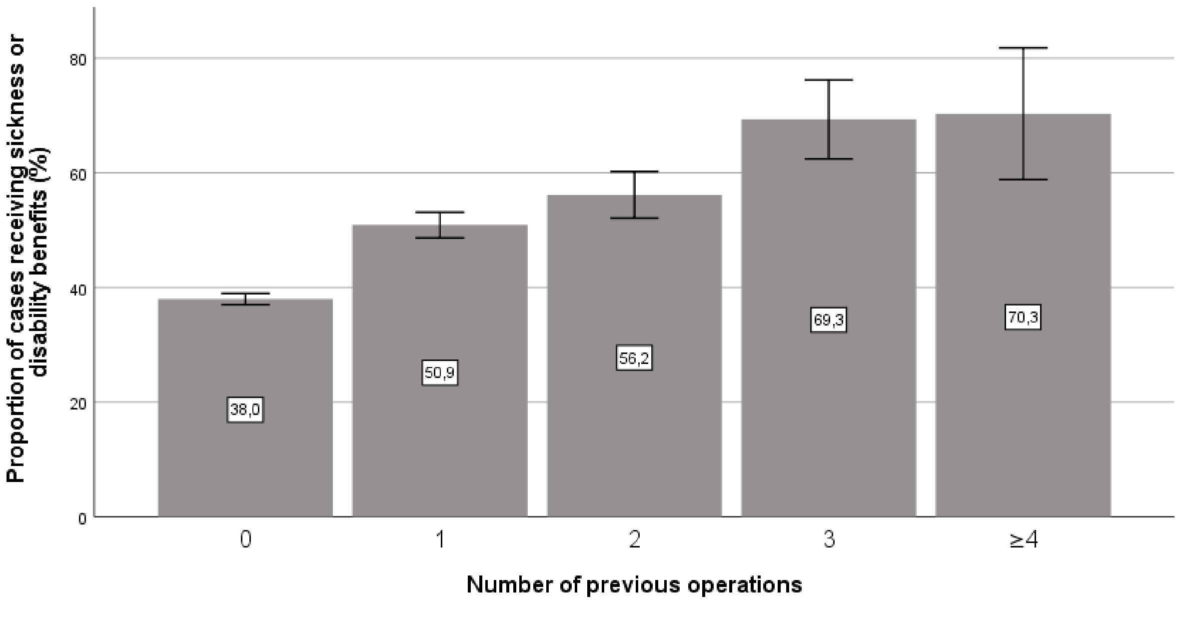

Figure 9 - Proportion of cases who received sickness or disability benefits preoperatively who still receive sickness or disability benefits at 12 months follow-up, stratified by the number of previous operations. Error bars represent 95 % CI`s.

To what degree did you benefit from the operation?	No previous operation	One previous operation	Two previous operations	Three previous operations	Four or more previous operations
Completely recovered, n (%)	4 898 (24.1 %)	591 (14.5 %)	125 (11.0 %)	23 (7.0 %)	4 (3.1 %)
Much improved, n (%)	9 078 (44.7 %)	1 569 (38.5 %)	416 (36.7 %)	111 (33.6 %)	41 (32.3 %)
Slightly improved, n (%)	3 669 (18.1 %)	954 (23.4 %)	300 (26.5 %)	86 (26.1 %)	40 (31.5 %)
Unchanged, n (%)	1 199 (5.9 %)	404 (9.9 %)	121 (10.7 %)	45 (13.6 %)	21 (16.5 %)
Slightly worsened, n (%)	742 (3.7 %)	263 (6.5 %)	91 (8.0 %)	22 (6.7 %)	11 (8.7 %)
Much worsened, n (%)	493 (2.4 %)	202 (5.0 %)	64 (5.7 %)	30 (9.1 %)	7 (5.5 %)
Worse than ever, n (%)	220 (1.1 %)	90 (2.2 %)	15 (1.3 %)	13 (3.9 %)	3 (2.4 %)

Table 4 - The Global Perceived Effect scale at 12 months follow up, stratified by the number of previous operations

	Beta (exposition)	Odds ratio (OR) (exposition)	95% CI OR (exposition)	p-value (exposition)	Confounder (1 yes, 0 no)	Significant association between covariate and dependent variable? (1 yes, 0 no)
Dependent variable						
Reaching a Patient Acceptable Symptom State (PASS) at 12 months follow up (no or yes)						
Exposition variable						
Number of previous operations	0.55	1.74	1.67-1.81	0.000		
Possible confounders						
Age (5 year categories)	0.54	1.71	1.64-1.78	0.000	0	1
Female gender (yes or no)	0.57	1.77	1.70-1.84	0.000	0	1
Smoking (yes or no)	0.55	1.74	1.67-1.81	0.000	0	1
College or university education (yes or no)	0.56	1.74	1.67-1.81	0.000	0	1
Living alone (yes or no)	0.56	1.74	1.68-1.82	0.000	0	1
Native Norwegian language (yes or no)	0.56	1.75	1.68-1.82	0.000	0	1
Body Mass Index (BMI)	0.55	1.73	1.66-1.81	0.000	0	1
Sickness or disability benefit recipient (yes or no)	0.56	1.74	1.67-1.82	0.000	0	1
Have applied or planning to apply for disability pension (yes/no)	0.55	1.74	1.67-1.82	0.000	0	1
Numeric Rating Scale (NRS) score for back pain (0 - 10)	0.52	1.68	1.61-1.75	0.000	0	1
NRS score for leg pain (0 - 10)	0.54	1.72	1.65-1.79	0.000	0	1
Oswestry Disability Index (ODI) (0 - 100)	0.52	1.68	1.61-1.75	0.000	0	1
EuroQoL 5 Dimensions (EQ-5D) (-0.594 - 1)	0.53	1.70	1.63-1.77	0.000	0	1
Longer than 12 months duration of back pain (yes or no)	0.56	1.76	1.68-1.83	0.000	0	1
Longer than 12 months duration of radiating pain (yes or no)	0.55	1.74	1.67-1.81	0.000	0	1
Use of painkillers (yes or no)	0.54	1.71	1.64-1.78	0.000	0	1
Any comorbidity (yes or no)	0.52	1.68	1.61-1.75	0.000	0	1

American Society of Anaesthesiologists` (ASA) classification > 2 (yes or no)	0.54	1.72	1.65-1.79	0.000	0	1
Moderate to severe anxiety and/or depression (yes or no)	0.56	1.75	1.68-1.83	0.000	0	1
Paresis (yes or no)	0.56	1.75	1.68-1.82	0.000	0	1
Fusion surgery (lumbar spinal stenosis) (yes or no)	0.51	1.66	1.57-1,75	0.000	0	1

Table 5 - Bivariate analysis of associations between the exposition variable and possible confounders

Number of previous operations	Beta	p-value	Odds ratio	95 % CI for odds ratio
0		0.000		
1	0.73	0.000	2.1	1.9 – 2.2
2	0.97	0.000	2.6	2.3 – 3.0
3	1.47	0.000	4.4	3.4 – 5.5
≥ 4	1.93	0.000	6.9	4.5 – 10.5

Table 6 - Univariate analysis of number of previous operations as a predictor of reaching Patient Acceptable Symptom State (no or yes) at 12 months follow up

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Appendix

<table>
<tr><td colspan="3">Referanse:
Sobottke et al. Predictors of improvement in quality of life and pain relief in lumbar spinal stenosis relative to patient age: a study based on the Spine Tango Registry</td><td>Design: Kohortestudie
Dokumentasjonsnivå: Very low
GRADE: 1</td></tr>
<tr><th>Formål</th><th>Materiale og metode</th><th>Resultater</th><th>Diskusjon/kommentarer</th></tr>
<tr><td>To evaluate the improvement in quality of life and pain relief after open decompression for LSS in relation to patient age.

Konklusjon
All age groups significantly benefit from the open decompressive treatment for LSS. Age group had no significant influence on any outcome.

Land
International
År data innsamling
??</td><td>The study is based on data from the Spine Tango Registry, using the last three iterations of the Spine Tango surgery form (2005, 2006 and 2011). n = 4768 patients from 40 international Spine Tango centres. The patients were subdivided into three age groups: (1) 20-64, (2) 65-74, and (3) >75 years. In multivariate logistic regression models, predictors for improvement in QoL and achievement of the minimum clinically relevant change in pain of two points were analysed. The following co-variates were included in the regression models: age group, sex, ASA-classification, extent of lesion, number of previous surgeries, most severely affected segment, rigid stabilization, fusion, dynamic stabilization and the duration of COMI-interval.</td><td>The overall follow-up rate for the COMI assessment in this study population was 46 %. There was no significant difference between age groups in the proportion of patients that improved by at least one QoL category (p = 0.86) and achieved the MCRC in back pain (p = 0.19) and leg pain (p = 0.94). In all age groups, a significant reduction in back and leg pain, and an improvement in the quality of life was documented (p < 0.001 for all outcomes in all groups).The pre- and postoperative back- and leg pain levels were different between age groups. Neither back pain relief, nor leg pain relief were significantly different between age groups. The multivariate logistic regression analysis revealed that worse preoperative quality of life, fewer previous surgeries, lower ASA status and the use of rigid stabilization were significant predictors increasing the likelihood of improvement in quality of life postoperatively. Rigid and dynamic stabilization, and fewer previous surgeries were significant predictors increasing the likelihood of achieving a MCRC in back pain. Higher preoperative leg pain, rigid and dynamic stabilization, and fewer previous surgeries were significant predictors increasing the likelihood of achieving a MCRC in leg pain.</td><td>Comments from the authors:
The findings of the study are similar to what several other studies addressing the influence of age on clinical outcome has found.
Large sample size and routine clinical settings from which the data were drawn are the major strength of the analysis.
The overall follow-up rate of 46 % is considered a weakness. Furthermore, cultural and health care differences may have influenced the results of the study, as data from nine different countries were included.
There is little reason to believe that a potential selection bias would affect the studied age groups in a differential way.</td></tr>
</table>

Kommentarer:

-The fact that the Spine Tango Registry includes patients operated in different countries, reporting to the registry is voluntary and follow up rates are low, raises the concern that the patients included may not be representative for the population of patients undergoing lumbar spine surgery. In the pool of patients registered in Spine Tango, only 46 % had a COMI at baseline and at least 3 months after surgery, making them eligible for inclusion. This further increases the concern of selection bias. The risk of selection bias is therefore very high.

-The observational study design gives the reported effects a low level of quality of evidence. The high risk of selection bias gives the study a very low quality of evidence.

Referanse: **Zehnder et al. Influence of previous surgery on patient-rated outcome after surgery for degenerative disorders of the lumbar spine.**	**Design: Kohortestudie**	
	Dokumentasjonsnivå	Low
	GRADE	2

Formål	Materiale og metode	Resultater	Diskusjon/kommentarer
To quantify the effect of multiple previous spine surgeries on patient-oriented outcome after spine surgery. **Konklusjon** **There is a dose-response effect of prior surgery on patient-reported outcome for lumbar spine surgery: the greater the number of prior spine surgeries, the systematically worse the outcome at 12 months`follow-up.** **Land** **International** **År data innsamling** **2004 - 2015**	**Multicenter retrospective analysis of prospectively collected data within the EUROSPINE Spine Tango Registry. The outcome measure is COMI-score, reported by patients preoperatively and 12 months postoperatively. They included patients operated for degenerative disorders in the lumbar spine. They excluded patients who did not have both preoperative and postoperative COMI-questionnaires, cases where the COMI form did not exist in the national language, surgery in other parts of the spine, non-degenerative main pathology, missing information on ASA-status, missing information on smoking status, missing information on BMI and cases where fewer than 100 patients from a given hospital was fulfilling the criteria. n = 4940.**	**The number of previous surgeries had a significant negative influence on the 12-month COMI-score: for each step-increase in the number of previous surgeries, the COMI-score at 12 months increased by 0.37 (95 % CI 0.29-0.45; p < 0.001).** **A higher preoperative COMI-score, greater extent of lesion, greater comorbidity, greater BMI, smoking, younger age and female gender were independently and significantly associated with the 12-month COMI-score.** **The effect of previous surgery on the 12-month COMI-score was more pronounced in the group with lumbar disc herniation, where, compared with first-time surgery, a single previous surgery resulted in a 0.52-point (95 % CI 0.27-0.77; p < 0.001) higher COMI score. The corresponding value for lumbar degenerative spondylolisthesis was 0.40 points (95 % CI 0.17 – 0.64; p = 0.001), and for lumbar spinal stenosis without spondylolisthesis, 0.27 points (95 % CI 0.12 – 0.42; p < 0.001). For the other lumbar diagnostic subgroups, the B coefficients for the effect of previous surgery failed to achieve statistical significance.**	**Comments from the authors:** • **The minimal clinically important change for individual improvement for the COMI-score is 2-3 points. Thus, the size of the stand-alone effect of prior surgery, although statistically significant, was not large. However, there may be an important additive effect when combined with other patient characteristics that are associated with worse outcome.** • **Large sample size is a strength of the study.** • **Data from an international registry are more representative than data from a single institution.** • **There may be other confounding factors not identified in this study affecting the 12-month COMI score.** • **The statistical significance reported for many of the findings resulted from the very large sample size. The small size of some of the diagnostic subgroups may have rendered the subgroup analyses underpowered.**

Kommentarer:

-They excluded cases where fewer than 100 patients from a given hospital was fulfilling the criteria, presumably to reduce the risk of selection bias. Still, the fact that the Spine Tango Registry includes patients operated in different countries, reporting to the registry is voluntary and follow up rates are low, raises the concern that the patients included may not be representative for the population of patients undergoing lumbar spine surgery The risk of selection bias is high.

- The quality of evidence for an observational study like this is low to begin with. The fact that they were able to find a dose response gradient improves the quality of evidence. The serious risk of selection bias lowers the quality of evidence.