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Karolinska Institutet, Stockholm, Sweden

LONG TERM EFFECTS OF LUMBAR DISC HERNIATION SURGERY IN ADOLESCENTS

Tobias Lagerbäck

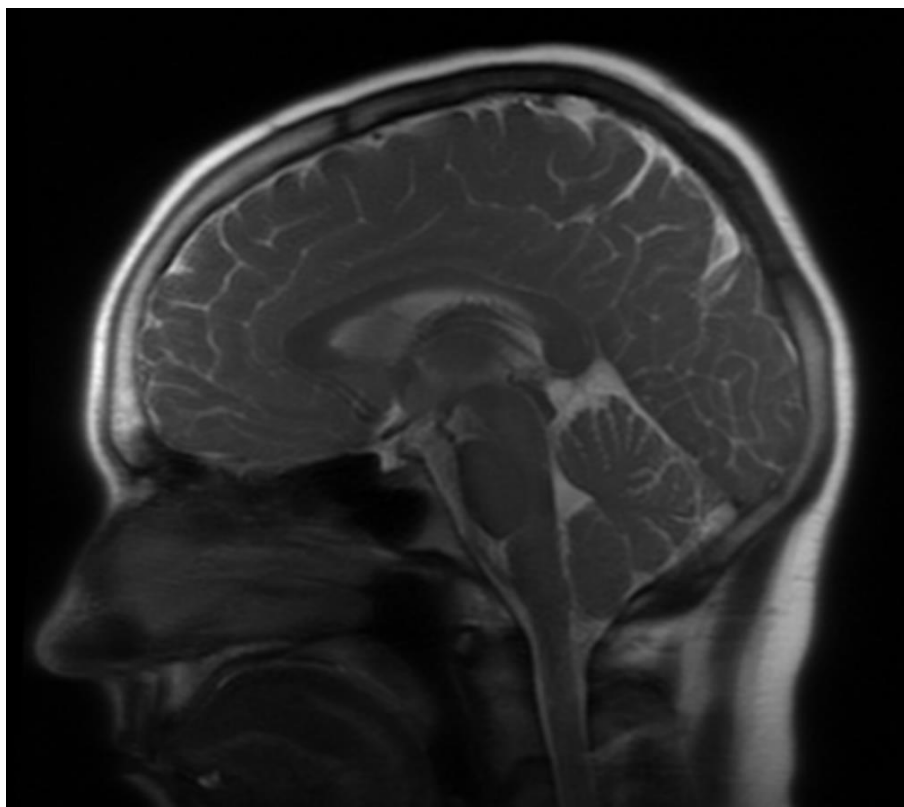


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The images on the cover show the lumbar spine of the author at age 18 (left) and age 28 (right). In the image on the left-hand side, lumbar disc herniations at level L4-L5 and level L5-S1 are seen and in the image on the right-hand side, the lumbar spine is seen 10 years after surgery of the L4-L5 disc herniation. Images provided by Granit Kastrati and Tobias Lagerbäck.

The image below shows the brain of the author, a brain that was very involved in this thesis. Image provided by Granit Kastrati.



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To my parents who have always supported me and had faith in me.

ABSTRACT

Background: In Sweden, about 2,900 surgeries due to a lumbar disc herniation are performed yearly, and the surgical incidence is low compared to the incidence in Denmark and Norway. Surgery for lumbar disc herniation in adolescence is rare and few reports on the outcome of surgery exist.

Aims: To investigate if preoperative patient characteristics and the one-year patient-reported outcomes differ between three Nordic countries with different incidence of surgery for lumbar disc herniation. To describe the short and long-term outcomes in adolescents and adults treated surgically for lumbar disc herniation.

Study population: Individuals treated surgically for lumbar disc herniation and registered in the nationwide spine registers in Sweden, Denmark and Norway. Age and sex-matched controls for adolescents treated surgically due to a lumbar disc herniation.

Methods: Data on surgery and patient-reported outcome were acquired from the spine registers. Magnetic resonance imaging (MRI) was performed in a subgroup of the adolescent patients and in all controls.

Results: When comparing Sweden, Denmark and Norway, we found no clear association between incidence of surgery for lumbar disc herniation, patient characteristics and outcome, despite of an up to two-fold variation in surgical incidence.

Adolescents (≤ 18 years old) account for only 1.4% of the lumbar disc herniation surgeries in Sweden. At short-term follow-up, adolescents are more satisfied with their treatment compared to adults (≥ 19 years old). All groups benefitted significantly from their surgery but the mean values for quality of life were still lower than the average of the general population.

At long-term follow-up, adolescents have a similar risk to young adults (19-39 years old) of having to undergo additional lumbar spine surgery, with about 16% of the adolescents and 18% of the young adults needing repeat surgery. When comparing elderly patients (60 years and older) to adults aged 40-59 years old, the elderly had a slightly smaller risk of additional lumbar spine surgery, with repeat surgery occurring in about 11% of the elderly and 14% of the adults. Within all age groups, there were no clinically relevant changes between short and long-term follow-up.

More than a decade after surgery, individuals operated on due to a lumbar disc herniation in adolescence have more degenerative signs, as seen on MRI, at the two lower lumbar levels compared to controls. The operated individuals are satisfied to a high degree, but they experience more back disability, more back pain and a lower quality of life compared to controls.

Conclusions: Differences in surgical incidence of lumbar disc herniation is not reflected in differences in preoperative patient characteristics and one-year patient-reported outcome.

Surgery for lumbar disc herniation is associated with a 11-18% risk of additional lumbar spine surgery, with a similar risk among adolescents and young adults. There are no clinically relevant changes in outcome between short and long-term follow-up within all age groups, putting into question the need for a long-term follow-up after surgery for lumbar disc herniation. Even though the rate of satisfaction is high, and surgery seems to be a viable alternative, operated adolescents have a higher prevalence of spinal degeneration in the two lower lumbar spine segments and experience slightly more back disability, more back pain and a lower quality of life than age and sex-matched controls more than a decade after their operation.

SUMMARY IN SWEDISH (SAMMANFATTNING PÅ SVENSKA)

Bakgrund: I Sverige genomförs cirka 2900 lumbala diskbråcksoperationer årligen. Incidensen (förekomsten) av kirurgi för lumbala diskbråck i Sverige är låg jämfört med incidensen i Danmark respektive Norge. Kirurgi för lumbala diskbråck förekommer sällan hos ungdomar och bara ett fåtal studier av utfallet efter kirurgi har tidigare gjorts.

Syfte: Att undersöka om patienternas besvärsbild innan operation och utfall ett år efter operation skiljer sig mellan tre nordiska länder med olika incidens av kirurgi för lumbala diskbråck. Att beskriva utfallet av kirurgi för lumbala diskbråck hos ungdomar och vuxna på kort och lång sikt.

Studiepopulation: Individer som behandlats kirurgiskt för lumbala diskbråck och registrerats i de nationella ryggregistren i Sverige, Danmark och Norge. Ålders- och könsmatchade kontroller för ungdomar som genomgått lumbal diskbråckskirurgi.

Metoder: Data om kirurgi och patientrapporterade utfall inhämtades från ryggregistren. Magnetresonanstomografi genomfördes för en undergrupp av ungdomarna som opererats och för alla kontroller.

Resultat: Vid jämförelse av tre nordiska länder hittade vi inga tydliga samband mellan incidensen av kirurgi för lumbala diskbråck, patienternas besvärsbild innan operation och utfallet efter ett år. Detta trots att incidensen av kirurgi varierade med upp till en faktor två.

Ungdomar (18 år och yngre) står för endast 1,4% av de operationer av lumbala diskbråck som genomförs i Sverige. Vid korttidsuppföljningen av lumbal diskbråckskirurgi i Sverige var ungdomarna i en högre utsträckning nöjda med sin behandling än de vuxna (19 år och äldre). Alla åldersgrupper gagnades signifikant av kirurgi men det patientrapporterade medelvärde för livskvalitet var ändå lägre än hos normalbefolkningen.

Vid långtidsuppföljningen hade ungdomarna en risk för ytterligare ländryggskirurgi som var liknande risken som sågs hos unga vuxna (19–39 år gamla) och cirka 16% av ungdomarna och 18% av de unga vuxna hade genomgått ytterligare kirurgi. Vid jämförelsen av äldre (60 år och äldre) och vuxna i åldrarna 40–59 år hade de äldre en något lägre risk för ytterligare ländryggskirurgi och ytterligare kirurgi förekom hos cirka 11% av de äldre och 14% av de vuxna. Inom alla åldersgrupper fanns det inga kliniskt relevanta skillnader i patientrapporterat utfall mellan kort- och långtidsuppföljningarna.

Mer än ett decennium efter kirurgi för lumbala diskbråck hos ungdomar ses mer tecken till degeneration i de två nedersta lumbala nivåerna på magnetresonanstomografi jämfört med hos kontroller. Ungdomarna som opererats var i hög utsträckning nöjda med sin behandling men upplevde mer ryggrelaterad funktionsnedsättning, mer ryggsmärta och hade en lägre livskvalitet jämfört med kontrollerna.

Slutsatser: Skillnader i incidens av kirurgi för lumbala diskbråck reflekteras inte i patienternas besvärssbild innan operation eller på utfallet efter ett år. Kirurgi för lumbala diskbråck innebär en risk på 11–18% för ytterligare kirurgi, en risk som är liknande i storlek hos ungdomar och unga vuxna. Det var inga kliniskt relevanta skillnader i utfall mellan kort- och långtidsuppföljningarna inom alla åldersgrupper, vilket ifrågasätter behovet av en långtidsuppföljning efter kirurgi för lumbala diskbråck. Kirurgi ses som ett bra alternativ vid lumbala diskbråck hos ungdomar men även om ungdomar som opererats för lumbala diskbråck i hög utsträckning är nöjda med operationen så har de, mer än ett decennium senare, mer degeneration i de två nedersta lumbala nivåerna, mer ryggrelaterad funktionsnedsättning, mer ryggsmärta och en lägre livskvalitet jämfört med ålders- och könsmatchade kontroller.

LIST OF SCIENTIFIC PAPERS

- I. **An observational study on the outcome after surgery for lumbar disc herniation in adolescents compared with adults based on the Swedish Spine Register.**

Tobias Lagerbäck, Peter Elkan, Hans Möller, Anna Grauers, Elias Diarbakerli, Paul Gerdhem

The Spine Journal. 2015 Jun 1;15(6):1241-7

- II. **Effectiveness of surgery for sciatica with disc herniation is not substantially affected by differences in surgical incidences among three countries: results from the Danish, Swedish and Norwegian spine registries.**

Tobias Lagerbäck, Peter Fritzell, Olle Hägg, Dennis Nordvall, Greger Lønne, Tore K. Solberg, Mikkel Ø. Andersen, Søren Eiskjær, Martin Gehrchen, Wilco C. Jacobs, Miranda L. van Hooff, Paul Gerdhem

European Spine Journal. 2019 Nov;28(11):2562-2571.

- III. **Lumbar disc herniation surgery in adolescents and young adults: a long-term outcome comparison.**

Tobias Lagerbäck, Hans Möller, Paul Gerdhem

The Bone and Joint Journal. 2019 Dec;101-B(12):1534-1541.

- IV. **Outcome after lumbar disc herniation surgery in adults and elderly – Risk of additional surgery and PROM change over time.**

Tobias Lagerbäck, Hans Möller, Paul Gerdhem

Manuscript

- V. **MRI characteristics mean 13 years after lumbar disc herniation surgery in adolescence - a case control study.**

Tobias Lagerbäck, Granit Kastrati, Hans Möller, Karin Jensen, Mikael Skorpil, Paul Gerdhem

Manuscript

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LIST OF ABBREVIATIONS

AD	Anno Domini, i.e. after Christ
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BC	Before Christ
BMI	Body mass index
CI	Confidence interval
CSF	Cerebrospinal fluid
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
IPAQ-SF	International Physical Activity Questionnaire – Short Form
MCID	Minimal clinically important difference
MCS	Mental component summary score
MRI	Magnetic resonance imaging
NRS	Numerical rating scale
ODI	Oswestry disability index
PCS	Physical component summary score
PROM	Patient-reported outcome measure
QALY	Quality-adjusted life years
SD	Standard deviation
SF-36	Short-form health survey, 36 items
TEP-score	Total endplate score
VAS	Visual analogue scale

1 INTRODUCTION

The human spine is formed of 32-34 vertebrae; seven cervical vertebrae (C1 to C7), 12 thoracic vertebrae (T1 to T12), five lumbar vertebrae (L1 to L5), five sacral vertebrae (S1 to S5, which are fused to form the sacrum) and three to five coccygeal vertebrae (which are fused fully or in segments to form the coccyx) (1, 2). Except for the 1st and the 2nd cervical vertebra, the vertebrae are separated by an intervertebral disc which, together with the two intervertebral joints on each level, allows motion (Figure 1). The intervertebral discs between the sacral vertebrae collapse when aging and the sacrum is formed by the time of adolescence (3).

The intervertebral disc consists of the outer fibrous part, the anulus fibrosus, and the inner gelatinous mass, the nucleus pulposus. The anulus fibrosus consists of concentric lamellae of fibrocartilage, mainly type I collagen (1, 4). The outer third of the anulus fibrosus is the only part of the intervertebral disc that is innervated, and this causes some patients to experience back pain when the disc herniates (1, 5, 6). The nucleus pulposus is avascular and mainly consists of large proteoglycans and type II collagen (4, 6). The nucleus pulposus and the inner part of the anulus fibrosus are separated from the adjacent vertebral bodies by the cartilaginous endplate (7). The endplate also serves as the epiphyseal growth plate (8). The endplate is sometimes classified as a part of the intervertebral disc and sometimes as a part of the vertebral body.

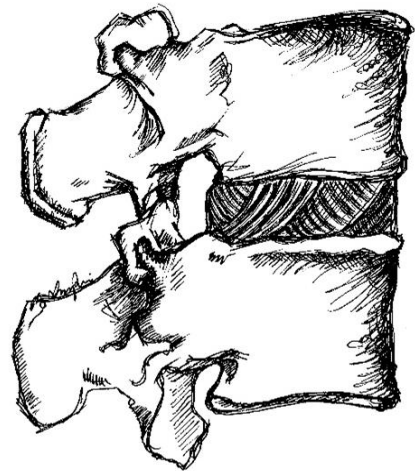


Figure 1. Lateral view of two lumbar vertebrae separated by an intervertebral disc. Figure courtesy of Lucy Bai.

The combination of the fibrous anulus fibrosus, the gelatinous nucleus pulposus and the cartilaginous endplate give the intervertebral discs their principal biomechanical properties; to stabilize the spine, to allow small movements and to evenly transmit axial loading forces between adjacent vertebrae (7).

When a disc herniates, it can cause radicular pain by compression of the spinal nerve root and due to exposure of inflammatory substances from the nucleus pulposus to the nerve root (1, 6, 9, 10). Nevertheless, in many cases a herniated disc is asymptomatic (11). A lumbar disc herniation that affects a spinal nerve root, most often affects the spinal nerve that exits at the level below, i.e. a herniation of the L4-L5 disc most often affects the L5 spinal nerve.

1.1 EMBRYOLOGY AND EARLY DEVELOPMENT OF THE INTERVERTEBRAL DISC

The nucleus pulposus derives from the notochord while the anulus fibrosus, the cartilaginous endplate and the vertebral body derive from the sclerotome, a derivation of the somite (12, 13). The nucleus pulposus is avascular during the fetal period and remains so throughout life (8, 12, 14). The cartilaginous endplate and the outer parts of the anulus fibrosus are vascularized at the beginning of life. Whether the inner parts of the anulus fibrosus are avascular throughout life or remain vascularized in the fetal and early postnatal period has however been debated (8, 12, 14). The vascular supply in the cartilaginous endplates and the possible supply in the inner parts of the anulus fibrosus are lost within the first years of life while the outermost part of the anulus fibrosus has been seen vascularized in all age groups (14). This leaves most of the intervertebral disc without blood supply, making it the largest avascular structure in the body. Being avascular, the only source of nutrition to the majority of the intervertebral disc is the diffusion of nutrients from the outermost part of the anulus fibrosus and the vessels of the vertebral endplate (7, 15, 16).

1.2 DEFINITION AND CLASSIFICATION OF LUMBAR DISC HERNIATION

The definition of lumbar disc herniation varies and the term is used to describe various abnormalities of the disc, from a disc bulge symmetrically extending beyond the intervertebral space to an extrusion of nucleus pulposus (17). In this thesis, the term lumbar disc herniation includes protrusion, a focal or asymmetric extension of the disc and extrusion, an escape of disc material.

Lumbar disc herniations are classified according to their position, the degree of injury to the anulus fibrosus and the possible leakage of material from the nucleus pulposus (5, 6). The position is decided in relation to the spinal canal and divided into central, paramedian, far lateral and extraforaminal (5, 6). The degree of injury to the anulus fibrosus is divided into two main groups; “contained” and “non-contained” herniations. Contained herniations, also known as protrusion, have an intact anulus fibrosus and the disc is bulging. The non-contained herniations can be of two types, “extrusion”; the anulus fibrosus is ruptured and the escaped material from the nucleus pulposus is still connected to the originated disc, and “sequestration”; the anulus fibrosus is ruptured and the escaped material from the nucleus pulposus is no longer connected to the disc it originated from (5, 6).

In adolescent lumbar disc herniation, there is a risk of ring apophysis fracture, but the condition is rare. The ring apophysis is a secondary ossification centre that encircles the margin of the endplate (18, 19). The most superficial part of the anulus fibrosus is connected to the ring apophysis by collagen fibres, and a separation of the ring apophysis and the vertebral body can occur (7, 20, 21). The ring apophysis typically ossifies in the late teens

and the majority of ring apophysis fractures are found in adolescents and young adults (7, 18, 20-22).

1.2.1 History

The Greek physician, Hippocrates of Kos (460–377 BC) has been crowned as “the father of medicine” (23). Hippocrates made major contributions to the knowledge about spinal anatomy and spinal diseases and their treatment, specifically the treatment of spinal deformities, altogether also earning him the title as “the father of spine surgery” (23, 24). It should also be borne in mind that all Hippocrates' findings were made during a time when dissection of the human body was prohibited (23, 24). Based on the works of Hippocrates, another Greek physician, Galen of Pergamum (129–200 AD), made further discoveries and descriptions regarding the spine (25, 26). Galen accurately described the vertebral column, the spinal cord, nerves emerging from the spine and the neurological deficits following transection of the spinal cord at different levels (26). Furthermore, Galen described a “mucous and ligamentous connection” between the vertebral bodies, which joins them together (26).

In the 18th century the Italian physician, Domenico Felice Antonio Cotugno (1736–1822), differentiated radiating pain, sciatica, as either originating from the hip “arthritic sciatica” or as a nervous disease “neurogenic sciatica” (27). Furthermore, he divided neurogenic sciatica into anterior and posterior, approximately corresponding to the dermatomes of L3-L4 and L5 respectively, but the pathomechanism of lumbar disc radiculopathy remained unknown (27). The true cause was not revealed until the 1930s when the two American surgeons William Jason Mixter (1880–1958) and Joseph Seaton Barr (1901–1963) proved that a herniated disc was the cause of sciatica (27, 28). Their results and the surgical procedure for removal of lumbar disc herniations were published in the *New England Journal of Medicine* in 1934 (29).

The first successful surgery for lumbar disc herniation in children and adolescents was not described in the literature until 1945 when the Swedish surgeon Herman Wahren (1897-1985) described an operation on a 12-year-old girl (30).

1.2.2 Clinical characteristics and diagnosis

The most common symptoms of lumbar disc herniation are back pain and leg pain (31). Patients usually present with back pain, followed by leg pain. This order can be due to the outer third of the anulus fibrosus being innervated, causing a sensation of pain in the back when the disc herniates (1, 5, 6, 31). The most sensitive symptom for a clinically relevant lumbar disc herniation, having a sensitivity of 0.95, is sciatica (32). Other symptoms are reduced spinal mobility, motor deficits and sensory deficits (31, 33). The most common

levels for a symptomatic lumbar disc herniation are the two lower levels, L4-L5 and L5-S1 (34).

The symptoms in adolescents are similar to the ones seen in adults; 65-100% of the adolescents who undergo surgery for lumbar disc herniation present with low back pain and 41-100% experience sciatica (35-41). Other symptoms include neurogenic claudication (37-40%), motor deficit (4-26%) and sensory deficit (8-31%) (35-40).

There are several other disorders causing sciatica (42). The most common differential diagnoses are spondylolisthesis, lumbar spinal stenosis, infections (including epidural abscess and herpes zoster), tumours, vertebral fractures, cysts, diabetic radiculopathy, multiple sclerosis and aortoiliac occlusive disease (42-45).

In adults, the most specific test for lumbar disc herniation that can be performed during physical examination is the crossed straight leg raise test (31, 33). However, this test has a rather low sensitivity. On the contrary, the straight leg raise test has a low specificity but a high sensitivity. Other tests and observations include flexion and extension of the spine, dorsal flexion of the ankle and hallux, Achilles tendon reflexes, sensory deficits and non-structural scoliosis (33).

When examining adolescents, the most common findings are; positive straight-leg raise test (41-99%), paravertebral spasm and/or non-structural scoliosis (10-82%), motor deficit (19-60%), sensory deficit (6-59%), tenderness in the lower back (31-53%) and loss of deep tendon reflexes (12-33%) (35-41). Scoliosis in conjunction with lumbar disc herniation most often disappears after treatment and is often a reaction to the pain and/or muscle spasm (39).

The mean time from onset of symptoms to diagnosis in adolescents has been found to be between 7.7 and 10 months, compared to 4.7 months in adults (5, 35-37). However, some studies report a mean time from onset of symptoms to surgery for lumbar disc herniation in adolescents of between 6 and 12.2 months, while the majority of adults undergo surgery within 3 to 12 months (38-41, 46, 47). The delay in diagnosis is believed to be because of the rarity of lumbar disc herniation in adolescents and the sometimes different symptomatology compared to adults, often leading to misdiagnosis (36, 38).

Cauda equina syndrome is a rare disorder that can evolve due to a lumbar disc herniation, and it accounts for approximately 1-2% of all lumbar disc herniation surgeries (48, 49). Cauda equina syndrome is rarely reported in studies of adolescent lumbar disc herniation, but one larger study reported that 2 out of 199 (1%) of the adolescents undergoing surgery had cauda equina syndrome (41). The syndrome occurs when the cauda equina (bundle of spinal nerves and spinal nerve rootlets located in the lumbar spine) is compressed and it can cause several symptoms including sciatica (most often bilateral), sensory deficits in the saddle region (including genitalia) and deficits in the bladder, bowel and sexual function (48). Patients with cauda equina syndrome should be operated on as soon as possible, however, no optimal timing has been proven (48, 50-52).

1.2.3 Imaging

Among patients with severe and/or progressive neurological deficits or suspicion of acute causes for sciatica (e.g. cauda equina syndrome, infections or tumours) an early imaging investigation should be undertaken (43). If other causes are ruled out, imaging of lumbar disc herniations should be performed if there is a clinical suspicion of a lumbar disc herniation with indication for surgery (11, 34, 43, 48, 53). There are three main imaging modalities for examination of lumbar disc herniation; MRI, CT and CT myelography (54). As compared to CT and CT myelography, MRI provides better soft tissue contrast, better visualization of the ligaments, vertebral marrow and the spinal canal, and does not use any ionizing radiation (34). CT myelography is an invasive procedure associated with a risk of complications (54). The specificity and sensitivity for diagnosis of a lumbar disc herniation in MRI, CT and CT-myelography is similar, but MRI is nevertheless generally recommended as the first choice for patients with suspected lumbar disc herniation (34, 54). MRI is also the most common modality for assessing spinal degeneration (55-57). If there are any contraindications for MRI, then CT or CT myelography are feasible alternatives.

1.2.4 Pathophysiology

Of all musculoskeletal tissues, the intervertebral disc is the tissue that undergoes the most degenerative changes with age (58). The degeneration starts in the second decade of life and progresses with age, and lumbar disc herniation is often considered a part of the degeneration among adults (11, 15, 59, 60). However, Lama et al. found that degenerative changes do not necessarily precede a lumbar disc herniation, and that the changes instead could be a consequence of the herniation (61).

During ageing and degeneration, several biochemical changes occur (60, 62-64). Notochordal cells in the nucleus pulposus are replaced by chondrocyte-like cells during maturation, and notochordal cells have been reported to be seen until roughly the age of 10 years while others have identified notochordal cells until the beginning of the fourth decade of life (60, 62). The most significant change is the dehydration of the intervertebral disc, occurring due to degradation of proteoglycans causing a loss in water pressure (63). The decrease of proteoglycans also appears in the cartilaginous endplate (64). As degeneration progresses, the intervertebral disc stiffens due to a changed composition of collagen fibres (64). In combination with the dehydration, the stiffening makes the intervertebral disc less capable of withstanding load and more vulnerable to mechanical stress. These changes can be seen at a histological level as fissures, fibrosis and cell clusters in the nucleus pulposus, as disruption of lamellar structure, fissures and increased vascularization and innervation in the anulus fibrosus and as thinning, microfractures and sclerosis of subchondral bone and reduction in the number of vascular channels in the cartilaginous endplate (64).

It has been suggested that the factors mediating these changes are genetic, nutritional and mechanical (65, 66). Several twin studies of disc degeneration exist, most of them conducted by Battié et al. (67). The studies by Battié et al. are based on the “Twin Spine Study” and in a review from 2009 they summarized their findings (66). Battié et al. found that 61% of the variability in disc degeneration at levels T12-L4 in monozygotic twins was explained by genetic influences and early shared environment, while age and occupational physical loading accounted for 16% (66, 68). Corresponding numbers for levels L4-S1 were 34% and 9% respectively. Sambrook et al. conducted a study of mono- and dizygotic twins and found that 74% of the overall score of disc degeneration in the lumbar spine was due to genetic factors (69). The studies of Battié et al. and Sambrook et al. lead to new knowledge; the variability of disc degeneration is to a high extent explained by genetics (66, 69).

Degeneration of the intervertebral disc has been strongly linked to a fall in nutrient supply (16). Nutrition reaches the intervertebral disc by diffusion from the outermost part of the anulus fibrosus and the vessels of the vertebral endplate (7, 15, 16). Conditions and exposures disturbing the blood supply to the vertebral body and endplate can cause nutrients to not reach the intervertebral disc (16). Other obstacles include calcification of the endplate and sclerosis of the subchondral bone. The fall in nutrients causes a fall in oxygen and glucose concentrations in the disc and lactic acid builds up (16). This will cause a degeneration of the matrix through cell death and change in cellular activity, which ultimately causes the mechanics of the disc to change. The nutrient diffusion has been studied with MRI, and Rajasekaran et al. found that degenerated discs had an altered pattern of nutrient diffusion compared to normal discs irrespective of age (15).

Mechanical stress, such as trauma or repeat loading causing fatigue, has traditionally been considered as a factor in disc degeneration, though genetic and nutritional factors have been given more space in the later years (70, 71). Adams et al. have suggested that there are two different phenotypes for disc degeneration, caused by different mechanisms, the endplate phenotype and the anulus phenotype (72, 73). The endplate phenotype manifests in the thoracic and upper lumbar spine, is more heritable than the anulus phenotype and often occurs before the age of 30 (72). It is associated with endplate defects and is thought to be caused by spinal compression. The anulus phenotype manifests in the lower lumbar spine, is less heritable and seldom occurs before the age of 30. It is associated with fissures of the anulus fibrosus and thought to be caused by spinal bending (72). Both phenotypes lead to disc bulging and decreased stability of the spine (73). Others have also found endplate defects to be both an initiating factor, and a risk factor for progression, of disc degeneration (74, 75).

The disc's decreased capability to withstand load and its vulnerability to mechanical stress can cause the disc to herniate. The lower lumbar intervertebral discs experience the highest mechanical forces and have the highest prevalence of disc degeneration, this may explain why most symptomatic lumbar disc herniations occur at levels L4-L5 and L5-S1 (34, 73, 76).

When a disc herniates, the mechanical pressure on the nerve root, in combination with an inflammatory process, can cause sciatica, sensory deficits and motor deficits (1, 6, 9, 10).

Since one nerve root is usually affected, the sensory deficits and motor deficits are specific to the level of the nerve root. In 1958, Smyth et al. found that nerve roots that had been pressed upon by a disc herniation were hypersensitive compared to adjacent nerve roots (77). Material from the nucleus pulposus has been shown to cause inflammation and attract leukocytes (78). It has also been shown in animal studies that the combination of mechanical pressure and exposure to nucleus pulposus causes more nerve injury than pressure or exposure alone (79). The need for a combination of pressure and inflammation to cause radiating pain is also supported by the fact that many lumbar disc herniations are asymptomatic and that the severity of symptoms is poorly correlated with the size of the herniation (9, 11). Furthermore, in support of an inflammatory involvement, in patients with disc degeneration, in patients with lumbar disc herniation with sciatica, and in patients with previous lumbar disc herniation and current chronic sciatica, several proteins associated with inflammation have been found in the epidural space (as close to the suspected nerve root as possible), in cerebrospinal fluid or in serum (80-82).

1.3 EPIDEMIOLOGY

1.3.1 Prevalence of lumbar disc herniation

Disc-related sciatica is a common disease with a life-time prevalence of up to 40% and a point prevalence of about 2-5% (83-86). Heliovaara et al. found sciatica to be more frequent in men than women, a difference that diminished when adjusting for anthropometrics (87). In adults, lumbar disc herniation and typical sciatica have been calculated to attribute to about 6% of the population's work disability and about 95% of the patients with disc-related sciatica are in need of health care interventions (84, 85). Even though these numbers are high, more than a third of the general population have an asymptomatic lumbar disc protrusion, a prevalence which increases with age (11).

1.3.2 Prevalence of disc degeneration

Radiological signs of spinal degeneration have been reported to be present in 37% of 20-year-old asymptomatic individuals and to increase with age to 96% of 80-year-old asymptomatic individuals (11). In a group of adults (mean age of 53 years, SD \pm 16 years) with symptomatic lumbar disc herniation, spinal stenosis, or degenerative spondylolisthesis, 95% were found to have disc degeneration (88). Degeneration has been reported to be present in 19% of 15-year-olds without low-back pain compared to 42% of 15-year-olds with low back pain (89). At a follow-up of the same subjects at age 18, corresponding numbers were 26% for the initially asymptomatic cases and 58% for the cases initially reporting low-back pain (90). Disc degeneration was also more frequent among subjects with low-back pain at follow-up compared to asymptomatic cases at follow-up (90).

Lee et al. found that 15 out of 15 adolescents, treated surgically for lumbar disc herniation, showed histological signs of degeneration (91). Whether the degeneration progresses faster in adolescents operated on due to lumbar disc herniation compared to those treated non-surgically or without lumbar disc herniation is unknown. Gelalis et al. investigated the degeneration five years postoperatively in adults and found an increased degeneration (92). However, due to the lack of a control group (preferably two groups; one receiving non-surgical treatment and one without lumbar disc herniation), it remains unclear if this is an effect of surgery, the lumbar disc herniation itself or ageing.

1.3.3 Incidence of surgical intervention

The current yearly incidence of surgery for lumbar disc herniation in Sweden is 29/100,000 inhabitants (93). During the late 80s and the 90s, the mean yearly incidence was 24/100,000 inhabitants, suggesting an increase during the beginning of the 21st century (94). In Sweden, the median age for surgical treatment due to lumbar disc herniation is 45 years, and surgery for lumbar disc herniation is slightly more common among men than among women (46).

The incidence of surgery for lumbar disc herniation varies worldwide. In two of Sweden's neighbouring Nordic countries, Denmark and Norway, the yearly incidence is 46/100,000 and 58/100,000 inhabitants respectively (95, 96). For comparison, between 1978 and 1983 the yearly incidence of lumbar disc herniation surgery in the United States was approximately 70/100,000 (97, 98) whilst the estimated incidence in Great Britain was 14/100,000 in 1970 (99). Cherkin et al. compared the number of back surgeries in the United States to other countries and found, for instance, the following ratios; England 0.19, Sweden 0.33, New Zealand 0.40, Norway 0.49, Finland 0.54, Denmark 0.64 (100). This furthermore describes a large variation in surgical incidence and indicates a higher incidence in the United States compared to other countries.

Even though surgery for lumbar disc herniation is common, it is rare in adolescents and adolescents account for approximately 0.8-2.8% of the lumbar disc herniation surgeries (36, 101, 102).

1.3.4 Risk factors

Several risk factors for disc-related sciatica have been suggested. Among the adult population these include smoking, obesity, height, anxiety and depression, a history of lower back problems and male gender (85, 103). Occupational factors have also been investigated showing an increased risk in heavy manual labour, heavy lifting, exposure to vibrations and jobs that require prolonged standing and bending forwards (85, 103). Wahlström et al. found that construction workers run a higher risk of hospitalization for lumbar disc herniation than white-collar workers and foremen. For example, a plumber has a relative risk of 1.68 (95%

confidence interval 1.39–2.02) of hospitalization due to lumbar disc herniation compared to white-collar workers and foremen (103). Interestingly Wahlström et al. found height to be a more significant risk factor than smoking. For lumbar disc degeneration, there is a genetic predisposition (see “1.2.4 Pathophysiology”) as well as an association with BMI (overweight and obese) (104).

Among adolescents, the risk factors described in the literature differ from the risk factors found in adults. The most common factors are previous trauma, athletic activity, a family history of lumbar disc disease and lifting of heavy objects (35, 36, 39, 105). Kumar et al. suggested that a family history of lumbar disc disease might be due to a hereditary predisposition to early degenerative changes in the spine or weak connective tissue (35). The genetic suggestion is supported by other findings, for example, in a study of 40 patients, aged 18 years and younger, who were operated on due to a lumbar disc herniation, Matsui et al. found an odds ratio of 5.61 for a family history of lumbar disc herniation in the cases compared to controls (106). Furthermore, there are three case-reports of lumbar disc herniation occurring in pairs of adolescent monozygotic twins (107-109). Studies have shown a predominance of female adolescents undergoing surgery for lumbar disc herniation, indicating female sex as a risk factor at youth, but contradicting studies exist (5, 37-39, 110). Lavelle et al. interpreted this predominance as a consequence of differences in peak growth velocity, weight and height (5).

In line with the suggestion of Kumar et al. about hereditary predisposition, the findings of Matsui et al. and the three case-reports, there are indications that genetics play a major part in disc degeneration among adults (see “1.2.4 Pathophysiology”). Similar to what has been found in adults, there is an association between BMI (overweight and obese) and disc degeneration in adolescents (111).

1.4 TREATMENT OF LUMBAR DISC HERNIATION

The natural course of a symptomatic lumbar disc herniation is generally benign (43). For patients with a lumbar disc herniation without severe neurological deficits, the first in line treatment is non-surgical, and 80% of patients experience pain relief within 8 weeks and as many as 90-95% of patients recover without surgery within 1 year (112, 113). In adolescents, the success rate of non-surgical treatment is lower and has been reported to be 25% to 50% (5, 38, 114). Among adults, two months of non-surgical treatment reduces the number of patients requiring surgery, particularly for non-contained herniations (115). Interestingly, Ebersold et al. found that most lumbar disc herniations in adolescents are contained (116). This may be the reason why many authors have found that non-surgical treatment is not as effective in adolescents as in adults (5, 36, 38, 114). However, in adults, even though specific non-surgical treatments may offer slight relief of symptoms, there is no evidence that the measures of non-surgical treatment change the natural course of a symptomatic lumbar disc herniation (43).

In a randomised controlled study of 283 adult patients with sciatica for 6-12 weeks due to lumbar disc herniation, Peul et al. compared prolonged non-surgical treatment and early surgery (117). The non-surgical treatment included information about the favourable prognosis, prescription of analgesics, advice to resume daily activities if feasible and guidance from physiotherapist if needed. Of the cases assigned to early surgery, 11% recovered spontaneously before surgery was to be carried out. Among the cases assigned to prolonged non-surgical treatment, 39% underwent surgery within one year and another 5% within the second year. In an “intention to treat” analysis, they found that patients assigned to early surgery made a faster recovery but that the results of the interventions were similar after one and two years. In a cost-utility analysis of the same material, the faster recovery probably makes early surgery more cost-effective than prolonged non-surgical treatment both on a societal level and in quality-adjusted life years (QALYs) (118). Lequin et al. conducted a five-year follow-up of the individuals included in the study and found no significant differences between the groups regarding disability, leg pain or back pain (119). At five-years, a total of 66 patients (46%) assigned to non-surgical treatment had been operated on due to intractable sciatica. Within the five-year period, eight (12%) of these 66 patients needed repeated disc surgery, compared to nine (7%) of the patients assigned to early surgery (119). In a more recent randomised controlled trial, 128 patients with sciatica persisting for 4-12 months were enrolled 1:1 to either surgery or non-surgical treatment for six months followed by surgery if needed (120). The non-surgical treatment included education in daily functioning, activity and exercise, analgesics, active physiotherapy and patients could receive an epidural glucocorticoid injection. In the surgical group, 56 patients underwent surgery at a mean time of 3.1 weeks after enrolment, seven patients (11%) improved spontaneously and therefore cancelled their surgery and one patient had the surgery cancelled due to heart arrhythmia. In the non-surgical treatment group, 22 (34%) patients underwent surgery at a median time of 11 months after enrolment (none of these within the first 6 months except two who underwent surgery at another facility and were lost to follow-up). In an “intention to treat analysis”, the study showed a superior result of the primary outcome (visual analogue scale (VAS) for leg pain) in the surgery group compared to the non-surgical treatment group at 6 months (120). The primary outcome at 12 months and the secondary outcomes at 6 and 12 months followed the same trend, with a superior result in the surgery group, but comparative analyses were not carried out since they were not included in the original statistical plan. In summary, in patients with sciatica for 6-12 weeks and patients with sciatica for 4-12 months, surgery renders superior results at 6 months compared to non-surgical treatment (117, 120). Contrary to the results of Peul et al., Bailey et al. found a trend suggesting that these differences also persist after 12 months.

For adolescents, only retrospective and small studies comparing the long-term outcome between surgical treatment and non-surgical treatment exist (105, 121). The studies agree that surgical treatment in adolescent patients should only be considered if non-surgical treatment is ineffective.

1.4.1 Non-surgical treatment

Non-surgical treatment for lumbar disc herniation among adolescents is similar to the treatment for adults and includes limitation of strenuous physical activities, physical therapy and medications (5, 38, 114, 122-124). The medications aim to decrease inflammation and pain, to allow patients to participate in physical therapy. Medications include analgesics, muscle relaxants, anti-inflammatory agents and epidural steroid injections (5, 38, 114, 122).

If non-surgical treatment fails, the indications for surgery for lumbar disc herniation in adolescents is similar to adults and generally includes: 1) no improvement of severe pain after 4-6 weeks of non-surgical treatment, 2) disabling pain that affects daily activities, 3) cauda equina syndrome 4) progressive neurological deficits, and 5) associated spinal deformities (114).

1.4.2 Surgical treatment

There are several different surgical techniques when operating lumbar disc herniations. The three main techniques include microdiscectomy (with or without microscope), discectomy with laminotomy and percutaneous endoscopic discectomy (114, 125). The first two techniques are sometimes referred to as the umbrella term “open discectomy”. The main difference between microdiscectomy and discectomy with laminotomy is the need for removal of the lamina. In microdiscectomy, the lamina is preserved or only minimal bone resection occurs while in discectomy with laminotomy, a hemi-laminectomy or laminectomy is performed (125). Microdiscectomy is the standard treatment of lumbar disc herniation in all age groups and discectomy with decompression by laminotomy is most common in patients with a combination of lumbar disc herniation and spinal stenosis (5, 38, 126). In a systematic review of randomised controlled trials, Gotfryd et al. found that all three techniques were effective for the treatment of single-level lumbar disc herniations with no statistically significant difference regarding improvement or patient satisfaction (125). Furthermore, they found microdiscectomy and percutaneous endoscopic discectomy to be superior to discectomy with laminotomy with regard to blood loss, systemic repercussions and duration of hospital stay (125). In a randomised study from Sweden, there were no differences in perioperative bleeding, length of hospital stay or outcome when surgery was performed with microscope compared to without microscope (127). In 2011 in Sweden, about 45% of the surgeries were discectomies without the use of microscope and 41% were discectomies with the use of microscope, the overall mean stay in hospital (time from surgery to discharge) was 2.73 days (46). In 2017, corresponding numbers in Sweden were 50% and 38%, respectively, with a mean stay in hospital of 1.06 days (126).

1.4.3 Ring apophysis fracture

The existence of a ring apophysis fracture in adolescents with lumbar disc herniation is not an indication for surgery, but if non-surgical treatment is unsuccessful, surgery is an option (20, 21). There is no consensus regarding surgical technique or whether to include removal of bone fragments or not in these patients, but one study has shown similar and satisfactory results in patients undergoing discectomy and patients undergoing discectomy with removal of bone fragments (21, 22). However, large apophyseal fragments have been suggested as a risk of chronic back pain (21).

1.4.4 Complications and additional surgery following surgery for lumbar disc herniation

Complications following lumbar disc herniation surgery are rare. In a previous review the most common complications were; incidental durotomy (4-5%), intraoperative nerve root injury (1-3%), new or worsening neurological deficit (1-3%), wound complications (1-2%), postoperative leakage of cerebrospinal fluid (1%) and wound hematoma (1%) (128).

Repeat lumbar spine surgery, after surgery for lumbar disc herniation, is associated with a worse patient-reported outcome (129-134). At long-term, the prevalence of repeat surgery has been reported to be between 9% and 25% among adults and 10% and 28% among adolescents (39, 40, 47, 116, 130, 132, 135-138). In a study of individuals aged 18 years and older, younger age was a risk factor for additional surgery due to reherniation (130, 139).

1.5 RATIONALE FOR THE STUDIES

Lumbar disc herniation is a common disease among adults, but it is rarely seen in adolescents. Surgery is widely used as a treatment in adults, and adolescents only account for about 0.8-2.8% of all lumbar disc herniation surgeries (36, 101, 102). Due to its rarity, only retrospective studies of the results after surgery in adolescents existed. Information on the quality of life before and after treatment, including short and long-term results would be beneficial for patients and health care personnel in the guidance of treatment.

The incidence of surgery for lumbar disc herniation in Sweden is increasing, but there is a large variation worldwide, a variation even seen within Nordic countries, with Sweden having a lower incidence than Denmark and Norway respectively.

We hypothesised that adolescents have a similar outcome of surgery as adults at short (paper I) and long-term follow-up (paper III). We also investigated the occurrence of additional lumbar spine surgery among adolescents and young adults (paper III).

We investigated whether the above-mentioned variation in surgical incidence among three Nordic countries was associated with differences in preoperative patient characteristics and patient-reported outcomes (paper II).

The similar risk of additional lumbar spine surgery among adolescents and young adults in paper III encouraged us to investigate whether the risk was similar in older adult groups (paper IV).

Results from paper III suggested that lumbar disc herniation in adolescence is a sign of an early progressive spinal degeneration. To investigate the degeneration, we conducted the study in paper V.

2 AIMS

The overall aim of this project was to increase the knowledge of the short and long-term outcomes after surgical treatment of lumbar disc herniation in adolescence.

To achieve the overall aim, we had several specific aims. Our first specific aim was to describe the short-term patient-reported outcome measures after surgery for lumbar disc herniation in adolescents compared to adults.

Secondly, we aimed to describe and compare the risk of additional lumbar spine surgery and to describe any long-term changes in patient-reported outcomes after surgery for lumbar disc herniation in adolescents and different adult age groups.

Thirdly, we aimed to investigate whether an up to two-fold national variation in surgical incidence of lumbar disc herniation was associated with differences in preoperative patient characteristics and short-term patient-reported outcomes.

Lastly, we aimed to describe the prevalence of lumbar spine degeneration after lumbar disc herniation surgery in adolescence.

3 PATIENTS AND METHODS

3.1 DATA SOURCES

3.1.1 The spine registers

All papers included in this thesis are based, or partly based, on data from the Swedish spine register, Swespine. Papers I, III, IV and V originate from the same cohort collected from Swespine between January 1st, 1998 and March 31st, 2011. Paper II used a cohort of patients collected between January 1st, 2011 and December 31st, 2013 from three Nordic spine registers; Swespine, the Danish spine register (DaneSpine) and the Norwegian spine register (NORspine).

With the aim of prospectively collecting data on lumbar spine surgeries, Swespine started in 1993. In 1998 Swespine became nationwide and started to include patients operated on due to lumbar disc herniation (46). Since the late 90s, the register is managed by the Swedish Society of Spinal Surgeons (<http://www.4s.nu/>). Since its implementation, the coverage, i.e. the proportion of operating centres reporting to Swespine, and the completeness, i.e. the proportion of operated patients reported to Swespine, have increased. During 2011 the coverage was approximately 90%, the completeness was approximately 75% and the register had a one-year follow-up rate of approximately 75-80% (46). Today the completeness is approximately 85% (personal communication, the Swespine register). The accuracy of registered diagnoses in Swespine is 97% (140).

DaneSpine was created based on Swespine and has, since 2009, been sequentially implemented (141). From 2011 to 2013 the coverage was approximately 80%, the completeness was approximately 64%, and the follow-up at one year was approximately 57% (95, 142).

NORspine was established in 2007, based on a local clinical registry and experiences from Swespine (143). From 2011 to 2013 the coverage was approximately 95%, the completeness was approximately 65%, and the follow-up at one year was approximately 66% (143). The accuracy of registered diagnoses in NORspine is 97% (144).

Swespine collects patient-completed questionnaires at admission for surgery (baseline), then after one year, two years, five years and ten years (46). The baseline questionnaire includes self-assessed information on anthropometrics, work status, smoking, duration of leg and back pain, co-morbidity, physical back function, leg and back pain and quality of life. At the follow-ups, a similar questionnaire, including satisfaction and global assessment, is mailed to the patient. All questionnaires are completed without the assistance of health care personnel. The surgeon registers diagnosis, type of surgical procedure and any complications occurring during the hospital stay on a separate form. All reoperations and new lumbar spine surgeries are registered by the surgeon performing the additional surgery. In Swespine, a reoperation is classified as a new surgery on the same level and laterality and due to the same diagnosis as

the index surgery. All other additional surgeries are classified as new index surgeries. In the case of a new index surgery, the follow-up of the original index surgery is terminated, and questionnaires will be mailed to the patient at one, two, five and ten years after the new index surgery.

DaneSpine and NORspine use a similar data collection as Swespine, but in NORspine, follow-ups are done at three and 12 months postoperatively as compared to one, two, five and ten years in Swespine and DaneSpine (46, 142, 143). All registers contain the patient-reported outcome measures; patient satisfaction, global assessment, Oswestry disability index (ODI) and EuroQol-5 Dimensions-3 Levels (EQ-5D-3L). Swespine and DaneSpine contains the visual analogue scale (VAS) for leg and back pain while NORspine contains the numerical rating scale (NRS) for leg and back pain. Swespine and DaneSpine also contain the Short-form health survey, 36 items (SF-36).

3.1.2 Controls

The controls in paper V were collected through local advertisement on the Karolinska Institutet, the Karolinska University Hospital and three private companies within the Stockholm County (two within the telecom business and one within the mechanical industry). Exclusion was made for controls with any known previous lumbar disc herniation or any previous spine surgery.

3.1.3 Magnetic resonance imaging

In paper V, imaging data was produced for all participants between May 2019 and January 2020. Collection of identical sequences for all participants was done using a 3.0 T scanner (Discovery MR750, GE Healthcare) at MR Research Center, Karolinska Institutet, Stockholm, Sweden. Imaging included sagittal T1-weighted, T2-weighted and Short Tau Inversion Recovery (STIR) sequences of the lumbar spine.

3.2 OUTCOME MEASURES

3.2.1 Patient satisfaction and global assessment of leg and back pain

Patient satisfaction and global assessment of leg and back pain were the primary outcomes in paper I and have also been used in papers III-V. The patient satisfaction question is formulated as “Are you satisfied with the surgical result?” and the possible answers are “satisfied”, “uncertain” and “dissatisfied”. For analyses in papers I, III and IV, the answers were dichotomized into “satisfied” vs. “uncertain” and “dissatisfied”.

The global assessment questions for leg and back pain are formulated as “How is your leg pain today when compared to before surgery?” and “How is your back pain today when compared to before surgery?”. The possible answers to both questions are “pain free”, “much better”, “somewhat better”, “unchanged” and “worse”. For analyses in papers I, III and IV, the answers were dichotomized into “pain free” and “much better” vs. “somewhat better”, “unchanged” and “worse”. Global assessment has been proven as a viable overall patient-reported outcome measure within spine surgery, especially for pain and function but also for mental state and quality of life (145, 146).

3.2.2 ODI, EQ-5D-3L, VAS, NRS, and MCS and PCS of SF-36

Oswestry disability index (ODI), EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) and visual analogue scale (VAS) were used in all papers (VAS was converted into numerical rating scale (NRS) in paper II). Mental component summary score (MCS) and physical component summary score (PCS) of Short-form health survey, 36 items (SF-36) were used in papers III, IV and V.

ODI is a back specific index measuring disability due to back pain on a scale from 0; no disability to 100; maximum disability (147). ODI is condition-specific and by some considered the gold standard in measuring outcome in spinal disorders (147). ODI consists of 10 questions with six choices for each question. Each answer gives a point from zero to five and the index is calculated by dividing the total score by the maximum possible score times 100. If a question is not answered, the maximum possible score is adjusted appropriately according to the formula below. Different thresholds for postoperative ODI and ODI improvement after spine surgery have been suggested. These are; acceptable symptom state (postoperative ODI ≤ 22), minimal clinically important difference (MCID) (improvement of 10-14) and successful result (improvement of ≥ 20) (148-153).

$$\frac{\text{Total score}}{\text{Answered questions} \times 5} \times 100 = ODI$$

EQ-5D-3L is an instrument for classifying the patient’s health status in three levels of five dimensions (154). The five dimensions are; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension gives a score between 1; no problems and 3; severe problems. Between an individual answering one to all questions (perfect health) and an individual answering three to all questions (worst possible state of health) there are 241 other different health states in this system (154-156). By using a tariff based on scores in a general population, all 243 health states correspond to a single index value where 1 is perfect health and 0 is death. Swespine uses the United Kingdom time trade-

off (UK-TTO) tariff. The UK-TTO was used for all papers in this thesis and ranges from -0.59 to 1, with a negative score meaning that the current state of health is worse than death (154, 155). The MCID for EQ-5D-3L has been suggested to be 0.20 (153). For EQ-5D-3L, an improvement corresponding to a successful result has been suggested to be ≥ 0.30 (149).

The VAS was used for measuring leg pain and back pain. The VAS is a 100 mm long horizontal line, marked with “no pain” on the left side (corresponding to 0) and “worst possible pain” marked on the right side (corresponding to 100) (157). The VAS used in the papers of this thesis asks the individual to mark their pain intensity during the last week on the horizontal line. It has been suggested that by allowing the individual to freely mark their pain on the line, VAS, with its scale from 0-100, is more sensitive than scales with fewer, set options (158). The MCID for VAS back pain has been suggested at 15-19 while MCID for VAS leg pain after spine surgery is missing (151, 152). However, there are suggested MCID values for NRS leg pain which can be used if multiplied by 10. An improvement in VAS back pain of 23 and an improvement in VAS leg pain of 58 have been suggested to correspond to a patient-reported outcome as “much better” in back and leg pain respectively (159).

The NRS was also used for measuring leg pain and back pain. The NRS is a visual scale with the numbers 0 to 10 written and the labels “no pain” to the left of the 0 and “worst possible pain” to the right of the 10 (160). In NORspine the individual marks a number corresponding to their pain intensity during the last week. In paper II, NRS was used for leg pain and back pain but since Swespine and DaneSpine uses VAS, the VAS was converted to NRS by dividing the VAS score by 10 with stochastic approximation of decimals to the closest integer. The suggested MCID for NRS leg pain and back pain are 1.6-1.7 and 1.2 to 2.0, respectively (150, 152, 153). An improvement corresponding to ≥ 3.5 for leg pain and ≥ 2.5 for back pain has been suggested as threshold for a successful result (149).

The MCS and PCS of SF-36 measures the individual’s mental and physical health on a scale from 0; poorest health to 100; best health (161). SF-36 consists of 36 questions from which eight domains are calculated; Vitality, Social functioning, Role-emotional, Mental health, Physical functioning, Role-physical, Bodily pain and General health. From these domains, two summary measures can be calculated, the MCS and PCS. MCS is derived from the first four domains and PCS from the last four domains (161). The MCID for MCS has been suggested to be 6.8 and for PCS 4.6 to 4.9 (150, 162).

3.2.3 Additional lumbar spine surgery and additional lumbar disc herniation surgery

In paper III and paper IV, data from Swespine on reoperations and new index surgeries were used and divided into additional lumbar disc herniation surgery (i.e. reoperations and new index surgeries due to a lumbar disc herniation) and additional lumbar spine surgery (i.e. all

additional lumbar spine surgeries, including reoperations and lumbar disc herniation surgeries).

3.2.4 Pfirrmann grade, Modic changes and TEP-score

In paper V, we assessed and compared disc degeneration according to the morphologic and semi-quantitative Pfirrmann grading system and we assessed and compared changes in the vertebral endplate and body according to Modic and total endplate score (TEP-score) (55-57). All three measures have sufficient intra- and interobserver reliability (57, 74, 88).

According to the Pfirrmann grading system each level was scored from Grade 1: homogeneous disc with bright hyperintense white signal intensity and normal disc height (no degeneration) to Grade 5: inhomogeneous disc with a hypointense black signal intensity, no difference between nucleus and anulus and the disc space is collapsed (severely degenerated) (55). For analysis, the Pfirrmann grades were dichotomized into no/moderate degenerative changes (grade 1-3) and severe degenerative changes (grade 4-5) (57).

Changes in the vertebral endplate and body were assessed according to Modic (56, 163). The four types of Modic changes are; Type 0: no changes, Type 1: oedema, Type 2: fat replacement, Type 3: subchondral bony sclerosis. For analysis the Modic changes were dichotomized for each segment (highest grade above or below each disc was used) into absence (grade 0) and presence (grade 1-3).

Endplate defects were assessed for each endplate and graded 1 to 6 according to Rajasekaran et al. (57). Endplate defects are classified according to the severity of endplate damage: Type 1: no endplate defects, uniform symmetrically concave hypointense band; Type 2: focal thinning of the endplate but no breaks; Type 3: focal disc marrow contact regions with normal contour of the endplate; Type 4: endplate defect up to 25% of the width and typical depression; Type 5: endplate defect up to 50% of the width and typical depression; Type 6: complete endplate damage with endplate irregularity or sclerosis (57). Endplate defects were then converted into total endplate score (TEP-score) for each segment (the sum of the grades above and below each disc, range 2 to 12). For analysis, the TEP-score was dichotomized into <6 and ≥ 6 (57).

3.2.5 IPAQ-SF, smoking and occupational strain

In paper V, for a better comparison of the patients and controls, we used additional questions regarding physical activity, smoking and occupational strain. The International Physical Activity Questionnaire – Short Form (IPAQ-SF) (translated to Swedish) was used to assess physical activity. Activity at three different levels (walking, moderate and vigorous) performed for at least 10 minutes during the last 7 days when filling in the questionnaire was

recorded (164). Activities exceeding 180 minutes per day was coded as 180 minutes, all according to the guidelines of data processing of IPAQ-SF. Activity level and Metabolic Equivalent Task (MET) minutes per week were calculated (165).

In Swespine, only smoking at admission for surgery, and not at follow-up, was recorded before 2016. For a better comparison we added a detailed question about smoking status. The three alternatives were non-smoker, current smoker and previous smoker. If the participant was a current or previous smoker there were questions regarding cigarettes per day and years of smoking. Calculation was made for “pack years” with the following formula.

$$\frac{\text{Number of cigarettes per day} \times \text{years smoking}}{20 \text{ (one pack of cigarettes)}} = \text{Pack years}$$

Occupational strain was evaluated by a four-level question; predominantly sedentary occupation, sitting or standing with some walking, walking with some handling of material and heavy manual work (166).

3.3 POPULATION

3.3.1 Papers I, III and IV

The patients in papers I, III and IV originate from the same Swespine cohort. The flowchart for the three papers is shown in Figure 2. In all three papers, patients with first-time spine surgery, operated on with discectomy only due to a lumbar disc herniation, were included. Exclusion was made for missing short-term follow-up (i.e. missing both one and two-year follow-up).

Paper I includes 10,615 patients of all ages and the patients were divided into three groups; age ≤ 18 years (n=151), age 19-39 years (n=4,386) and age ≥ 40 years (n=6,078) and the patients were monitored for the short-term outcome.

In paper III patients aged 39 years and younger were included and divided into two groups; age ≤ 18 years (n=151) and age 19-39 years (n=4,386). All patients were monitored for the risk of additional lumbar spine surgery. Patients with long-term follow-up (consisting of five- and ten-year follow-up) were monitored for PROMs (n=88 and n=2,628 respectively).

In paper IV patients aged 40 years and older were included and divided into two groups; age 40-59 years (n=4,844) and age 60 years and older (n=1,234). All patients were monitored for the risk of additional lumbar spine surgery. Patients with long-term follow-up (consisting of five- and ten-year follow-up) were monitored for PROMs (n=3,209 and n=852 respectively).

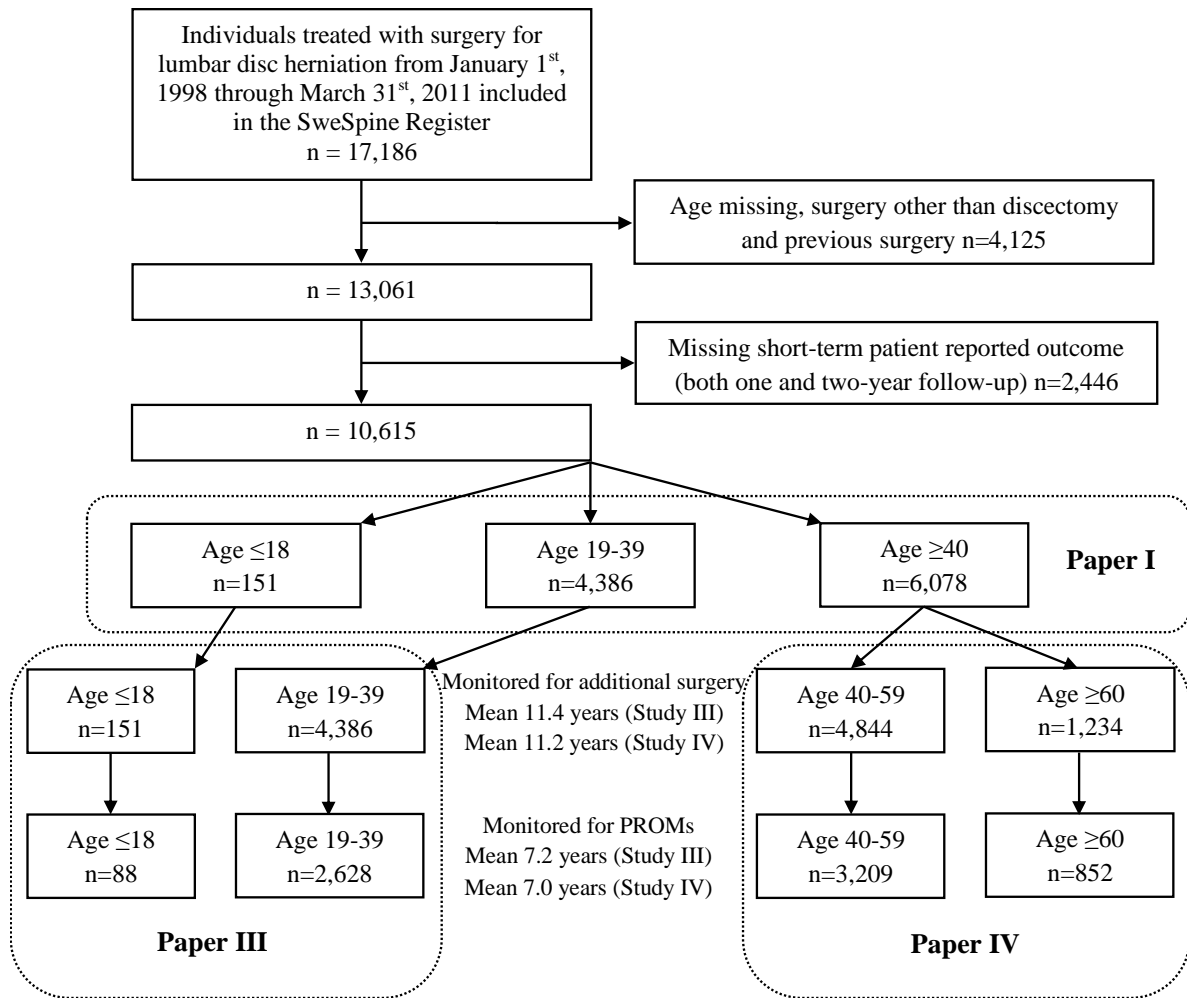


Figure 2. Flowchart of the participants in papers I, III and IV.

3.3.2 Paper II

The patients in paper II originate from a pooled cohort from Swespine, DaneSpine and NORspine. The flowchart for paper II is shown in Figure 3. Patients aged 18-65 years, without previous spine surgery, operated on with discectomy only were included. Exclusion of patients with values considered outliers for weight, height and BMI was carried out as was exclusion of patients missing the one-year follow-up (Figure 3.). In total, 6,468 patients were included and separated by country, giving a total of 2,408 patients from Sweden, 1,631 patients from Denmark and 2,429 patients from Norway.

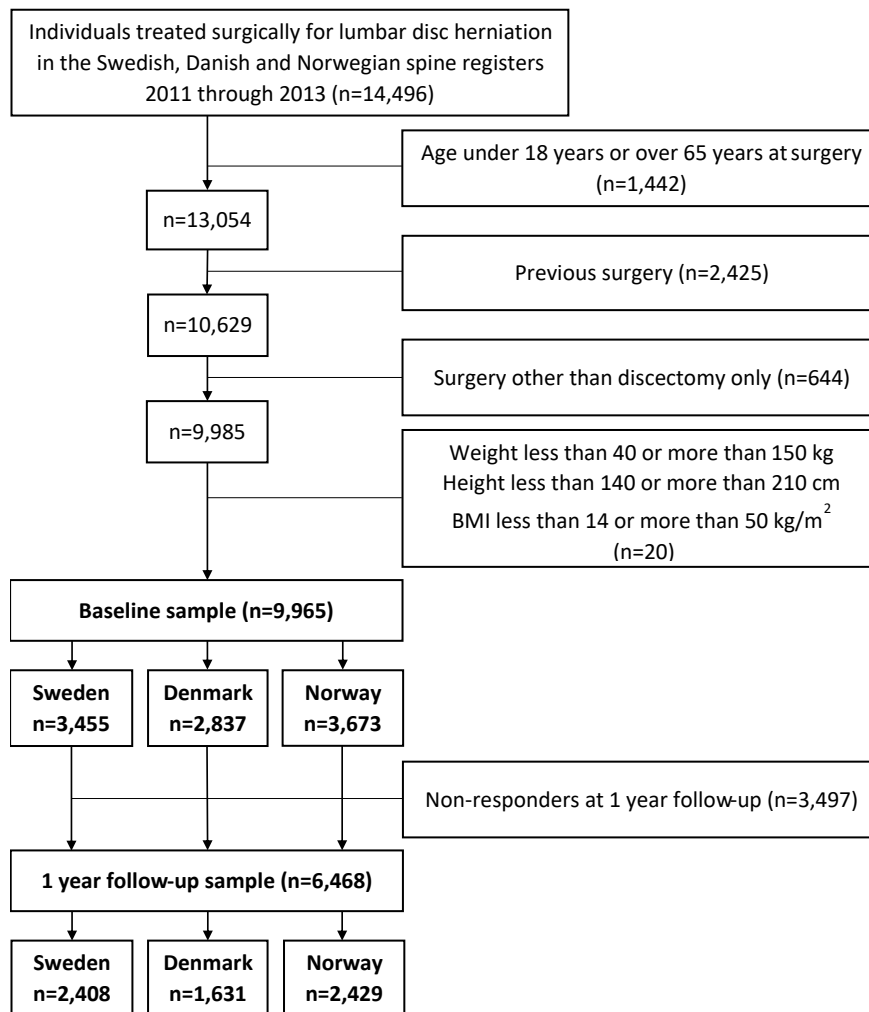


Figure 3. Flowchart of the participants in paper II.

3.3.3 Paper V

The participants in paper V originate from two different sources, patients and controls. The flowchart for paper V is shown in Figure 4. The patient material was collected from the 151 patients aged ≤ 18 years used in papers I and III. The unique Swedish social security number system makes it possible to track and, if necessary, contact patients even a long time after their surgery. Of the 151 individuals, 40 had a current postal address within Stockholm County and were contacted for participation in the study. Eleven individuals did not reply despite three attempts. Of the 29 individuals who replied, six had a relative contraindication for MRI, declined to participate or were unavailable for MRI during the study period. The remaining 23 individuals were included in the study and had a mean follow-up time of 13.8 years.

In total, 58 individuals without exclusion criteria replied to the advertisement to act as controls (see “3.1.2 Controls”). For each of the 23 operated individuals, one control was matched for age, sex and if possible current occupation.

All participants included (n=46) underwent the same MRI sequence and replied to the same questionnaire, containing questions about anthropometrics, physical activity, smoking habits, occupational strain and PROMs.

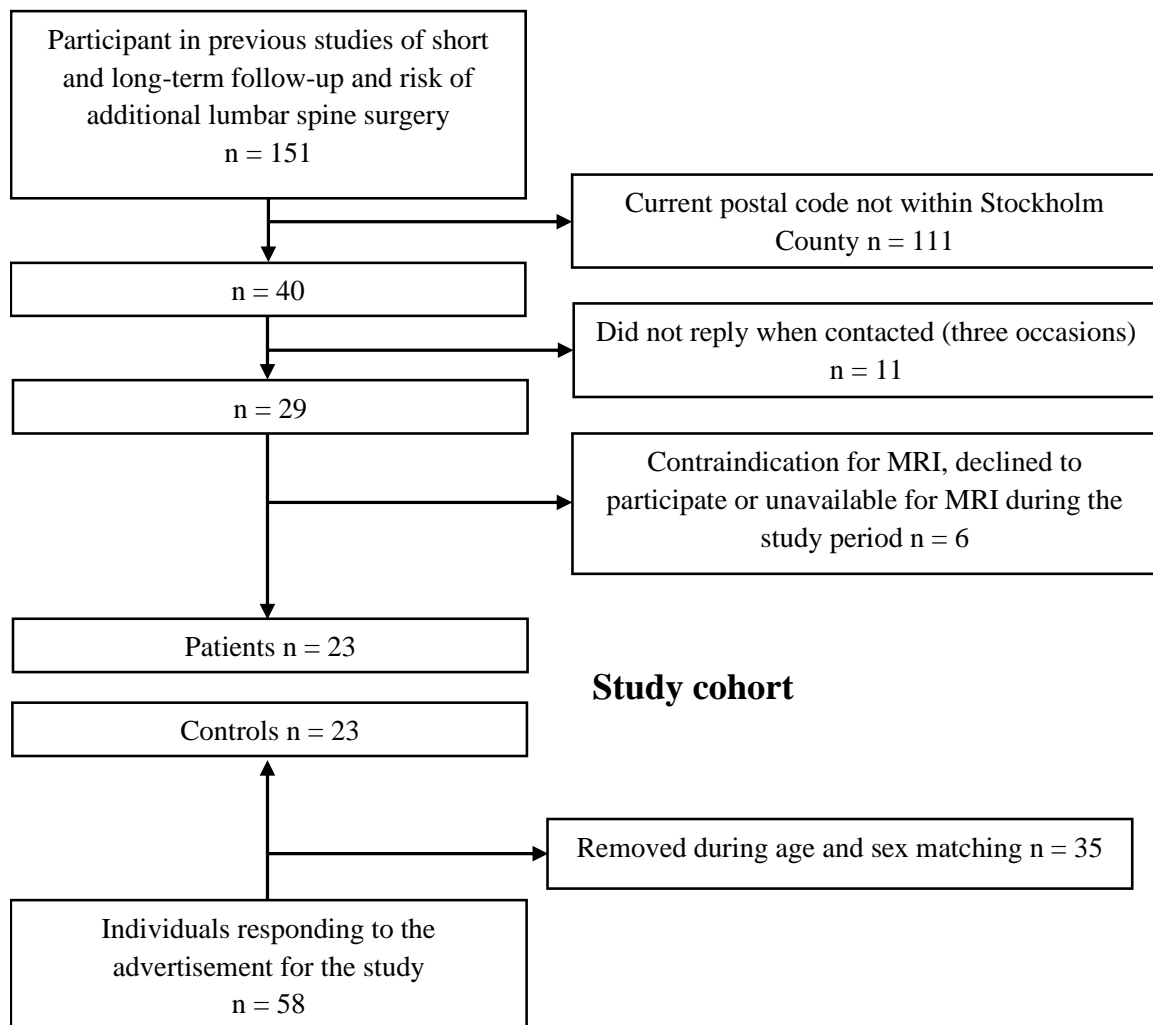


Figure 4. Flowchart of the participants in paper V.

3.4 STUDY DESIGN AND STATISTICAL METHODS

3.4.1 Choice of study design

Papers I, II, III and IV are all observational cohort studies of prospectively collected material, even though the study designs are retrospective. Paper V has an observational case-control study design.

It has been suggested that observational studies overestimate the treatment effect (167) but in rare conditions, like severe spinal disorders in adolescents, it is difficult, or even impossible, to achieve the highest level of evidence for treatment, i.e. randomised controlled trials. In these cases, prospective observational studies may be a feasible alternative. Jacobs et al.

compared randomised controlled trials and observational studies within spine surgery and concluded that important and valid conclusions can be drawn from observational studies (168). Within other fields, observational studies have also shown results similar to randomised controlled trials (169, 170). The use of multicentre studies increases the external validity of the findings. In papers I, III and IV, different age groups are compared, which could be a source of bias since there are naturally occurring differences between age groups (171). In papers I, III, IV and V, outcomes, such as global assessment, that are dependent on the individual's ability to recall their condition before surgery were used. These questions are subject to a risk of recall bias, i.e. recalled information may not be fully accurate (172).

Paper V is a case-control study comparing the long-term MRI findings and PROMs in patients collected from Swespine to age and sex-matched controls. When constructing a case-control study, it is essential to have a representative control group (172, 173). The target with a control group is to collect a group that would have been the same as the cases, if the cases had not had an exposure (in our case, surgery due to a lumbar disc herniation in adolescence). By excluding controls with any known disc herniation or prior spine surgery, but not excluding those with current or prior back pain or other back conditions, and matching by age, sex and, if possible, current occupation, we aimed to produce a representative control group. To avoid selection bias, the controls were collected from the same geographic area as the operated individuals. To avoid observer bias, the primary outcome (MRI) was analysed randomly and blinded, i.e. without knowledge of patient characteristics and group belonging (174). However, even if MRI assessments were blinded, group belonging may have been assumed due to the nature of the condition, causing a risk of observer bias. Furthermore, we cannot exclude the possibility that other factors, such as where we advertised for controls, might have caused a selection bias (172). Neither can we exclude the possibility that there was a self-selection bias, i.e. that the individuals who chose to participate were not representative of the operated group or of the general population (175). In the study, we compared all known variables between the groups in order to investigate whether we had collected a representative control group. All participants were asked about their smoking status and, if they were smokers or previous smokers, they were asked for detailed information about cigarettes per day and years smoking. This question is subject to a risk of response bias (e.g. participants might have under-reported their smoking in fear of being criticised) and the remembrance of cigarettes per day and years smoking are also subject to a risk of recall bias (172).

3.4.2 Statistics

Data were presented as median (25th and 75th percentiles and range) (paper I), mean (95% confidence interval (95% CI)) (papers II, III, IV and V) or number (%) (all papers). In case of missing data, cases were excluded analysis by analysis (all papers). Analyses in papers I, III, IV and V were done using IBM SPSS Statistics versions 22 to 26 (IBM Corp., Armonk, NY,

USA) and analyses in paper II were done using R version 3.3.3 (R Foundation for Statistical Computing).

Exclusion of cases analysis by analysis was used in all papers. This method preserves more information compared to complete deletion of cases with some missing data (176). However, the different statistical tests might use different sets of data and use different sample sizes, which will affect the standard error. This method is less likely to be biased if the data is missing at random (176). A study of Swespine indicates that the cases not responding at follow-up are mostly missing at random (177) and we believe that the majority of the missing values in our material were missing at random.

Papers I and II were subject to a statistical limitation. When analysing more than two groups within the same statistical test, the test only says whether there is a difference, not where the difference occurs (e.g. between group one and two, two and three or one and three) (178). This limitation could have been eliminated by adding group-to-group comparison. However, this was not done in papers I and II.

Group comparisons of categorical data (i.e. nominal and ordinal data) were done using the Pearson's chi-square test in all papers. The Pearson's chi-square test examines if there is a similar distribution between the groups (178).

The Welch's F test (paper I) and the Welch-Satterthwaite t-test (also known as the Welch's t-test or the unequal variance t-test) (papers III, IV and V) were used for group comparison of continuous variables. The Welch's t-test is an adoption of the Student's t-test (179). Welch's t-test is more reliable than the Student's t-test when the groups have unequal variances and/or unequal sample sizes (179, 180).

The analysis of covariance (ANCOVA) was used for testing of covariates (paper I). ANCOVA is a general linear model that can be seen as a combination of analysis of variance (ANOVA) and regression analysis (181).

For tests of differences within groups, the Wilcoxon signed-rank test was used for continuous dependent variables (papers I, III and IV) and the McNemar test was used for categorical variables (papers III and IV). These tests are designed for testing differences in related or paired samples (182, 183).

The ANOVA F test, the Student's t-test, the Likelihood ratio chi-square test and linear regression tests were used in paper II. The ANOVA F test is sensitive to non-normality and tests the equality of means in three or more groups (184). The Student's t-test tests the difference between means in different groups and can be used when equal variances can be assumed (179, 180). The Likelihood ratio chi-square test tests the significance of the null hypothesis (185). A linear regression test was used to predict the impact of risk factors on the tested variable (186). Significance was presented as unadjusted p-values and adjusted p-values obtained after case-mix adjustments.

The Cox cumulative hazard function and the Cox proportional hazard regression were used to describe the risk of additional lumbar spine surgery (papers III and IV). The Cox cumulative hazard function was used to illustrate the risk over time and the Cox proportional hazard regression was used to calculate the hazard ratio for one group in relation to another group (e.g. adolescents in relation to young adults) (187). The Cox proportional hazard regression was also done with the addition of sex and smoking (yes/no) as covariates. Cases were censored at the end of follow-up or in case of death.

4 ETHICS

Ethical approval for all studies included in this thesis has been obtained from the relevant Ethical Review Boards.

In all papers, the interventions had already been made as part of the regular treatment of the disorder and answering questionnaires with patient-reported outcome measures before and after treatment may be considered a relatively small intrusion in the individual's privacy. Swespine and DaneSpine apply the opt-out method but answering questionnaires is voluntary. NORspine applies the opt-in method and informed consent is collected.

In paper V, previously operated cases were contacted, which may be considered a breach of privacy, however since all participation was voluntary, we considered it to be small. All cases and controls were given, and signed, an informed consent before the MRI examination and completion of the questionnaire. All participating cases in paper V were offered a clinical examination if wanted. Magnetic resonance imaging is considered safe.

All participants could, at any time, withdraw their participation without giving any reason. All data are kept under secure conditions. Data were anonymized when analysed.

5 RESULTS

5.1 PAPER I

The patients included were divided into three groups (≤ 18 years old, 19-39 years old and 40 years and older) according to Figure 2.

There were significant differences in the proportion of patients with a duration of back and leg pain ≥ 3 months between the groups (both $p=0.001$), with the adolescent group having the highest proportion. Differences between the groups were also seen for the proportion of women ($p=0.030$) and proportion of smokers ($p<0.001$) with the adolescent group having the highest and lowest proportion, respectively. At baseline, there were no significant differences between the groups regarding VAS leg and back pain ($p=0.37$ and $p=0.18$, respectively) while there were significant differences in ODI and EQ-5D-3L (both $p<0.001$) with lower ODI and higher EQ-5D-3L among the adolescents.

At short-term follow-up, the primary outcomes, satisfaction and global assessment of leg and back pain, differed between the groups (all $p<0.001$, Table 1). There was a higher proportion of satisfied patients and a higher proportion of patients reporting “pain free” or “much better” for both leg and back pain in the adolescent group. The p -values remained significant after adjustment for sex, smoking, type of disc herniation and duration of preoperative leg and back pain.

Table 1. Satisfaction and global assessment one to two years after surgery. Data are given as numbers (%). Unadjusted p -values are given for the Pearson’s chi-square test, and adjusted p -values are given for analysis of covariance after adjustment for sex, smoking, type of disc herniation and duration of preoperative leg and back pain for the differences between the three groups. Numbers in the table do not always correspond to group numbers due to missing data.

	Age ≤ 18 years (n=151)	Age 19-39 years (n=4,386)	Age ≥ 40 years (n=6,078)	Unadjusted p-value	Adjusted p-value
<u>Satisfaction</u>					
Satisfied	128 (86%)	3,362 (78%)	4,479 (76%)	$p<0.001$	$p=0.043$
Uncertain/dissatisfied	21 (14%)	925 (22%)	1,436 (24%)		
<u>Global assessment leg pain^a</u>					
Pain free/much better	130 (87%)	3,337 (78%)	4,191 (71%)	$p<0.001$	$p<0.001$
Somewhat better/unchanged/worse	20 (13%)	951 (22%)	1,691 (29%)		
<u>Global assessment back pain^b</u>					
Pain free/much better	120 (88%)	3,025 (73%)	3,959 (70%)	$p<0.001$	$p<0.001$
Somewhat better/unchanged/worse	17 (12%)	1,108 (27%)	1,714 (30%)		

^aThere were 0 adolescents, 43 younger adults and 94 older adults who did not experience leg pain before surgery.

^bThere were 12 adolescents, 189 younger adults and 312 older adults who did not have back pain before surgery.

All groups improved significantly from baseline to short-term follow-up in all secondary outcomes (all $p < 0.001$, Figure 5). At short-term follow-up, significant differences were seen between the groups for all secondary outcomes (all $p < 0.001$). The adolescent group had the lowest VAS for leg and back pain, the lowest ODI and the highest EQ-5D-3L (Figure 5). Adjustment for sex, smoking, type of disc herniation and duration of preoperative pain did not change the outcomes substantially.

The rate of reoperation within two years after surgery did not differ between the three groups ($p = 0.12$).

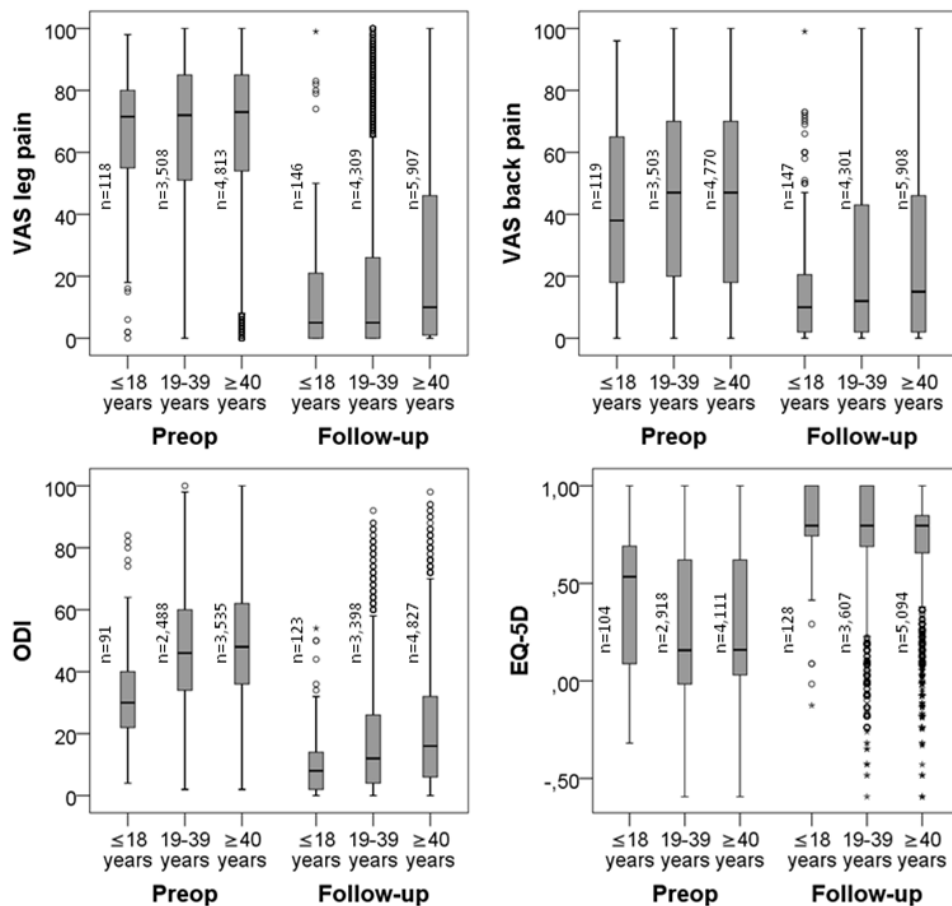


Figure 5. Comparison of secondary outcomes preoperatively and at follow-up. The boxes show median and interquartile ranges; inner fences represent minimum and maximum values or 1.5 times the interquartile range. Outliers are indicated, and “n” denotes the number of patients available in each group.

5.2 PAPER II

The flowchart for the study is shown in Figure 3. Preoperatively, there were significant differences between the countries in age ($p < 0.001$), BMI ($p < 0.001$), sex ($p = 0.003$), smoking status ($p < 0.001$), presence of any co-morbidity ($p < 0.001$) and preoperative duration of leg and back pain (both $p < 0.001$). In Sweden, a lower proportion of the patients were smokers (16% vs 33% and 30%) and the patient had a longer duration of leg pain compared to the patients in Denmark and Norway. Significant differences were also seen for the baseline

patient-reported outcome measures ODI, NRS leg pain, NRS back pain and EQ-5D-3L (Figure 6). The Danish patients had the lowest NRS leg and back pain, the highest EQ-5D-3L and, together with the Norwegian patients, the lowest ODI. The Norwegian patients also had the highest NRS back pain. The Swedish patients had the highest ODI and NRS leg pain and the lowest EQ-5D-3L.

At follow-up (one year), significant differences between the countries were observed in all outcome variables except for EQ-5D-3L (Figure 6). The Norwegian patients had less disability according to ODI but more back pain according to NRS compared to the patients from Denmark and Sweden. The Swedish patients had less leg pain according to NRS compared to the patients from Denmark and Norway. After case-mix adjustment, the significance was unchanged for ODI, attenuated for NRS leg and back pain and the difference in EQ-5D-3L was now significant.

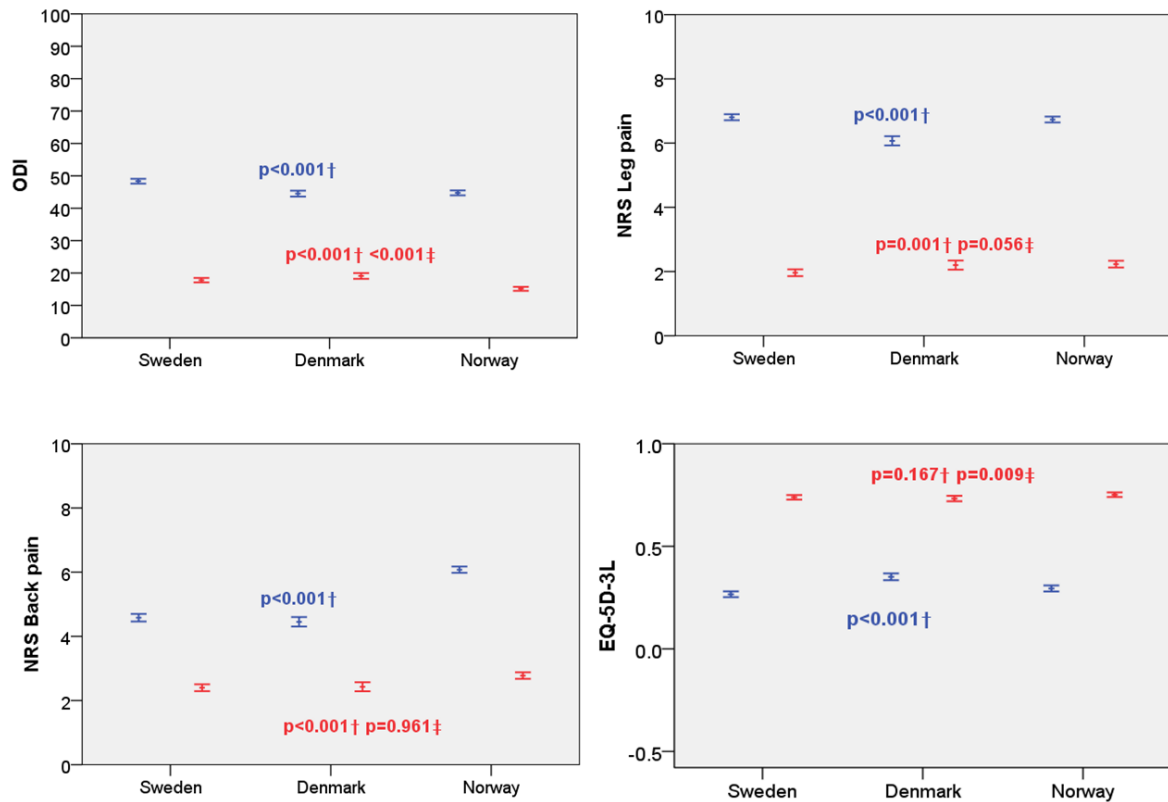


Figure 6. Preoperative and postoperative absolute values. Comparison of absolute outcome values at baseline (blue) and at follow-up (red). Data are presented as mean and 95% confidence interval. p values are given for the ANOVA F test for the comparison between the countries. † Non-adjusted p-value, ‡ Adjustment for baseline age, sex, BMI, smoking, any co-morbidity, duration of leg pain and preoperative value of the dependent variable.

In mean improvement from baseline to follow-up, there were significant differences between the countries in all outcomes (Table 2). The patients from Denmark had smaller mean improvements in all outcomes compared to the patients from Norway and Sweden. After

case-mix adjustment, the differences were attenuated except for ODI which remained unchanged and significant. The difference in EQ-5D-3L also remained significant.

Table 2. Change in outcome from baseline to one-year postoperative. Data is shown as mean (95% CI). P values are given for the ANOVA F-test for the comparison between the countries.

	Sweden	Denmark	Norway		
Total (n = 6468)	(n = 2408)	(n = 1631)	(n = 2429)	p-value [†]	p-value [‡]
ODI	-31 (-31 to -30)	-25 (-27 to -24)	-30 (-31 to -29)	<0.001	<0.001
NRS leg pain	-4.8 (-5.0 to -4.7)	-3.9 (-4.0 to -3.7)	-4.5 (-4.6 to -4.4)	<0.001	0.056
NRS back pain	-2.2 (-2.3 to -2.0)	-2.0 (-2.2 to -1.9)	-3.3 (-3.4 to -3.2)	<0.001	0.961
EQ-5D-3L	0.47 (0.46 to 0.49)	0.38 (0.36 to 0.40)	0.46 (0.44 to 0.47)	<0.001	0.009

[†]Non-adjusted p-value [‡]Adjustment for baseline age, sex, BMI, smoking, any co-morbidity, duration of leg pain and preoperative value of the dependent variable.

In an extended analysis of the primary outcome, ODI, there was a smaller proportion of patients from Denmark reaching a clinically relevant outcome compared to patients from Norway and Sweden.

In linear regression analyses, predictors for the outcome in ODI, NRS leg pain and NRS back pain were examined. The predictors examined were; country, sex, age, BMI, smoking, any co-morbidity, preoperative duration of leg pain ≥ 3 months and the preoperative value of the dependent variable. The three predictors with the strongest association to a poor outcome were the same in the three analyses; smoking status, any co-morbidity and preoperative duration of leg pain ≥ 3 months.

5.3 PAPER III

The flowchart for the study is shown in Figure 2. At baseline, the patient characteristics for all included patients (n=4,537) differed between the adolescent group (≤ 18 years old) and the young adult group (19-39 years old). The adolescent group had a larger proportion of L4-L5 disc herniations, a smaller proportion of L5-S1 disc herniations and a smaller proportion of smokers. The adolescent group had a significantly better baseline condition according to ODI, EQ-5D-3L, and MCS and PCS of SF-36 while there were no differences between the groups in VAS leg and back pain.

At a mean follow-up of 11.4 years, 24 (16%) of the adolescents had undergone at least one additional lumbar spine surgery compared to 772 (18%) of the young adults. Corresponding numbers for additional lumbar disc herniation surgery was 16 (11%) and 455 (10%) respectively. With the young adult group as a reference, the risk of at least one additional lumbar spine surgery and the risk of additional lumbar disc herniation surgery in the adolescent group were 0.9 (0.6-1.4) and 1.0 (0.6-1.7) respectively (Figure 7). Adjustment for smoking did not alter the results in a substantial way.

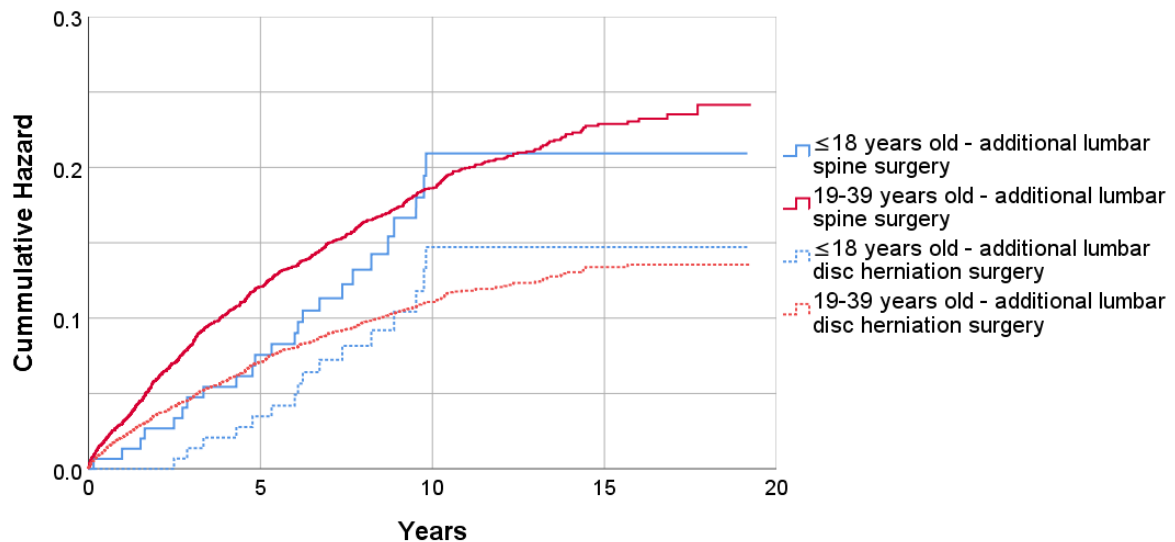


Figure 7. Cox cumulative hazard functions for the probability of at least one additional lumbar spine surgery (unbroken line) and additional lumbar disc herniation surgery (dotted line) in the two age groups. Patients are censored in case of death or at last date of follow-up.

A total of 2,716 patients were monitored for long-term (mean 7.2 years) patient-reported outcome measures. Within this sub-cohort, both age groups improved significantly from preoperative to short-term follow-up according to ODI, VAS for leg and back pain, EQ-5D-3L, and MCS and PCS of SF-36 (all $p < 0.001$). At short-term follow-up of these patients, the adolescent group had a higher proportion of patients being “pain free” or “much better” according to global assessment for both leg and back pain, a lower ODI, a lower VAS for back pain, a higher EQ-5D-3L and a higher PCS of SF-36 (all $p \leq 0.037$).

Within the adolescent group, there were no significant differences between short and long-term follow-up in any patient-reported outcome measure (all $p \geq 0.061$) except for global assessment where a smaller proportion reported themselves as “pain free” or “much better” at long-term follow-up ($p = 0.021$). In the young adult group, a larger proportion were satisfied at the long-term follow-up compared to the short-term follow-up ($p = 0.003$). In the young adults, there were also the following significant changes between the short and long-term follow-up (all $p \leq 0.013$); ODI -1 point, VAS leg pain -1 mm, VAS back pain -1 mm, EQ-5D-3L index +0.01 points, SF-36 MCS -1 point and PCS +1 point.

5.4 PAPER IV

The flowchart for the study is shown in Figure 2. In the group of elderly patients (60 years and older) and in the group of adult patients (40-59 years old), 139 (11%) and 683 (14%), respectively, had undergone at least one additional lumbar spine surgery at a mean follow-up of 11.2 years (Figure 8). Corresponding numbers for additional lumbar disc herniation surgery were 56 (5%) and 320 (7%) respectively. With the adult group as a reference, the hazard ratio for at least one additional lumbar spine surgery in the elderly group was 0.83 (0.69-0.99). The ratio was attenuated after adjustment for sex and smoking status at baseline to 0.88 (0.72-1.07). Corresponding numbers for the hazard ratio for additional lumbar disc herniation surgery in the elderly group were 0.70 (0.53-0.93) and 0.69 (0.51-0.95) respectively.

A total of 4,061 patients responded to the long-term follow-up questionnaire and were monitored for long-term patient-reported outcome (mean 7.0 years). At baseline, within this sub-cohort, there was a significant difference with more L4-L5, less L5-S1, more other single level and more unknown or multiple level lumbar disc herniations among the elderly compared to the adults ($p < 0.001$). The elderly group also had a lower proportion of smokers, a higher ODI, a higher VAS for both leg and back pain, a higher EQ-5D-3L and a lower PCS of SF-36 (all $p \leq 0.049$). Within both groups, there was a significant improvement from baseline to short-term follow-up in all patient-reported outcomes (all $p < 0.001$). At short-term follow-up, the elderly group had a smaller proportion of individuals reporting global assessment for leg pain as “pain free” or “much better” and a poorer outcome in VAS for leg pain and PCS of SF-36 compared to the adults (all $p \leq 0.001$).

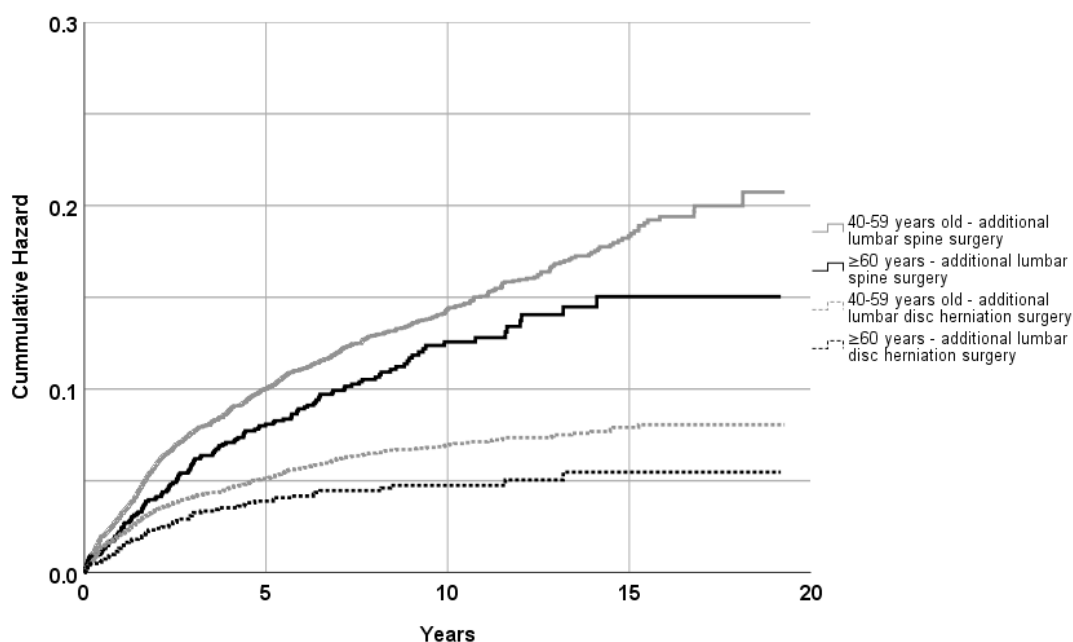


Figure 8. Cox cumulative hazard functions for the probability of at least one additional lumbar spine surgery (unbroken line) and additional lumbar disc herniation surgery (dotted line) in the two age groups. Patients are censored in case of death or at last date of follow-up.

Within the adult group, the following significant differences were observed between the short and long-term follow-up, an increase in patients being satisfied, an increase in the proportion of individuals being “pain free” or “much better” in global assessment back pain, ODI -1 point, EQ-5D-3L index +0.03 points and SF-36 PCS +1 point (all $p \leq 0.001$). In the elderly group, there was a decrease in the proportion of individuals being “pain free” or “much better” in global assessment leg pain ($p=0.041$) while no other significant differences were observed between the short and long-term follow-up (all $p \geq 0.074$).

Compared to the adults, the elderly group had a poorer outcome at the long-term follow-up in all patient-reported outcome measures (all $p \leq 0.012$) except for MCS of SF-36 ($p=0.523$). When comparing the mean change in outcome (mean Δ -score), there were no differences between the groups in ODI, VAS for leg and back pain and MCS of SF-36 (all $p \geq 0.054$) while the adult group had a larger Δ -score for EQ-5D-3L and PCS of SF-36 (both $p \leq 0.001$).

5.5 PAPER V

The flowchart for the study is shown in Figure 4. At the time of MRI examination, no significant differences were seen between the cases (mean 13.8 years postoperatively) and the controls regarding age, height, body mass index (BMI), activity level, metabolic equivalent task-minutes (MET-minutes), occupational strain and smoking. Among the cases, 9 of 23 (39%) had undergone at least one additional lumbar spine surgery. The corresponding number among the 17 individuals operated on due to a lumbar disc herniation in adolescence, who were contacted but did not participate, was 6 (35%). Degeneration at level L5-S1 was not assessed in one of the cases due to fusion of the segment.

At level L4-L5 and level L5-S1 the cases had a larger proportion of individuals with severe degeneration (grade 4 and 5) according to Pfirrmann compared to the controls ($p=0.007$ and $p=0.002$ respectively, Figure 9). No significant differences in the proportion of individuals with severe degeneration were seen for the other lumbar levels (all $p \geq 0.295$).

Similar findings were made for the prevalence of Modic changes, the cases had a larger proportion of individuals with the presence of Modic changes at level L4-L5 and level L5-S1 compared to the controls ($p=0.022$ and $p=0.031$ respectively). At the remaining lumbar levels, the presence of Modic changes were similar among cases and controls (all $p \geq 0.550$).

There were significantly more individuals among the cases with a total endplate score (TEP-score) ≥ 6 at level L5-S1 compared to the controls ($p=0.001$). No other significant differences were seen regarding TEP-score.

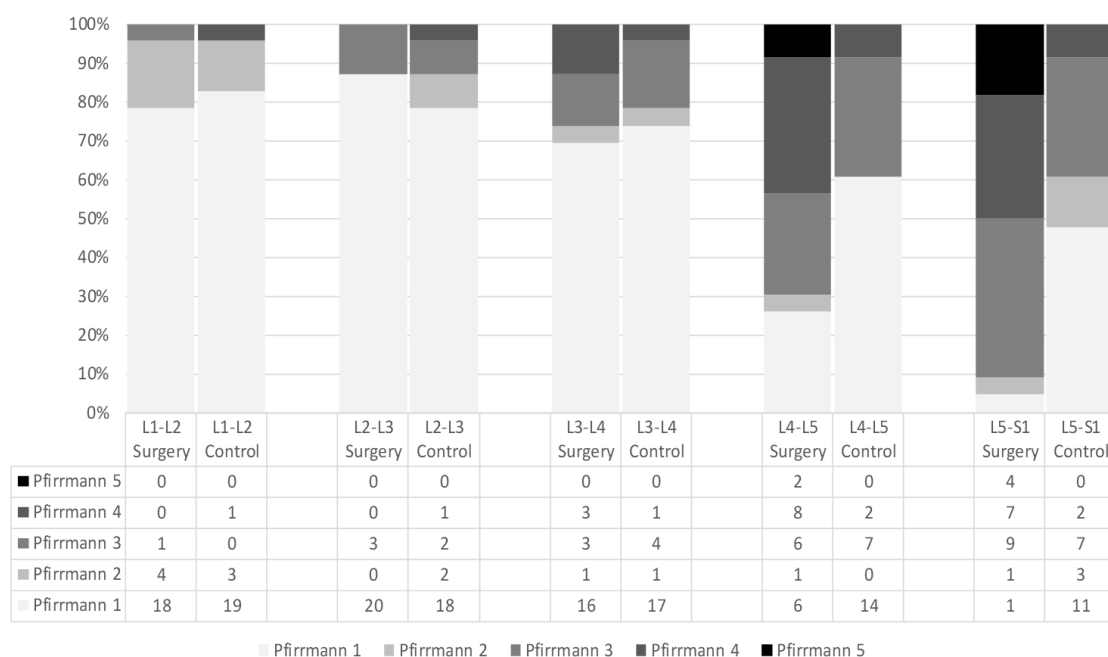


Figure 9. Pfirrmann grading for each lumbar disc level. Pfirrmann grading for level L5-S1 was not assessed in one of the cases due to fusion of the segment. Ranging from Grade 1: homogeneous disc with bright hyperintense white signal intensity and normal disc height (no degeneration) to Grade 5: inhomogeneous disc with a hypointense black signal intensity, no difference between nucleus and anulus, and the disc space is collapsed (severely degenerated).

Compared to the controls, the cases had more disability according to ODI (mean 12 vs 1, $p < 0.001$), more back pain according to VAS (mean 18 vs 3, $p = 0.002$), lower quality of life according to EQ-5D-3L (mean 0.83 vs 0.94, $p = 0.010$) and lower physical function according to PCS of SF-36 (mean 50 vs 56, $p < 0.001$). There were no significant differences between the groups for VAS leg pain ($p = 0.093$) and MCS of SF-36 ($p = 0.844$). Despite the poorer state of health, 22 (96%) of the cases were satisfied with their surgery and 1 (4%) uncertain. In global assessment for leg pain, 5 (23%) of the cases reported themselves as “pain free”, 14 (64%) as “much improved” and 3 (14%) as “somewhat improved”. Corresponding numbers for global assessment of back pain were 9 (39%), 12 (52%) and 2 (9%), respectively. None of the cases were dissatisfied with their surgery and none reported a global assessment as “unchanged” or “worse”.

6 DISCUSSION

6.1 STRENGTHS AND LIMITATIONS

There are several strengths and limitations in all five papers. The common strength is the use of validated outcome instruments and the use of these instruments in Swespine; a prospective nationwide register with high external and internal validity (140). All five papers were dependent on the reporting surgeon giving the correct diagnosis. However, studies of Swespine and NORspine have shown that the diagnosis submitted corresponds to the surgical file in 97% of the cases and in paper V the diagnosis was confirmed for the patients included (140, 144). Hence, the number of incorrectly included patients in papers I to IV should be small and likely randomly distributed between the groups. All papers were limited by the termination of follow-up in case of a new index surgery. If patients had undergone a new index surgery before their first short-term follow-up (one or two-year follow-up) they would not be included in any of the papers. If a patient had undergone a new index surgery before their first long-term follow-up (five or ten-year follow-up) they would not be included in the analyses of patient-reported outcome measures in papers III and IV but would still be included for the primary outcome in papers III and IV and would have the possibility to participate in paper V. This could bias the patient-reported outcome measures to a slightly better result, but it is probably evenly distributed between the groups. All papers had a loss to follow-up, nevertheless, two studies of Swespine have shown that Swespine outcome data is fairly representative (177, 188). In addition, a Norwegian study found that a loss to follow-up of 22% would not bias conclusions of the overall treatment effect after spine surgery (189).

Paper I had at the time, to our knowledge, the largest prospectively collected material for outcome in adolescents after lumbar disc herniation surgery. A large sample size, which is also seen in papers II, III and IV, gives a high precision of the estimates. Paper I was limited due to the questionnaires not being validated for adolescents but the primary outcomes (satisfaction and global assessment) were chosen because of their simplicity and we believe they were easily interpreted, by adolescents too. Global assessment has been found to aggregate important dimensions and give a reliable assessment of the outcome (145).

Paper II further benefits from the use of two additional nationwide registers with similar data collection and use of validated patient-reported outcome measures. The relatively high coverage, completeness and follow-up in the three registers give a high external validity. The registers have small differences in data collection, for example, co-morbidities are reported by the physician in Norway and by the patient in Denmark and Sweden. This was likely the cause of a higher rate of co-morbidities in Norway, but it was not reflected in a negative impact on the outcomes for the Norwegian patients. The registers also differ in instruments measuring back and leg pain. The VAS data from Denmark and Sweden was converted to NRS which could be a source of bias (160). However, despite conversion, the results of NRS had a pattern similar to the results in other patient-reported outcome measures. The questionnaires were given to the patients in the native language of the operating country and

even though they have been cross-validated against other languages, we cannot exclude the possibility of this influencing the results (190). To avoid differences in country-specific conversion of EQ-5D-3L, all EQ-5D-3L answers were translated into indexes using the same tariff (UK-TTO).

Papers III and IV had the advantage of the comparably long follow-up time. Furthermore, the primary outcome was not affected by the loss of patients due to a new index surgery if the new index surgery did not occur before the first short-term follow-up. However, there might be data missing on additional surgery, but given Swespine's high coverage and completeness, only a few surgeries are expected to be missing. The secondary outcomes could be biased towards better results since patients undergoing a new index surgery before long-term follow-up could not be included due to termination of the follow-up. However, the rate of termination was similar in the different groups and should therefore not have a significant influence on the group comparison.

Paper V benefits from the long follow-up time, matched controls, fulfilment of the pre-planned power analysis, the blinded MRI evaluation, the use of recognised MRI measures with sufficient intra and interobserver reliability and the use of validated outcome instruments (57, 74, 88). Paper V was limited by the lack of preoperative MRI for the cases, though these are set to be collected.

The strengths and limitations of the study designs and possible biases are discussed under "3.4.1 Choice of study design". Since the lion's share of patients with lumbar disc herniation improve without surgery, all papers, and specifically paper V, would have profited from a group of non-surgically treated patients.

6.2 GENERAL DISCUSSION

This thesis includes the first study with prospectively collected data on the outcome of lumbar disc herniation surgery among adolescents. The rarity of surgical intervention among adolescents was confirmed, and in Sweden adolescents account for about 1.4% of the surgeries. At short-term follow-up we found significant improvements in all age groups and better results among adolescents compared to adults. The improvements were more than the suggested minimal clinically important difference (MCID) for each outcome (150-153). The improvements also exceeded the suggested threshold for defining the surgical result as successful (149). Even though the surgical result in all age groups could be defined as successful at short-term follow-up, when comparing the mean score of EQ-5D-3L for each group to age-corresponding population-based mean values, inferior results were seen in all age groups (171, 191).

In line with the findings in a review by Lavelle et al., who reported that more than 90% of adolescents experience a good or excellent short-term result, we found that among the adolescents in paper I, 86% were satisfied, 87% experienced significantly reduced leg pain

and 88% experienced significantly reduced back pain at short-term (5). In the secondary patient-reported outcome measures at short-term follow-up, the adolescents also had a better result compared to the adults, but the differences were smaller than the suggested MCID and therefore the clinical relevance of the differences could be questioned.

We found a significantly longer duration of pain before surgery, especially duration of leg pain, in the adolescent group, findings similar to what others have observed (38). Among adults, a longer duration of leg pain has been associated with a poorer outcome after surgery for lumbar disc herniation (192). In paper II we found support for this association, and a duration of leg pain ≥ 3 months was a predictor for poorer short-term outcome in ODI, NRS back pain and NRS leg pain in adult patients. In paper II we also found smoking to be a predictor of poorer outcome, which has been described earlier (193, 194). Neither in paper I nor paper II, did adjustments for these factors affect the results substantially. It is likely that the longer duration of leg pain, and its associated poorer outcome, was counteracted by the significantly smaller proportion of smokers among adolescents in paper I and that the same counteracting effect occurred in paper II, where adult Swedes had a longer duration of leg pain but a smaller proportion of smokers compared to adult Danes and Norwegians. Similar to paper I, the short-term outcomes in paper II exceeded the thresholds for a successful surgical result for all groups (countries).

One can speculate that the results among adolescents would have been even better compared to adults if they were operated on earlier. Earlier surgery would, however, most likely increase the number of operated adolescents, since the natural course is usually beneficial, and more patients have time for spontaneous improvement if the time to surgery is longer. However, with the results from paper II in mind, where a higher incidence of surgery for lumbar disc herniation was not associated with clinically relevant differences in outcome compared to a lower incidence, earlier surgery could still be beneficial for adolescents as a group, even if the numbers of surgeries would increase. This is further supported by the fact that prolonged non-surgical care has not been proven superior to surgery among adults, especially if symptoms have persisted for 4 to 12 months (120, 195, 196). Nevertheless, to draw firm conclusions for adolescents regarding this, there is a need of an adolescent group treated non-surgically as comparison.

The lower incidence of surgery in Sweden and the longer duration of leg pain seen in paper II, could reflect differences in accessibility to surgical care and/or a more conservative treatment tradition compared to Denmark and Norway. At least in Stockholm County today, where index operations for spine disorders increased by 17% between 2013 and 2016, after the introduction of a new reimbursement system, accessibility is not likely to be a problem (197). Furthermore, in regard to accessibility in Stockholm, in paper V we collected individuals from the Stockholm area and observed a higher rate of at least one additional lumbar spine surgery among the previously operated individuals invited to participate in paper V than the national average found in paper III. However, in paper V it is not certain that

the additional surgery was performed in Stockholm or if any individuals moved there after their additional surgery.

In paper III we found a 16% long-term prevalence of at least one additional lumbar spine surgery after surgery for lumbar disc herniation in adolescence. The prevalence is in line with the 10-28% prevalence for adolescents previously reported (39, 40, 47, 116, 138). Even though younger age has been reported as a risk factor for recurrent lumbar disc herniation among adults, we found a similar risk of additional lumbar spine surgery and additional lumbar disc herniation surgery among adolescents and young adults (130). The most common cause of repeat surgery in adolescents and young adults was a new lumbar disc herniation, supporting previous finding (116).

When comparing the risk of a new lumbar disc herniation surgery or at least one additional spine surgery after surgery for lumbar disc herniation, it is important to take the follow-up time into account. However, results from other studies differ, although the follow-up time was similar. For example, at a mean follow-up of 9 years Parisini et al. found that 10% of the adolescents operated on due to a lumbar disc herniation underwent additional spine surgery while Durham et al. reported that 24% of the operated adolescents underwent surgery for recurrent lumbar disc disease at a mean follow-up of 8.5 years (40, 47). Nevertheless, the United States, where Durham et al. conducted their study, has high rates of spine surgery compared to other countries and the difference in additional spine surgery could be due to differences in accessibility of spine surgery or a more liberal view on spinal surgery in the United States (100). Paper III had a slightly longer follow-up time (mean 11.4 years) than previous studies and a comparably large sample size. One may speculate that surgeons refrain from additional surgery in younger cases. This was not reflected in a lower risk in paper III, however.

Similar findings of non-time-dependent variations have also been seen in adults. Atlas et al. had a shorter follow-up time than paper III and paper IV, but still reported that 25% of the patients underwent at least one additional lumbar spine surgery as compared to 11-18% in papers III and IV (132). Like the study by Durham et al., Atlas et al. conducted their study in the United States, a country with high rates of spinal surgery (100). The prevalence of additional lumbar spine surgery among adults in papers III and IV is similar to previous studies, with the reservation that some of them only report the prevalence of surgery for recurrent lumbar disc herniation (94, 133, 135, 136, 198).

When comparing the risk of at least one additional lumbar spine surgery and additional lumbar disc herniation surgery after surgery for lumbar disc herniation among adults 40-59 years old and individuals aged 60 years and older, we found a similar risk of at least one additional lumbar spine surgery while the risk of additional lumbar disc herniation surgery was lower among the elderly. Similar findings, with a lower prevalence of additional lumbar disc herniation surgery among patients 60 years and older, have been made in a previous Swedish study (94). In paper IV, the adult group had a larger proportion of smokers than the elderly group (25% vs 16%) and smoking has been found to be a risk factor highly associated

with recurrent lumbar disc herniation (199). However, this was not reflected in our study, since the risk of additional lumbar disc herniation surgery was not affected after adjustment for sex and smoking. When the risk of at least one additional lumbar spine surgery was adjusted for sex and smoking, the difference was attenuated, however. We cannot exclude the possibility that older age might be a reason for both the patient and the surgeon to refrain from additional surgery, which could be reflected in the slightly lower risk among the elderly patients.

Among adolescents, the patient-reported outcome measures have been reported to deteriorate between short and long-term follow-up, while the patient-reported outcomes among adults have been reported to be steady as soon as after three months, though some report that important individual differences occur between three and 12 months (47, 200-203). In papers III and IV, we found a stable patient-reported outcome between short (mean 1.9 years) and long-term (mean 7.0 to 7.2 years) follow-up in all age groups. Only minor or insignificant differences were seen and none of the significant differences were close to the described minimal clinically important difference (150, 151, 153).

Since only small or clinically insignificant changes occur between short and long-term follow-up after surgery for lumbar disc herniation, it might be possible to obtain representative group-level data for all age groups with only one or two-year follow-up. Since one and two-year follow-up data were combined as short-term follow-up in papers I, III and IV, we cannot conclude whether there are any relevant changes in patient-reported outcome measures between these time-points. However, previous Swespine-based studies have not found any clinically relevant changes between one and two-year follow-up (177, 204). One could therefore speculate that characteristic group-level data could be obtained with only one or two-year follow-up.

Despite the risk of additional lumbar spine surgery seen in papers III and IV, all age groups improved significantly, on a group level, from preoperatively to short-term follow-up and the changes between short and long-term follow-up were only small or insignificant. In combination with a maintained, or for some groups even higher, satisfaction at long-term follow-up this suggests that surgery for lumbar disc herniation is feasible in all age groups, including adolescents and the elderly. Furthermore, with regard to surgery in elderly patients, when comparing the changes in outcome (mean Δ -score) between preoperative and long-term follow-up to adults 40-59 years old, the elderly group only had inferior results in EQ-5D-3L and PCS of SF-36. In the elderly, the mean Δ -score for all outcomes exceeded the suggested minimal clinically important difference for each outcome and the Δ -score for mean ODI, VAS for leg pain and EQ-5D-3L exceeded the suggested threshold corresponding to a successful surgical result (149-151, 162, 205).

The similar risk of at least one additional lumbar spine surgery among adolescents and young adults operated on due to a lumbar disc herniation, seen in paper III, indicated that a lumbar disc herniation at youth is a sign of a beginning spinal degeneration. In paper V we compared spinal degeneration, as seen on MRI, and patient-reported outcome measures between

individuals operated on due to a lumbar disc herniation in adolescence, mean 13.8 years earlier, and controls.

Compared to the controls, the cases had a significantly higher proportion with a total endplate score (TEP-score) ≥ 6 at level L5-S1 and we observed a trend towards a higher proportion also at level L4-L5. Endplate defects have been suggested as the initiating factor for the cascade of degeneration of Pfirrmann grade and Modic changes, with Modic changes being the last to occur on MRI (74, 75, 206). In line with this suggestion, we found a significantly higher prevalence of severe degeneration according to Pfirrmann and presence of Modic changes in the same levels among cases compared to controls.

The link between disc degeneration and lumbar back pain have been debated (207-211). By using a grading system similar to Pfirrmann, Bendix et al. found a higher prevalence of low back pain in subjects with severe degeneration compared to subjects with moderate degeneration and subjects with normal discs (207). In line with the findings of Bendix et al. we observed a higher mean VAS back pain among the cases, who had approximately five times more individuals with severe degeneration at level L4-L5 and level L5-S1, compared to controls (none of the controls had Pfirrmann grade 5).

Modic changes are found in asymptomatic individuals and are to some degree dependent on age. The evidence for the presence of Modic changes as an association to low back pain is conflicting (11, 209-214). Two reviews have found Modic type 1 changes to be relatively correlated to low back pain (211, 212). Modic type 1 was also observed in a larger proportion at level L4-L5 and particularly level L5-S1 among the cases compared to controls. This could further explain the observation of more back pain among the cases.

Despite inferior results in patient-reported outcome measures compared to controls, adolescents operated on due to a lumbar disc herniation are satisfied to a high degree and the majority still experience an improvement according to global assessment for leg and back pain more than a decade after surgery. This leads to a belief that surgery, regardless of the degeneration seen 13.8 years postoperatively, could be a feasible alternative for adolescents. However, it remains unclear whether it is the lumbar disc herniation, degeneration at baseline, or the surgery performed, that causes a higher prevalence of degeneration. To delineate this further, and to test this belief, we are already in the process of including baseline MRIs and collecting a group of individuals treated non-surgically for lumbar disc herniation in adolescence.

7 CONCLUSIONS

This thesis provides detailed and new information on lumbar disc herniation surgery in all age groups, but particularly the long-term effects in adolescents. Surgery for lumbar disc herniation in adolescence is associated with a risk of additional lumbar spine surgery similar to the risk seen in young adults. Lumbar disc herniation surgery in adolescence is also associated with a higher prevalence of spinal degeneration in the two lower segments of the lumbar spine in adulthood compared to controls. Even though the rate of satisfaction is high and surgery seems to be a viable alternative, adolescents operated on due to a lumbar disc herniation experience slightly more back disability, more back pain and a lower quality of life compared to age and sex-matched controls more than a decade after their operation.

Differences in surgical incidence of lumbar disc herniation is not reflected in differences in patient-reported outcome. Patient-reported outcome measures in all age groups are stable between short and long-term follow-up, putting into question the need for a long-term follow-up to evaluate the results of lumbar disc herniation surgery.

7.1 CLINICAL IMPLICATIONS

This thesis clarifies the long-term results and the risk of additional lumbar spine surgery in different age groups. It is important to inform the patients not only about benefits, but also risks, for them to be able to make an informed decision whether to undergo surgery or not.

By increasing the surgical incidence in Sweden, patients with a lumbar disc herniation might benefit from earlier surgery. However, without more knowledge of the outcome of non-surgically treated patients this is an observation rather than a recommendation.

The stable results between short and long-term follow-up seen among all age groups in papers III and IV, indicate that there is little value in long-term patient-reported outcome collection after surgery for lumbar disc herniation. With this in mind, registers could focus their resources on a high follow-up rate at short-term rather than a long-term follow-up. Data on additional surgeries would not be affected by this since it is reported by the surgeon.

7.2 FUTURE PERSPECTIVES

For a better understanding of the impact of surgery for lumbar disc herniation in adolescence, there is a need to examine the progress of degeneration after surgery and to compare the operated cases to patients treated non-surgically. A prospective register of patients treated non-surgically could also help to examine the indications for surgery and to provide guidance on which patients, both adolescents and adults, that should and should not be operated on. The first of the perspectives is already ongoing and I hope that my future studies will bring further clarity to this extremely interesting field.

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