Decompression alone or with fusion for degenerative lumbar spondylolisthesis (Nordsten-DS): five year follow-up of a randomised, multicentre, non-inferiority trial

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ABSTRACT

OBJECTIVE

To assess whether decompression alone is non-inferior to decompression with instrumented fusion five years after primary surgery in patients with degenerative lumbar spondylolisthesis.

DESIGN

Five year follow-up of a randomised, multicentre, non-inferiority trial (Nordsten-DS).

SETTING

16 public orthopaedic and neurosurgical clinics in Norway.

PARTICIPANTS

Patients aged 18-80 years with symptomatic lumbar spinal stenosis and a spondylolisthesis of 3 mm or more at the stenotic level.

INTERVENTIONS

Decompression surgery alone and decompression with additional instrumented fusion (1:1).

MAIN OUTCOME MEASURES

The primary outcome was a 30% or more reduction in Oswestry disability index from baseline to five year follow-up. The predefined non-inferiority margin was −15%. Secondary outcomes included the mean change in Oswestry disability index, Zurich claudication questionnaire, numeric rating scale for leg and back pain, and EuroQol Group 5-Dimension (EQ-5D-3L) questionnaire.

RESULTS

From 12 February 2014 to 18 December 2017, 267 participants were randomly assigned to decompression alone (n=134) and decompression with instrumented fusion (n=133). Of these, 230 (88%) responded to the five year questionnaire: 121 in the decompression group and 109 in the fusion group. Mean age at baseline was 66.2 years (SD 7.6), and 69% were women. In the modified intention-to-treat analysis with multiple imputation of missing data, 84 (63%) of 133 people in the decompression alone group and 81 (63%) of 129 people in the fusion group had a at least a 30% reduction in Oswestry disability index, a difference of 0.4 percentage points (95% confidence interval (CI) −11.2 to 11.9). The respective results of the per protocol analysis were 65 (65%) of 100 in the decompression alone group and 59 (66%) of 89 in the fusion group, a difference of −1.3 percentage points (95% CI −14.5 to 12.2). Both 95% CIs were higher than the predefined non-inferiority margin of −15%. The mean change in Oswestry disability index from baseline to five years was −17.8 in both groups (mean difference 0.02 (95% CI −3.8 to 3.9)). Results of the other secondary outcomes were in the same direction as the primary outcome. From two to five year follow-up, a new lumbar operation occurred in six (5%) of 123 people in the decompression group and 11 (10%) of 113 people in the fusion group, with a total from baseline to five years of 21 (16%) of 129 people and 23 (18%) of 125, respectively.

CONCLUSIONS

In participants with degenerative spondylolisthesis, decompression alone was non-inferior to decompression with instrumented fusion five years after primary surgery. Proportions of subsequent surgeries at the index level or an adjacent lumbar level were no different between the groups.

TRIAL REGISTRATION

ClinicalTrials.gov NCT02051374.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Two year follow-up data indicate that additional instrumented fusion is a superfluous adjunct to decompression surgery for patients operated on for lumbar stenosis and degenerative spondylolisthesis

Still, in most countries, additional fusion surgery prevails as the first treatment option despite disadvantages such as increased risk and costs

The little of change in surgical practice may be due to concerns about inferior outcomes and higher reoperation rates for people operated with decompression only

WHAT THIS STUDY ADDS

Nordsten-DS is the first trial with a sufficient sample size and follow-up rate to investigate outcomes in the longer term

At five year follow-up, surgery with decompression alone gave non-inferior clinical results and similar reoperation rates compared with additional fusion surgery

This new evidence supports surgeons, patients, and administrators to choose the simpler, cheaper, and safer type of surgery

Introduction

Degenerative lumbar spondylolisthesis is a forward slippage of one vertebra relative to the next vertebra below, caused by degeneration of facet joints and discs, and vertical shear forces between the vertebrae.[1] Degenerative lumbar spondylolisthesis commonly occurs in the population aged 50 years and older, and is more frequent in women.[2] People with a narrowing of the spinal canal at the same lumbar level (spinal stenosis) often have leg and back pain, neurogenic

claudication, and impaired physical function. In clinical practice, patients with degenerative spondylolisthesis have symptomatic spinal stenosis and a concomitant spondylolisthesis.[3 4]

Surgery is recommended in selected patients who have had no improvement after non-surgical care.[3] Decompression of the narrowed spinal canal has traditionally been the main objective of operative treatment.[4] Following suggestions from studies from the early 1990s,[5-7] adding instrumented fusion (the use of bone grafts, screws, rods, and other devices to fuse the slipped vertebrae) became the preferred surgical method.[8 9] More recently, evidence from randomised controlled trials and meta-analyses have indicated that decompression alone is sufficient for up to two years of follow-up.[10-14]

By contrast, one randomised controlled trial found that additional instrumented fusion gave superior results to decompression alone.[15]

Results from randomised controlled trials that include outcomes from more than two years after surgery are sparse and contradictory.[11 15 16] In this study, we present the five year results of the Norwegian degenerative spondylolisthesis and spinal stenosis (Nordsten-DS) trial to assess whether decompression alone is non-inferior to decompression with instrumented fusion.

Methods

Trial oversight

Nordsten-DS is an investigator initiated, multicentre, randomised, open label trial designed to evaluate the non-inferiority of decompression alone compared with decompression with instrumented fusion at two, five, and 10 years after the initial surgery.[17] The Regional Committee for Medical and Health Research Ethics of Central Norway (project identifier 2013/366) approved the trial. The trial reporting follows the consolidated standards of reporting trials (CONSORT) guidelines.[18] We previously published the trial protocol and the statistical analysis plan.[17 19] Information regarding patient involvement is provided in section 2 of appendix.

An interim analysis at two years was conducted during patient recruitment when 150 included participants had completed the one-year follow-up to ensure trial safety and efficacy, following the protocol.[10 17]

Enrolment and randomisation

The complete inclusion and exclusion criteria have been reported previously,[10 17] and are provided in table S2 in appendix. In brief, eligible patients were 18-80 years of age, with clinical symptoms of lumbar spinal stenosis (neurogenic claudication or radiating leg pain) verified by magnetic resonance imaging, and an at least 3 mm spondylolisthesis solely at the stenotic level on standing radiographs. We included patients regardless of whether they presented with signs of instability, such as predominant back pain, higher grade of spondylolisthesis, slippage or angulation of vertebral bodies on flexion-extension radiographs, and facet joints with increased fluid or high sagittal angle.[15 20 21] Patients were excluded if they had a thoracolumbar scoliosis of more than 20 degrees, excessive foraminal stenosis (ie, a deformed nerve root in the intervertebral foramen), were previously operated at the level of spondylolisthesis, or had a former fracture or fusion surgery in the thoracolumbar region. We included patients referred to public orthopaedic and neurosurgical departments by the primary care givers for surgical evaluation. The surgeons who conducted the trial surgeries were involved in screening for patient eligibility. The decision to undergo surgery or further non-surgical care was based on shared decision making. The shared decision making process was not explicitly outlined in the study protocol but is well anchored in the Norwegian clinics' best practices and patient rights laws.[22] Participating surgeons were well versed in balancing patient's expectation and potential gain from surgery with the risks of complications or an undesirable outcome. Patients who opted for surgery after shared decision making were invited to participate in the trial. They received the best available information for and against fusion surgery and on the scarcity of evidence for one treatment being superior, both in oral and written form. All patients who accepted trial participation gave written consent before randomisation. Section 2 in the appendix provides information about the surgical departments' contribution to the enrolment of participants.

The Medinsight database hosted by the clinical trial unit at Oslo University Hospital allowed for the computer generated random assignment of the eligible participants in a 1:1 ratio to undergo either decompression alone or decompression with instrumented fusion. The sequence was concealed from the investigators and stratified according to site using random block sizes of four and six participants. The trial coordinating centre at the research and communication unit for musculoskeletal health at Oslo University Hospital forwarded the treatment assignments by email to local trial coordinators who documented this information in patients' records and informed the surgeons. Individual participants and their surgeons were not masked to the treatment assignment.

The routines for the collection and storage of data have been previously described.[10] All data, stored at the clinical trial unit at Oslo University Hospital, were inaccessible to the research group until 23 March 2023; confirmation is provided in section 4.1 in appendix.

Interventions

The participants assigned to decompression alone were operated with a decompression preserving the posterior midline (without removal of the spinous process or the supraspinous-interspinous ligament complex). The approach could be bilateral, ipsilateral, or ipsilateral with a crossover to the contralateral side. For the participants assigned to decompression with instrumented fusion, a posterior decompression

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(with or without preserving midline structures, at the surgeon's discretion) was followed by implantation of pedicle screws with rods and bone grafting across the level of spondylolisthesis, and optional use of an intervertebral fusion device. Implants were selected according to established practices at the trial centres. All participating surgeons routinely performed the procedures used in the trial. A microscope or magnifying glass was recommended for the decompression procedure in both treatment groups.

Outcome measures

The primary outcome was a reduction in the Oswestry disability index (version 2.0) of 30% or more from baseline to five year follow-up,[23] defined as a clinically important outcome. [24] The disability index comprises 10 items that assess functional impairment with a total score from 0 to 100, with higher scores indicating more disability.

Secondary outcomes were the mean score changes in the Oswestry disability index, the Zurich claudication questionnaire,[25] which assesses symptom severity (range 1-5, higher scores indicating more severity), functional impairment (1-4, higher scores indicating more impairment), and satisfaction with treatment (1-4, higher scores indicating lower satisfaction); the numeric rating scale[26] for leg pain and for back pain, which assesses pain experienced during the past week (range 0-10, with higher scores indicating more pain), and the score on the three level version of the EuroQol Group 5-Dimension (EQ-5D-3L) questionnaire (ranging from −0.59 to 1.0, with higher scores indicating better health related quality of life).[27] A seven point global perceived effect scale measuring the self-perceived benefit of the surgery was used, and participants' responses of "much worse" or "worse than ever" were also used to assess adverse outcomes. All questionnaires were translated into Norwegian and validated for psychometric properties (section 4.2.1 in appendix). To evaluate adverse events and treatment during follow-up, we assessed the frequency of complications, patient reported neurological symptoms (sensory, motor, or both) in the lower limbs, subsequent surgeries on the index level or adjacent lumbar levels, use of pain medication, and use of other health services related to the participants' spine health (ie, physiotherapy chiropractor, acupuncture, and visits to hospitals and general practitioners).

Statistical analysis

All primary and secondary outcomes were analysed in a full analysis set, that is, the modified intention-to-treat set consisting of all the participants who received the trial treatment assigned at randomisation and had available data at one or more time point after randomisation.[28] The null hypothesis (H_0) was that the proportion of participants who met the primary outcome (a reduction of 30% or more in the Oswestry disability index) should be 15 percentage points lower in the decompression group than in the fusion group. The predefined non-inferiority margin was based on established knowledge that decompression alone is less extensive, less invasive, cheaper, and possibly safer,[29 30] which would justify an acceptable loss of effectiveness. A difference of 15 percentage points corresponds to a number needed to benefit from additional fusion of seven (number needed to treat was 100/15=6.67).[31] This means that at least seven patients need instrumented fusion in addition to decompression to meet one additional patient with a successful outcome. To reject H_0, 116 participants were required in each group to be 80% certain (power) that the lower limit of a 95% confidence interval (CI) of the difference (decompression alone minus decompression with instrumented fusion) in the percentage of participants with a successful outcome on Oswestry disability index was above −15 percentage points.[32] Considering a possible dropout of 10%, 128 participants were required in each group.

To declare non-inferiority for decompression alone, the null hypothesis had to be rejected in the analyses of both the modified intention-to-treat set with multiple imputation of missing data (information provided in section 4.3.1 in appendix) and in a per protocol set. The per protocol set consisted of all the participants in the modified intention-to-treat set who did not undergo a subsequent surgery at the index level or an adjacent lumbar level during the follow-up period and had available data for the primary outcome. Two sensitivity analyses were performed: one in the modified intention-to-treat set with complete cases (without imputation for missing data) and one in which missing values at five years were replaced by values recorded at two years, when available.

The primary outcome and all categorical secondary outcomes were analysed with Newcombe hybrid score confidence intervals.[33] This included the proportion of participants with a clinically meaningful improvement as assessed by the Zurich claudication questionnaire and numeric rating scale for leg and back pain. All repeated continuous outcomes (scores on the Oswestry disability index, Zurich claudication questionnaire, numeric rating scale for leg pain, numeric rating scale for back pain, and EQ-5D-3L) were analysed with linear mixed models. The linear mixed models contained fixed effects for treatment, time, the interaction between treatment and time, the trial centre, and a random intercept at the patient level. Time was modelled as piecewise linear with knots at three months and two years. Based on the fitted models, mean values were estimated with 95% CIs at baseline (inclusion), three months, one year, two years, and five years after surgery, the change from baseline to five years within each treatment group, and the between group difference (with 95% CIs) in change from baseline to five years.

The assumption of normally distributed data was assessed with visual inspection of histograms and descriptive statistics, and no major deviations were observed. We did not predefine any method for adjustment of confidence intervals for multiple comparisons of secondary outcomes. These results

are presented as point estimates with unadjusted confidence intervals from which no definite conclusions can be made. The analyses were done using Stata/SE software, version 17.0.

Patient and public involvement

Patient involvement is an important factor in the Nordsten trials. This paper's patient representative and co-author (IL) is a member of the Nordsten scientific board and working group. She regularly participates in discussions to ensure that the patients' perspectives and involvement are adequately integrated into the research process. She bridges the gap between researchers and the Norwegian Back and Spine Patients Association, facilitating communication and collaboration. In furtherance of this, she has created the first draft of a popular science piece covering the present five year results, which will be distributed by letter to the study participants and the funders.

Results

From 12 February 2014 to 18 December 2017, we screened 738 patients who were referred to 16 Norwegian public orthopaedic and neurosurgical clinics for degenerative spondylolisthesis, of whom 267 were enrolled in the Nordsten-DS trial (fig 1). The randomisation assigned 134 participants to the decompression group and 133 to the fusion group. At five year follow-up, seven participants (3%; three from the decompression group and four from the fusion group) had died and 25 (10%; nine to the decompression group and 16 to the fusion group) were lost to follow-up, resulting in available data for patient reported outcome measurements from 121 participants in the decompression group and 109 in the fusion group. The modified intention-to-treat set consisted of 133 participants assigned to the decompression group and 129 participants in the fusion group (one patient withdrew consent before surgery, and four did not receive the assigned treatment). The per protocol set consisted of 189 participants: 100 in the decompression group and 89 in the fusion group (44 were reoperated), of which seven had missing data for primary outcome (two at baseline and five at five years). Primary outcomes were missing in 29 people (three at baseline and 26 at five years) (fig 1).

Primary outcome

In the analysis of participants in the modified intention-to-treat set with multiple imputation, 84/133 (63%) in the decompression group and 81/129 (63%) in the fusion group met the primary outcome (an Oswestry disability index reduction of at least a 30% from baseline to five year follow-up). The difference between the groups was 0.4 percentage points (95% CI −11.2 to 11.9). In the per protocol set, the results were 65/100 (65%) in the decompression group and 59/89 (66%) in the fusion group, a difference of −1.3 percentage points (−14.5 to 12.2). The 95% CIs were within the predefined non-inferiority margin of −15 percentage points in both analysis sets. The lower bounds of the 95% CIs corresponded to numbers needed to treat of 8.9 (100/11.2) in the modified intention-to-treat set with multiple imputation and 6.9 (100/14.5) in the per protocol set, which means that at least seven to nine patients needed to be fused to have one additional patient meet at least a 30% improvement in functional status. The results of the sensitivity analyses were in the same direction as the primary analysis and did not cross the non-inferiority margin (fig 2).

Table 1 shows that the treatment groups had similar patient characteristics, outcome measurements, and radiological parameters at baseline.

Secondary outcomes

The mean change in Oswestry disability index from baseline to five years was −17.8 in the decompression group and −17.8 in the fusion group (mean difference −0.02 (95% CI −3.9 to 3.8)). The mean change in leg pain measured by the numeric rating scale showed values of −3.5 in the decompression group and −2.9 in the fusion group (mean difference −0.59 (95% CI −1.36 to 0.18)). For back pain the results were −2.8 and −2.6 (−0.22 (−0.95 to 0.52)), respectively. Mean change in Zurich claudication questionnaire and the EQ-5D also had similar small differences (table 2). Figures in the appendix show the results of complete cases analyses of patient reported continuous outcomes from baseline to five year follow-up. The between-group differences in percentages of participants meeting a clinically meaningful improvement according to the Zurich claudication questionnaire and numeric rating scale pain scales from baseline to five years after surgery were in line with the results of the primary outcome (table 2).

Estimated values are based on linear mixed models. The modified intention-to-treat set consisted of all the participants who were operated according to the randomisation and had available data at baseline.

Table 3 shows the recorded adverse events from two to five year follow-up, 16 (13%) of 119 in the decompression group and 21 (19%) of 109 in the fusion group reported new neurological sensory and/or motor symptoms of the lower limbs. About 5% in each group perceived themselves to be substantially deteriorated ("much worse" or "worse than ever") according to the GPE score (table S4 in appendix).

Except for higher blood loss during surgery and incidence of dural tears in the fusion group, no significant between group differences were observed regarding adverse events. Neither the consumption of pain medication nor the use of health services was different during follow-up (table 3 and tables S4 and S6 in appendix). A subsequent lumbar surgery was done in 21 (16%) of 129 participants in the decompression group and in 23 (18%) of 125 participants in the fusion group. Of these, comparing people in the decompression group and fusion group, 11 and 15 had subsequent surgery from index surgery to two year follow-up, and 6 and 11 had surgery from two to five years. Some participants had more than one reoperation, giving a total number of 28 subsequent surgeries in each group.

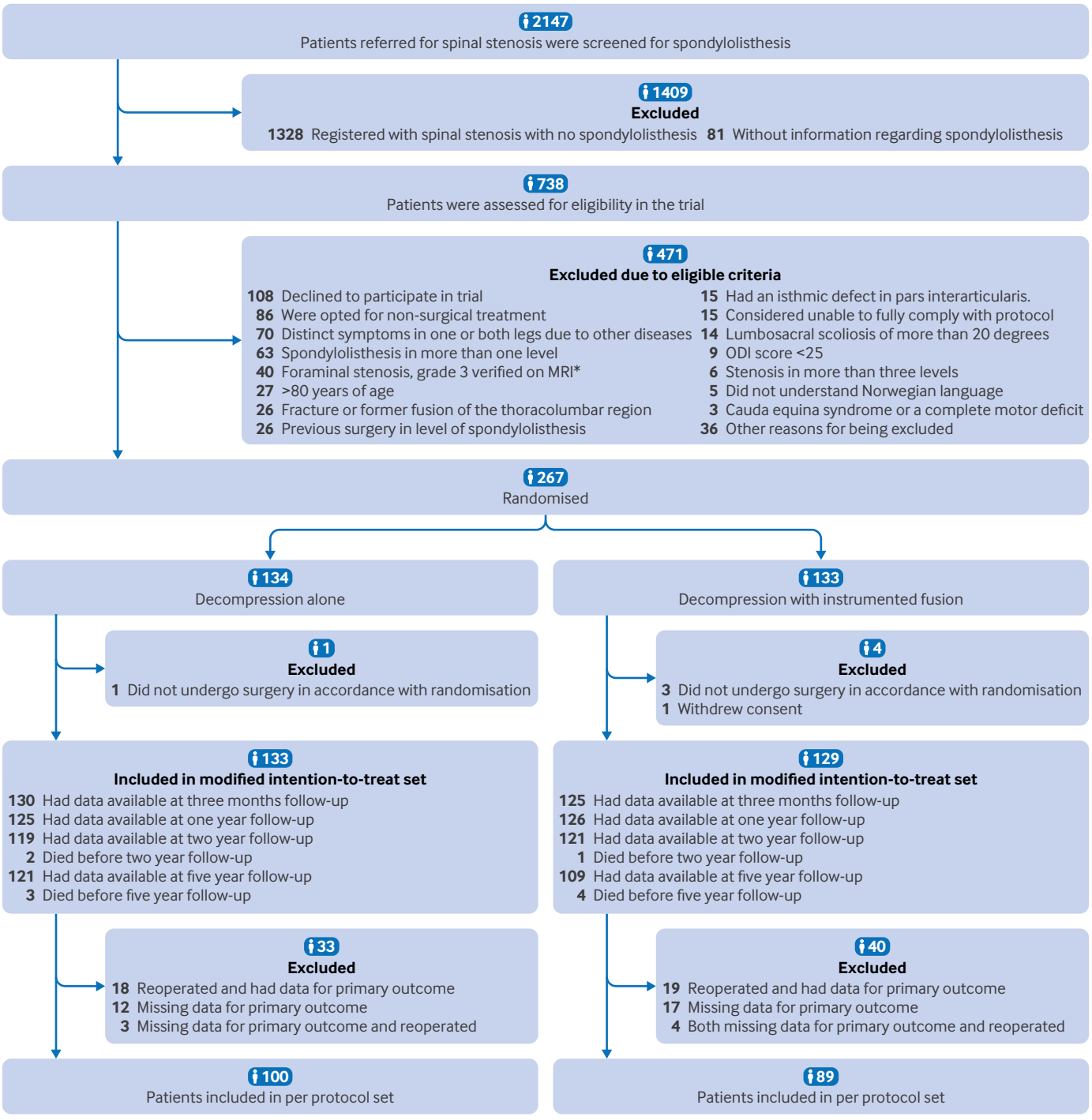

Fig 1 | Screening, randomisation, and follow-up of the trial participants. Patients who were referred with the diagnosis of lumbar spinal stenosis were screened for the presence of spondylolisthesis. 738 patients who were assessed for eligibility in the trial could have been excluded for more than one reason. The diagnosis of foraminal stenosis of grade 3 was made according to the classification of Lee et al.[34] From 15 April 2014 (the start of inclusion) to 29 August 2015, a score of less than 25 on the Oswestry disability index (ODI) was an exclusion criterion. MRI=magnetic resonance imaging

Discussion

The Nordsten-DS randomised controlled trial involving 267 participants with lumbar spinal stenosis and degenerative spondylolisthesis showed that surgery with decompression alone was non-inferior to surgery with decompression and instrumented fusion at five year follow-up. Results of secondary outcomes concerning pain, symptom severity, functional status, and reoperation rates were in accordance with the primary outcome.

Strengths and limitations

Some major strengths of this trial were its large sample size, the external data monitoring, the use of validated outcomes, the high follow-up rate, and the strong involvement of a patient representative (IL).[40] The

Table 1 | Patient characteristics at baseline (modified intention-to-treat set). Values are numbers (percentage) unless stated otherwise

Characteristics	Decompressionalone (n=133)	Decompression and instrumented fusion (n=129)
Age, years (SD)	66.0 (7.4)	66.5 (7.9)
Female sex	92/133 (69)	88/129 (68)
≥3 years of education	30/129 (23)	36/125 (29)
Married/partner	91/129 (71)	99/127 (78)
Smoker (yes)	24/130 (19)	21/127 (17)
Body mass index, mean (SD)	27.7 (4.4)	27.9 (4.3)
Lumbar spine surgery but not spondylolisthesis	4/130 (3)	4/127 (3)
Duration of leg pain >1 year	91/125 (73)	95/127 (75)
Duration of back pain >1 year	107/130 (82)	112/129 (87)
Use of analgesics (yes)	103/130 (79)	107/126 (85)
American Society of Anesthesiologists score:		
Score 1, no disease	16/129 (12)	11/124 (9)
Score 2, mild systemic disease	97/129 (75)	88/124 (71)
Score 3 severe, non-life threatening systemic disease	16/129 (12)	25/124 (20)
Coexisting conditions (yes)		
Hypertension	46/133 (35)	44/129 (34)
Diabetes	9/133 (7)	9/129 (7)
Cardiovascular disease	23/133 (17)	26/129 (20)
Lung disease	13/133 (10)	10/129 (8)
Rheumatoid disease	5/133 (4)	8/129 (6)
Anxiety or depression	6/133 (5)	7/129 (5)
Other musculoskeletal diseases	13/133 (10)	11/129 (9)
Hopkins Symptom Checklist-25,* mean (SD)	1.6 (0.4)	1.6 (0.4)
Oswestry disability index,† mean (SD)	39.3 (14.0)	39.4 (12.4)
Zurich claudication questionnaire		
Symptom severity,‡ mean (SD)	3.3 (0.6)	3.4 (0.6)
Physical function,§ mean (SD)	2.5 (0.5)	2.5 (0.5)
Numeric rating scale leg pain,¶ mean (SD)	6.7 (2.1)	6.7 (1.8)
Numeric rating scale back pain,¶ mean (SD)	6.7 (2.0)	6.6 (2.0)
EuroQol Group 5-Dimension,** mean (SD)	0.43 (3.0)	0.38 (3.0)
Radiological parameters		
Degree of spondylolisthesis in standing x rays, mm mean (SD)[35]	7.6 (3.2)	7.2 (2.8)
Facet joint fluid gap, mm mean (SD)[36]	1.1 (1.0)	1.2 (1.0)
Facet joint fluid gap >2mm	24/125 (19)	25/125 (20)
Modic changes (type I, II, and mixed)[37]	23/127 (18)	15/124 (12)
Disc degeneration††	12/129 (9)	8/125 (6)
Foraminal stenosis‡‡	12/111 (11)	11/113 (10)
Segmental instability, assessed on standing x ray (extension minus flexion)[20]		
≥3 mm forward translation	26/121 (22)	19/112 (17)
≥10 degrees loss of lordosis	9/121 (7)	8/119 (7)
Orientation of the facet joint,§§ degrees mean (SD)	56 (9)	57 (9)
Disc height in the level of olisthesis,¶¶ mm mean (SD)	7.6 (2.0)	8.0 (2.1)
Lumbal lordosis,*** degrees mean (SD)	54 (11)	54 (11)

The modified intention-to-treat set consisted of all the participants who received the trial treatment assigned by the randomisation and had available data after randomisation. Percentages may not total 100 because of rounding.
SD=standard deviation.
* The 25 item Hopkins Symptom Checklist is a patient administered questionnaire for the assessment of symptoms of anxiety and depression. Score range 1-4, with lower scores indicating less severe symptoms.
† Score range 0-100, with higher scores indicating more severe disability.
‡ Scores for symptom severity, range 1-5, with lower scores indicating less symptom severity.
§ Scores for physical function, range 1-5, with lower scores indicating less impairment.
¶ Scores for leg pain and for back pain, range 0-10, with lower scores indicating less pain.
** Health-related quality of life, including mobility, self-care, usual activity, pain or discomfort, and anxiety or depression. Score range −0.59 to 1.0, with higher scores indicating better health-related quality of life.
†† Refers to grade 5 according to Pfirmann classification (range 1-5, where higher grade indicates more extensive degeneration).[38]
‡‡ Refers to foraminal stenosis grades 2 and 3 according to Lee classification (range 0-3, where higher grade indicates more extensive stenosis).[39]
§§ Refers to the angle (mean of right and left joint assessed by MRI, axial plane) at the level of spondylolisthesis.
¶¶ Refers to the middle disc height (distance between mid-inferior and mid-superior disc borders assessed on a mid-sagittal MRI plane).
*** Refers to the angle between upper endplate S1 and lower endplate L1 on standing x-ray.

pragmatic design, wherein patients were recruited from 16 public institutions and surgery was performed by both orthopaedic and neurosurgical spine surgeons, improved the generalisability of the results.

Due to the eligibility criteria, one cannot generalise the trial results to patients with degenerative scoliosis, severe foraminal stenosis, and previous surgery at the index level or with spondylolisthesis at multiple levels. Another limitation was the absence of double blinding; only the data analyst was masked to treatment assignments.

An evidence based margin of non-inferiority for this research question does not exist, which is why the predefined −15 percentage points limit was chosen

Analysis set	No of patients/total (%)		Difference in percentage point (95% CI)	Difference in percentage point (95% CI)
	Decompression alone group	Fusion group		
Modified intention-to-treat set with multiple imputation	84/133 (63.2)	81/129 (62.8)		0.4 (-11.2 to 11.9)
Per protocol set	65/100 (65.0)	59/89 (66.3)		-1.3 (-14.5 to 12.2)
Modified intention-to-treat set with complete cases	77/118 (65.3)	71/108 (65.7)		-0.5 (-12.7 to 11.8)
Modified intention-to-treat set with imputation of two year data if missing	78/123 (63.4)	78/121 (64.5)		-1.1 (-12.9 to 10.9)

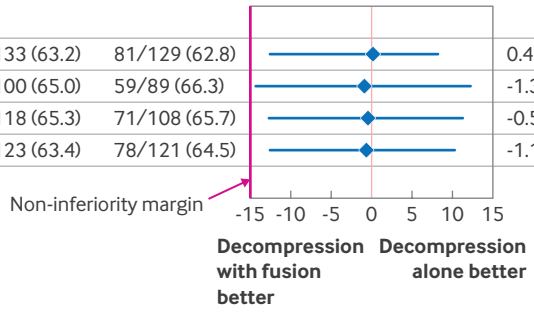

Fig 2 | Primary outcome. No of patients/total no (%) refers to the proportion of patients with 30% or more reduction in Oswestry disability index in each specified analysis. The between group differences in percentage points and its 95% confidence intervals (CIs) were calculated as decompression alone minus decompression with fusion. For patients in the modified intention-to-treat set with imputation of missing data at five year, the missing values were replaced by multiple imputation

empirically. The 95% CI of the between group difference in percentages reaching the primary outcome did not cross the non-inferiority margin in this analysis. However, the sample size for the per protocol analysis was below the a priori required sample size.

Comparison with other studies

Two randomised controlled trials from 2016 of patients with degenerative spondylolisthesis included longer term follow-ups, similar to the current trial.[11 15] One included participants from seven Swedish hospitals.[11] The trial had a superiority design, did not present

Table 2 | Secondary patient reported outcome measurements (modified intention-to-treat set). Data are mean (95% confidence interval)

Outcome	Baseline	Three month	One year	Two year	Five year	Change from baseline to year five	Difference (decompression minus fusion) in change from baseline to year five (95% CI)
Oswestry disability index							
Decompression alone	39.2 (36.5 to 41.8)	17.3 (14.8 to 19.8)	17.9 (15.7 to 20.1)	18.8 (16.1 to 21.4)	21.4 (18.7 to 24.1)	−17.8 (−20.4 to −15.1)	−0.02 (−3.85 to 3.80)
Decompression with fusion	39.6 (37.0 to 42.3)	19.5 (16.9 to 22.1)	19.0 (16.8 to 21.2)	18.3 (15.6 to 21.0)	21.9 (19.1 to 24.7)	−17.8 (−20.5 to −15.0)	
Zurich claudication questionnaire symptom severity							
Decompression alone	3.32 (3.19 to 3.45)	2.21 (2.09 to 2.33)	2.26 (2.16 to 2.37)	2.33 (2.20 to 2.46)	2.26 (2.13 to 2.39)	−1.06 (−1.19 to −0.92)	−0.07 (−0.26 to 0.13)
Decompression with fusion	3.42 (3.29 to 3.55)	2.25 (2.13 to 2.37)	2.33 (2.22 to 2.43)	2.43 (2.30 to 2.56)	2.43 (2.29 to 2.56)	−0.99 (−1.13 to −0.85)	
Zurich claudication questionnaire physical function							
Decompression alone	2.52 (2.41 to 2.62)	1.65 (1.55 to 1.75)	1.66 (1.58 to 1.75)	1.68 (1.58 to 1.79)	1.79 (1.68 to 1.90)	−0.73 (−0.84 to −0.61)	0.06 (−0.11 to 0.22)
Decompression with fusion	2.52 (2.41 to 2.62)	1.62 (1.52 to 1.72)	1.66 (1.57 to 1.75)	1.71 (1.60 to 1.81)	1.73 (1.62 to 1.85)	−0.78 (−0.90 to −0.67)	
Zurich claudication questionnaire patient satisfaction							
Decompression alone	—	1.71 (1.58 to 1.83)	1.74 (1.63 to 1.86)	1.78 (1.66 to 1.91)	1.86 (1.73 to 2.00)	—	—
Decompression with fusion	—	1.73 (1.60 to 1.85)	1.73 (1.61 to 1.85)	1.73 (1.60 to 1.86)	1.85 (1.71 to 1.98)	—	
NRS leg pain							
Decompression alone	6.64 (6.19 to 7.09)	2.68 (2.26 to 3.10)	2.74 (2.40 to 3.08)	2.83 (2.38 to 3.27)	3.12 (2.66 to 3.59)	−3.52 (−4.06 to −2.98)	−0.59 (−1.36 to 0.18)
Decompression with fusion	6.71 (6.26 to 7.16)	2.47 (2.05 to 2.90)	2.73 (2.39 to 3.07)	3.08 (2.64 to 3.52)	3.78 (3.29 to 4.27)	−2.93 (−3.49 to −2.37)	
NRS back pain							
Decompression alone	6.72 (6.29 to 7.15)	3.38 (2.97 to 3.78)	3.36 (3.04 to 3.69)	3.35 (2.92 to 3.78)	3.89 (3.44 to 4.33)	−2.84 (−3.35 to −2.33)	−0.22 (−0.95 to 0.52)
Decompression with fusion	6.61 (6.17 to 7.04)	3.25 (2.84 to 3.65)	3.42 (3.09 to 3.75)	3.66 (3.23 to 4.09)	3.99 (3.52 to 4.45)	−2.62 (−3.15 to −2.09)	
EQ-5D-3L							
Decompression alone	0.44 (0.39 to 0.49)	0.72 (0.67 to 0.76)	0.71 (0.67 to 0.75)	0.70 (0.65 to 0.75)	0.68 (0.63 to 073)	0.24 (0.18 to 0.30)	−0.06 (−0.14 to 0.02)
Decompression with fusion	0.38 (0.33 to 0.43)	0.70 (0.66 to 0.75)	0.71 (0.67 to 0.75)	0.72 (0.67 to 0.77)	0.68 (0.63 to 0.73)	0.30 (0.25 to 0.36)	

Table 3 | Additional secondary outcomes (modified intention-to-treat set) Values are number (percentage), unless stated otherwise

	Decompression alone (n=133)	Decompression and instrumented fusion (n=129)	Difference (95% CI)
Duration of surgery, min (SD)	104 (4.2)	174 (6.15)	−70 (−84 to −55)
Length of hospital stay, days	3.3 (0.21)	5.0 (0.23)	−2 (−2 to −1)
Clinically important improvement:			
Assessed by the Zurich claudication questionnaire*	93/133 (70)	96/129 (74)	−5 (−15 to 6)
Assessed by the NRS† for leg pain	78/133 (59)	70/129 (54)	4 (−8 to 16)
Assessed by the NRS† for back pain	73/133 (55)	68/129 (53)	2 (−10 to 14)
Complications:			
Incidental dural tear	7/132 (5)	17/128 (13)	8 (1 to 15)
Blood loss per operative, mL (SD)	141 (134)	429 (278)	292 (235 to 348)
Blood transfusion	0/132	4/128 (3)	3 (−0 to 8)
Operated on the wrong side/level	1/132 (1)	1/128 (1)	0.0 (−4 to 4)
Hematoma requiring reoperation during hospital stay	1/132 (1)	1/128 (1)	0.0 (−4 to 4)
Wound infection:			
During hospital stay	0/132	0/128	0.0 (−3 to 3)
From hospital discharge to three months	3/129 (2)	6/125 (5)	3 (−3 to 8)
Reoperation due to deep infection	1/129 (1)	4/129 (3)	
Cardiovascular complications:			
During hospital stay	3/132 (2)	0/128	−2 (−7 to 1)
From hospital discharge to three months	1/129 (1)	0/125	−1 (−4 to 2)
Venous thromboembolism:			
During hospital stay	0/132	0/128	0.0 (−3 to 3)
From hospital discharge to three months	0/129	0/125	0.0 (−3 to 3)
Urological complication:			
During hospital stay	4/132 (3)	6/128 (5)	2 (−4 to 7)
From hospital discharge to three months	2/129 (2)	5/125 (4)	2 (−2 to 8)
Respiratory complication:			
During hospital stay	0/132	2/128 (2)	2 (−2 to 6)
From hospital discharge to three months	1/129 (1)	0/125	−1 (−4 to 2)
Patient reported neurological deterioration‡:	32/132 (24)	45/128 (35)	−11 (−22 to 0)
During hospital stay	1/132 (1)	2/128 (2)	−1 (−5 to 3)
From hospital discharge to three months	3/129 (2)	7/125 (6)	−3 (−9 to 2)
From three months to two years	12/120 (10)	15/121 (12)	−2 (−11 to 6)
From two years to five years	16/119 (13)	21/109 (19)	−6 (−16 to 4)
Substantially deteriorated§	6/119 (5)	5/108 (5)	0 (−6 to 7)
Had another operation¶:			
First reoperation before three months	2/129 (2)	7/125 (6)	−4 (−10 to 1)
First reoperation between three months and two years	13/120 (11)	5/121 (4)	7 (−0 to 14)
First reoperation two years to five years	6/123 (5)	11/113 (10)	−5 (−12 to 2)
Participants with at least one reoperation	21/129 (16)	23/125 (18)	−2 (−12 to 7)
Total numbers of reoperations	28/129 (22)	28/125 (22)	−1 (−11 to 10)
Primary outcome in participants reoperated**	12/18 (67)	12/20 (60)	7 (−23 to 34)

The modified intention-to-treat set consisted of all the participants who were operated according to the randomisation and had available data at baseline.
NRS=numerical rating scale; SD=standard deviation
* Two of three defined criteria had to be met at the five year follow-up: a decrease from baseline in the score on the symptom severity scale ≥0.46, a decrease from baseline in the score on the physical function scale of ≥0.42, and a score on the patient-satisfaction scale of ≤2.42.
† The criteria for a clinically important improvement were a decrease from baseline of ≥40% in the score on the leg pain and a decrease from baseline of ≥33% in the score on the back pain, both at five year follow-up.[24 25]
‡ Neurological deterioration was reported by the participants to the local coordinators at follow-ups, specified as a sensory, motor or combined sensory/motor disturbance emerged since the previous follow-up. No clinical examinations were performed.
§ Participants who responded that their condition was "much worse" or "worse than ever" on the global perceived effect seven point Likert scale.
¶ Participants who underwent one or more subsequent operations from the time of the primary operation to five year follow-up.
** Shown are participants who underwent one or more subsequent lumbar operations from the time of the primary operation to five year follow-up and had a reduction in Oswestry disability index score ≥30% from primary operation to five year follow-up.

information about radiological instability, and had available data for 80 (59%) of 135 participants at five year follow-up. The Swedish trial found no between group differences in Oswestry disability index and pain scores, corresponding to our findings. The reoperation rate over the course of five years from index surgery was 22% in the decompression group and 21% in the fusion group, quite similar to our findings.

The other trial recruited 66 patients from five US spine centres, 51 of whom were from one site.[15] Each centre had one surgeon who performed all the surgeries in the trial. At four year follow-up, 45 participants (68%) had data for analysis. Compared with our trial, the US trial had a less pragmatic design. They only included grade 1 lumbar spondylolisthesis (slip of 3-14 mm). Furthermore, they did not include patients who had a dynamically unstable condition, defined as motion of the spondylolisthesis of more than 3 mm measured on dynamic radiographs, or those with mechanical low back pain in the upright posture. Their results at a four year follow-up favoured fusion, as assessed by the generic physical component summary score of the 36-item short-form health survey. The reoperation rate of that study at four years was 34% in

the decompression alone group, and all patients were deemed to have clinical instability. In the fusion group, 14% had a subsequent surgery, and all had adjacent level degeneration. In our trial, there were slightly more reoperations in the decompression group during the first two years, mainly operated with a subsequent fusion at the index level, while more participants in the fusion group had a subsequent operation between two and five year follow-up, mainly at a new lumbar level.

The reasons for the noticeable difference in reoperation rates between the US trial compared with the present trial and the Swedish trial are unknown. Diverging reoperation rates could partially be explained by differences in treatment traditions and radiological assessment. If a patient operated on without additional fusion complains of persisting back pain, the threshold for offering reoperation with fusion could be low. A surgical alternative is less apparent when the patient is primarily operated with fusion. The rationale might be that the back pain is caused by spondylolisthesis so-called instability.[15 20 21]

In this trial, non-inferiority for decompression alone was maintained over five years and the reduction in back pain was similar between the groups, even though a high number of participants had radiological and clinical signs of instability. A secondary exploratory Nordsten-DS study on treatment effect modifiers did not find that participants with more typical preoperative signs of instability and back pain benefited from an additional fusion.[41] The high prevalence of non-specific low back pain in the general population and the scarcity of evidence for a causal relationship between back pain and degenerative spondylolisthesis are valid arguments for not routinely offering subsequent fusion surgery for persistent back pain.[42 43]

Decompression without fusion is a faster,[10 11 15] less invasive,[44] safer,[13] and more cost-effective treatment for patients with degenerative spondylolisthesis.[44] Despite the two year results from randomised controlled trials and meta-analyses recommending decompression alone as primary treatment for these patients,[10-15 34 45] only a few countries have reported a change in surgical practice.[46 47] In the US, the fusion rate for degenerative spondylolisthesis continued to increase from 67% in 2016 to 90.4% in 2019.[48] To ensure implementation of evidence from follow-ups longer than two years, the results from the present trial need to be acknowledged by patients and healthcare providers as well as by decision and policy makers. Selective use of information supporting fusion surgery will lead to patients receiving more extensive and risky surgery than is necessary.

For successful shared decision making, clinicians should thoroughly inform patients about the pros and cons of alternative surgical and non-surgical treatments and communicate corresponding realistic prognoses for reaching pain and functional goals. Unfortunately, very little is known about patients' goals regarding spine surgery. A recent study[49] showed that patients' preoperative expectations may be higher than the commonly reported outcomes of spinal surgery.[10 11 15 50] Future investigations should assess patients' functional and pain goals before surgery relative to their perceived benefits after surgery.

The results of this five year analysis cannot exclude the possibility that subgroups of patients may benefit from an additional fusion (eg, age, gender, socioeconomic status, and different radiological variables). At the two year follow-up, we did not identify any subgroups that would favour one of the two treatments.[41] Following the Nordsten-DS trial protocol, we will also investigate potential treatment effect modifiers in a separate study related to the five year follow-up, as well as alongside the 10 year follow-up.[17]

Conclusion

In this multicentre, randomised trial of patients with degenerative lumbar spondylolisthesis, the five year results of decompression alone were non-inferior to those of decompression with instrumented fusion. A subsequent reoperation occurred in about one in five participants in both groups. The results expand on the current evidence that, for most of these patients, fusion surgery is superfluous.

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Contributors: CH, MVF, TS, JIB, KS, EH, KI, and IMA were responsible for study conception and trial design. MVF was responsible for the statistical analysis. ELK and IMA were responsible for the first draft of the manuscript. All authors were responsible for the interpretation of the data and for drafting and approving the final submitted manuscript. EK, CH, and IMA are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The corresponding author had full access to all the data in the study and was responsible for deciding to submit it for publication.

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Competing interests: All authors have completed the ICMJE uniform disclosure form www.icmje.org/disclosure-of-interest/ and declared that they have had no financial relationships with any organisation that may have a financial interest in the submitted work in the previous three years and no relationships or activities that could have influenced the submitted work.

Ethical approval: The Regional Committee for Medical and Health Research Ethics of Central Norway (project identifier 2013/366) was approved on 8 May 2013.

Data sharing: All data requests should be submitted to ivar.magne.austevoll@helse-bergen.no for consideration. The NORDSTEN scientific board may grant access to anonymised data following a research protocol review. The statistical analysis plan can be found on the clinicaltrials.gov website: https://storage.googleapis.com/ctgov2-large-docs/74/NCT02051374/SAP_001.pdf.

Transparency: ELK and IMA affirm that the manuscript is an honest, accurate, and transparent account of the Nordsten-DS five year trial being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as explained in the original statistical analysis plan (27 December 2022). The database lock approval form provided in appendix confirms that data were inaccessible to the research group until 13 March 2023.

Dissemination to participants and related patient and public communities: The patient representative (IL), along with ELK, KS, and IMA are responsible for a lay summary of the results of the study that will be made available on the trial website, in the annual letter to the research participants and the Norwegian Back and Spine Patients Association's magazine. An English translation of the information letter is available in section 2 of the appendix. As with the two year results, the five year results will be disseminated through public media channels.

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