THE OPTIMAL PATHWAY TO LUMBAR SPINAL FUSION

Esther R.C. Janssen

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Improving perioperative health and care with patients opting for lumbar spinal fusion surgery

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1

Introduction

SOCIETAL CHALLENGE

The societal burden of low back pain (LBP) is substantial. In the Netherlands, we spent 937 million euros on healthcare for people with LBP (62% of which was spent on hospital care) in 2017.[1] Moreover, there is a huge personal burden for people who suffer from LBP, as LBP accounts for most years lived in disability around the globe.[2] However, governments and policy makers have failed to prioritize the problem of LBP, regardless of its increasing prevalence and burden on society.[3, 4] Reasons for this neglect might be: LBP is a non-lethal disorder; the challenge of diagnostic (a-)specificity; the persistent lack of effective prevention and curative treatment options; and the firm between disease-group competition for funding and investments within the limited healthcare and research budget. Nonetheless, in the previous decades great advances in research and healthcare towards predictive, preventive, personalized and participatory (P4) medicine in spinal healthcare have improved the health of people with LBP.[5] To accelerate these ongoing developments towards better health of people with LBP, prioritizing and investments in research on LBP with patients with LBP are necessary. As such, we can generate new evidence and translate it into clinical practice, as has been shown to be effective in well-funded research areas like cardiovascular disease, cancer and diabetes.[6] Already a wealth of options in prevention methods, conservative treatment and surgical techniques have become available to patients with LBP, due to innovation and research advances,. Still, a substantial part of the population of people with LBP have chronic complaints (prevalence rates between 3.9-25.4%).[7] For these people operative treatment can be considered, if non-operative management is unable to relieve their symptoms and disability. Lumbar spinal fusion (LSF) is an increasingly popular surgical treatment that can be considered by people suffering from degenerative disorders of the lumbar spine. Making the decision for LSF is not easy, as treatment effects of LSF remain variable, despite advancements in spinal surgery and anesthesiology. On average 56% of patients who opted for LSF gain a clinically relevant reduction of at least 1.1 points on the Numeric Pain Rating Scale two years after surgery.[8] Consequently, making a strong case for continuous improvements in preoperative decision making and perioperative care for patients considering LSF.

To implement P4 medicine in perioperative care for people opting for LSF in the near future, analysis of data that reflects real-world variation and aggregation of knowledge is necessary. Fortunately, the amount of data and knowledge on spinal health(care) and perioperative care has grown explosively, especially in the last few decades.[9] By effectively mining existing real-world data and knowledge, and generating new evidence by applying real-world research strategies that incorporate context, interpersonal and disease heterogeneity (real-world variation), we can gain information to achieve P4

spinal care.[10, 11] As a consequence, health of individual patients with LBP can be improved and the societal burden will be reduced.[3]

CENTRAL MISSION

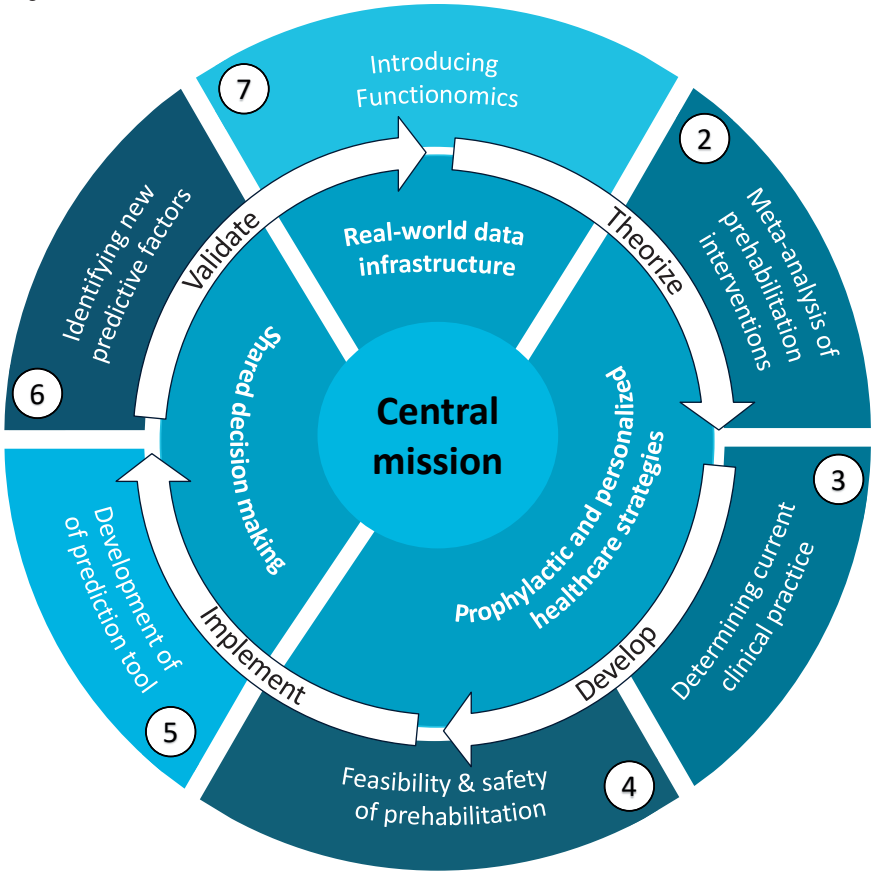
Transformation and adaptation of our health and healthcare research systems are necessary and ongoing in different (surgical) research fields such as oncology, orthopedics and cardiology.[12-15] Scientific critics from the recent past ('Science in Transition', 'P4 medicine' and 'without context no evidence') [5, 16-19] and major advances in research technologies and analyses techniques illustrate how this transformation should be established: transitioning from a traditional rather passive and siloed care system, focusing on population health, towards a proactive communal health system, adopting a proactive personalized approach. Until now, these adaptions are only sparsely implemented in the perioperative care pathway of patients opting for LSF.[4]

The ongoing transition in health, healthcare and research is continued in this thesis, specifically concerning the complex and multi-facetted perioperative care period of patients opting for LSF. Hereto, *we formulated a mission*; Improving the health of people opting for elective LSF by adopting ongoing advancements in healthcare towards an increasingly predictive, preventive, personalized and participatory (P4 medicine) perioperative healthcare approach.[5, 20] In this thesis, we made the mission actionable by theorizing, developing, validating and implementing methods and tools in real-life perioperative healthcare practice with patients opting for elective 1-3 level LSF, covering three themes (Figure 1):

I) Preventive and personalized perioperative risk management strategies (*chapters 2-4*);
II) Innovative methods to guide evidence based shared decision making within the perioperative healthcare pathway (*chapters 5 & 6*);
III) First steps towards integration of a modern real-world perioperative data technology and expanding the 'omics-family', by introducing functionomics (*chapter 7*);

We used real-world data and analysis techniques that enabled us to extract valid conclusions from real-world data, because context for scientific evidence matters and learning from real-world data and variation is essential for the personalization of medicine.[21]

Figure 1. Transition towards participatory, predictive, preventive and personalized (P4 medicine) perioperative healthcare with people opting for elective lumbar spinal fusion (inner circle). Through iterative theorizing, development, implementation and validation (white arrows) of: I) preventive and personalized risk management strategies, II) improved personalization in treatment decision making and prognostics, and III) towards integration of a modern real-world perioperative data infrastructure and expanding the 'omics-family', by introducing functionomics (middle circle). Operationalized in chapters 2 through 7 in this thesis (outer circle).

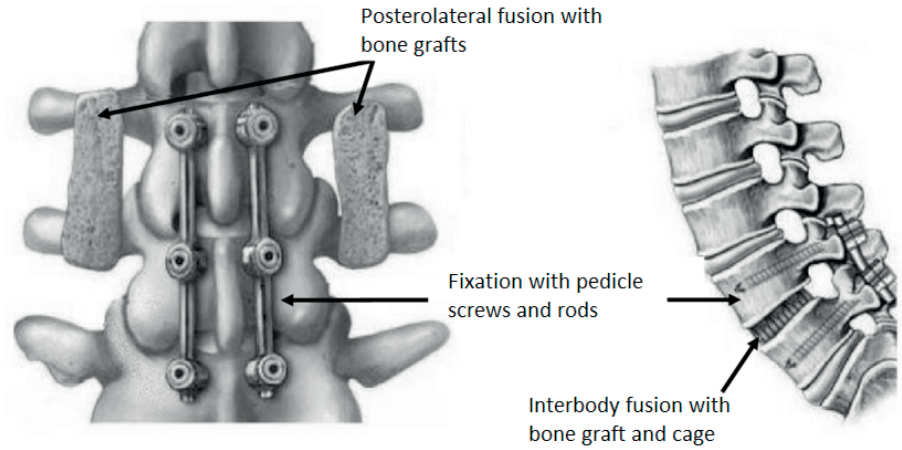


LUMBAR SPINAL FUSION

LSF is one treatment option people with LBP might consider and is often viewed as a last-resort treatment, when conservative treatment or pain interventions did not benefit the patient. Imaging of patients with an indication for undergoing LSF usually shows findings of disc degeneration, facet joint degeneration and/or spondylolisthesis. The indication for LSF based on imaging alone can be insufficient, as degenerative signs can also be seen in asymptomatic patients.[22, 23] Until now, the indication for LSF is therefore often based on patient preferences and surgeon experience.

LSF is a surgical technique in which two or more vertebrae are fixed using screws and rods to restrict motion of the affected spinal segment(s), with the ultimate goal of bony fusion between these fixed segments. Spinal fusion can be obtained either by placing bone graft between the transverse processes of the vertebrae or by inserting an interbody cage with autologous or synthetic bone graft placed between the vertebrae (Figure 2).

Figure 2. Posterolateral fusion (left) and interbody fusion (right) of the lumbar spine. (Adapted from Abbott 2010 [24])

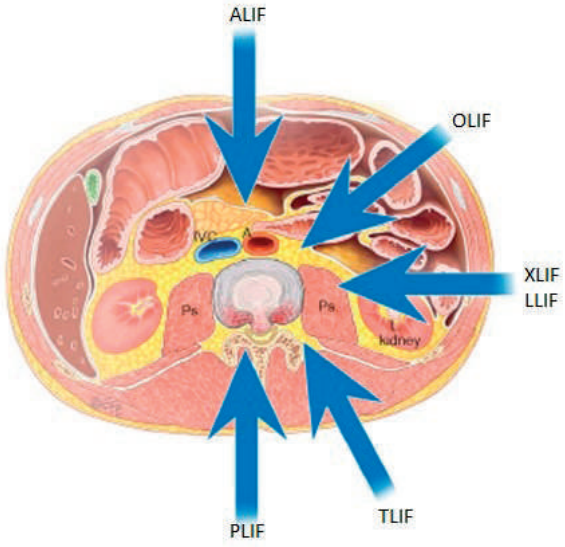


There are multiple surgical approaches for LSF, such as posterior lumbar interbody fusion (PLIF), transforaminal interbody fusion (TLIF), extreme lateral interbody fusion (XLIF/LLIF), oblique lumbar interbody fusion (OLIF) and anterior interbody fusion (ALIF) (Figure 3). PLIF, TLIF and ALIF are the most commonly used, although there is no evidence showing a clear advantage of one technique over the other.[25] Moreover, both open and minimally invasive techniques can be applied. In the Netherlands, major variation in surgical approach and operative technique is apparent among spine surgeons (either orthopedic or neurosurgeons): 67-69% prefer open fusion above minimally invasive fusion, and most surgeons use the PLIF approach (44%).[26] In the Maastricht University Medical Centre (MUMC+), an open PLIF or TLIF procedure is commonly applied in patients with degenerative disorders of the lumbar spine.

Undergoing major surgery, like LSF, is considered to be a major life event for patients, involving significant health risks and causing temporary deconditioning. Major surgery induces a systemic stress response, caused by surgical tissue injury, resulting in an inflammatory reaction, which drives metabolic, hormonal and immunological processes in the body.[27, 28] These processes are necessary to stimulate tissue repair, however are

accompanied by an increased demand for oxygen.[29] To cater to this increased oxygen demand, adequate physiological reserve of a patient is imperative.[30] Moreover, surgery also has an impact on a patient's mental state, asking for an adequate mental capacity as well.[31, 32] On top of that, patients with chronic LBP often already have gone through long periods of disuse and deconditioning, which negatively impacts both the physical and psychological state of a patient.[33] This makes it difficult to adequately cope with the surgery induced stress, which could possibly lead to a permanent deterioration in health. Variation in severity of deconditioning, mental state and other physical and socio-economic factors, leads to large interindividual differences in the risks for adverse outcomes. Especially frail, deconditioned and elderly patients seem to experience trouble in coping with the physiological and mental stressors of undergoing surgery, as their reserves are inherently smaller.[34] Although recent advances with regard to surgery and anesthesiology reduce the intraoperative stressors, a large proportion of the patients still do not benefit from undergoing LSF. This leaves us with the question for which patients undergoing LSF is worthwhile, and if it is, what can we do to limit the risk of negative postoperative outcomes?

Figure 3. Surgical approaches for lumbar interbody fusion. (Adapted from Mobbs et al. [25])



Abbreviations: PLIF= posterior lumbar interbody fusion, TLIF= transforaminal interbody fusion, XLIF/LLIF= extreme lateral interbody fusion, OLIF= oblique lumbar interbody fusion, ALIF= anterior interbody fusion.

PREDICTION MODELLING

Prediction modelling can be of great assistance in decision making for patients and healthcare professionals considering LSF, and is a major aspect of creating a P4 care pathway.[35, 36] Prediction models can help patients and healthcare professionals in making accurate treatment decisions,[37] by calculating the probability of a certain outcome while taking into account the risk factors of that individual patient and their context.[38] The calculated probability can be used to help both patient and surgeon to make better informed treatment decisions and manage expectations.[39] Prediction modelling is not new in medical research and consists of three phases: 1) development of the prediction rule, 2) external validation of the prediction rule, and 3) assessing the impact of implementation the prediction rule on clinical practice.[39]

Prediction modelling is especially useful for patients considering major surgery, as the stakes are high, the outcomes are for LSF are variable and well-informed shared decision making will ultimately result in more satisfied patients. Moreover, personalizing peri- and intraoperative care pathway components according to an individual's preoperative predicted outcomes can help minimize risks, thus tipping the scales of risks and benefits in favor of LSF.

Research on risk factors in this population identified patient characteristics like Body Mass Index (BMI), comorbidities and smoking status, as well as health perceptions on pain, disability and mental health to be predictive for postoperative outcomes.[40-42] Due to the limited number and variety of variables included in these studies, prediction accuracy of the prediction models were limited. Moreover, major methodological issues were apparent (e.g., unrepresentative population, no external validation or absence of an easily adaptable tool). Therefore, these models are not suitable for application in clinical practice.[43, 44] However, these models are still valuable, as the knowledge on predictive factors can be applied in the development of a new externally validated model.[44] Exploring new patient and context specific variables can improve predictive accuracy and make new prediction models more suitable for application in clinical practice. Of specific interest for exploration are variables that can be modified before surgery, like physical fitness. Physical fitness is an important predictive variable in major surgery like cardiac, oncological and abdominal surgery, which could also hold true for LSF.[45-47] This seems logical, as good physical fitness or cardiorespiratory capacity is an important aspect of high physiological reserve necessary to adequately deal with surgical stress.[48]

After the development phase, rigorous external validation should be performed, as often prediction models show reduced accuracy when applied to new populations.[39, 44] Preferably, after external validation, an impact assessment should be commenced to determine whether the prediction rule is used by the intended audience and thereby has its intended effect: better postoperative outcomes, reduced costs and/or more accurate patient selection. Moreover, patient and surgeon should consider which risk factors can be influenced by pre- and postoperative interventions, thus could reduce risks for negative outcomes when opting for LSF.

PERIOPERATIVE HEALTH

The perioperative care pathway contributes to the success of surgery probably just as much as the surgery itself. During the perioperative care pathway a positive or negative impact on a patient's physiological and mental reserve can be accomplished. A rather passive one-size-fits-all approach could lead to higher risk of negative postoperative outcomes. For example, a passive waiting period before joint replacement surgery can cause decline in a patient's physical capacity by 25%, a decline in quality of life by 53% and a aggravation of pain in 84% of patients.[49] As the waiting-period for elective LSF can be long, 37% waits nine months or longer, this 'waiting' time could be well spent by preparing for the surgery.[50]

Postoperative periods after LSF are also still characterized by immobility and passiveness; care is mostly bed-centered, one-size-fits-all, and patients are not genuinely motivated to be active during hospitalization. This hospitalization induced disability or iatrogenic disability is largely preventable and can mainly be attributed to healthcare management, rather than the underlying disease or treatment.[51] The introduction of enhanced recovery after surgery (ERAS) protocols have made a positive impact here by improving postoperative rehabilitation and anesthesiology.[52] On top of that, the application of prehabilitation in other types of orthopedic surgery is becoming more common and has positively influenced postoperative outcomes as well.[53, 54] The hospitalization period after LSF is relatively long, compared to total joint replacement surgery: seven days vs. four days on average at the start of this thesis in the MUMC+, with a national average of 4.8 days vs. 3.7 days, respectively.[55] Here the large interindividual differences in people undergoing LSF becomes apparent again, as hospitalization periods ranged from two to 64 days during the period of this thesis in the MUMC+. Long – most of the time medically necessary – hospitalization and/or rehospitalization can cause more iatrogenic disability and can have serious consequences for postoperative recovery rate, complication rate and long term outcomes. Thus, a proactive personalized perioperative care pathway, implementing both pre- and postoperative rehabilitation

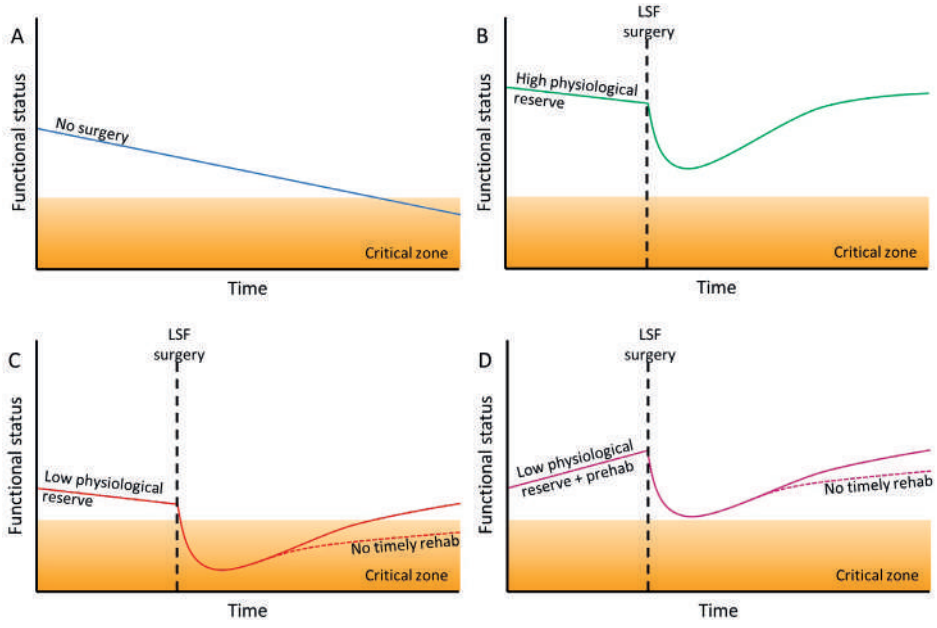
strategies is paramount in optimizing outcomes after surgery. The question is: can we mitigate the impact of the (pre)hospitalization period? Who will benefit most from these interventions? And what are the most appropriate interventions for patients opting for LSF?

Proactive Perioperative Care

Previous studies have shown that it is possible to reduce the impact of surgery and hospitalization by optimizing adaptable patient and context specific risk factors.[13] For example, rehabilitation interventions improving physical fitness in patients undergoing major elective surgery (such as total hip and knee replacement surgery, cardiothoracic surgery and oncological surgery) are known to be capable of shortening functional recovery by specific well administered preoperative therapeutic interventions.[53, 56-63] However, evidence on the effectiveness of pre- and post-operative rehabilitation for patients undergoing LSF is very limited.

Because of the large interindividual differences in this population, a more personalized approach is warranted. Research on interventions should specifically focus on patients with increased risk of negative outcomes.[34, 56, 57] Undergoing major surgery in people with low physiological reserve may push them into the critical zone, where

Figure 4. Possible courses of functional status over time in patients with degenerative disorders of the lumbar spine eligible for lumbar spinal fusion surgery, who A) do not opt for surgery (blue line), B) opt for surgery and have a high physiological reserve (green line), C) opt for surgery and have a low physiological reserve (red line), and D) opt for surgery, have a low physiological reserve and undergo prehabilitation before surgery (pink line). (adapted from Hulzebos et al. [12])



expectations of good functional recovery over time will mitigate.[13] A prehabilitation intervention boosts a patient's physiological reserve, with the aim not to reach the critical zone threshold. Moreover, timely start of postoperative rehabilitation can decrease the postoperative loss of functional status and speed up recovery time. The context and content of the interventions should be personalized, as one-size-fits-all strategies tend to be less effective.[64] A focus on pre-operative training or prehabilitation, together with timely postoperative recovery (e.g., fast track recovery) might lead to improved outcomes, as it increases a patient's physiological reserve and speeds up recovery (Figure 4). Moreover, it could mitigate the iatrogenic disability induced by a passive waiting list period.[65]

TECHNOLOGICAL DEVELOPMENTS

All non-experimental research in essence could already benefit from the collection and analysis of large amounts of real-world data, be it within in single patient or within a population.[66] However, manual big data collection and analysis is burdensome and time consuming for the patient, clinician and researcher. Hereto, relatively new technological developments will need to come into play.

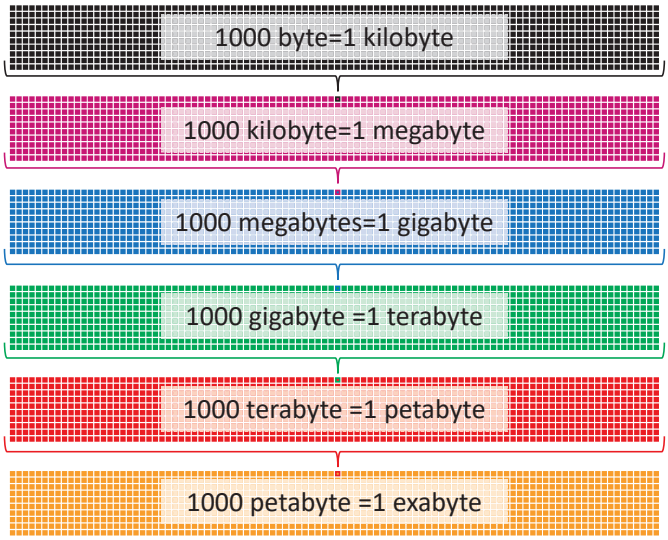
Real-world (Big) Data

More than 2.310 exabytes of healthcare data will be produced in 2021 (Figure 5).[67] Although data collection and analysis are a mere means to a greater goal, it is an essential part in the discovery of new knowledge and the driving force behind innovations. Apart from people themselves in real life, in the field of orthopedics, physiotherapy and spinal care the amount of (automatically) recorded data is growing exponentially. More data means better generalizability and personalizability through previously mentioned prediction modelling and accompanying interventions, whilst more details can unlock new hypothesis and a deeper understanding of underlying disease and functioning mechanism. However, mining and analyzing this vast amount of data, which is locked away in a multitude of data siloes is not an easy task. Here innovative methods to acquire and analyze data need to be applied to uncover useful knowledge that can be integrated into clinical practice and ultimately improve a patient's well-being.

FAIR Data

Methods for acquiring real-world (big) data are rapidly developing. Current real-world and research datasets are often siloed and hard to find, share and interpret by others. Every hospital, physical therapy practice and GP practice has its own method for registering and storing data. Sharing data between health professionals and/or researchers

Figure 5. How big is one exabyte.



is therefore time consuming. Often the same data are registered multiple times, leading to an unnecessarily large burden for the patient as well.

In 2016 the FAIR (findable, accessible, interoperable and reusable) guiding principles were introduced, to improve the usability of (research)data.[18] These principles describe what 'good data-management' should look like. One of the major advantages, when these principles are applied, is that data become 'machine readable', which results in computers being able to mine data from these siloes. A multitude of data can be retrieved relatively easy from different sources, like hospitals, patients, GP practices and national registries. In turn, these data could automatically be shared with patients, healthcare professionals and researchers, greatly reducing the registration burden. If the FAIR principles are applied accurately, these data can be also used for data analysis in research and improvement of patients' health(care).

Machine Learning

As more and more data become available, more powerful selective and calculative analytics need to be applied. Although machine learning is not new, it is especially in recent years widely applied in medical research.[68] Machine learning is a type of artificial intelligence (AI) in which algorithms are used to identify patterns in large and/or complex datasets.[35] These algorithms can leverage the variety and richness of the data and offer new insights for applying personalized medicine. However, a model can only be as good as the data it was built on. Moreover, the adoption of machine learning may also pose ethical and legal issues, such as liability in case of errors, understanding of the algorithm and privacy issues when data are used from multiple sources. Therefore,

adhering to the FAIR principles is an important first step towards effective application of machine learning in clinical practice. Appropriate application and further development of machine learning in healthcare promises a great return on investment.

THESIS OUTLINE

The central mission of this thesis was to improve the health of people opting for elective LSF by adopting ongoing advancements in healthcare towards an increasingly predictive, preventive, personalized and participatory (P4 medicine) perioperative healthcare approach.

To achieve this mission, we started with assembling information on the current variety of expert perioperative physiotherapeutic care for patients opting for elective LSF. We conducted a systematic review and meta-analysis in c*hapter 2* to summarize the available latest evidence of perioperative interventions with patients opting for spinal surgery. The aim was to make recommendations on how to apply the latest evidence into clinical practice and identify gaps in knowledge for future scientific research.

In chapter 3 we used a cross-sectional survey design to elicit standard physiotherapy practice in hospitals in the Netherlands that were involved in care for patients opting for LSF.

In *chapter 4* we assessed the feasibility and preliminary effectiveness of a community-based prehabilitation exercise training in multiple high-risk cases. Hereto, we applied a pragmatic propensity matched cohort approach and interrupted time series analysis. High-risk patients were identified using the risk factors found in *chapter 5* and were subsequently offered a preoperative functional high-intensity interval training program.

In *chapter 5* we aimed to derive and externally validate a prediction tool for clinically relevant pain reduction 1-2 years after LSF. This tool was derived from classical predictive factors such as patient characteristics and PROMs and was translated into a tool that can easily be implemented in clinical practice. We built this tool to support patients and surgeons in the difficult process of decision making for undergoing LSF.

In *chapter 6* we explored the importance of physical fitness as a predictor for short term in-hospital and one year postoperative outcomes after LSF. Specifically, we explored physical fitness parameters collected via a standard care screening in our hospital to identify patients who are at high risk for delayed in-hospital recovery, discharge and change in pain one year after LSF.

To take first steps towards applying the FAIR principles and thereby providing a real-world example on the possibilities of federated learning. In *chapter 7* we propose a strategy describing how to apply linked data and sematic web technology, within the context of real-world data collection of *chapter 5*. Moreover, we introduced a functio-

nomics as an addition to the current 'omics' family to enable better, faster and smarter analysis of real-world data.

Finally, a summary of our findings, their implications for P4-oriented clinical practice, prospects for future research and the impact on society are discussed in *chapter 8 and 9*.

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2

Current prehabilitation programs do not improve the postoperative outcomes of patients scheduled for lumbar spine surgery: A systematic review with meta-analysis

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ABSTRACT

Objective

To assess the effectiveness of prehabilitation in patients with degenerative disorders of the lumbar spine who are scheduled for spine surgery.

Design

Intervention systematic review with meta-analysis.

Literature Search

Seven electronic databases were systematically searched for randomized controlled trials or propensity-matched cohorts.

Study Selection Criteria

Studies that measured the effect of prehabilitation interventions (i.e., exercise therapy and cognitive behavioral therapy [CBT]) on physical functioning, pain, complications, adverse events related to prehabilitation, health-related quality of life, psychological outcomes, length of hospital stay, use of analgesics, and return to work were included.

Data Synthesis

Data were extracted at baseline (preoperatively) and at short-term (six weeks or less), medium-term (greater than six weeks and up to six months), and long-term (greater than six months) follow-ups. Pooled effects were analyzed as mean differences and 95% confidence intervals (CIs). Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Results

Cognitive behavioral therapy interventions were no more effective than usual care for all outcomes. Pooled effect sizes were –2.0 (95% CI= –4.4, 0.4) for physical functioning, –1.9 (95% CI= –5.2, 1.4) for back pain, and –0.4 (95% CI= –4.1, 0.4) for leg pain. Certainty of evidence for CBT ranged from very low to low. Only one study focused on exercise therapy and found a positive effect on short-term outcomes.

Conclusion

There was very low–certainty to low-certainty evidence of no additional effect of CBT interventions on outcomes in patients scheduled for lumbar surgery. Existing evidence was too limited to draw conclusions about the effects of exercise therapy.

INTRODUCTION

Treatment for individuals with degenerative disorders of the lumbar spine is usually nonsurgical. Surgery may be considered when patients have persistent symptoms and nonsurgical treatment fails.[1, 2] However, lumbar spine surgery carries the risk of complications, (temporary) decline in physical capacity, and unsatisfactory results.[3, 4] Prehabilitation (i.e., exercise therapy and cognitive behavioral therapy [CBT]) before undergoing major elective surgery may accelerate recovery and diminish complication rates.[5, 6] Cognitive behavioral therapy and exercise therapy have efficacy in other orthopaedic surgery populations, such as total hip or knee replacement.[7-10] A previous review of prehabilitation for patients undergoing lumbar spine surgery only included three interventions, did not perform a meta-analysis, and focused only on functional and economic outcomes.[11] Therefore, what should be considered best practice in terms of the effect, timing, and content of prehabilitation programs is unclear. Given that prehabilitation before spine surgery is gaining popularity,[12, 13] further investigation is needed to determine the best approach to prehabilitation for patients undergoing lumbar spine surgery. The aim of our systematic review was to assess the short-term (six weeks or less), medium-term (greater than six weeks and up to six months), and long-term (six months or greater) effects of prehabilitation compared to usual care in patients with a degenerative disorder of the lumbar spine who were scheduled for spine surgery. We focused on physical functioning (self-reported and observed), back and leg pain, complications after surgery, adverse events related to prehabilitation, health-related quality of life (HRQoL), psychological outcomes, length of hospital stay, use of analgesics, and returnto-work outcomes, to give clinicians and researchers a complete overview of the potential benefits and pitfalls of current prehabilitation interventions.

METHODS

The review protocol was prospectively registered in the PROSPERO database (CRD42017050598).

Data Sources and Searches

Three reviewers (EJ, IP, MC) systematically searched the MEDLINE, Embase, PEDro, Zetoc, and CINAHL databases. Additional unpublished or ongoing studies were identified by searching the OpenGrey database and the clinical trial registry at http://www.clinicaltrials.gov/. Using the Boolean terms "AND" and "OR," we combined search terms related to prehabilitation and lumbar spine surgery.[14] The search was not limited by language or date. We manually searched the reference lists of eligible studies and reviews on the

same topic and conducted a systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[15]

Study Selection

Two reviewers (EJ, IP) independently evaluated titles and abstracts of eligible articles using Covidence systematic review software (Veritas Health Innovation Ltd., Melbourne, Australia). No blinding was used in this selection. When the title and abstract provided insufficient information to include or exclude the study, the full text was requested. Two reviewers (EJ, IP) evaluated full-text articles for inclusion. Uncertainty was solved by consulting an expert spine surgeon and a researcher (PW, TH). Duplicates and articles for which the full text was unavailable were excluded. The inclusion criteria were (1) a study design of randomized clinical trial or propensity-matched cohort, (2) measurement of the effect of preoperatively initiated structured rehabilitation or prehabilitation (i.e., physical therapy, exercise therapy, and/or CBT) in adult patients who were scheduled to undergo spine surgery for a degenerative disorder of the lumbar spine, and (3) measurement of at least one of the outcomes of physical functioning (self-reported or observed), back and leg pain, complications after surgery, adverse events related to prehabilitation, HRQoL, psychological outcomes, length of hospital stay, use of analgesics (quantitative measures), or return to work. Studies of patients with nondegenerative disorders (spinal tumors, fractures, discitis, or scoliosis) were excluded.[16] Studies that were identified as substudies of included trials were used to complete outcome measures if these were not reported in the publication of the main study.

Data Extraction

Two reviewers (EJ, IP) independently extracted data from every eligible article in duplicate, using a standardized form created using Microsoft Access 2013 (Microsoft Corporation, Redmond, WA). In the case of errors or discrepancies, differences were resolved in a consensus meeting. The primary outcome measure was physical functioning (self-reported), reported as mean ± SD. Secondary outcomes of interest were reported as mean ± SD values for back and leg pain, complications, adverse events related to prehabilitation, HRQoL, psychological outcomes, length of hospital stay, use of analgesics, and return to work. Data were extracted for every intervention group of interest at all available measurement points: at baseline (preoperatively) and at short-term (six weeks or less after surgery), medium-term (greater than six weeks and up to six months after surgery), and long-term (six or more months after surgery) follow-ups. When multiple follow-up data were available in the same time frame, the longest follow-up time was used for the meta-analyses. If necessary, the outcome measures of interest and their distribution were extracted from figures using the WebPlotDigitizer tool.[17] If data were missing, a maximum of two attempts via e-mail were made to contact the cor-

responding author. If missing variance estimates (SDs) of a study could not be retrieved, multiple imputation was used to impute likely replacement values where meta-analysis was performed. Means, SDs, and sample sizes were used as predictor variables to impute the missing SDs.[18] Missing SDs were randomly imputed using predictive mean matching across the range of SDs available from the studies with no missing variance estimates.[19] This was completed five times, using the mice package[20] in R Version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).[19] Imputation was used to prevent bias resulting from exclusion of studies with missing variance estimates.[21] Information on the characteristics and context of the interventions was assessed using the Template for Intervention Description and Replication (TIDieR) checklist.[22]

Risk of Bias

The Cochrane tool was used to assess individual study risk of bias. We evaluated six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.[23] Two researchers (EJ, IP) independently rated included studies as high, low, or unclear risk of bias. Zero to two unclear or biased domains represented a low risk of bias, three to four unclear or biased domains represented an unclear risk of bias, and five or more unclear or biased domains represented a high risk of bias. Conflicts were resolved by consensus.

Data Synthesis and Analyses

We analyzed the effect of prehabilitation on all retrieved outcomes. If two or more studies reported the same outcome in the same time frame, meta-analysis was performed using a random-effects model.[24] Statistical heterogeneity of the treatment effect among studies was tested using the inconsistency I^2 test. Reporting bias was explored by a funnel plot and Egger's test for funnel plot asymmetry if more than 10 comparisons were available.[25] All analyses were conducted using the R Version 3.6.1 meta package (R Foundation for Statistical Computing).[26, 27] Besides statistical significance, we assessed whether the mean difference between the prehabilitation intervention and usual care reported in the studies reached a minimal clinically important difference (MCID). The following MCIDs were used: 12.8 to 14.9 points for physical functioning (measured with the Oswestry Disability Index), 12 to 21 points for back pain, 16 to 28 points for leg pain, and 0.46 points for HRQoL (measured with the EuroQol-5 dimensions scale [EQ-5D]).[28, 29]

Certainty of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to appraise the certainty of the evidence.[30] Evidence from randomized controlled trials began as high-certainty and observational studies as low-

certainty evidence.[30] Certainty was downgraded due to risk of bias, inconsistency of results, indirectness of evidence, imprecision, and reporting bias. Certainty was upgraded when the magnitude of the treatment effect was high, there was evidence of a dose-response relation, or all plausible biases would have reduced the magnitude of the treatment effect.[30]

RESULTS

A total of 8249 records were identified in all databases (Figure 1). After discarding duplicates, 5328 studies remained for title and abstract screening. Of these, 31 studies were eligible for full-text screening. Sixteen studies did not meet our inclusion criteria. Fifteen studies met the inclusion criteria and were included in the systematic review. The 15 included studies described 12 interventions (Table 1). There were 12 randomized controlled trials,[31-42] two lagged controlled trials,[43, 44] and one matched cohort study.[45]mSample sizes ranged from 39 to 197 patients, with a mean age ranging from 36 to 63 years. Types of surgery included laminectomy, interlaminar decompression, microdiscectomy, and spinal fusion. Most interventions (11/12) were CBT interventions.[31-35, 38-42] Only the studies by Nielsen et al.[36, 37] described an intervention focusing on exercise therapy and were not included in any meta-analyses. Effects of CBT interventions were pooled, but the effect of the exercise intervention was analyzed separately, due to heterogeneity in the content of the interventions. One study reported on return to work[36] and no study reported on complications or adverse events related to the prehabilitation. Therefore, no meta-analyses were conducted for these outcomes. Characteristics and context descriptions of the individual interventions according to the TIDieR checklist can be found in Appendix A (available at www.jospt.org).

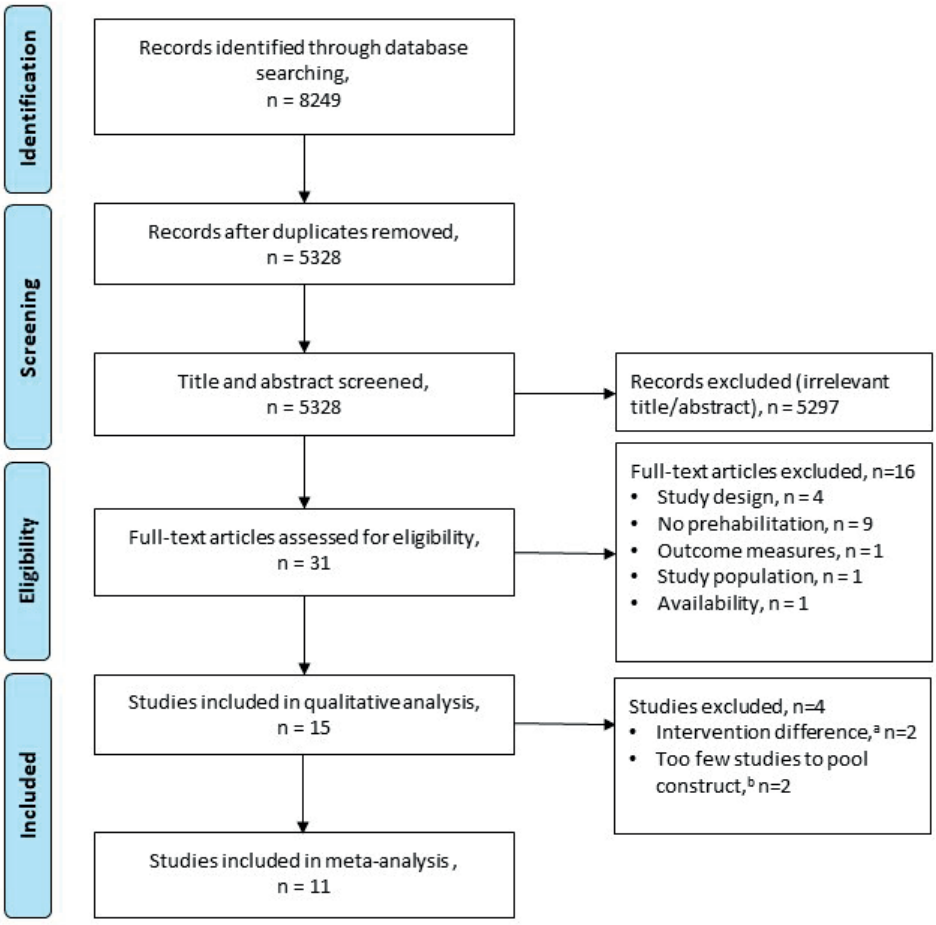
Risk of Bias

Figure 2 presents the outcomes of the Cochrane risk-of-bias tool for each of the 15 studies. None of the studies blinded participants and personnel due to the nature of the interventions. Twelve studies had no allocation concealment, 11 had no blinding of outcome assessment, 10 had incomplete outcome data, and 10 had selective reporting or did not report on this. Two studies had low risk of bias,[34, 41] four studies had unclear risk of bias,[35, 37, 39, 40] and nine studies had high risk of bias.[31-33, 36, 38, 42-45]

Effects of Prehabilitation

Standard deviations were not reported in three studies and had to be imputed using multiple imputation.[31, 33, 42] Forest plots for HRQoL, psychological outcomes, length of hospital stay, and analgesic use can be found in Appendix B (available at www.jospt.org).

Figure 1. PRISMA flowchart of study selection process for the systematic review.



[a] The studies of Nielsen et al. 2008 & 2010 reported on exercise therapy, this intervention was not comparable to the interventions of other included studies and was therefore, excluded from the meta-analysis.

[b] The studies of Gavin et al. and Reichart et al. measured constructs that were measured by only one study and therefore could not be pooled.

Effects of CBT on Self-reported Physical Functioning

Self-reported physical functioning data were reported in five studies at short-term follow-up, in 7 studies at medium-term follow-up, and in four studies at long-term follow-up.[31, 33-35, 39, 42-45] There was no additional effect of prehabilitation compared to usual care on postoperative self-reported physical functioning at short-term, medium-term, or long-term follow-up (Figure 3). There was heterogeneity at medium-term follow-up (I^2= 65%). Certainty of evidence was very low at short-term follow-up (very serious risk of bias and imprecision) and medium-term follow-up (very serious risk of bias and inconsistency, and serious imprecision) and low at long-term followup (serious risk of bias and imprecision) (Appendix C, available at www.jospt.org).

Table 1. Characteristics of included studies.

Study/Country/ Reported Design	Surgery type	Sample[a]	Recruit-ment rate	Outcomes
Gavin et al.[32] United States Single-blind RCT	Lumbar laminectomy or lumbar fusion	Intervention: n= 27 (male, n= 7; female, n= 20); age, 56 ± 16 y Control: n= 22 (male, n= 7; female, n= 15); age, 56 ± 18 y	Unknown	Overall pain, analgesics
Louw et al.[35] United States Multicenter RCT	Lumbar surgery	Intervention: n= 32; age, 49.59 y Control: n= 35; age, 49.65 y	0.73	Back pain, leg pain, perceived PF
Nielsen et al.[36] Denmark RCT	Lumbar spinal fusion	Intervention: n= 28 (male, n= 11; female, n= 17); age, 48 (31-72) y Control: n= 32 (male, n= 13; female, n= 19); age, 52 (31-88) y	0.83	HRQOL, RTW
Nielsen et al.[37] Denmark RCT	Lumbar spinal fusion	Intervention: n= 35 (male, n= 14; female, n= 21); age, 48 (31-80) y Control: n= 38 (male, n= 16; female, n= 22); age, 52 (23-88) y	0.83	Back pain, leg pain, observed PF, perceived PF, LOS, HRQOL
Rolving et al.[39] Denmark RCT	Lumbar spinal fusion	Intervention: n= 59 (male, n= 23; female, n= 36); age, 51.4 ± 9.2 y Control: n= 31 (male, n= 16; female, n= 15); age, 47.7 ± 8.9 y	0.61	Back pain, leg pain, observed PF, perceived PF
Rolving et al.[41] Denmark RCT	Lumbar spinal fusion	see previous	0.61	HRQOL
Rolving et al.[40] Denmark RCT	Lumbar spinal fusion	see previous	0.61	Back pain, leg pain, LOS, analgesics
Boote et al.[31] United Kingdom Pilot RCT	Unilateral, single-level lumbar micro-discectomy surgery	Intervention: n= 29 (male, n= 14; female, n= 15); age, 38 ± 6 y Control: n= 30 (male, n= 15; female, n= 15); age, 36 ± 7.4 y	0.64	Back pain, leg pain, perceived PF, HRQOL
Lindbäck et al.[33] Sweden RCT	Surgery for degenerative lumbar spinal disorder	Intervention: n= 99 (male, n= 45; female, n= 54); age, 58 ± 13.3 y Control: n= 98 (male, n= 47; female, n= 51); age, 61 ± 11.5 y	0.81	Back pain, leg pain, perceived PF, HRQOL, psychological outcomes
Reichart et al.[38] Germany Randomized prospective longitudinal study	Posterior lumbar interbody fusion.	Intervention: n= 19 (male, n= 8; female, n= 11); age, 59.4 y Control: n= 20 (male, n= 9; female, n= 11); age, 58.8 y	0.91	Overall pain, perceived PF
Skolasky et al.[44] United States Lagged controlled trial	Lumbar decompression and fusion procedures.	Intervention: n= 63 (male, n= 25; female, n= 38); age, 59 ± 13.2 y Control: n= 59 (male, n= 20; female, n= 39); age, 58.1 ± 13.5 y	0.90	Perceived PF, HRQOL
Skolasky et al.[43] United States Lagged controlled trial	Decompression surgery	Intervention: n= 63 (male, n= 25; female, n= 38); age, 60 ± 13 y Control: n= 59 (male, n= 20; female, n= 39); age, 58 ± 13.5 y	0.68	Overall pain, perceived PF, HRQOL

Table 1. Characteristics of included studies. (continued)

Study/Country/ Reported Design	Surgery type	Sample[a]	Recruitment rate	Outcomes
Lotzke et al.[34] Sweden RCT	Lumbar spinal fusion	Intervention: n= 59 (male, n= 26; female, n= 33); age, 44.8 ± 8.2 y Control: n= 59 (male, n= 29; female, n= 30); age, 46.7 ± 8.5 y	0.55	Back pain, leg pain, observed PF, perceived PF, HRQOL, psychological outcomes
Strøm et al.[42] Denmark RCT	Instrumented lumbar spinal fusion	Intervention: n= 48 (male, n= 22; female, n= 26); age, 53 y Control: n= 51 (male, n= 13; female, n= 38); age, 55 y	0.54	Back pain, leg pain, perceived PF, HRQOL, psychological outcomes, LOS
Yi et al.[45] United States Matched cohort study	1- to 4-level decompression and/or fusion	ntervention: n= 24 (male, n= 11; female, n= 13); age, 61.4 ± 6.86 y Control: n= 24 (male, n= 11; female, n= 13); age, 63.17 ± 8.45 y	Unknown	Back pain, leg pain, perceived PF, HRQOL, LOS, analgesics

Abbreviations: HRQoL= health-related quality of life, LOS= length of hospital stay, PF=physical functioning, RCT=randomized controlled trail, RTW=return to work.
Age values are mean, mean ± SD, or median (range).

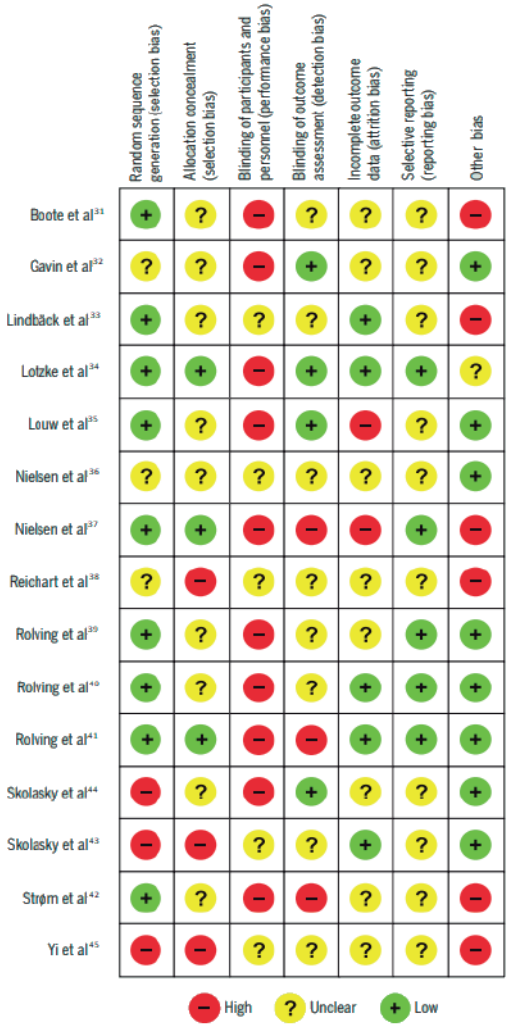
Effects of CBT on Observed Physical Functioning

Two studies reported on observed physical functioning.[34, 40] However, measurement instruments used in these studies measured different constructs of physical functioning and could therefore not be pooled. There was no additional effect of CBT on any of the tests measuring observed physical functioning (i.e., the 5-minute walk test, 15-m walk test, timed up-and-go test). Rolving et al.[40] found a significant difference in the number of patients who reached independent mobility (reaching functional milestones like performing transfers and walking) within three days after surgery between the intervention and control groups, in favor of the intervention group.

Effects of CBT on Back Pain

Of studies that investigated the effect of prehabilitation on postoperative back pain using the visual analog scale (VAS) or the numeric rating scale (NRS), there were six at short-term follow-up, five at medium-term follow-up, and three at long-term followup. [31, 33-35, 39, 42, 45] There was no additional effect of prehabilitation compared to usual care on back pain (Figure 4). There was heterogeneity at short-term follow-up (I^2= 61%). Certainty of evidence was very low at short-term (very serious risk of bias and imprecision), medium-term (very serious risk of bias and imprecision, and serious inconsistency), and long-term follow-up (serious risk of bias and very serious imprecision) (Appendix C, available at www.jospt.org).

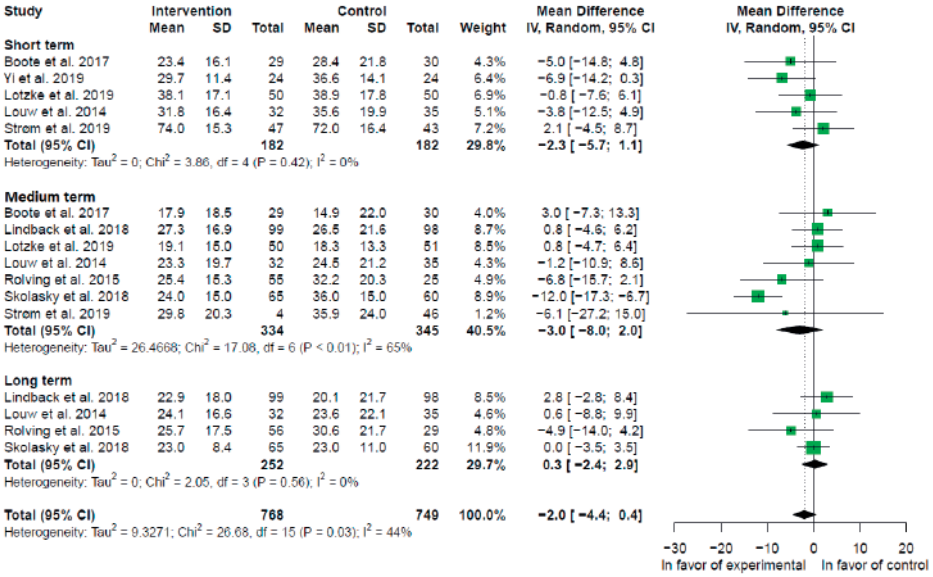
Figure 2. Risk of bias assessment results for included studies.



Effects of CBT on Leg Pain

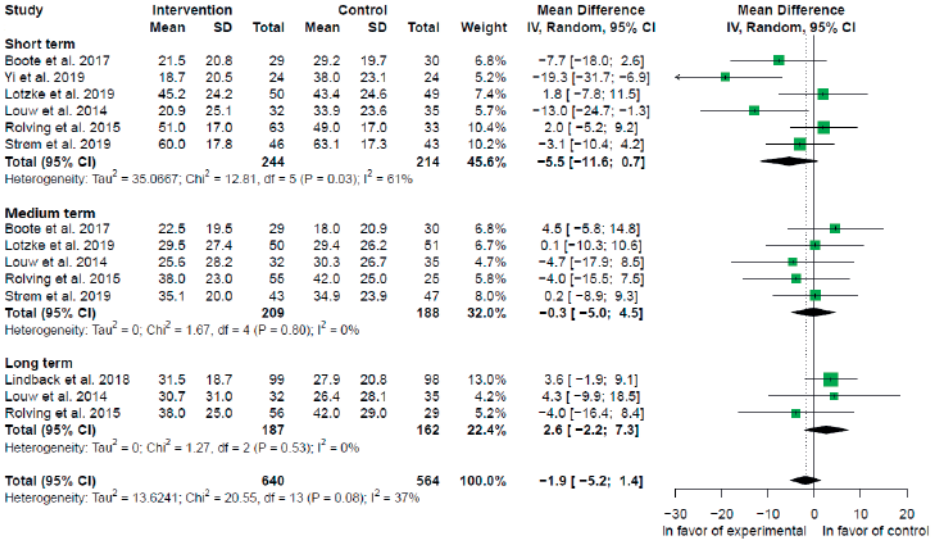
Five studies investigated the effect of prehabilitation on postoperative leg pain, using a VAS or NRS, at short-term and medium-term follow-ups, and three at long-term follow-up.[31, 33-35, 39, 42, 45] There was no additional effect of prehabilitation compared to usual care on leg pain. There was heterogeneity at short-term and long-term follow-ups (I^2= 41% and 37%, respectively). Certainty of evidence was very low at short-term (very serious risk of bias and imprecision, and serious inconsistency), medium-term (very serious risk of bias and imprecision), and long-term follow-up (serious risk of bias and very serious imprecision) (Appendix C, available at www.jospt.org).

Figure 3. Forest plot of the effect of prehabilitation compared to usual care on self-reported physical functioning (0-100) on short-, medium-, long-term and overall effect.



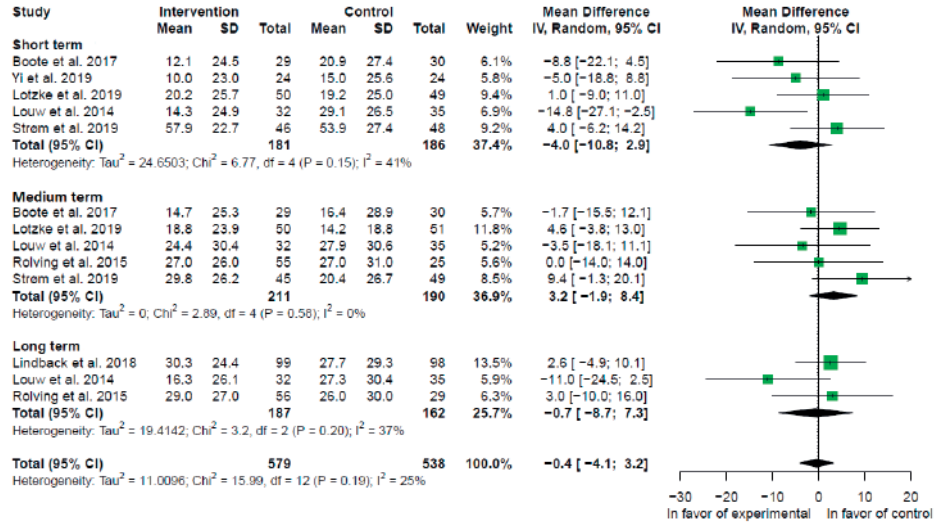
Abbreviations: SD= standard deviation; IV= weighted mean difference; CI= confidence interval

Figure 4. Forest plot of the effect of prehabilitation compared to usual care on back pain (0-100) on short-, medium-, long-term and overall effect.



Abbreviations: SD= standard deviation; IV= weighted mean difference; CI= confidence interval

Figure 5. Forest plot of the effect of prehabilitation compared to usual care on leg pain (0-100) on short-, medium-, long-term and overall effect.



Abbreviations: SD= standard deviation; IV= weighted mean difference; CI= confidence interval

Effects of CBT on Pain

Three studies reported on the effect of prehabilitation on overall pain, using different measurement methods: verbal patient-reported pain,[32] the German pain questionnaire,[38] and the Brief Pain Inventory.[43] As these three methods measure different constructs of pain, they could not be pooled. The mean difference in pain at short-term follow-up was –0.2 (95% CI= –1.21, 0.81) in the study by Gavin et al.[32] The mean difference in pain at medium-term follow-up was –1.83 (95% CI= –4.35, 0.66) in the study by Reichart et al.[38] and –0.90 (95% CI= –1.49, –0.31) in the study by Skolasky et al.[43] The mean difference in pain at long-term follow-up was –1.00 (95% CI= –1.36, –0.64) in the study by Skolasky et al.[43]

Effects of CBT on HRQOL

Five studies reported on HRQoL at shortand medium-term follow-ups, using the EQ-5D.[31, 33, 34, 42, 45] There was no additional effect of prehabilitation compared to usual care on HRQoL at short-term or medium-term follow-up (Appendix B, available at www.jospt.org). There was heterogeneity in the short-term data (I^2= 63%). Certainty of evidence was very low for short-term (very serious risk of bias and imprecision, and serious inconsistency) and medium-term follow-ups (serious risk of bias and very serious imprecision) (Appendix C, available at www.jospt.org). Two studies also reported on HRQoL at long-term follow-up.[33, 43] Skolasky et al.[43] used the Medical Outcomes Study 12- Item Short-Form Health Survey; Lindbäck et al.[33] used the Medical Out-

comes Study 36-Item Short-Form Health Survey. From Lindbäck et al.[33] SDs could not be retrieved; therefore, meta-analysis was omitted. Mean differences for the physical component summary (0-to-100 scale) were 3 (95% CI= 0.04, 5.96) and 0 (95% CI could not be calculated) for Skolaksy et al.[43] and Lindbäck et al.[33] respectively. The mean difference for the mental component summary was –1.5 (95% CI could not be calculated) in the study by Lindbäck et al.[33] Skolasky et al.[43] did not report the mental component summary score.

Effects of CBT on Psychological Outcomes

All studies that reported on psychological outcomes used the Hospital Anxiety and Depression Scale (HADS); the depression and anxiety subscores of the HADS were included in the meta-analyses.[33, 34, 42] Two studies investigated the effect of prehabilitation on postoperative psychological outcomes using the HADS at short-term follow-up, three at medium-term follow-up, and one at long-term follow-up (Appendix B, available at www.jospt.org).[33, 34, 42] There was no additional effect of prehabilitation compared to usual care on psychological outcomes. There was heterogeneity in the HADS depression score at short-term followup (I^2= 86%). Certainty of evidence was very low at short-term (serious risk of bias and inconsistency, and very serious imprecision) and medium-term followups (serious risk of bias and very serious imprecision) for the HADS depression score. For the HADS anxiety score, certainty of evidence was very low at short-term (serious risk of bias and very serious imprecision) and medium-term followups (serious risk of bias and very serious imprecision) (Appendix C, available at www.jospt.org). The Pain Catastrophizing Scale, Tampa Scale of Kinesiophobia, and Fear-Avoidance Beliefs Questionnaire physical activity subscale outcomes were measured.[33, 34] However, there were insufficient data to perform meta-analysis. Lindbäck et al.[33] reported a mean difference of 0.7 (95% CI= –1.2, 2.6) on the Fear-Avoidance Beliefs Questionnaire physical activity subscale at long-term follow-up. Lotzke et al.[34] reported a mean difference of –0.4 at short-term followup and –0.8 at medium-term follow-up on the Pain Catastrophizing Scale. For the Tampa Scale of Kinesiophobia, there was a mean difference of 0.1 at short-term follow-up and –0.2 at medium-term follow-up.

Effects of CBT on Length of Hospital Stay

Three studies reported on length of hospital stay.[40, 42, 45] There was no additional effect of prehabilitation compared to usual care on length of hospital stay (Appendix B, available at www.jospt.org). There was evident heterogeneity between studies (I^2= 55%). Certainty of evidence was very low (very serious risk of bias and imprecision, and serious inconsistency) (Aappendix C, available at www.jospt.org).

Effects of CBT on Analgesic Use

Three studies reported on analgesic use.[32, 40, 45] The study by Gavin et al.[32] could not be pooled, as they reported milligrams of intravenous morphine equivalents per hour instead of opioid equivalents per day. Results from Gavin et al.[32] did not favor the intervention group, with a mean difference on postoperative day 1 of 0.6 and on postoperative day two of 0.36 mg of intravenous morphine equivalents per hour. There was no additional effect of prehabilitation compared to usual care on opioid equivalent intake (Appendix B, available at www.jospt.org). There was no evident heterogeneity. The certainty of evidence was very low (serious risk of bias and very serious imprecision) (Appendix C, available at www.jospt.org).

Effects of Excercise on Postoperative Outcomes

Only the studies by Nielsen et al.[36, 37] focused on exercise as an intervention in combination with improved diet, smoking cessation, and optimized pain control, and were therefore not included in the meta-analyses. Nielsen et al.[36, 37]only reported short-term follow-up data and found that the prehabilitation group had a shorter length of hospital stay and faster recovery of physical functioning ($P<.05$) compared to the control group. There were no differences in complication rates, adverse events, pain, or HRQoL, and no effect on the timed up-and-go test or the sit-to-stand test.

Clinically Important Differences

None of the pooled mean differences in physical functioning, back and leg pain, HRQoL, and psychological functioning between usual care and prehabilitation interventions reached MCID thresholds.[29, 46, 47] In other words, no clinically important effects were identified. Yi et al.[45] and Louw et al.[35] reached the lower threshold of the MCID for back pain at short-term follow-up.

DISCUSSION

We assessed the effect of prehabilitation in patients suffering from a degenerative disorder of the lumbar spine who were scheduled for spine surgery. There was very low to low certainty of evidence of no additional effect of CBT prehabilitation interventions on any outcome when compared to usual care. No clinically important differences (MCIDs) in meta-analyses were found for any of the outcomes. A single exercise prehabilitation intervention found a significant effect on length of hospital stay and self-reported physical functioning.[36, 37] A previous systematic review[11] evaluated the effect of prehabilitation on physical functioning and economic outcomes following spine surgery. This review included only three of the 12 interventions included in our review. Our results for

functional outcomes were similar: no effect of prehabilitation. Prehabilitation (exercise interventions) can reduce postoperative length of hospital stay and possibly improve physical functioning in a predominantly orthopaedic population (mainly knee or hip arthroplasty for osteoarthritis),[48] although there may not be significant postoperative benefits of prehabilitation on HRQoL, pain, and other outcomes,[49] which supports our results. In systematic reviews of prehabilitation in other surgery populations, prehabilitation interventions have a beneficial effect on postoperative outcomes when compared to usual care. For major abdominal, cancer, and cardiac surgery, there are positive effects of prehabilitation on (pulmonary) morbidity.[47, 50-52] The evidence is conflicting when it comes to the effect of prehabilitation interventions on postoperative outcomes. Preoperatively improving psychological health and physical functioning may improve postoperative outcomes, as both are prognostic factors for worse outcomes after spine surgery.[53] Surprisingly, this was not the case for the interventions in our review. This may be explained by differences in populations or in the nature of the interventions under study. Prehabilitation interventions capable of reducing morbidity after other types of surgery were mainly exercise interventions.[10, 52] In our review, there was only one intervention that focused on exercise therapy, which showed some benefits of prehabilitation on short-term outcomes. Some authors suggest that effective prehabilitation interventions should focus on high-risk patients, as some patients are at higher risk for worse postoperative outcomes than others.[6] Patients who are at high-risk (e.g., frail, deconditioned, or obese individuals) may have trouble meeting the increased physiological demands of surgery and are therefore in need of preoperative interventions to improve their physiological reserves.[54] Including both high- and low-risk patients in a prehabilitation study may lead to weaker effect estimates, as effects of prehabilitation are logically smaller in a low-risk population. None of the studies in our review described a preselection of high-risk patients or performed a sensitivity analysis on possible risk groups. Some of the included studies may have excluded patients at high risk for poor postoperative outcomes, as recruitment rates ranged between 0.54 and 0.91, 7 of 15 studies had a maximum inclusion age,[31, 33-35, 39-41]1,21-23,39-41 9 of 15 studies excluded patients with specific comorbidities,[31, 33-37, 39-41] and five of 15 studies excluded patients who had undergone previous spine surgery.[31, 34, 38, 43, 44] If studies only included patients at high risk for poor postoperative outcomes (or performed sensitivity analysis on a highrisk subgroup), effects of prehabilitation compared to usual care might have been different.

Strengths and Limitations

Strengths of this review are the broad inclusion of eligible outcome measures and the stratification into different time frames. This helps to identify for which outcomes and at which time points prehabilitation may be most effective, and where there is still a gap

in knowledge. Our approach is clinically relevant, as interventions may only have an effect on a subset of outcomes and can change over time. We mainly had homogeneous populations in terms of age, sex, and surgery type. The division made in our review between CBT and exercise interventions was arbitrary. For example, the study by Lindbäck et al.[33] had both exercise and behavioral components; however, we chose to classify the intervention in the CBT comparator. Our results were not influenced by this decision, as pooling of treatment effects from the studies by Lindbäck et al.[33] and Nielsen et al.[36, 37] was not possible due to differences in the timing of outcome measurement, and Lindbäck et al.[33] did not find a treatment effect. We made this decision to improve homogeneity between pooled interventions. Most studies had a high risk of bias and described a variety of CBT interventions, such as behavioral counseling and relaxation therapy, with great variation between interventions in terms of intensity, ranging from a 30-minute session to 18 contact hours with a physical therapist. There may be a dose-response relationship between intervention intensity and the outcomes, with more intense interventions being more effective. The difference in intensity is only one example of the variety between the studied interventions. Variety in terms of location of the intervention and adherence was also present between CBT interventions, which could have influenced the effectiveness of prehabilitation. Another limitation is the relatively small total sample size of the meta-analyses and small sample sizes of individual studies, as well as the incoherence of several effect estimates, leading to downgrading of the certainty of evidence. In the meta-analysis we used mean ± SD estimates of individual studies, though some authors specifically mentioned that the data were not normally distributed, which might have influenced the results. We could not detect the presence of reporting bias, as there were too few studies available to adequately test for reporting bias.

Recommendations

Prehabilitation does not seem to have an added benefit for postoperative outcomes after lumbar spine surgery. However, larger, high-quality trials (with improved randomization procedures, allocation concealment, and blinding) are needed to improve the certainty of our findings on the possible effects of prehabilitation interventions. Future studies should take into account concerns raised in this review: (1) high-quality studies on exercise interventions and CBT for patients undergoing spine surgery are needed to evaluate effectiveness, especially on long-term outcomes; and (2) inclusion of, or sensitivity analysis on, high-risk subgroups of patients (e.g., frail, deconditioned, or obese individuals) who may be more likely to benefit from prehabilitation interventions.[55]

CONCLUSION

There was very low to low certainty of evidence of no additional effect of CBT compared to usual care on postoperative outcomes in patients undergoing surgery for a degenerative disorder of the lumbar spine. Existing evidence was too limited to draw conclusions about the effect of exercise therapy.

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Determining clinical practice of expert physiotherapy for patients undergoing lumbar spinal fusion: a cross-sectional survey study

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ABSTRACT

Purpose

To determine the content of current Dutch expert hospital physiotherapy practice for patients undergoing lumbar spinal fusion (LSF), to gain insight into expert-based clinical practice.

Methods

At each hospital where LSF is performed, one expert physiotherapist received an e-mailed questionnaire, about pre- and postoperative physiotherapy and discharge after LSF. The level of uniformity in goals and interventions was graded on a scale from no uniformity (50–60%) to very strong uniformity (91–100%).

Results

LSF was performed at 34 of the 67 contacted hospitals. From those 34 hospitals, 28 (82%) expert physiotherapists completed the survey. Twenty-one percent of the respondents saw patients preoperatively, generally to provide information. Stated postoperative goals and administered interventions focused mainly on performing transfers safely and keeping the patient informed. Outcome measures were scarcely used. There was no uniformity regarding advice on the activities of daily living.

Conclusion

Dutch perioperative expert physiotherapy for patients undergoing LSF is variable and lacks structural outcome assessment. Studies evaluating the effectiveness of best-practice physiotherapy are warranted.

INTRODUCTION

In the past decades surgical interventions, especially lumbar spinal fusion (LSF), have gained popularity.[1] In the United States the number of LSFs increased between 1998 and 2007 by 237% (from 174,223 to 413,171 procedures).[2] LSF is a procedure in which two or more vertebrae are fixated to restrict painful spinal motion. Regaining function after LSF is very important for the patient. Clinical rehabilitation, in particular physiotherapy, may be an important factor in regaining functional independence. There is little knowledge on the optimal physiotherapy practice in patients undergoing LSF. In a systematic review of the literature, Rushton et al. [3] demonstrated that studies on the effectiveness of physiotherapy after LSF are of low quality and too heterogeneous to pool. Consequently, physiotherapists have to depend on their own competence and experience in their day-to-day practice. This results in highly variable clinical care with unknown effectiveness, as demonstrated by Rushton et al. [4] in the UK. Thus, best clinical physiotherapy practice in LSF remains to be elucidated.[3, 5] We hypothesised that studying clinical practice for patients undergoing LSF provided by expert physiotherapists would establish a better understanding of the current best practice. These data could serve as temporary guidelines for hospital physiotherapists working with people undergoing LSF and as a usual care arm in future randomised studies. Therefore, the purpose of this study is to describe the content of Dutch inpatient expert physiotherapy before and after LSF.

METHODS

Design and Population

In this cross-sectional survey study, we asked expert physiotherapists who perform inpatient treatment before and after LSF to complete a survey on their practice routines. To select the expert physiotherapists, we contacted all heads of physiotherapy departments who were registered with the Dutch Association for Physiotherapy in Hospitals (NVZF) by e-mail (02/06/2014). The NVZF represents 67 general hospitals, academic hospitals and specialised care centres in the Netherlands.[6] Hospitals where LSF was not performed were excluded. Department heads were informed about the content of the study and were asked to forward the survey to their expert physiotherapist concerning LSF (i.e., the physiotherapist they would want to be treated by if they underwent LSF). Return of the questionnaire was considered as informed consent. A reminder was sent after one month. This manuscript is reported according to the STROBE guideline for cross-sectional studies [7] and the CHERRIES checklist for reporting the results of internet E-surveys.[8] Assessment by a medical ethics review board was not necessary.

Survey

The survey comprised 46 questions (nine open and 37 multiple-choice) on four domains: (1) demographic data (nine questions), (2) preoperative diagnostics and treatment (seven questions), (3) postoperative diagnostics and treatment (26 questions), and (4) information for discharge (four questions). The questions in the survey were based on a similar study in the UK by Rushton et al.[4] However, we adapted the survey to the Dutch healthcare context. Moreover, we based the answer options for the questions on diagnostic procedures on the ICF core set for low back pain (LBP).[9] Finally, we added 17 questions in order to obtain information regarding multidisciplinary cooperation, discharge criteria and referral information after discharge. The survey (translated into English; i.e., not an official cross-cultural adaptation) is available as an appendix to this manuscript (available at https://doi.org/10.1007/s00586-016-4433-4).

Data Collection

To collect the data, we used Qualtrics (http://www.qualtrics.com), a commonly used internet-based program for administering surveys.[10] To minimise the chance of incomplete responses due to skipped and/or forgotten questions, the function "Force Response" was used. "Skip Logic" was added to increase the efficiency of the questionnaire (completion time was approximately 15 min). Respondents were able to review and change their given answers using a back button. To prevent multiple answers from the same individual we checked from which hospital the questionnaire originated and their IP-address. In the case of duplicate entries, only the first entry was kept for analysis. The IP-addresses were deleted before the data were analysed. The questionnaire was pre-tested by five peers.

Data Analysis

First of all, two researchers (ES and EJ) categorised the answers of the open questions and labelled them. Differences in categories between the two assessors were resolved by a third researcher (TH). In case of disagreement, the respondent was re-approached for further clarification. All data were analysed anonymously and presented as such. Completeness of the questionnaire was checked; forms were not included in the analysis if over 50% of the data were missing. Descriptive statistics were used to describe the study population and the survey answers [i.e., numbers and percentages, means and standard deviations (SD), and medians and interquartile ranges (IQR)]. To determine the level of uniformity between the physiotherapists on relevant goals and interventions used in expert standard practice, we used categories ranging from No uniformity to Very strong uniformity (see Table 1). Uniformity shows the percentage of participants choosing one answer option (per question). The more participants choosing one answer option, the higher the level of uniformity for a specific goal or intervention.

Table 1. Grading of level of uniformity on goals and interventions

50%–60%	61%–70%	71%–80%	81%–90%	91%–100%
No uniformity	Low uniformity	Moderate uniformity	Strong uniformity	Very strong uniformity

RESULTS

A total of 67 expert physiotherapists in 67 different hospitals were approached to participate in this study. In 33 of the hospitals LSF surgery was not performed and they were therefore excluded from the study. Of the resulting 34 respondents, 29 (85%) responded to our survey. One survey was excluded from the analysis due to missing data. Thus, a total of 28 questionnaires (82% of eligible respondents) were included in the analysis. Figure 1 shows the number of respondents at each stage of the study. Table 2 provides information concerning the respondents' demographics.

Figure 1. Flowchart indicating the number of participants in the study.

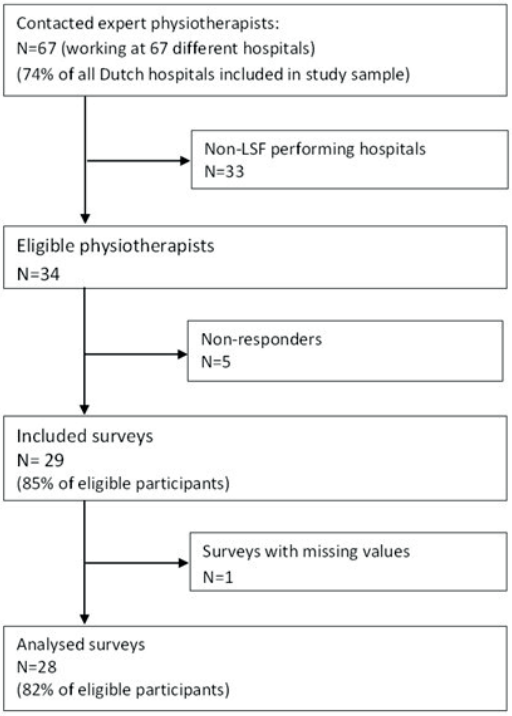

Table 2. Demographic profile respondents.

Characteristics	N (%)	Mean (SD)	Median (IQR)
Type of hospital			
Academic hospital	5 (18)		
General hospital	21 (75)		
Specialised care centre	2 (7)		
Care pathway implemented in hospital			
Yes	2 (7)		
No	26 (93)		
Physiotherapy according to protocol			
Yes	23 (82)		
No	5 (18)		
Number of LSF patients per year per hospital			
1-10 per year	3 (11)		
11-25 per year	8 (29)		
26-50 per year	8 (29)		
>50 per year	9 (32)		
Surgeon performing LSF*			
Neurosurgeon	16 (57)		
Orthopaedic surgeon	23 (82)		
Trauma surgeon	2 (7)		
Combined ortho/neuro surgeon	1 (4)		
Experience with LSF rehabilitation (years)		14.8 (8.4)	15 (8-21)
Treatment duration per session (minutes)		20 (5)	20 (18-25)
Treatment frequency per patient			
Once a day	14 (50)		
Twice a day	10 (34)		
Three times a day	0 (0)		
Once every two days	0 (0)		
Depends on the patient	4 (14)		
Length of hospital stay (days)		3.8 (1.3)	4 (3-5)

Abbreviations: LSF= Lumbar Spinal Fusion, IQR= Interquartile Range, SD= Standard Deviation.
*Multiple answer options possible.

Preoperative Physiotherapy

The majority of the respondents, representing 22 hospitals (79%), did not provide preoperative physiotherapy care for patients undergoing LSF. In the six cases where preoperative care was provided, it was mainly group-based (five respondents) and aimed at informing the patient about the postoperative phase (six respondents). Regarding preoperative diagnostics and instructions there was no uniformity or low uniformity in goals and interventions such as performing a preoperative functional assessment (67%), instructing patients on how to perform postoperative transfers (50%) or taking a history (67%) (see Table 3).

Table 3. Preoperative goals and interventions (n=6).

Level of uniformity	Performed[a]		Not performed[b]	
	Goals/Intentions	**Intervention/Therapy**	**Goals/Intentions**	**Intervention/Therapy**
Very strong uniformity (91%-100%)	Informing about postoperative phase	-	Mobilise	Pulmonary-function exercises Blood circulation exercises
Strong uniformity (81%-90%)	-	Advice and information on postoperative PT	Teaching exercises Assessing living environment Goal setting Risk inventory through coping questionnaire	-
Moderate uniformity (71%-80%)	-	-	-	-
Low uniformity (61%-70%)	Assessing functioning	Anamnesis Psychosocial assessment Information concerning the surgery Answering questions	-	Physical examination
No uniformity (50%-60%)	Measuring preoperative status	Provide instructions on postoperative transfers	-	-

Abbreviations: PT= physiotherapy.

[a]Goals/intentions and interventions/therapies that are reported as being relevant by ≥50% of the respondents.

[b]Goals/intentions and interventions/therapies that are reported relevant by <50% of the respondents.

Postoperative Inpatient Physiotherapy

Inpatient physiotherapy for patients recovering from LSF was standard care in 22 hospitals (79%). In four (14%) cases, patient-specific needs were first assessed to establish the necessity of inpatient physiotherapy. In the remaining two cases it was unclear how physiotherapy was initiated and under which circumstances it was provided. Commonly, patients were treated once (50%) or twice (34%) a day by a physiotherapist for an average (SD) of 3.8 (1.3) days and a median (IQR) of 20 (18–25) min per session. In the majority of the hospitals (61%) mono-disciplinary care was provided (i.e., by the physiotherapist). In the case where multidisciplinary treatment was reported in hospitals, the other professions most frequently involved were: family caregivers (11%), nurses (11%), and occupational therapists (7%).

Respondents agreed to a great extent on the goals and interventions that are part of the inpatient rehabilitation process after LSF surgery (Table 4). Postoperative goals with strong to very strong uniformity were: getting the patient to function safely (93%), getting the patient out of bed (93%), informing the patient on the rehabilitation process (93%), getting the patient to walk (96%) with an optimal gait pattern (93%), getting the patient to climb stairs (89%) and getting the patient to carry out (bed) transfers (89%). Postoperative interventions with very strong uniformity were: getting out of bed (93%), walking (96%) and climbing stairs (93%). Interventions with strong uniformity were: taking patient history (86%), giving advice on functional activities and restrictions (89%), instructing and training patients about transfers (89%), answering questions (89%) and giving instructions for exercises at home (82%).

No uniformity or low uniformity among respondents was seen for several goals and interventions, including: performing a physical examination (57%), instructing how to lift and carry objects (32%), and instructing how to use the restroom (32%). Moreover, there was no uniformity regarding when to resume the activities of daily life after discharge (Table 5). Finally, a minority of respondents used questionnaires (4%) or observational measurements (18%) to guide or evaluate their therapy during the inpatient rehabilitation.

Discharge Information

Of the responding physiotherapists 32% always referred patients for outpatient physiotherapy and 50% only if deemed necessary. Typically, according to the respondents, the decision to refer depends on the patient's physical capacity, coping ability or on the physician's advice. Our respondents stated that the majority of patients are discharged to their home with a referral to primary care physiotherapy (78%). At which practice the rehabilitation process after discharge is continued is mainly decided by the patient (67%) and primarily based on the distance from their house to the practice (67%).

Table 4. Postoperative goals and interventions (n= 28).

Level of uniformity	Performed[a]		Not performed[b]	
	Goals/Intentions	**Intervention/Therapy**	**Goals/Intentions**	**Intervention/Therapy**
Very strong uniformity (91%–100%)	Patient can function safely Patient can get out of bed (d420) Patient is informed on the rehab process Walking (d450) Patient attains an optimal gait pattern functions (b770)	Getting out of bed Walking Climbing stairs	Assess motoric reflex functions (b750) Managing Using walking tools Assess pulmonary situation Neurologic examination Gaining self-confidence (b126) Functional training	Mobilizations of the muscles Mobilizations of the joints (b710) Improve aerobic endurance (b455) Teach how to use a corset Informing
Strong uniformity (81%–90%)	Patient can climb stairs (d4551) Patient can carry out transfers (d420)	Anamnesis Advice concerning functional activities and restrictions Instructing and training transfers Answering questions Instructing home exercises	Performing measurements Normalise muscle tonus (b735) Assess AC of the pelvis (s740) Assess AC of the lower extremities (s750) Assess AC of the trunk (s760) Assess AC of additional structures irt movement (s770) Implement hand and arm function (d445) Using means of transportation (d470) Washing oneself (d510) Resume domestic tasks (d640) Resume recreation and leisure (d920) Usage of a corset	Breathing exercises
Moderate uniformity (71%–80%)	Patient can move around (d455)	Inform regarding the surgery Inform regarding pain management	Improve muscle strength (b730) Improve muscle endurance (b740) Handling stress and other mental requirements (d240) Getting dressed (d540) Looking after one's health (d570)	Train muscle strength (b730) Train trunk stability (s7601)

Table 4. Continued.

Level of uniformity	Performed[a]		Not performed[b]	
	Goals/Intentions	**Intervention/Therapy**	**Goals/Intentions**	**Intervention/Therapy**
Low uniformity (61%–70%)	Patient can maintain/change their body position (d415)		Improve propriocepsis (b260) Improve exercise tolerance (b455) Improve joint stability (b715) Lifting and carrying objects (d430) Toileting (d530)	Teaching exercises to stimulate blood circulation
No uniformity (50%–60%)	Therapist assesses the patient's pain perception (b280)	Physical examination Assessment of ADL	Performing exercises (b455) Improve joint mobility (b710) Improve bone mobility (b720) Sensations related to muscles and movement (b780)	

Abbreviation: AC= Anatomic Characteristic, irt= in relation to, ADL= Activities of Daily Living, Rehab= Rehabilitation, (ICF core set number).

[a]Goals/intentions and interventions/therapies that are reported as being relevant by ≥50% of the respondents.

[b]Goals/intentions and interventions/therapies that are reported relevant by <50% of the respondents.

Table 5. Content of postoperative advice.

Activity	NA	1 wk (%)	2 wk (%)	3 wk (%)	4 wk (%)	5 wk (%)	6 wk (%)	7 wk (%)	8 wk (%)	3 mo (%)	6 mo (%)	12 mo (%)
Sitting	2(7)	22(79)	0	0	1(4)	3(11)	0	0	0	0	0	0
Driving a car	3(11)	2(7)	2(7)	1(4)	1(4)	16(57)	1(4)	2(7)	0	0	0	0
Making love	22(79)	3(11)	0	0	0	3(11)	0	0	0	0	0	0
Resuming work	9(32)	2(7)	1(4)	0	0	13(46)	0	3(11)	0	0	0	0
Resuming sports	8(29)	1(4)	0	0	0	7(7)	1(4)	8(29)	1(4)	0	2(7)	0
Resuming contact sports	12(43)	0	0	0	0	0	0	5(18)	5(18)	2(7)	4(14)	0
Jogging/running	13(46)	0	0	0	0	1(4)	0	8(29)	3(11)	1(4)	2(7)	0
Training muscle strength	8(29)	3(11)	0	0	0	7(7)	0	5(18)	2(7)	0	3(11)	0
Heavy lifting	6(21)	1(4)	0	0	0	3(11)	0	8(29)	5(18)	1(4)	4(14)	0
Extreme lumbar movements	13(46)	1(4)	0	0	0	1(4)	0	4(14)	3(11)	0	6(21)	0

Abbreviations: NA= No Advice, wk= weeks, mo= months.

DISCUSSION

This study assessed current inpatient treatment before and after LSF surgery in Dutch hospitals from the perspective of expert physiotherapists. We established that preoperative physiotherapy is uncommon and mainly limited to providing information on postoperative rehabilitation. Inpatient postoperative physiotherapy is common after LSF surgery and in most cases a standard procedure. Physiotherapists primarily aim to help patients to function safely (i.e., get out of bed, get into a chair, walk and climb stairs) by practicing functional activities (typically after an anamnesis) and providing information. Questionnaires and performance measures were scarcely used, and there was no uniformity among physiotherapists concerning giving advice on resuming the activities of daily life. Outpatient care is prescribed mainly if deemed necessary by the hospital physiotherapist.

Strengths and Limitations

A number of strengths and weaknesses are apparent in this study. The strengths include the validity of our findings regarding the Dutch inpatient physiotherapy practice, as 74% (67 out of 91) of the Dutch hospitals [6] were approached with a response rate of 93%. Furthermore, we focused only on expert physiotherapists, allowing an overview of expert based care as reported both before and after LSF. We believe we were successful in doing so, as the majority of physiotherapists had 8 or more years of experience treating patients undergoing LSF.

Some limitations include the external validity of our findings. After all, the data might not be generalisable to some other countries due to differences in cross-cultural health care, educational systems and curricula, although the findings might be relevant to other European countries due to their similarities in culture and healthcare systems. Furthermore, questionnaires rely on self-reported data and therefore do not guarantee an accurate reflection of daily clinical practice. Ideally, observations of clinical practice would be performed; however, due to time and budgetary constraints, this method was not feasible. Finally, we aimed to include expert physiotherapists through asking the department heads to select the therapist who they would want to be treated by after an LSF procedure. A better method for selecting experts would be based on their clinical outcomes; unfortunately these data are not available.[11]

Comparison to the Literature

There is just one other study that describes the current practice of physiotherapy for patients undergoing LSF.[4] This study investigated physiotherapy practice for patients undergoing LSF in the UK.[4] The authors administered a nationwide survey, targeting all physiotherapists that were involved in the management of patients before or after LSF within the UK National Health Service trusts. Our findings overlap considerably with theirs. For instance, in both the UK and the Netherlands: (a) physiotherapy care is provided structurally after surgery (70 vs. 79%, respectively); (b) few centres used questionnaires and performance measures to evaluate or monitor the treatment (6 and 19 vs. 4 and 18%, respectively); and (c) interventions such as providing information (98 vs. 89%, respectively), answering questions (95 vs. 89%, respectively), and instructing and supervising walking (98 vs. 96%, respectively) were most common.

A notable difference between practice in the Netherlands and the UK is the use of therapeutic protocols; 49% in the UK and 82% in the Netherlands. In the Netherlands it is common for hospital physiotherapists to protocolise their postoperative care.[12] Through the use of protocols, physiotherapists who are unfamiliar with working practices in other departments, can still deliver care as best as possible. Unfortunately, these protocols carry the risk that all therapists will deliver protocolised and therapist centred (one-size-fits-all) care instead of the currently favoured patient centred and personalised care,[13, 14] as demonstrated by the high number of expert therapists using protocols to guide their day-to-day practice therapy in our study. We specifically included expert physiotherapists in our survey population to distil best (physiotherapy) practice in LSF.[13, 14] Interestingly, we found that factors essential for clinical reasoning (such as functional diagnosis) were often not evaluated, therapy was either never or always provided (regardless of the patient's need), and therapy was typically delivered on time-based principles (not goal-based). It seems that now is the time for best practice guidelines to be established.

General Findings

In the Netherlands it may be necessary to reconsider the approach of the (expert) hospital physiotherapist in the management of individuals undergoing LSF. Considering that: (1) there is a (small) number of hospitals where LSF surgery is routinely performed without involving physiotherapists in the clinical care pathway, possibly due to the lack of evidence on benefits of clinical physiotherapy after lumbar surgery;[14] (2) physiotherapy in the management of LSF is mainly characterised by one-size-fits-all care, rather than care based on evaluating the specific functional needs of the patients;[15, 16] and (3) there is no uniformity or low uniformity in the different aspects of the content of the physiotherapy management (e.g., the necessity of preoperative care, multidisciplinary treatment and the contents of advice); the current physiotherapy practice needs to be reconsidered.

A shift from postoperative care to preoperative care in patients undergoing major surgery and at-risk for poor outcomes could decrease costs, improve functional outcomes, and in some cases, prevent complications and death.[17] This may hold true for individuals undergoing LSF surgery as well.[18, 19] Preoperatively predicting which patients will not benefit from LSF has proven to be quite challenging, as most medical and surgical factors have very little predictive value.[20, 21] Our data demonstrated that pre- or postoperative risk-stratification and/or optimisation are not utilised in daily clinical practice. Nonetheless, evidence tells us that functional measures are vital for risk assessment and provision of optimal care before and after major surgery.[22-24]

An interesting finding was that there is little agreement on the "dos and don'ts" after LSF surgery. Even though nearly all physiotherapists report that they provide information and recommendations, we found there is not only little uniformity in the content of recommendations but also in when to resume the activities of daily life. Topics that are almost never discussed are: (when to) return to sports and (when to) return to work, despite these being absolutely crucial for reintegration and participation in society. This apparent dissensus among health professionals on the timing of postoperative activities might be caused or at least maintained by the scarce, and somewhat counter-intuitive, literature on this topic.[25, 26]

CONCLUSION

Literature on the current rehabilitation policy of physiotherapy treatment before and after LSF is scarce. Nonetheless, many patients who undergo LSF are treated by a physiotherapist. Expert physiotherapy practice before and after LSF in the Netherlands is mainly aimed at getting patients back onto their feet by teaching and training transfers, walking and stair climbing. However, in terms of diagnostic procedures, the type of

recommendations given to the patient, outcome valuation/monitoring and discharge logistics we found considerable differences between therapists' responses. Considering the latter, we think that best evidence/practice guidelines are needed to help guide physiotherapists in the management of people undergoing LSF.

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4

Preoperative community based functional high intensity interval training (*f*-HIIT) with high-risk patients opting for lumbar spinal fusion: a pilot study

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ABSTRACT

Study Design

Pilot cohort study.

Objectives

The aim of this study is to determine the feasibility, safety and preliminary effectiveness of preoperative functional high-intensity interval training (*f*-HIIT) for high-risk patients undergoing lumbar spinal fusion (LSF).

Methods

High-risk patients eligible for elective 1-3 level LSF were included. Feasibility and safety of the preoperative *f*-HIIT program was determined by measuring participation and attrition rates, training adherence, adverse events, reached training intensity and pre-operative progression in physical fitness. A propensity matched Mann-Whitney U test and Interrupted Time Series Analysis (ITSA) were used to estimate the preliminary effect of the preoperative *f*-HIIT program on time to postoperative functional recovery and length of hospital stay (LoS) between high-risk patients who did and did not participate in the prehabilitation program.

Results

Eleven out of 23 high-risk patients opted to participate in the *f*-HIIT program, which was safe and feasible, as no adverse events occurred and only one out of 74 sessions was missed (1.4%). Trained high-risk patients improved their physical fitness with 21.2% on average and obtained faster time to functional recovery compared to matched untrained patients (median 4.5 vs. 7.5 days; P= 0.013). No effect was seen on LoS (median 7 vs. 8 days (P= 0.58)). ITSA showed a positive effect of participation in the preoperative *f*-HIIT program on time to functional recovery (relative risk (RR)= 0.54 (95% CI= 0.32-0.92)), but no effect on LoS (RR= 0.65 (95% CI= 0.41-1.03)).

Conclusion

This preoperative *f*-HIIT program is feasible, safe and shortened time to postoperative functional recovery in patients who underwent LSF.

INTRODUCTION

Undergoing lumbar spinal fusion (LSF) is associated with a risk of (temporarily) decreased functioning, morbidity and mortality.[1] Patients undergoing LSF are at various stages of deconditioning due to their chronic back pain restraining physical activities, resulting in large interindividual differences in risks for these negative outcomes.[2] Patients who are less deconditioned have a higher physiological reserve, which is a prerequisite for withstanding surgical stress and achieving satisfactory postoperative outcomes.[3] Consequently, patients who are more deconditioned (i.e., have a lower physiological reserve) are more at risk for negative postoperative outcomes. These so-called "high-risk" patients could benefit from preoperative exercise training to improve their physiological reserve.[3] Preoperative high intensity interval training (HIIT) for high-risk patients is an effective intervention for improving postoperative outcomes of high-risk patients in different types of major surgery, such as total hip and knee replacement,[4, 5] elective cardiac surgery [6] and elective oncological surgery.[7] Studies on prehabilitation in LSF mainly focused on low-risk patients and cognitive behavioural therapy, and showed inconclusive results.[8] Research on the effect of preoperative exercise training of high-risk patients opting for LSF is lacking. However, training frail and deconditioned patients might prove difficult, as for these patients exercise training, especially in a high intensity mode seems quite be contra-intuitive as many may think that there are health risks are involved with high-intensity training. Moreover, training should be functional and community-based, as training tasks specific to a patient's context will accomplish more sustainable results.[7] Therefore, the primary objective of this pilot study was to investigate if a preoperative functional high-intensity interval training (*f*-HIIT) program was feasible and safe for high-risk patients undergoing elective LSF. The secondary objective was to investigate the feasibility of participating in the risk stratification and *f*-HIIT program procedures. The third objective was to explore the preliminary effect of the preoperative *f*-HIIT program on functional recovery and length of hospital stay (LoS) of high-risk patients undergoing elective LSF.

METHODS

Study Design

From February 2017 onwards, as part of standard care, patients scheduled for elective LSF underwent a preoperative risk screening. This population was used to determine baseline levels of the outcome and provide control patients for analysing preliminary effectiveness. From November 2018 onwards, the preoperative *f*-HIIT program became part of standard care and was offered to all high-risk patients undergoing LSF. Data on patients undergoing LSF until February 2020 was collected and analysed prospec-

tively. The STROBE statement and CONTENT scale for therapeutic validity were used as reporting guidelines. The study was assessed by the local ethics committee and was considered not applicable to the Medical Research Involving Human Subject (WMO) Act (case numbers 2020-1838, 2019-1426).

Population

Patients were included if they underwent a preoperative risk screening after they opted for elective one to three level LSF surgery between February 2017 and January 2020. Inclusion criteria were: ≥18 years old patients diagnosed with a degenerative disorder of the lumbar spine. Patients were excluded from the analysis if they had undergone LSF previously.

Risk Assesment

To identify a patient's risk level (high or low risk) they underwent a preoperative screening assessing their physical capacity four to six weeks before surgery. This preoperative risk screening was performed at a single university hospital by a hospital physiotherapist with experience in treating patients undergoing LSF (T0) (Figure 1) and consisted of tests for: aerobic capacity (steep ramp test (SRT)), muscle strength of the lumbar spine (Sorensen test), lumbar movement control (sitting one leg knee extension, posterior pelvic tilt, waiter's bow and the one leg stance test), flexibility (finger-floor distance) and functional status (Timed Up and Go (TUG) and Morton Mobility Index (DEMMI)).

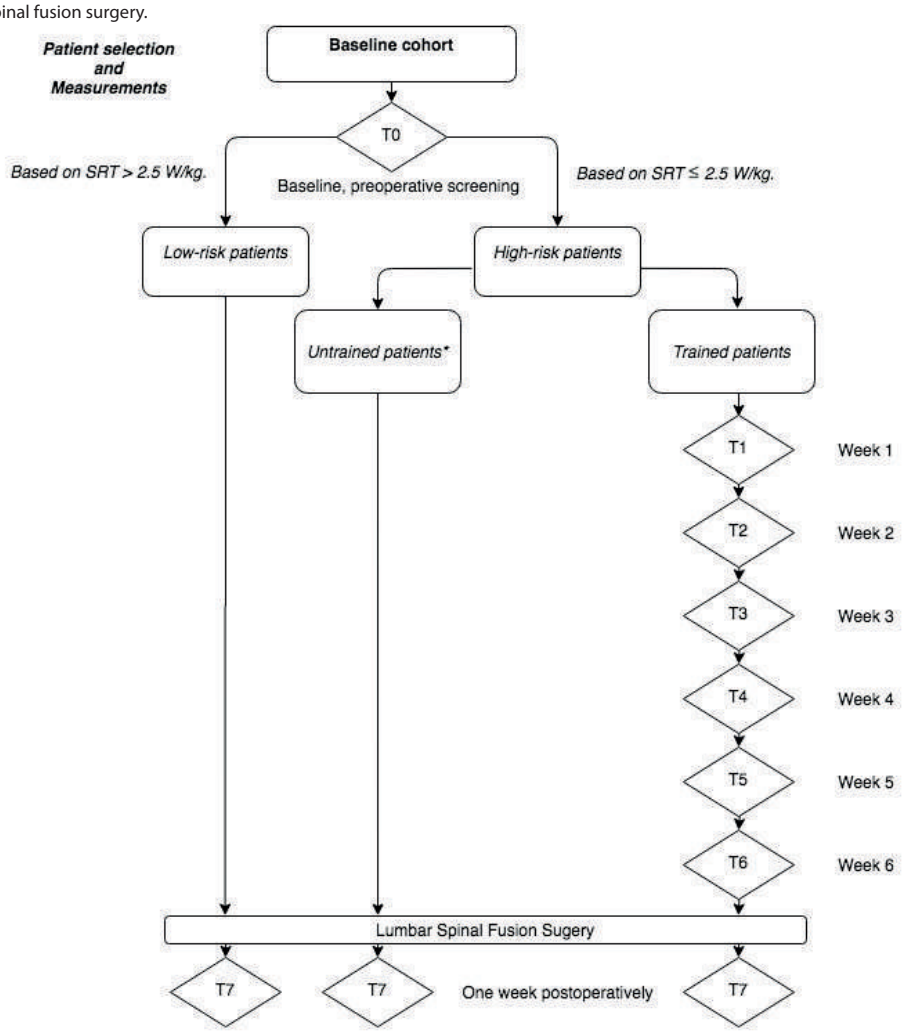
Trained Patients

From November 2018 onwards all high-risk patients were offered a preoperative *f*-HIIT program as part of standard care. This preoperative training consisted of a maximum of eight community based training sessions of thirty minutes, guided by a trained primary care physiotherapist. The physiotherapists who guided the program had completed a three-day training course on *f*-HIIT prehabilitation. Each guided training session consisted of a five-minutes low to moderate intensity warm up phase, followed by 25 minutes of high intensity patient-specific functional interval training. Training intensity was monitored and adjusted using the BORG Rating of Perceived Exertion Scale (BORG RPE on a 0-10 scale) [9] and heart rate (in beats per minute). Adequate intensity was achieved at a BORG RPE ≥7 and/or 90% of maximum heart rate (HR) (208-(0.7*age)).[9, 10] Next to the supervised sessions, patients were instructed to incorporate functional exercises into their everyday life. Training progression was monitored weekly (Figure 1) by the physiotherapist using: the two-minute walk test (2MWT),[11] TUG[12] and 30-second chair-stand test (30CST).[13] The SRT was measured at screening (T0) and in the last week of training (T6) by the hospital physiotherapist to measure changes improvements in physiological reserve.

Usual Care

High-risk patients undergoing LSF before November 2018, patients who opted not to train and all low-risk patients received usual care. Data from high-risk patients undergoing LSF before November 2018 were used as a control group in the effectiveness analysis. Preoperative usual care included: information about the surgery and advice to stay physically active. Postoperative care was the same for both the trained and untrained patients. They received daily postoperative physiotherapy sessions during hospitalization. Physiotherapy after discharge was not recommended. Measurements in the untrained patients were performed at the preoperative screening (T0), by the hospital physiotherapist (Figure 1).

Figure 1. Flowchart of measurement time points (diamonds) of trained and untrained patients opting for 1-3 level lumbar spinal fusion surgery.



Abbreviations: SRT= Steep Ramp Test, T=time point.

Outcome Measurements

Postoperative time to functional recovery was measured using the modified Iowa Level of Assistance Scale (mILAS).[14] This instrument was scored daily during hospitalization by a physiotherapist to score the degree of independent functioning of a patient. Five functional tasks are scored on this scale: supine to sit, sit to supine, sit to stand, transfer, walking and stair climbing. Each task was scored on a five-point scale whereby the sum score zero (or six in case the patient does not have stairs at home) meant the patient was recovered. LoS was defined as the number of days until discharge from the hospital, starting at the day of surgery.

Statistics

SPSS, Version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics. Armonk, NY: IBM Corp.) and R (version 3.3.2; http://www.r-project.org) were used for statistical analysis. A p-value of <0.05 was considered statistically significant. Patients were excluded from the analysis if they had missing data on the outcomes.

Feasibility f-HIIT for high-risk patients

Safety of the preoperative *f*-HIIT program was evaluated by the registration of the number of adverse events during the preoperative training period. Feasibility was assessed through adherence to the program by number of guided sessions missed, the maximum training intensity reached during the guided sessions and the progress of physical fitness made during the preoperative training period. *Feasibility participation in the f-HIIT into clinical practice*

Feasibility of participation of the risk stratification procedure was evaluated by calculating the attrition rate for screening and for risk stratification. Moreover, the participation rate for the *f*-HIIT program after implementation was calculated.

Preliminary effectiveness

Preliminary effectiveness was measured by 1) calculating mean-differences between matched trained and untrained high-risk patients, and 2) an interrupted time series analyses (ITSA) before and after implementation of the *f*-HIIT program, on time to functional recovery and LoS. An independent samples t-test, or its non-parametric equivalent a Mann-Whitney U test, was used for calculating mean-differences. Untrained high-risk patients from the cohort up to November 2018 were used as a control group and matched with trained patients, using Propensity Score Matching based on a patient's age, American Society of Anaesthesiologists (ASA) score, preoperative pain score (Visual Analogue Scale, VAS) and smoking status (smoker/non-smoker). These variables were identified in literature as potential confounding factors and thus required correction

through propensity score matching.[15] ITSA was used to demonstrate the impact of implementation of the preoperative *f*-HIIT program on time to functional recovery and LoS. Here, differences in results before and after implementation are compared using a regression analysis correcting for secular trends.[16] For ITSA we assumed a level change (relative risk reduction) to occur when the *f*-HIIT program was implemented without lag (no transition period).[16] No slope change was expected to occur. This assumption was based on results from a previous pilot study.[17] The ITSA was applied in the matched high-risk population to show the effect of prehabilitation in a real-world setting.

RESULTS

During the study period a total of 183 patients opting for LSF entered the clinic of which 135 patients could be stratified into risk profiles, from which 46 were identified as high-risk and 89 as low-risk (Figure 2). Baseline characteristics and pre-operative physical fitness levels of both risk groups can be found in Table 1. After implementation of the preoperative *f*-HIIT program in November 2018 eleven out of 23 high-risk patients opted to undergo prehabilitation.

Feasibility *f*-HIIT for High-risk Patients

None of the eleven patients who participated in the preoperative *f*-HIIT program dropped out (0.0%). Patients took part in six preoperative supervised training sessions on average, only 1/74 sessions was missed (1.4%), due to an unrelated illness. Based on the BORG RPE-score, on average patients reached adequate training intensity in 71.2% of the supervised sessions. Based on 90% maximum HR 0.0% reached adequate training intensity. All patients showed improvements in preoperative physical fitness on at least two out of four tests (TUG, 2MWT, 30CST and SRT) during the preoperative training period, see Figure 3. On average patients improved 32.9% on the TUG, 22.4% on the 2MWT, 48.27% on the 30CST and 21.2% on the SRT.

Feasibility Implementation f-HIIT into Clinical Practice

The attrition rate for screening was 0.89 (158/178), twenty patients did not undergo risk screening, due to logistical reasons. Attrition rate for risk stratification was 0.84 (135/158), as 23 patients did not perform the SRT. Participation rate for training was 0.48 (11/23). Twelve patients did not train, due to: opted not to train (n= 3), run-up time to surgery was too short (n= 5) and they lived outside of the catchment area of the training network of physiotherapists (n= 4).

Table 1. Baseline characteristics for high-risk and low-risk patients undergoing elective level one to three LSF.

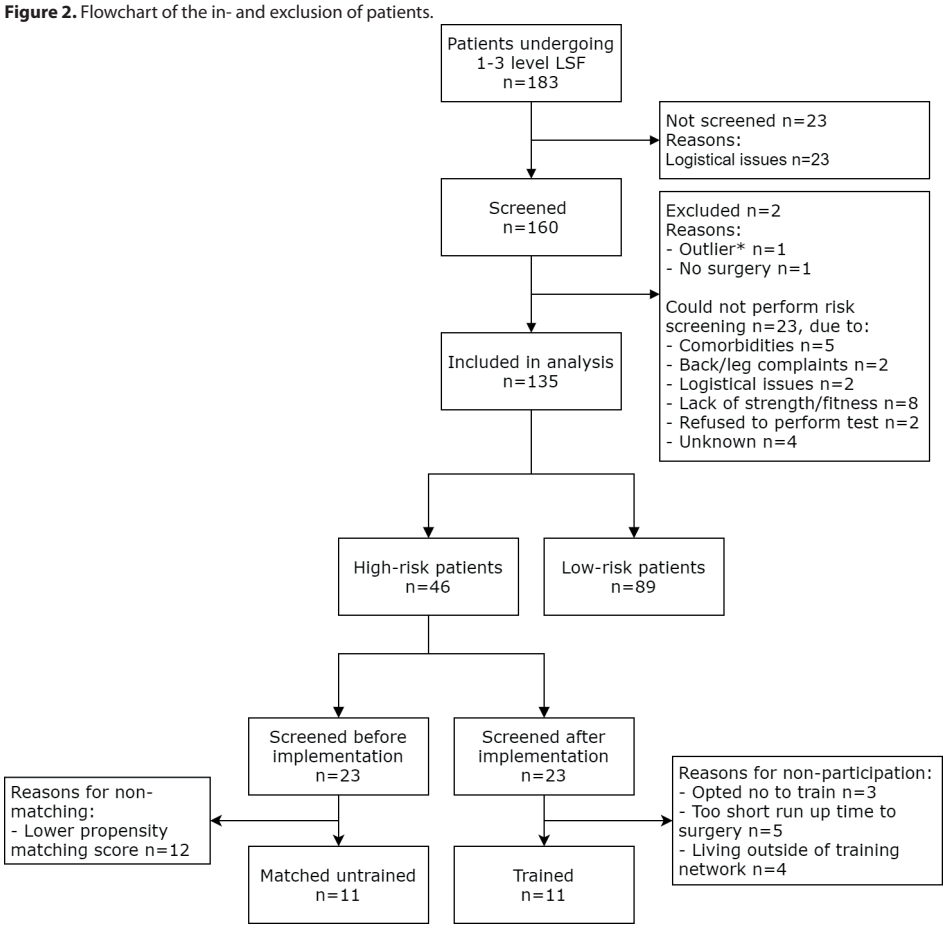
	Total (n= 135)	Low-risk (n= 89)	High-risk (n= 46)	P-value difference high and low-risk group
Sex, n women (%)	84 (62.2)	45 (50.6)	39 (84.8)	<0.001[a]
Age in years, mean (SD)	60.6 (11.7)	58.7 (11.1)	64.2 (5.0)	0.009[b]
BMI, mean (SD)	26.8 (4.7)	25.9 (4.3)	28.7 (5.0)	<0.001[a]
Smoking status, n smoker/ n observed* (%)	44/127 (29.7)	29/84 (34.5)	7/43 (16.3)	0.032[a]
ASA-score, n (%)				<0.001[a]
ASA-1	29 (21.4)	25 (28.1)	4 (8.7)	
ASA-2	85 (63.0)	56 (62.9)	29 (63.0)	
ASA-3	21 (15.6)	8 (9.0)	13 (28.3)	
Pain duration, n >1 year/ n observed (%)	67/122 (49.6)	45/80 (50.6)	22/42 (52.4)	0.15[a]
Surgery indication, n (%)				0.86[a]
Spondylolisthesis	83 (61.5)	56 (62.9)	27 (58.7)	
Degenerative disc disease	52 (38.5)	33 (37.1)	19 (41.3)	
N levels fused, n (%)				0.28[a]
1	98 (72.6)	67 (75.3)	31 (67.4)	
2	32 (23.7)	20 (22.5)	12 (26.1)	
3	5 (3.7)	2 (2.2)	3 (6.5)	
Preoperative pain in 0-100, mean (SD), (n observed)	76.8 (18.6), (125)	74.9 (19.9), (82)	80.7 (15.2), (43)	0.15[a]
Flexibility in cm, mean (SD), (n observed)	9.7 (11.4), (128)	8.9 (10.2), (87)	11.6 (13.5), (41)	0.36[a]
Motor control 0-4, n (%)				0.011[a]
0	2 (1.5)	1 (1.1)	1 (2.2)	
1	7 (5.2)	3 (3.4)	4 (8.7)	
2	18 (13.3)	8 (9.0)	10 (21.7)	
3	55 (40.7)	37 (41.6)	18 (39.1)	
4	53 (39.3)	40 (44.9)	13 (28.3)	
Back muscle endurance strength in sec., mean (SD), (n observed)	35.4 (39.8), (91)	41.5 (42.5), (65)	20.5 (27.8), (26)	0.006[a]
Max. back muscle extensor strength in % from norm, mean (SD), (n observed)	-12.8 (35.0), (108)	-8.7 (34.5), (76)	-22.5 (35.0), (32)	0.040[a]
Estimated aerobic capacity, mean (SD)	2.8 (0.9)	3.2 (0.6)	1.8 (0.5)	<0.001[b]
mILAS= 0 in days, mean (SD)	5.2 (2.6)	4.6 (1.6)	6.3 (3.8)	0.005[a]
LOS in days, mean (SD)	7.2 (3.4)	6.7 (2.8)	8.2 (4.1)	0.021[a]

* Number of observations within cohort if missing data were apparent

a) Mann-Whitney U test, b) independent sample t-test

Abbreviations: ASA= American Society of Anesthesiologists score, cm= centimeters, sec.= seconds, max.= maximum, mILAS= modified Iowa Level of Assistance Score, LOS= length of stay.

Figure 2. Flowchart of the in- and exclusion of patients.



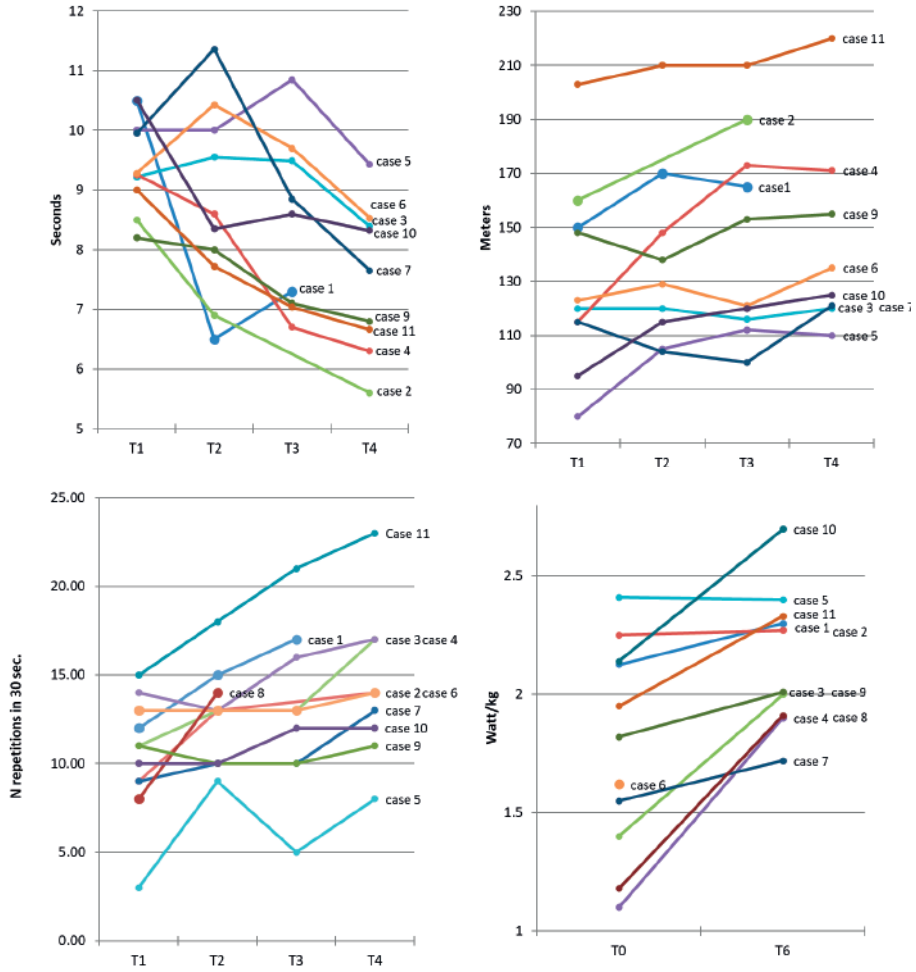
Abbreviations: LSF= lumbar spinal fusion

*Outliers were defined as any value that is more than 1.5 IQR below the first quartile or above the third quartile.

Preliminary Effectiveness

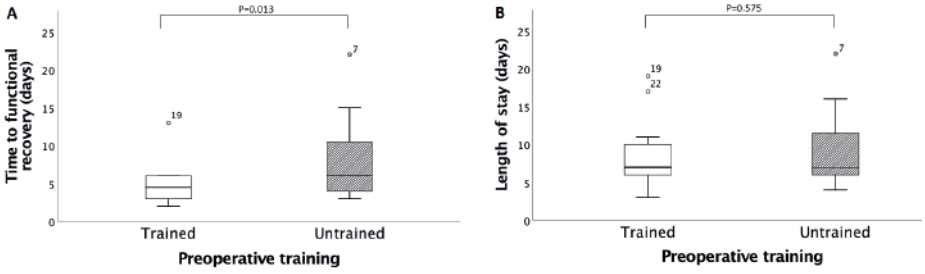
Trained and untrained high-risk patients were matched on their propensity score to correct for important confounders when assessing effectiveness. As a result matched trained and untrained cohorts did not differ on baseline characteristics (P= 0.11-1.00). The median (IQR) time to functional recovery for the trained group was 4.5 (3-6) days and for the matched untrained group was 7.5 (5.75-12.5) days (P= 0.01) (Figure 4a). The median LoS (IQR) for the trained group was 7 (6-11) days and for the untrained group 8 (6-13) days (P= 0.58) (Figure 4b).

Figure 3 A, B, C, D. Per patient progression on: a) the 30 seconds Chair Stand Test, b) the 2 Minute Walk Test and c) the Timed Up and Go test between week 0 and 4 of training, and d) per patient progression on the Steep Ramp Test between week 0 of training and directly preoperatively.



Abbreviations: T= time point, N= number, sec.= seconds, kg= kilogram.

Figure 4 A and B. A boxplot comparing the trained and untrained high-risk patients on postoperative: a) time to functional recovery and b) length of hospital stay.



The effect (expressed as a relative risk (RR)) of implementation on the preoperative *f*-HIIT program on time to functional recovery was: RR= 0.54 (95% CI= 0.32-0.92, P= 0.02) in the Propensity Score matched high-risk population (Figure 5). RR= 0.65 (95% CI= 0.41-1.03, P= 0.07) in the Propensity Score matched high-risk population (Figure 6).

Figure 5. Effect of implementation of preoperative f-HIIT program on time to functional recovery (in days) in the matched high-risk population (n= 22).

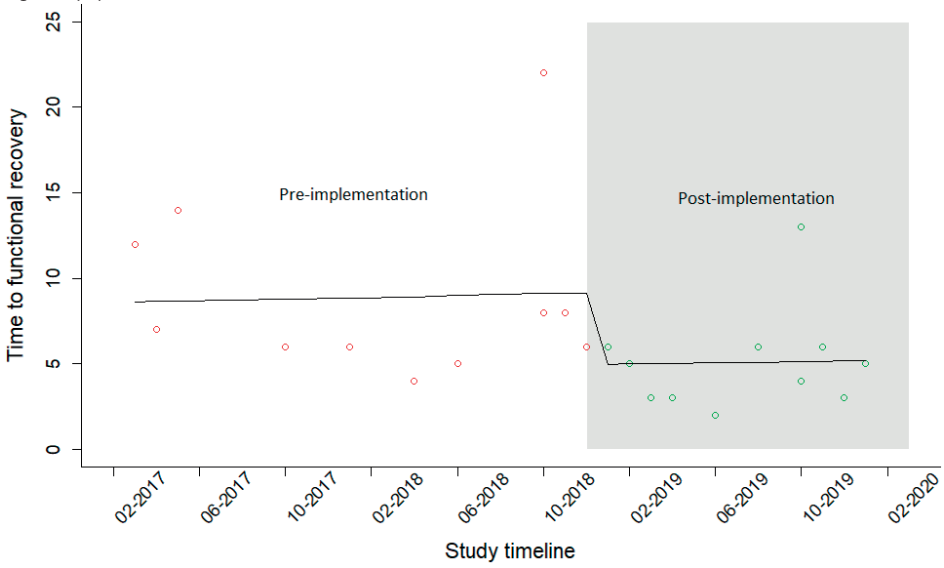
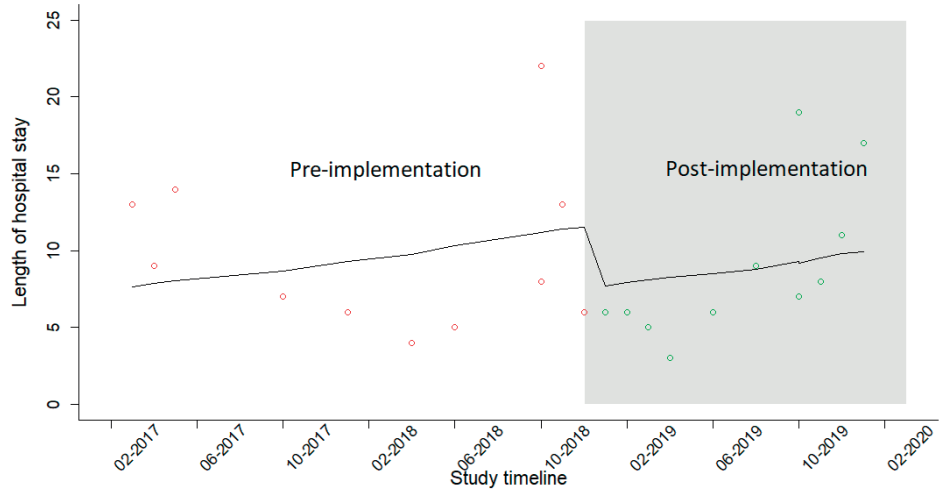


Figure 6. Effect of implementation of preoperative f-HIIT program on length of hospital stay in the matched high-risk population (n= 22).



DISCUSSION

The current pilot study demonstrated that preoperative community-based *f*-HIIT is feasible and safe for high-risk patients opting for elective 1-3 level LSF. No adverse events occurred and only one (1.4%) supervised training session was missed. High-intensity was achieved in most training sessions (71.2%) according to the BORG RPE, but not according to the maximum HR (0.0%). All trained patients showed progression during their preoperative training period, although results fluctuated. Implementation of the pre-operative screening and risk stratification was feasible (92.1% and 91.4% attrition rates). However, participation in the *f*-HIIT program could be improved, as only 47.8% of eligible high-risk patients were trained, mainly caused by the limited catchment area and logistic issues with surgical planning. Finally, preoperative *f*-HIIT may be able to shorten time to functional recovery in high-risk patients undergoing LSF.

Prehabilitation can be applied to improve outcomes after major surgery, such as LSF, by mitigating pre-existing deconditioning as a risk factor for worse postoperative outcome. A recent systematic review concluded that most studies on preoperative interventions before LSF show inconclusive results.[8] The marginal benefits could be caused by the inclusion of both high- and low-risk patients. Low-risk patients are likely to benefit less from undergoing preoperative training, as they do not suffer from pre-existing deconditioning. This was confirmed in our results, as low-risk patients had a significantly shorter time to functional recovery than high-risk patients in the total population (P= 0.005). Previously, two research groups investigated a preoperative exercise training program in patients undergoing spinal surgery.[18-20] Both interventions were largely similar to our intervention, as all applied a personalized prehabilitation program provided by a trained physiotherapist. However, their intervention differed from ours since they did not apply a preoperative risk screening identifying high-risk patients.[19, 20] Moreover, neither of the studies described a high-intensity interval training (HIIT). HIIT is be preferred over other types of exercise therapy since it elicits overload which results in benefits on physical functioning within a very short time span, making it very time-efficient in a preoperative period.[21, 22] Moreover, its effectiveness is established in other prehabilitation programs before major surgery.[21, 22]

Strengths and Limitations

A strength of this pilot study was the pragmatic design whereby the inclusion of the patients was based on real-life practice and detailed data were collected from individual cases to evaluate their response to training. This is an advantage over randomized controlled trials (RCT), as evidence reflects real-life variation and facilitates implementation into clinical practice.[23] Described results on feasibility can help improve the

intervention and aid other hospitals in the implementation of similar strategies. Thirdly, the process of selecting controls via matching is based on known confounding factors from a previously published prediction rule for postoperative success chance.[15] This means our results were controlled for likely confounders and thereby are less prone to confounding bias, similar to an RCT. However, a larger sample size is a prerequisite for valid conclusions on population effects.

Some limitations were apparent in this study. The *f*-HIIT program was a new method of training in a specific population for the local network of physiotherapists. Although all physiotherapists followed a three-day training course on *f*-HIIT prehabilitation, it is likely that a learning curve may have influenced the efficacy of training and its intensity.[24] Secondly, using LoS as an outcome measure for recovery after surgery is debatable, since it is highly dependent on external factors other than functional (e.g., logistics, planning) or medical recovery alone.[25] This could explain the lack of effect of the prehabilitation intervention on LoS.

Recommendations

Preoperative exercise training provides patients and surgeons with feasible and safe means for reducing the risk of negative surgical outcomes. Long-term effects (e.g., long-term recovery rate, HRQOL and pain) in a more representative population still need to be investigated. Recommendations for research are that 1) the risk stratification method should be validated externally, 2) surgical planning should be optimized to allow for preoperative screening and training, and 3) participation rates should be improved by enlarging the catchment area of physiotherapists providing prehabilitation.

CONCLUSION

The current study showed that a preoperative *f*-HIIT program is feasible and safe for high-risk patients undergoing 1-3 level elective LSF. Implementation of the preoperative *f*-HIIT program into clinical practice can and should be optimized by improving surgical planning and enlarging the prehabilitation catchment area. The preoperative *f*-HIIT program shortened time to functional recovery in our patient population.

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Development and validation of a prediction tool for pain reduction in adult patients undergoing elective lumbar spinal fusion: A multicentre cohort study

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ABSTRACT

Purpose

On average, 56% of patients report a clinically relevant reduction in pain after lumbar spinal fusion (LSF). Preoperatively identifying which patient will benefit from LSF is paramount to improve clinical decision making, expectation management and treatment selection. Therefore, this multicentre study aimed to develop and validate a clinical prediction tool for a clinically relevant reduction in pain one to two years after elective LSF.

Methods

The outcomes were defined as a clinically relevant reduction in predominant (worst reported pain in back or legs) pain one to two years after LSF. Patient-reported outcome measures and patient characteristics from 202 patients were used to develop a prediction model by logistic regression. Data from 251 patients were used to validate the model.

Results

Non-smokers (odds ratio= 0.41 [95% confidence interval= 0.19–0.87]), with lower Body Mass Index (0.93 [0.85– 1.01]), shorter pain duration (0.49 [0.20–1.19]), lower American Society of Anaesthesiologists score (4.82 [1.35–17.25]), higher Visual Analogue Scale score for predominant pain (1.05 [1.02–1.08]), lower Oswestry Disability Index (0.96 [0.93– 1.00]) and higher RAND-36 mental component score (1.03 [0.10–1.06]) preoperatively had a higher chance of a clinically relevant reduction in predominant pain. The area under the curve of the externally validated model yielded 0.68. A nomogram was developed to aid clinical decision making.

Conclusions

Using the developed nomogram surgeons can estimate the probability of achieving a clinically relevant pain reduction one to two years after LSF and consequently inform patients on expected outcomes when considering treatment.

INTRODUCTION

The number of elective lumbar spinal fusions (LSF) has increased 2.4-fold in the past decade,[1] although postoperative pain reduction often remains unsatisfactory.[2] Some patients have a considerably lower probability of achieving a reduction in pain postoperatively.[3] To improve clinical shared decision making, expectation management, and patient selection, it is important to predict expected outcomes after LSF and act upon this information.

Prediction tools are reliable tools that can predict the probability of outcomes after LSF. Patients and surgeons can consult such prediction tools to estimate probabilities of outcomes, such as pain reduction, after LSF for that specific patient. Factors that predict postoperative pain reduction have been reported previously.[4-6] Patient characteristics such as: age, smoking, American Society of Anaesthesiologists (ASA) score and preoperative patient reported outcome measures (PROMs) on pain, mental health and health related quality of life (HRQOL) are associated with postoperative pain reduction.[4-7] To the best of our knowledge only one study externally validated a prediction tool that predicts pain reduction after LSF, which has been translated into an easily implementable tool in the USA.[7] However, due to substantial differences in health care systems this tool probably cannot be applied to European countries. Moreover, potentially important predictors such as symptom duration and mental health were not incorporated in that model. For use in clinical practice, an externally validated and easily applicable prediction tool developed in a representative population is imperative.[8]

Thus, the aim of this multicentre cohort study is to develop and validate a prediction tool to predict the probability of clinically relevant reduction in pain one and two years after elective one- to three-level LSF.

METHODS

Since January 2011 until January 2015, baseline and one to two years postoperative questionnaires were collected 202 from patients undergoing elective LSF as part of routine care in the university hospital. In this cohort study this *derivation set* was used to develop and internally validate the logistic regression model. The *validation set* was used for external validation of the model and contained baseline and one to two years postoperative data on 251 patients collected since July 2014 until November 2016 in the general hospital. This study was assessed by the local Ethics Committee and was considered not applicable to the Medical Research Involving Human Subject Act (number: 16-4-262.1/ivb).

Population

Adult patients (≥18 years) eligible for elective one to three level LSF were included. Diagnosis and surgical procedure were verified from their medical records. Patients were included in the study if they were diagnosed with degenerative disc disease, spondylosis, spondylolysis/-olisthesis, spinal stenosis, adjacent level disease, post- herniotomy, post-laminectomy or (recurrent) disc herniation. Revisions of a spinal fusion within one year of the previous surgery, were excluded.

Data Collection

Patients preoperatively and postoperatively completed questionnaires on the following: back and leg pain using the Visual Analogue Scale (VAS),[9] physical functioning using the Oswestry Disability Index (ODI),[10] HRQOL using the RAND-36,[11] mental health using the Pain Catastrophizing Scale (PCS) and Hospital Anxiety and Depression Scale (HADS).[12, 13] From the three VAS scores (back pain, right leg pain and left leg pain) the predominant (worst reported) pain score was used as a predictor. The RAND-36 resulted in a mental component score (RAND-36 MCS) and a physical component score (RAND-36 PCS). The HADS provided anxiety and depression subscores.

Furthermore, the following demographic data were collected: sex, age, Body Mass Index (BMI), smoking status (yes/no), duration of pain (<2 years/ ≥2years) and ASA score (I-II/III).

In the validation set back and leg pain was measured using the 11-point Numeric Pain Rating Scale (NRS) instead of the VAS.[9, 14] The NRS score was transformed to a 0-100 scale by multiplying all scores by ten, to match with the VAS scale in the derivation set.

Dependent Variable

Pain relief is the main goal for most patients undergoing LSF.[15] Therefore, the primary outcome of the prediction tool was defined as a clinically relevant reduction in predominant pain in the back or (one of the) legs (worst reported pain in back or legs) as measured with the VAS at one to two years after surgery. The secondary outcome was defined as a clinically relevant reduction in leg pain at one to two years after surgery. The VAS for pain ranges from 0 to 100, with 0 indicating no pain and 100 indicating the most severe pain imaginable.[9] To make interpretation of the prediction tool more practical, the dependent variable was made binary: clinically relevant pain reduction or not. Minimal clinically important change (MCIC) for pain ranged between 0.28 and 2.88 on an eleven-point scale in the literature on spinal surgery, a reduction of 2.88 or more (28.8 on a 0-100 point scale) was a priori defined as a clinically relevant pain reduction to prevent overestimation.[16]

Statistics

Analyses were performed using SPSS (versions 24, SPSS Inc., Chicago, IL, USA) and R (version 3.3.2; http://www.r-project.org). In case of incomplete variables within a case, multiple imputation of missing values was used.[17]

The independent samples t-test for normally distributed variables or the Mann-Whitney U-test for non-normally distributed variables was used to analyse differences in baseline and outcome variables between subgroups within and between cohorts.

Multivariable logistic regression was used to develop the prediction model. Stepwise backward elimination was used to eliminate non-significant predictor variables from the logistic regression model. To prevent premature deletion of predictor variables a more liberal alpha for exclusion criterion of variables was used (alpha= 0.157).[18]

Discriminatory capacity of the prediction model was quantified by the area under the receiver operating characteristic curve (AUC). The discriminative capacity is perfect when the AUC is 1.0; there is no discriminative capacity when the AUC is 0.5 equivalent to a coin flip.

The logistic regression model was internally validated using standard bootstrapping techniques. As a result, a shrinkage factor was computed, which was used to penalize the regression coefficients of the logistic regression model. The internally validated model was applied to the validation set, for which a new AUC was calculated to evaluate its performance in the population of the second hospital. A nomogram was developed from the validated logistic regression model.

Power Analysis

As a general rule, ten events per predictor variable are necessary to find associations in logistic regression models.[19] The percentage of patients undergoing LSF achieving MCIC in pain on average was 56%.[20] A prediction model with eleven predictors could be developed based on a sample size of 197 patients (202 patients were available in the derivation set). Eleven independent variables were selected based on clinical relevance by literature review [4-7] and by expert opinion of five experienced spine surgeons. Selected variables include the following: sex, BMI, pain duration, smoking status, educational level, employment status, ASA score, VAS, ODI, PCS and RAND-36.[4-7]

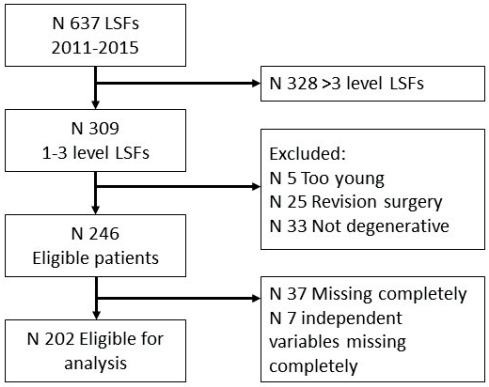
RESULTS

Population Characteristics

The derivation set consisted of 202 patients who were found eligible for analysis (Figure 1). Baseline characteristics are shown in Table 1. The mean reduction in predominant pain was 33/100 points (SD= 31.3) for leg pain it was 35/100 (SD= 35.5).

The validation set consisted of 251 patients (Table 1). The validation set differed from the derivation set in terms of the mean preoperative predominant pain score (P= 0.001), RAND-36 MCS (P= 0.047) and reduction in predominant pain (P= 0.044). The mean reduction in predominant pain in the validation set was 27/100 points (SD= 29.4), for leg pain this was 31/100 (SD= 34.6). No significant differences in terms of predominant pain reduction were found between categories of surgery type, primary diagnosis or number of levels fused (Table 2).

Figure. 1 Flowchart of number of patients included in the dataset used to develop the model



Abbreviations: LSF= lumbar spinal fusion.

Development of the Prediction Model

In total, 9.1% of values were missing in the derivation set; these values were imputed using 20 imputations. The clinical prediction model consisted of eight independent predictors after stepwise backward elimination: smoking, BMI, pain duration, educational level, ASA, predominant preoperative pain, physical functioning (ODI), HRQOL related to mental health (RAND-36 MSC). Patients had a higher probability (odds ratio [95% confidence interval]) of achieving a clinically relevant pain reduction if they were non-smoking patients (0.41 [0.19-0.87]) with lower BMI (0.93 [0.85-1.01]), short pain duration (0.49 [0.20-1.19]), low educational level (0.46 [0.19-1.12]), lower ASA score (4.82 [1.35-17.25]), higher VAS scores (1.05 [1.02-1.08]), lower ODI (0.96 [0.93-1.00]) and higher RAND-36 MCS (1.03 [0.10-1.06]) (Table 3). The model had an AUC of 0.77 (95% CI= 0.70-0.83).

The model for leg pain consisted of four independent predictors after stepwise backward elimination: smoking, pain duration, ASA, predominant preoperative pain. Patients had a higher probability of achieving a clinically relevant leg pain reduction if they were non-smoking (0.55 [0.27-1.12]), had short pain duration (0.59 [0.30-1.15]), lower ASA score (3.18 [0.82-12.34]) and higher VAS scores (1.03 [1.01-1.05]). The model had an AUC of 0.71 (95% CI= 0.63-0.77).

Table 1. Cohort characteristics and differences between derivation sample, complete case and external validation sample*

Variable	Derivation sample (n= 202)	Complete case sample (n= 73)	External validation sample (n= 251)	Difference complete/ incomplete cases derivation sample[a]	Difference derivation/ external sample[a]
Age in years, mean (SD)	58 (13.1)	59 (11.4)	57(11,1)	0.519[m]	0.199[m]
Sex, % female (n)	59.9% (121)	63.1%(65)	57.8% (145)	0.828[m]	0.647[m]
BMI, mean (SD)	27 (4.5)	27 (4.8)	28 (5,0)	0.902[t]	0.936[m]
Duration of pain					0.111[m]
<2 years	40.6% (82)	53.4% (39)	40.6% (102)	0.267[m]	
≥2 years	43.1% (87)	46.6% (34)	59.4% (149)		
Smoking (% yes)	31.7% (64)	38.4% (28)	35,5% (89)	0.426[m]	0.054[m]
Educational level			n/a		n/a
Low	38.1% (77)	42.5% (31)		0.562[m]	
High	46.5% (94)	57.5% (42)			
Employment status			n/a	0.545[m]	n/a
Employed	24.8% (50)	27.4% (20)			
Unemployed	62.9% (127)	72.6% (53)			
ASA score, mean (SD)					0.664[m]
I-II	86.6% (175)	87.7% (64)	88.0% (221)	0.745[m]	
III	13.4% (27)	12.3% (9)	12.0% (30)		
Pain score (0-100), mean (SD)	74 (17.5)	73 (16.7)	80 (14.1)	0.167[m]	0.001[m]
HADS (0-21), mean (SD)					n/a
Anxiety	7 (4.2)	7 (4.2)	n/a	0.790[m]	
Depression	7 (4.4)	7 (4.5)	n/a	0.491[m]	
PCS (0-52), mean (SD)	25 (12.3)	24 (12.5)	n/a	0.387[m]	n/a
ODI (0-100), mean (SD)	45 (12.7)	45 (14.1)	68 (154)	0.580[t]	0.121[t]
RAND-36 (0-100), mean (SD)					0.406[m]
PhCS	29 (7.7)	28 (6.1)	29 (7.6)	0.088[t]	0.047[m]
MCS	45 (12.7)	46 (12.1)	43 (12.2)	0.559[m]	
Change score pain, mean (SD) (-100-100)	-33 (31.3)	-32 (30.9)	-27 (29.4)	0.678[m]	0.044[m]
Change score leg pain, mean (SD) (-100-100)	-35 (35.5)	-34 (35.8)	-31 (34.6)	0.701[m]	0.293[m]

Abbreviations: ASA= American Society of Anaesthesiologists, VAS= Visual Analogue Scale, HADS= Hospital Anxiety and Depression Scale, PCS= Pain Catastrophizing Scale, ODI= Oswestry Disability Index, RAND-36 PhCS= Physical Component Score, RAND-36 MCS= Mental Component Score

* This table provides the mean and standard deviations for continuous variables and the percentage and counts for categorical variables. N= 202, derivation sample, for some participants baseline statistics were missing and are therefore not shown.

[a] P value: comparison of two samples. Statistical testing of pooled results, independent t-test (t), Mann-Whitney U test (m).

Internal Validation

The bootstrap validation yielded a shrinkage of 0.84 for predominant pain and 0.88 for leg pain, which was used to multiply the regression coefficients of the final model in order to correct for overfitting (Table 4). The optimism-corrected AUC of the internally validated model was 0.74 for predominant pain and 0.69 for leg pain.

Table 2. Surgery characteristics and subgroup distribution with regards to clinically relevant pain reduction one to two years after LSF

Variable	Derivation sample (N= 202), %(N)	External validation sample (N= 251), %(N)	Difference derivation/ external validation sample[a]
Type of surgery			0.444[k]
PLIF[b,c]	85,1% (172)	100%(251)	
Posterolateral fusion without decompression	4,0% (8)	0% (0)	
TLIF[b,c]	10,9% (22)	0% (0)	
MIS	0% (0)	0% (0)	
Primary diagnosis			0.058[k]
Deg. with listhesis	73,3%(148)	40,6%(102)	
Deg. without listhesis	14,4%(29)	34,3%(86)	
Prior spine surgery*	4%(8)	12,7%(32)	
Adjacent level disease	8,3%(17)	12,4%(31)	
Levels fused			0.460[k]
One	81,2% (164)	64,1%(161)	
Two	17,8% (36)	31,1%(78)	
Three	0,5% (1)	4,8%(12)	

Abbreviations: PLIF= Posterior Lumbar Interbody Fusion, TLIF= Transversal Lumbar Interbody Fusion, Deg.= degenerative disorders of the lumbar spine

[a] P value: comparison of two samples or more samples. Statistical testing of pooled results Kruskal-Wallis test (k).

[b] Surgery technique includes usage of interbody cage

[c] Inherent decompression

*Post herniotomy/-laminectomy

Table 3. Predictors of a clinically relevant reduction in predominant pain one to two years after LSF using logistic regression

Variable	Regression coefficient		P-value	Odds ratio	95% Confidence interval	
	β	S.E.			Lower	Upper
BMI	-0.075	0.045	0.094	0.927	0.848	1.013
Pain duration (long)	-0.718	0.455	0.114	0.487	0.199	1.188
Smoking status (yes)	-0.890	0.386	0.021	0.410	0.192	0.874
Educational level (high)	-0.772	0.454	0.089	0.461	0.189	1.123
ASA score (I-II)	1.574	0.650	0.015	4.825	1.349	17.254
VAS	0.051	0.015	0.000	1.052	1.021	1.083
ODI	-0.035	0.018	0.051	0.965	0.932	1.000
RAND-36 MCS	0.030	0.016	0.067	1.030	0.997	1.063
Constant	-1.558	1.895	0.411	0.210	0.005	8.637

Abbreviations: LSF= Lumbar Spinal Fusion, ASA= American Society of Anaesthesiologists, VAS= Visual Analogue Scale, ODI= Oswestry Disability Index, RAND-36 MCS= 36 Mental Component Scale

Table 4. Internally validated logistic prediction model for clinically relevant pain reduction one to two years after LSF

Variable	β-coefficients	
	Predominant pain	Leg pain
BMI	-0.063	n/a
Pain duration (long)	-0.603	-0.468
Smoking status (yes)	-0.748	-0.533
ASA score (I-II)	1.322	1.021
Max. pain	0.043	0.027
ODI	-0.029	n/a
RAND-36 MCS	0.025	n/a
Constant	-2.466	-3.679

Abbreviations: LSF= Lumbar Spinal Fusion, ASA= American Society of Anaesthesiologists, VAS= Visual Analogue Scale, ODI= Oswestry Disability Index, RAND-36 MCS= 36 Mental Component Scale

External Validation

After exclusion of patients who had not completed any preoperative PROMs, 0.18% of the values were missing and these were imputed. Educational level was missing in the validation cohort and was therefore omitted from the prediction model. In the validation set, the prediction model was able to discriminate between achieving relevant pain reduction or not in 68% of the cases, meaning that an AUC of 0.68 (95% CI= 0.66-0.69) was achieved. For leg pain the AUC in the validation set was 0.52 (95% CI= 0.44-0.59).

Development of the Prediction Tool

From the validated model for clinically relevant reduction in predominant pain a nomogram was plotted (Figure 2). Patients' score points per predictor variable, as visualized on the rulers. Explanation on how to use the nomogram and a practical example can be found in Appendix 1 (avaible at: https://doi.org/10.1007/s00586-020-06473-w).

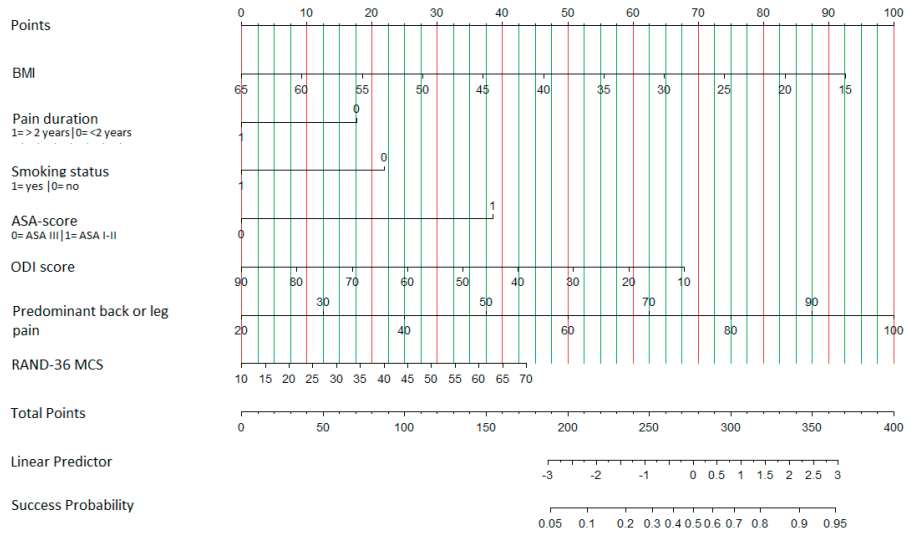
Sensitivity Analysis

Primary diagnosis, as categorized in Table 2, was added as a predictor to the clinical prediction model, to assess if variability in diagnosis within our population influenced the final prediction model. Primary diagnosis was excluded from the final prediction model after stepwise backward elimination.

DISCUSSION

We developed and validated a tool to preoperatively predict a clinically relevant reduction one to two years after LSF in an adequately powered analysis. A nomogram was developed from the externally validated model (for the primary outcome) for applica-

Figure. 2 Nomogram to predict the probability of a clinically relevant pain reduction for the individual patient.



Abbreviations: BMI= Body Mass Index, ASA= American Society of Anaesthesiologists, ODI= Oswestry Disability Index, MCS= Mental Component Scale

tion in clinical practice. With an AUC of 0.68 in an external population, this prediction tool possesses fair discriminatory ability to predict a clinically relevant reduction in predominant pain. We also developed and externally validated a model for clinically relevant reduction in leg pain which had an AUC of 0.52, thus possess low discriminatory ability. The clinical prediction tool for predominant pain could be implemented in clinical practice to improve shared decision making when considering LSF.

In agreement with our findings, previous studies reported that preoperative non-smoking status,[5, 7] better physical functioning [4, 6] and better mental health [4, 5] predict pain reduction one to two years after LSF. This strengthens the likelihood that the prediction tool developed in this study is able to predict pain reduction in other populations as well.

Surprisingly, our results showed that higher educational level indicated a lower probability of a clinically relevant pain reduction, whereas from literature high socioeconomic status is usually associated with a better health condition, especially in patients with chronic low back pain.[21, 22] Educational systems in various countries are different and definitions of high educational level can differ, therefore further research is needed to verify this finding.

The performance of our prediction non-validated model for reduction in predominant pain was similar to that of Abbott et al. (0.74 vs. 0.72 respectively); the externally validated model of Kohr et al. performed better compared to ours (0.79 vs. 0.68 respectively).[7, 23] However, they externally validated their model in a random sample from the same population it was built in, explaining the high performance. The model performance for reduction in leg pain was low (AUC= 0.52). Therefore, this model was not translated into a prediction tool. A possible explanation for the low AUC is that we excluded possibly important predictors too soon in the model development phase, leading to overfitting (data fit "too well") of the model to the derivation set.[18] The added value of our study lies in the fact that we externally validated a model predicting a clinically relevant reduction in predominant pain in a European setting and translated it into a concrete tool for use in clinical practice (see Figure 2).

Strengths and Limitations

A strength of the study is that our model is derived from an academic hospital population and externally validated on a population from a general hospital. Usually surgical populations from an academic hospital and general hospital differ in the sense of complexity of the surgery. From our external validation it is apparent the model can predict a clinically relevant reduction in predominant pain in both academic (AUC= 0.74) and non-academic settings (AUC= 0.68). However, for leg pain this was not the case as it did not perform well in the non-academic setting (AUC= 0.52). Further external validation of the prediction tool is necessary for applicability of the prediction tool to countries with different surgical populations and health care systems.

A limitation of this study is the amount of missing data in derivation set used to develop the model (9.1%). This was probably caused by the fact that the data were collected retrospectively from standard care records. Consequently, multiple imputation was to minimize to increase the power of our analysis. Secondly, in the general hospital the variable 'educational level' was missing.[24] We chose elimination of this predictor from the model rather than imputation, because the value of this predictor is considered untrustworthy without external validation. Finally, we acknowledge that the cut-off point for clinical relevance in our model, although based on literature, is arbitrary. Nevertheless, the primary outcome was defined as a clinically relevant reduction in predominant pain, as indications for elective LSF are both due to back and leg pain in our hospitals.

Future Implications of the Results

The validated prediction tool for estimating clinically relevant reduction in predominant pain can be used by clinicians as an aid to preoperatively inform individual patients about their expected outcomes. An example and explanation of the clinical application

and decision making with help of the nomogram can be found in Appendix 1 (available at: https://doi.org/10.1007/s00586-020-06473-w). Secondly, adding new variables able to predict clinically relevant pain reduction could improve the performance of the prediction models. A variable that is overlooked in all previously mentioned models is preoperative physical performance. In other types of surgery it has been proven physical performance can improve predictive power,[25, 26] which may also hold true for patients undergoing LSF. Thirdly, for patients who are less likely to achieve a clinically relevant pain reduction, care should be tailored to their specific needs in order to improve this probability. Using the nomogram a surgeon can identify which risk factors that are modifiable contribute least to the expected pain reduction for the individual patient and can inform the patient to improve these risk factors before surgery.

CONCLUSION

Using the validated prediction tool (nomogram) a patient's probability of a clinically relevant pain reduction can be estimated one to two years after undergoing LSF. This validated prediction tool can be implemented in clinical practice to aid patients and care professionals in the difficult process of clinical decision making when considering LSF.

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6

Exploring associations of preoperative physical performance with postoperative outcomes after lumbar spinal fusion: A machine learning approach

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ABSTRACT

Objective

Explore associations of preoperative physical performance with short and long-term postoperative outcomes in patients undergoing lumbar spinal fusion (LSF).

Design

Retrospective cohort.

Setting

University hospital.

Population

Seventy-seven patients undergoing elective LSF were preoperatively screened on: patient demographics, patient reported outcome measures and physical performance measures (movement control, back muscle endurance strength and extensor strength, aerobic capacity and flexibility).

Main Outcome Measures

Associations between preoperative variables and inpatient functional recovery, length of hospital stay (LOS) and 1-2 year postoperative pain reduction were explored using random forest analyses assessing the relative influence of the variable on the outcome.

Results

Aerobic capacity was associated with fast functional recovery <4 days and prolonged functional recovery > 5 days (median Z-scores= 7.1 and 12.0). Flexibility (median Z-score= 4.3) and back muscle endurance strength (median Z-score= 7.8) were associated with fast functional recovery <4 days. Maximum back extensor strength was associated with prolonged functional recovery >5 days (median Z-score= 8.6). Flexibility (median Z-score= 5.1) and back muscle endurance strength (median Z-score= 13.5) were associated with short LOS <5 days. Aerobic capacity (median Z-score= 8.7) was associated with prolonged LOS >7 days. Maximum back extensor strength (median Z-score= 3.8) was associated with 1-2 year postoperative pain reduction and aerobic capacity (median Z-score= 2.8) was tentative.

Conclusions

Physical performance measures were associated with both short and long-term outcomes after LSF. Adding these measures to prediction models predicting outcomes after LSF may increase their accuracy.

INTRODUCTION

Undergoing lumbar spinal fusion (LSF) can be considered a major life event[1] because it involves significant health risks and (temporary) physical deconditioning on top of the general poor physical health of these patients.[2] Large interindividual differences exist, and some patients are evidently more deconditioned than others,[1, 3] meaning that they have less physiological reserve to deal with surgery-induced physical stress and increased metabolic demand.[4] Consequently, these patients are considered to be at greater risk for poor outcomes after surgery.[5]

Prediction models are essential tools to aid in adequately identifying interindividual differences, and preoperative identification of a patient's risk level is imperative.[5, 6] However, current clinical prediction models with respect to LSF lack predictive power.[7, 8] This may be a consequence of using patient and surgery characteristics and patient-reported outcome measures only, whereas physical performance measures have been shown to hold robust predictive power in major surgery.[9, 10] Consequently, we have made an effort to identify candidate predictive physical performance measures known from literature and clinical practice to be related to deconditioning in patients with lower back pain.[2, 11] Movement control, back muscle strength, aerobic capacity, and flexibility are of interest because they are factors negatively affected in people suffering from the disuse syndrome which is common in patients with chronic low back pain and could therefore improve prediction for outcomes after LSF.[2, 11] Identifying which of these physical performance factors are associated with outcomes after LSF can help with treatment decision making and reduce the individual's risk factors, for example, by providing preoperative interventions like prehabilitation exercise training.[12] he aim of this study is to explore associations of preoperative physical performance measures with postoperative short- and long-term outcomes in adult patients undergoing LSF.

METHODS

This retrospective cohort study, used data collected between January 2017 and September 2018 from a single university medical center.

Population

As part of standard care, all adult patients (aged ≥18 years) with a degenerative disorder of the lumbar spine and scheduled for elective 1- to 3-level LSF underwent a preoperative screening to measure their physical performance. Primary surgical indications included were spondylolisthesis, degenerative disk disease, prior spine surgery (ie, previous spinal fusion, discectomy, laminectomy). Patients eligible for elective LSF had

previously received at least 1 type of conservative treatment (e.g., physiotherapy, pain medication, nerve block) that was not effective in relieving their complaints.

Physical Performance Screening

The physical performance screening assessed movement control, back muscle strength, aerobic capacity, and flexibility six weeks prior to surgery. A trained hospital physical therapist executed the screenings between January 2017 and July 2018.

First, movement control was assessed using four tests: (1) sitting knee extension (flexion control); (2) posterior pelvic tilt (extension control); (3) Waiter's bow (flexion control); and (4) 1-leg stance test (lateral flexion/rotation flexion control; supplemental Appendix S1, available at http://www.archives-pmr.org/).[13] he physical therapist scored the performance of the patient on these four tests as correct if the patient showed control of the spine or incorrect if the patient did not. This resulted in a score of 0-4 correct tests.

Second, back muscle strength was tested using the following (see supplemental Appendix S1, available at http://www.archives-pmr.org/):

i) The Sorensen test to assess back muscle endurance strength. During the test the patient laid on the examining table in a prone position with the upper body levitating over the edge of the table.[14] The patient was asked to isometrically maintain the upper body in a horizontal position for as long as possible. The number of seconds the patient was able to hold the test position was used in the analysis.
ii) A submaximal multiple-repetition test using a lumbar extension machine to assess maximum back extensor strength (MedX, Ocala, Florida, USA). he MedX machine measures maximal voluntary isometric torque (in Newton meters) of the back extensor muscles at 7 angles of the lumbar spine.[15] The average difference from the normal values (percentage of the norm) for the individual patient was calculated and used in the analysis.

Next, aerobic capacity was measured using the steep ramp test (SRT) (see supplemental Appendix S1, available at http://www.archives-pmr.org/).[16].= The SRT is a maximal exercise test on an exercise bicycle highly associated with the VO_2 max, which is the gold standard for measuring aerobic capacity.[16] The outcome from the test provided an estimation maximum short-time exercise capacity (Watt/kg), which was used in the analysis.

Finally, back flexibility was measured using the finger-floor distance (see supplemental Appendix S1, available at http://www.archives-pmr.org/). The measured distance between the patient's middle finger and the floor in centimeters was used in the analysis.

Baseline Characteristics

The following patient demographics were collected: sex, age, body mass index (BMI), smoking status (active smoker: yes/no), duration of pain (<2/≥2 years), and American Society of Anesthesiologists score (I/II/III). The following data on surgical characteristics were collected: primary surgical indication (spondylolisthesis/degenerative disk/prior spine surgery), single or multilevel fusion and type of surgery (posterior lumbar interbody fusion/transforaminal lumbar interbody fusion/posterolateral fusion without decompression/combination).

In addition, preoperative perceptions were collected during the first preoperative in hospital visit, via questionnaires on: back and leg pain (Visual Analogue Scale (VAS)),[17] physical functioning (Oswestry Disability Index (ODI)),[18] health related quality of life (HRQOL) (RAND-36 mental component score (RAND-36 MCS), and RAND-36 physical component score (RAND-36 PCS))[19] and mental health (Hospital Anxiety and Disability (HADS) anxiety and depression sub scores, and Pain Catastrophizing Scale (PCS)).[20, 21]

Outcome Variables

The primary short-term outcome was defined as inpatient functional recovery (in days) measured with the modified Iowa Level of Assistance Scale (mILAS) by a hospital physical therapist. The mILAS assesses the capability of patients to perform five activities of daily life (supine-to-sit, sit-to-supine, sit-to-stand, walking, stair climbing) and rates the amount of assistance necessary to perform the task on a scale from 0-30.[22, 23] Functional recovery was achieved on the day the patient had a score of 0 or 6 (if the patients did not have stairs at home) on the mILAS. The mILAS is valid and responsive and has excellent interrater reliability (intraclass correlation, 0.96).[24]

The secondary short-term outcome, hospital length of stay (LOS), was defined as days of hospitalization starting from the day of surgery to discharge.

There were no known cutoff points in the literature defining fast or prolonged functional recovery and LOS for patients undergoing LSF. Cutoff values for short or prolonged functional recovery and LOS were based on the distribution of these variables within this study. Cutoff values closest to the 25th percentile were used to identify associations with fast functional recovery and short LOS, whereas values closest to the 75th percentile were used to identify associations with prolonged functional recovery and LOS. The 25th and 75th percentiles were chosen, as suggested in the literature when there is no criterion standard available.[25]

The long-term outcome was defined as a clinically relevant reduction in predominant pain in the back or legs (worst reported pain in back or 1 of the legs) as measured with the VAS at 1-2 years after surgery. The VAS for pain ranges from 0-100, with 0 indicating no pain and 100 indicating the most severe pain imaginable.[17] This dependent variable was made binary: clinically relevant pain reduction or not. Minimal clinically impor-

tant change for pain ranged between 0.28-2.88 on an 11-point scale in the literature on spinal surgery[26]; therefore, a reduction of ≥2.88 (28.8 on a 0 to 100-point scale) was a priori defined as a clinically relevant pain reduction in order to prevent overestimation.

Statistics

Coded data were analyzed using SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) and R (version 3.3.2; http://www.r-project.org). Data were checked for completeness. In case of incomplete variables, we imputed all missing variables with multiple imputations using the multivariate imputation by chained equations (MICE) package. Correlation between preoperative variables was assessed, using a Pearson or Spearman correlation for normally or non-normally distributed data, respectively. If a correlation of r>0.7 was found, one of the correlated variables was chosen to use in the association analysis.

For the identification of stable associations among a large number of variables in a small sample we used the Boruta package (available from the Comprehensive R Archive Network at http://CRAN.R-project.org/package=Boruta) with 300 iterations, which implements criteria for identifying variables associated with the outcome in datasets with many variables. The Boruta package calculates a z score, which is a combination of variable importance and heterogeneity. Boruta is a feature selection method that uses the well-known random forest machine learning technique. This analysis can best be viewed as a rank order of variable influence (correlation) on the outcome, which is worthy of further investigation. The Boruta algorithm produces randomly shuffled duplicates of each variable in the original dataset (shadow variables). During each random forest run (each iteration), these shadow variables are also taken into account as possible predictor variables for the outcome. The shadow variables can be viewed as random noise. Some shadow variables will perform better than others. Preoperative variables consistently performing better than the shadow variable are qualified as important variables that should be investigated further. A P value <0.05 was viewed statistically significant.

RESULTS

During the study period, 87 patients with a degenerative disorder of the lumbar spine underwent elective 1- to 3-level LSF. In total 77 patients were preoperatively screened and 10 were not due to logistical issues. These 77 patients were eligible for analysis (88.5%). Table 1 shows baseline patient characteristics. Baseline characteristics of the 10 missing patients and the 77 screened patients differed only on surgery indication. Age ranged from 28-79 years. Functional recovery ranged from 2-15 days with a median of five days. LOS ranged from 3-23 days with a median time of 7 days. Pain reduction 1-2

years postoperatively was measured in 65 of the 77 patients (84%) because of loss to follow-up. VAS scores ranged from −100 to +50, with a median pain reduction of −20. The identified cutoff points for fast and prolonged inpatient functional recovery were recovery within four days and recovery in five days or more, representing the values closest to the 25th and 75th percentiles. Similarly, the cutoff points identified for short and prolonged LOS were discharge within five days and discharge in seven days or more. None of the baseline variables were highly correlated (r<0.7).

Functional Recovery

Fast functional recovery ≤4 days (Figure 1A): flexibility (median z score= 4.3; range, −0.5 to 9.1), aerobic capacity (median z score= 7.1; range, 3.5-12.2), and back muscle endurance (median z score= 7.8; range, 3.7-11.6) were associated with a functional recovery ≤4 days, because their z scores were consistently higher than that of the maximum shadow variable. Maximum back extensor muscle strength (median z score= 2.8; range, −1.5 to 6.4) was a tentative variable for functional recovery ≤4 days, because its z score was sometimes higher than that of the maximum shadow variable.

Prolonged functional recovery ≥5 days (fig 1B): HADS Depression subscale (median z score= 3.0; range, −1 to 8.7), PCS (median z score= 4.0; range, 0.5-8.7), surgical indication (median z score= 4.8; range, −1.4 to 9.6), maximum back extensor strength (median z score= 8.6; range, 4.2-13.1), and aerobic capacity (median z score= 12.0; range, 6.5-16.5) were associated with functional recovery ≥5 days.

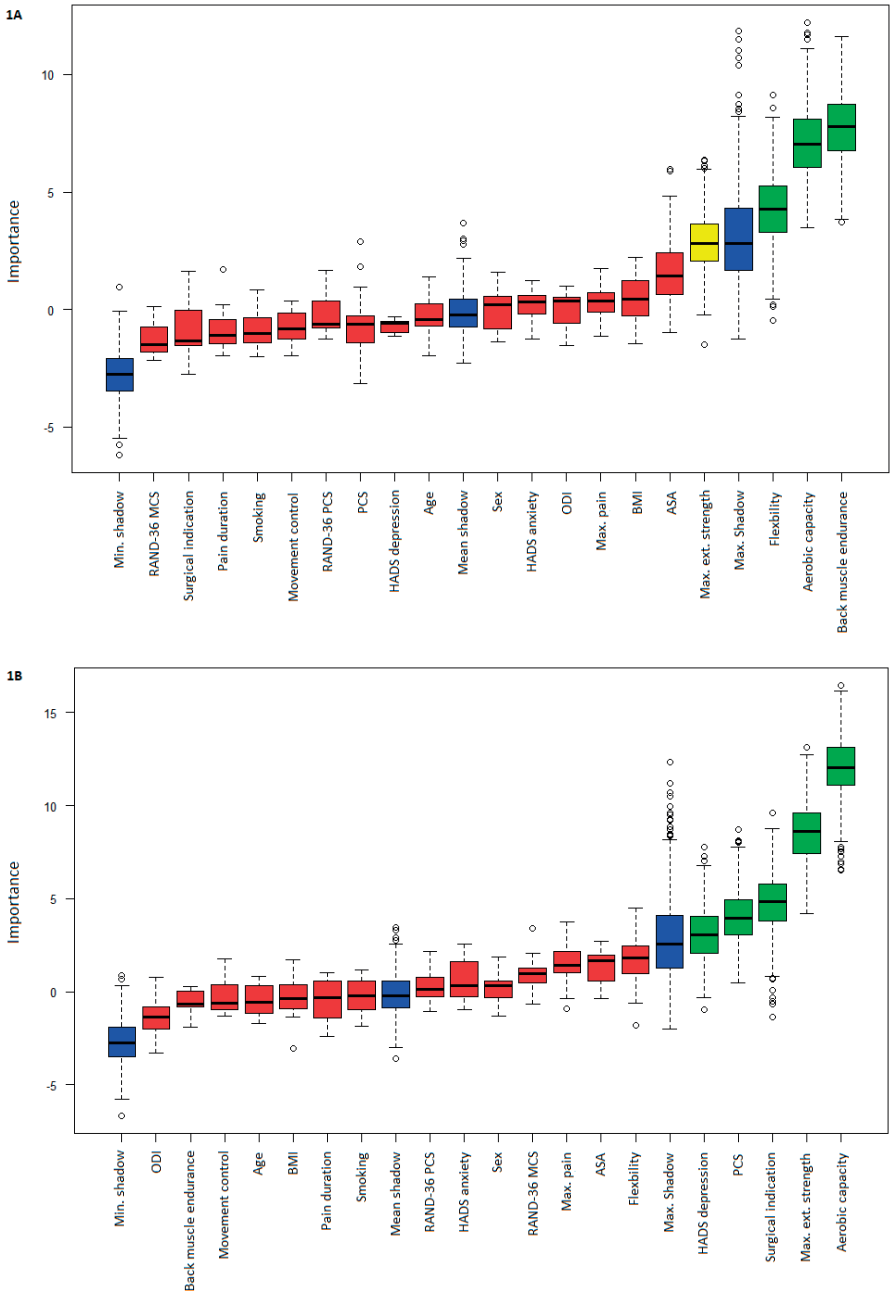
Length of Hospital Stay

Short LOS ≤5 days (Figure 2A): American Society of Anesthesiologists score (median z score= 3.6; range, −0.3 to 7.5), flexibility (median z score= 5.1; range, 0.2-9.2), and back muscle endurance strength (median z score= 13.5; range, 7.8-19.8) were associated with LOS ≤5 days.Prolonged LOS ≥ 7 days (Figure 2b): age (median Z-score= 3.7 (-0.9-7.9)), RAND-36 PCS (median Z-score= 4.0 (0.8-7.1)), maximum pain (median Z-score= 6.4 (3.1-10)) and aerobic capacity (median Z-score= 8.7 (4.0-12.6)) were associated with LOS ≥ 7 days.

ClinicallyRelevant Reduction in Predominant Pain

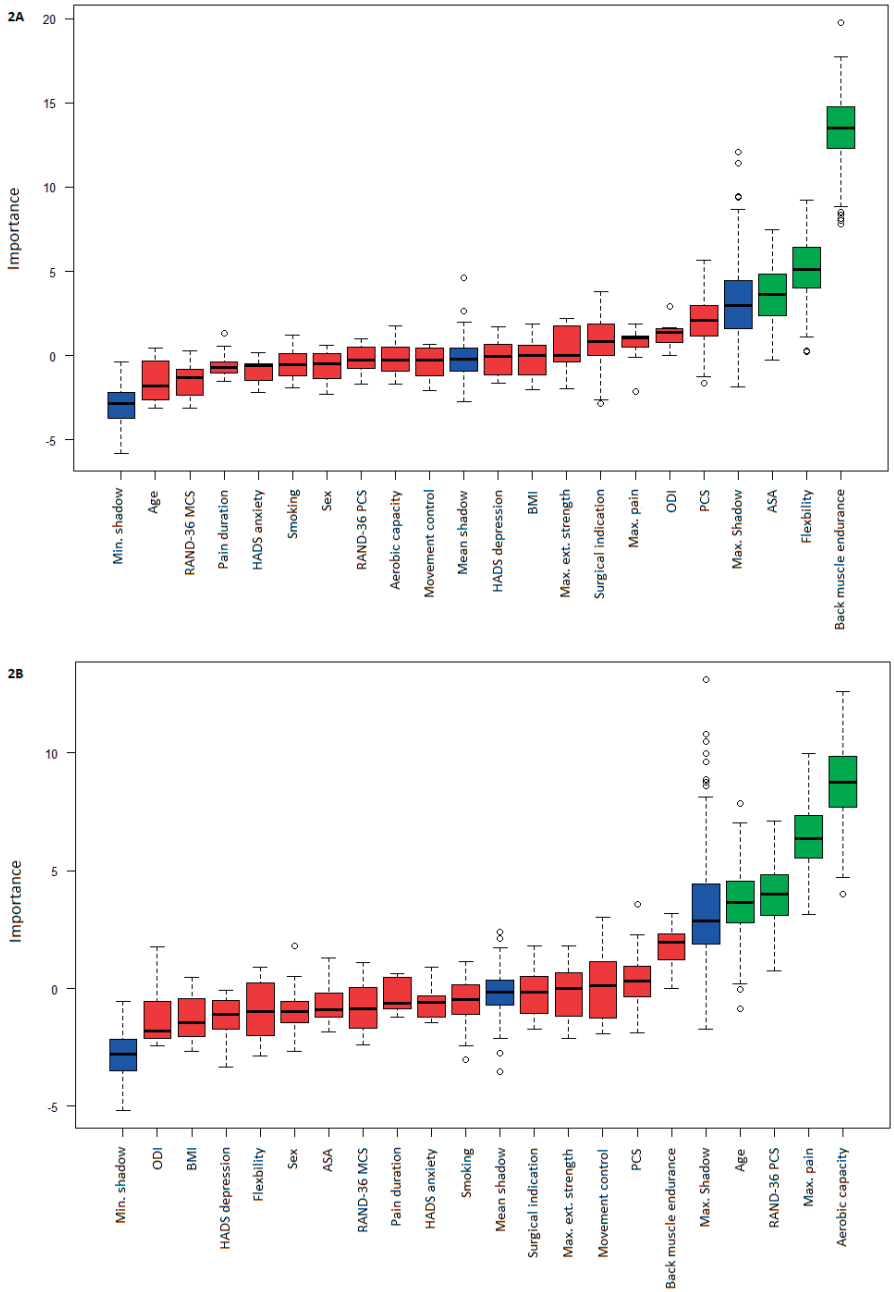
PCS (median z score= 4.1; range, −0.5 to 8.8) and maximum back extensor strength (median z score= 3.8; range, 0.2-7.6) were associated with a clinically relevant reduction in predominant pain 1-2 years after LSF. Aerobic capacity (median z score= 2.8; range, −2.2 to 8.7) and surgery indication (median z score= 2.8; range, −1.1 to 8.0) were tentative variables and therefore might be associated with a clinically relevant reduction in predominant pain one to two years after LSF.

Figure 1A and B. The relative ranked influence of variables on inpatient functional recovery within 4 days (A: fast functional recovery) and in 5 days or more (B: prolonged functional recovery) respectively



Red and green boxplots represent Z-scores of respectively rejected and confirmed attributes and yellow boxplots indicate tentative variables. Blue boxes represent minumum, mean and maximum Z-scores of shadow variables. Abbreviations: ASA= American Society of Anesthesiologists, BMI= Body Mass Index, Max.= maximum, ODI= Oswestry Disability Index, PCS= Pain Catastrophizing Scale, HADS= Hospital Anxiety and Depression Score.

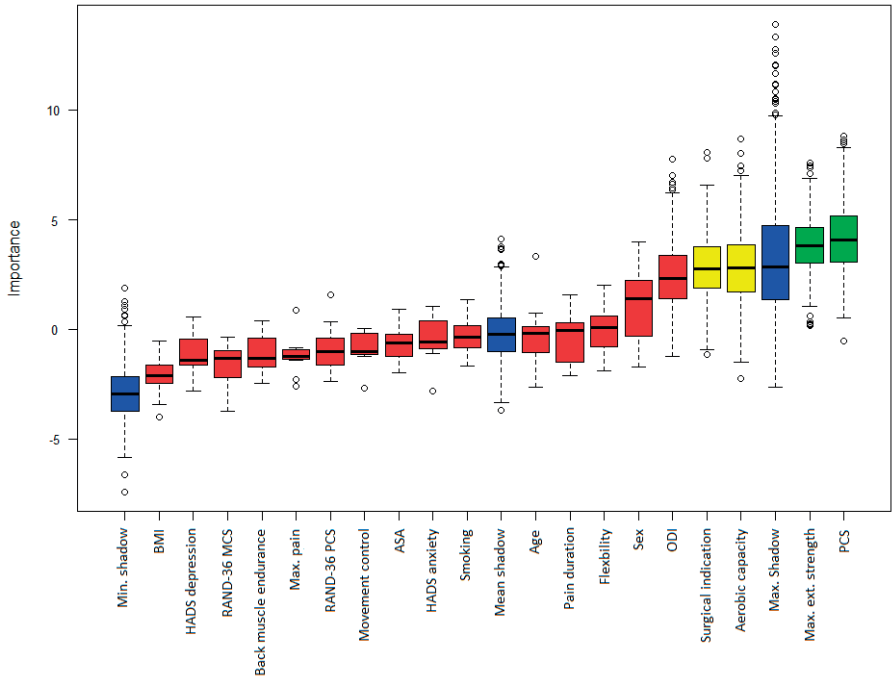
Figure 2A and B. The relative influence of variables on the risk of short and prolonged length of hospital stay (LOS) within 5 days (A: short LOS) and in 7 days or more (B: prolonged LOS) respectively



Red and green boxplots represent Z-scores of respectively rejected and confirmed attributes and yellow boxplots indicate tentative variables. Blue boxes represent minumum, mean and maximum Z-scores of shadow variables. Abbreviations: ASA= American Society of Anesthesiologists, BMI;= Body Mass Index, Max.;= maximum, ODI= Oswestry Disability Index, PCS= Pain Catastrophizing Scale, HADS= Hospital Anxiety and Depression Score.

Box 1 describes how Figures 1, 2 and 3 should be interpreted.

Figure 3. The relative influence of variables on the risk of a clincally relevant pain reduction 1-2 years postoperatively.



Red and green boxplots represent Z-scores of respectively rejected and confirmed attributes and yellow boxplots indicate tentative variables. Blue boxes represent minumum, mean and maximum Z-scores of shadow variables. Abbreviations: ASA= American Society of Anesthesiologists, BMI= Body Mass Index, Max.= maximum, ODI= Oswestry Disability Index, PCS= Pain Catastrophizing Scale, HADS= Hospital Anxiety and Depression Score.

Box 1. Interpretation aid Figure 1, 2 and 3

The Boruta algorithm produces randomly shuffled duplicates of each variable in the original dataset: *shadow variables*. During each random forest run (each iteration) these shadow variables are also taken into account as possible predictor variables for the outcome. The shadow variables can be viewed as random noise. Some shadow variables will perform better than others. The blue boxes represent the worst, mean and best shadow variable included in the random forest analysis. For each random forest run, a real variable gets a hit when it performs better than the best shadow variable. Variables consistently (at each iteration) performing better than the best shadow variable are confirmed (green boxes), variables that often perform better than the best shadow variable are tentative (yellow boxes).

DISCUSSION

This study explored the associations between preoperative physical performance and inpatient functional recovery, LOS, and a clinically relevant reduction in predominant pain 1-2 years after surgery in adult patients opting for elective 1- to 3-level LSF. Pre-operatively, aerobic capacity and back muscle strength were associated with both fast

and prolonged inpatient functional recovery and flexibility was associated only with fast functional recovery. Back muscle endurance strength and flexibility were associated with short LOS and aerobic capacity was associated with prolonged LOS. Maximum back extensor strength was associated with a clinically relevant reduction and aerobic capacity was tentative. To the best of our knowledge, this is the first study to show that better aerobic capacity, flexibility, and back muscle strength are associated with both short- and long-term outcomes in patients undergoing elective LSF.

There is strong evidence that aerobic capacity is a predictor of postoperative mortality and recovery after major surgery (ie, abdominal and cardiac surgery).[27] This is likely to be true for patients undergoing LSF as well because we found aerobic capacity to be positively associated with both functional recovery and LOS and tentative for a clinically relevant reduction in predominant pain. That is, the better the preoperative aerobic capacity, the better the postoperative outcomes. Functional cross-sectional area of the paraspinal back muscles assessed by magnetic resonance imaging, which is a measure for muscle quality, is a predictor of better postoperative outcomes after spinal decompression.[28] This poses the hypothesis that better muscle strength is associated with better outcomes after spinal surgery. In line with this hypothesis, our results show associations between back muscle strength and both short- and long-term postoperative outcomes. Additionally, like in our study, Huang et al showed a correlation between range of motion and postoperative outcomes,[29] suggesting that better flexibility is associated with better outcomes after spinal surgery. These studies, together with our results, provide presumptive evidence that good physical performance before LSF is associated with better postoperative outcomes. Thereby, adding these measures to a prediction model for postoperative outcomes after LSF may improve its accuracy, which can be helpful when patient and surgeon discuss different treatment options.

Before hospital discharge, it is generally advised that patients should achieve inpatient functional recovery first. On average, the time difference between achieving functional recovery and being discharged was two days in our study. For some patients this delay was up to 10 days. The delay between functional recovery and discharge was due to medical, organizational, and social issues, most commonly delayed postoperative radiographs, waiting for a postoperative brace, or wound leakage. This demonstrates the importance of distinguishing between functional recovery and LOS as outcome measures. Although LOS is an important outcome, it can be influenced heavily by several nonclinical factors and does not necessarily reflect a patient's recovery of function.[30] Therefore, outcomes like functional recovery, which reflect the physical effect of surgery on the individual patient, should play a more dominant role in research on surgical outcomes.

Strengths and Limitations

A strength of our study is that we were able to find stable associations between physical performance measures and postoperative outcomes in a relatively small population by applying random forest analysis. Random forest has several advantages that make it ideal for datasets with many variables; for example: (1) it has good performance when there are many variables with few observations; (2) it has good performance even when most variables are considered to be noise; and (3) it incorporates interactions among variables.[31] This addresses important disadvantages in traditional analysis techniques that cannot deal with datasets that consist of few observations and many variables: they require a preselection of variables, potentially excluding important variables from the analysis that were not identified a priori.

A limitation was that we analyzed our model using limited data from a single university medical center, which could lead to overfitting and lack of generalizability. We infer, however, that the importance of our work lies in identifying possible modifiable variables that affect outcomes after LSF, which could be replicated and built upon by others. Finally, due to the use of standard care data, we had some missing values in our dataset, as is ubiquitous in clinical research. For back muscle endurance strength more than half of the data were missing. This was because of logistical issues (n= 12), patients who did not perform test because of pain (n= 20), and patients who did not perform test because of lack of strength (n= 7). Therefore, results on this variable should be interpreted with caution. In a post hoc analysis we checked whether execution of the Sorensen test (yes or no) was associated with the outcomes but this was not the case. An easier method to perform back muscle endurance testing, like a pressure biofeedback unit, should be considered to improve executability.[32]

Implications for Future Studies

In future studies, our findings need to be confirmed in a larger cohort study. Preoperative physical performance screening is recommended for implementation in standard preoperative assessment. These physical performance measures can then be added to an externally validated preoperative prediction tool in addition to known patient and surgery characteristics, such as BMI, age, and patient-reported outcome measures, to estimate postoperative outcomes. If our findings are confirmed, patients with worse preoperative physical performance may benefit from additional prehabilitation training, whereas low-risk patients could be prepared for overnight admission routes.

CONCLUSION

Better preoperative physical performance (aerobic capacity, back muscle strength, flexibility) is associated with short- and long-term outcomes in patients undergoing elective LSF. Adding these performance measures in the exploration and validation of prediction tools for LSF outcomes is warranted. In this way, a positive effect on personalized medicine and shared decision making for patients undergoing LSF can be expected.

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8

General discussion

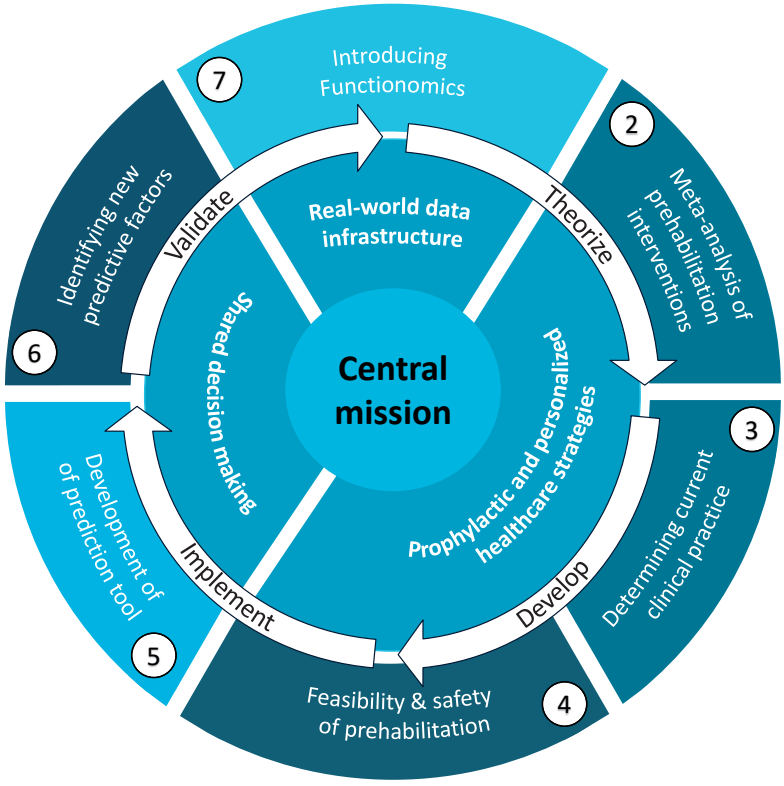
The central mission of this thesis was improving the health of people opting for elective lumbar spinal fusion (LSF) by adopting ongoing advancements in healthcare towards an increasingly predictive, preventive, personalized and participatory (P4 medicine) perioperative healthcare approach. We studied this with patients opting for elective 1-3 level LSF, by iteratively theorizing, developing, validating and implementing methods and tools in real-life perioperative healthcare practice, covering three themes (Figure 1):

I) Preventive and personalized perioperative risk management strategies (*chapters 2-4*);

II) Innovative methods to guide evidence based shared decision making within the perioperative healthcare pathway (*chapters 5 & 6*);

III) First steps towards integration of a modern real-world perioperative data technology and expanding the 'omics-family', by introducing *functionomics* (*chapter 7*).

Figure 1. Transition towards participatory, predictive, preventive and personalized (P4 medicine) perioperative healthcare with people opting for elective lumbar spinal fusion (inner circle). Through iterative theorizing, development, implementation and validation (white arrows) of: I) preventive and personalized risk management strategies, II) improved personalization in treatment decision making and prognostics, and III) towards integration of a modern real-world perioperative data infrastructure and expanding the 'omics-family', by introducing functionomics (middle circle). Operationalized in chapters 2 through 7 in this thesis (outer circle).



WHAT IS KNOWN

To position our findings in the correct context, we shortly recapitulate the health, healthcare and research landscape compartments relevant to this thesis in 2016 and earlier. Great advances had already been made in the decades before 2016 in improving perioperative healthcare with patients undergoing various types of elective surgery. For example, prediction tools and prehabilitation interventions had been developed, validated and implemented in the patient journey of people undergoing total hip- and knee replacement and major abdominal surgery.[1-5] The movement towards an increasingly predictive, preventive, personalized and participatory (P4 medicine) perioperative healthcare approach resulted in improved postoperative outcomes.[6] This thesis was initiated building on these developments and accomplishments, aimed at achieving similar positive results with people opting for LSF.

LSF is often the final treatment option for patients suffering from degenerative disorders of the lumbar spine who had no benefit from conservative treatment. Despite great advances in surgical techniques and anesthesiology, the success chance of LSF is still variable: on average 56% of patients experience a clinically relevant reduction in pain one year after LSF.[7] Due to the complexity and heterogeneity of symptoms and characteristics of these patients, it is difficult to estimate which patients will benefit from undergoing LSF in clinical practice. To aid in this difficult decision making process, a few prediction models for people opting for LSF were developed in the recent past. These models included biomedical and patient perception factors to preoperatively estimate a patient's postoperative outcome (e.g., pain, BMI, functioning).[8-10] These models were able to predict postoperative outcomes after LSF with moderate accuracy, leaving much room for improvement.

Likewise, the biomedical paradigm focusing on anatomy, physiology and symptom treatment, had been dominant in research on perioperative care with patients opting for LSF in the recent past. This led to great advancements in surgical techniques and anesthesiology. Utilization of the biomedical paradigm however disregards important information for improving health of patients opting for LSF. Meanwhile, in other types of major (orthopedic) surgery a transition towards a more biopsychosocial, P4-based perioperative care approach was ongoing and demonstrated substantial benefits in postoperative outcomes and patient satisfaction.[4, 5, 11, 12] Fortunately, during the course of the conduction of this thesis, this trend in international research and, in clinics, towards P4 medicine became more apparent in the context of perioperative patient journey in patients opting for LSF as well.[13, 14]

The ongoing advancements towards P4 medicine in general requires not only a shift in research paradigm, but also calls for new research methodologies. This transition is currently ongoing, extending the scope from a predominantly synthetic data collection methods such as by randomized controlled trials, towards real-world big data and open science.[15] To capture and process enough information for personalization, advances in information technology (IT) and new statistics are essential. For example, the internet of FAIR (Findable Accessible, Interoperable and Reusable) data and services was developed and will - in the coming years - stepwise enable us to gain access to data sources worldwide.[16] These 'big data' can be analyzed by using recently developed machine learning techniques able to process large amounts detailed real-world data.[17, 18]

In this thesis we first adopted the paradigm shift in perioperative healthcare and thereupon combined that shift with the newly developed – and for continuously developing – research methodologies to achieve our central mission.

In this chapter we will reflect on the study findings presented in this thesis and their implications for patients and professionals in their clinical practice. Next, challenges encountered during the conduction of this research and their implications for scientific research related to the perioperative patient journey in patients opting for LSF are discussed. Thereafter, future research directions building upon the findings of this thesis will be considered. Finally, we will discuss how this thesis contributed in achieving the central mission.

WHAT IS NEW

Main Findings, Their Interpretation and Clinical Implications

I. Preventive and personalized risk management strategies

Our systematic review (*chapter 2*) showed that current prehabilitation programs did not improve postoperative outcomes compared to usual care of the patients scheduled for LSF. Of 15 included studies, the results of 13 studies could be pooled in a meta-analysis, as they all described cognitive behavioral therapy (CBT) interventions. Two studies could not be pooled as they described a single exercise intervention and were deemed too heterogeneous. None of the pooled mean differences on pain, self-reported or observed physical functioning, health related quality of life (HRQOL), psychological outcomes, length of hospital stay, analgesics use and return to work were significant at any time point (short-, mid- and long-term). The level of certainty of the pooled results of our review was low to very low, as assessed using the Grading of Recommendations

Assessment Development and Evaluations (GRADE) framework,[19] which means that these results are not conclusive and new evidence could have an important impact.

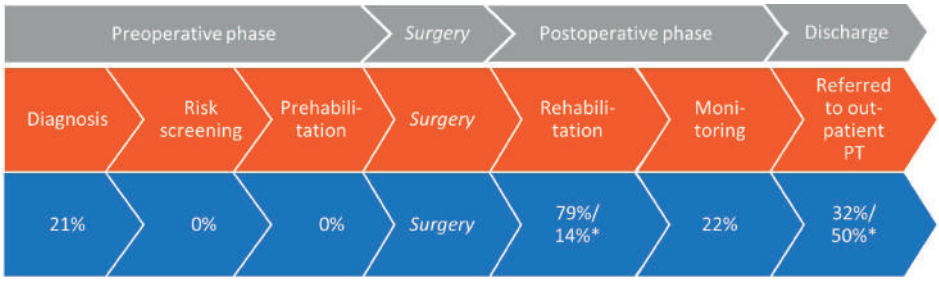
At first glance these results seems surprising, as in other types of major surgery prehabilitation interventions were shown to be effective for improving postoperative outcomes by reducing complication rates and improving recovery rates of physical functioning.[11, 20-27] Possible explanations for this conclusion could point to suboptimal intervention designs (variable types of CBT interventions were included) or inadequate patient selection criteria (as risk profiles of the included patients were almost always absent). Included CBT interventions ranged from one-size-fits-all web based anxiety reduction to intensive one-on-one multimodal therapy sessions. The two studies reporting on exercise interventions, not included in the meta-analysis, did suggest a positive effect of such an intervention on length of stay and self-reported physical functioning after LSF. Prehabilitation strategies for improving postoperative outcomes in other types of major surgery also described exercise therapy interventions to be effective in reducing morbidity.[28, 29] Exercise therapy may thus be considered as a more effective intervention for improving postoperative outcomes after LSF when compared to CBT. Next to treatment modality, population selection may also play an important role in validating the effectiveness of prehabilitation for people opting for LSF. Recent studies emphasize the importance of risk stratification before assigning patients to a prehabilitation intervention to achieve optimal outcomes of surgery.[1, 5, 11, 17, 30] None of the included studies performed an explicit preoperative risk stratification. A crucial step here, as patients opting for LSF are at various stages of deconditioning and show clinically relevant interindividual differences,[31] as we reported also in *chapter 4 and 5*. Bearing these interindividual differences in mind, the studies in the meta-analysis on average included relatively healthy patients. These patients obviously benefit less from prehabilitation than those who are deconditioned or have a vulnerable mental health. Therefore, tailoring care to the specific 'high-risk' patient profiles may be crucial to show its effectiveness; meaning that in future research those with worse physical fitness should be offered preoperative exercise therapy, whilst those suffering from diminished mental fitness should be offered CBT. Depending on the specific risks of patients a combination of both interventions should also be considered as the preferred preoperative intervention.[32] Personalizing the preoperative trajectory to better fit the patient's needs should thus involve preoperative identification of a patient's risk profile through preoperative screening and consequently acting upon this information.

Implication for clinical practice I: Preoperative cognitive behavioral therapy interventions, as evaluated in our systematic review, cannot be recommended for implementation in clinical practice in their current form. Alternatively, risk stratified exercise

prehabilitation should be studied as a treatment strategy with patients opting for LSF, as it has shown high potential in other surgical populations.

In 2014, we conducted a nationwide survey study to elicit the current state of expert perioperative physiotherapeutic care services for patients opting for LSF in Dutch hospitals (*chapter 3*). Most hospitals provided post-operative rehabilitation and referred patients who underwent LSF to outpatient physiotherapy (Figure 2).

Figure 2. Percentages of inpatient physiotherapy practices performing some type of service for patients opting for LSF in the Netherlands anno 2014.



Abbreviations: PT= physiotherapy
*Physiotherapists only provided rehabilitation or referral to outpatient physiotherapy to patients when deemed necessary.

However, some important dissimilarities between hospitals and discrepancies with recent evidence in physiotherapy practice were found. Especially, preoperative services and postoperative monitoring was seldom part of standard care in hospitals. These are key constructs described in the literature that aid the optimization and personalization of physiotherapy care.[33, 34] The preoperative phase should be used for both initial diagnosis and risk stratification to plan the perioperative care according to the patient's needs.[2, 5, 35] Investing in the preoperative period, by implementing a preoperative diagnosis and risk screening has specific advantages for postoperative hospital planning (e.g., estimating the length of hospital stay and estimating necessity of referral for postoperative rehabilitation), and as described in the previous paragraph, prehabilitation, according to a patient's risk profile, could also help improve postoperative outcomes. Furthermore, postoperative monitoring is essential for (re)evaluation of the preoperative prognoses, timely intervention, adjustment of treatment intensity and effect measurement. With the data collected through standardized monitoring of outcomes, perioperative care can be further improved.[36]

Of course, improvements in practice may have taken place since 2014, rendering these data not representable of the current state of perioperative physiotherapeutic care services for patients undergoing LSF. As part of the national 'Better in, Better out' (BiBo) learning community where national perioperative health and care strategies and their

evidence are presented and discussed among perioperative caregivers and scientists in several Dutch hospitals, we are making efforts in improving perioperative physiotherapeutic care for these patients. This led to a national BiBo guideline for physiotherapists, describing best practices.[37] For the population undergoing LSF, generation and imbedding of new evidence into the perioperative care pathway has made slow progress. Nationally more hospitals are taking up the developed screening and are implementing similar prehabilitation strategies. Moreover, from the review in chapter 2 we can see a positive international trend towards a more preventive care pathway for people opting for LSF as well.

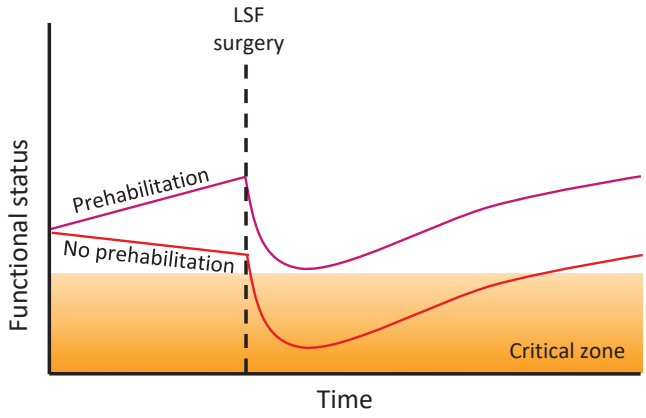
Implication for clinical practice II: Hospital physiotherapists should implement national best practice guidelines for perioperative care. Specifically, standardized preoperative diagnosis and risk screening, and postoperative monitoring should be implemented.

In 2017 we updated the perioperative physiotherapeutic care pathway in our own hospital, by implementing a preoperative risk screening and the year thereafter a community-based prehabilitation intervention for high-risk (i.e., deconditioned, unfit) patients opting for LSF (*chapter 4*). The goal of the improved pathway was to have all patients achieve an optimal physiological reserve so they would be able to withstand the surgically induced stress better and have faster postoperative recovery. Preoperative risk stratification of patients into high- and low-risk profiles relied on the results from chapter 6, where we identified predictive physical performance measures for outcomes after LSF. Preoperative risk screening together with recent evidence on the promising prehabilitation interventions before major surgery resulted the implementation of a community based functional high-intensity interval training (*f*-HIIT) program. This relatively new f-HIIT concept combines the high-intensity interval training principles, where >90% of the maximum heart rate is achieved in short time intervals,[38, 39] with functional training where patients together with their therapist decide on exercises that best fit the patient's individual needs and daily activities.[40] During this preoperative intervention period, frequent and standardized monitoring of progress by a physiotherapist was applied to ensure adequate training intensity. Standardized monitoring of postoperative recovery was performed as well. Standardized monitoring facilitated iterative evaluation, fine-tuning and validation of this new strategy.

In *chapter 4* we described the results from our pilot cohort study. We included 11 high-risk patients who participated in the *f*-HIIT prehabilitation intervention. The initial results during the preoperative training period, collected through frequent (self-)monitoring, showed that this type of prehabilitation was safe and feasible for all 11 high-risk patients who underwent the intervention. No adverse events occurred during training and all patients improved their fitness during the training period. Although none of the

patients reached >90% of their maximum heart rate during training, they did achieve high intensity according to the perceived exertion scale. Submaximal heart rates could be attributed to many patients taking heart rate reducing medication or to suboptimal training intensity. Nonetheless, immediate postoperative benefits on time to functional recovery were visible, with high-risk patients receiving prehabilitation achieving functional recovery three days faster than their propensity score matched untrained counterparts (Figure 3).

Figure 3. Visualization of the effect of the f-HIIT prehabilitation intervention in high-risk patients compared to high-risk patients who did not receive prehabilitation. (adapted from Hulzebos et al.[5])



Although these results seem promising, there were some initial implementation issues: I) We were only able to provide physiotherapists within the Maastricht-Heuvelland region with a *f*-HIIT education program, leading to any patients living outside of this region were not being eligible for training, and II) not all patients were screened due to either a too short preoperative time frame, logistic issues or patients being unable to perform certain screening tests. This is unfortunate as it may leave some high-risk patients with unfair chances of achieving an optimal preoperative physiological reserve and fast postoperative recovery.

Implication for clinical practice III: The *f*-HIIT prehabilitation program is feasible and safe for high-risk patients opting for LSF. Moreover, it may be able to shorten time to functional recovery. Although the effectiveness results are only preliminary, the costs and risks of the intervention are low, whilst benefits seems to be high. Therefore, prehabilitation can be recommended for implementation in clinical practice if combined with preoperative risk stratification. If hospitals want to implement prehabilitation they should firstly achieve a broad outpatient training network within the region of the

hospital to be able to offer training to all high-risk patients and have timely surgical planning to leave enough time for screening and prehabilitation.

II. Innovative methods to guide evidence based shared decision making within the perioperative healthcare pathway

An important element of P4 medicine involves the personalization of the care pathway by offering interventions that best fit the individual's needs while achieving the best possible outcomes.[41] Clinicians rely on their clinical experience and intuition to guesstimate a person's prognosis or diagnosis during a clinical consultation.[42] Clinical prediction models are tools that can help clinicians increase the accuracy of prognosis and diagnosis, by using an algorithm to formally calculate prognostic and diagnostic probabilities.[43] Prediction models are especially useful in treatment decision making when the stakes are high and decisions are ambiguous.[44] A good example is the decision whether or not to choose for LSF. For this decision the stakes are high: LSF is associated with a serious risk of complications and morbidity. Moreover, the choice is rather ambiguous, as success rates after LSF tend to be variable.[7] At the start of this thesis no externally validated prediction tool was available aiding in the decision making for or against LSF, by predicting the probability of achieving a clinically relevant pain reduction after LSF. We constructed and externally validated a clinical prediction tool (nomogram) in a Dutch population, which is ready to be implemented in clinical practice. The prediction tool calculates the probability of achieving a clinically relevant reduction (≥28.8 points on the VAS scale) in predominant pain in the back and/or (one of the) legs (worst reported pain in back or legs) at one to two years after surgery.[45] The area under the curve (AUC) of the externally validated model yielded 0.68. This roughly means the prediction model was able to accurately discriminate between achieving relevant pain reduction or not in 68% of the cases. Although this AUC is not bad, it does leave room for improvement. Moreover, the nomogram is rather easy to use, but implementation of this tool into clinical practice is limited due to time constraints during consultations. Automation of risk calculation through creation of a web based app and direct linkage with readily available input variables from the electronic health records (EHRs) into the algorithm could decrease time for risk calculation and could improve acceptance for use in clinical practice. By implementing and at the same time gradually improving the prediction tool, patients and surgeons are able to accurately calculate expected outcomes after LSF. This can help them make better informed treatment decisions for or against LSF.

Implication for clinical practice IV: The constructed prediction nomogram can aid patients and surgeons in the shared decision making process whether or not to choose for LSF. This provides patients and surgeons with objective information on the expected

reduction in pain one to two years after LSF. Users should keep in mind that calculated probabilities hold limited certainty.

Adding additional relevant variables could improve the accuracy of the prediction model. Preferably, such variables are chosen based on clinical and evidence based knowledge of the topic.[46] A variable that was overlooked previously is preoperative physical fitness. In other types of surgery, physical fitness was shown to be a strong predictor of postoperative outcomes.[1, 47, 48] Moreover, physical fitness is a variable that was already shown to be modifiable before surgery, as concluded in *chapter 4* and in studies with other types of surgical populations.[4, 5, 11, 12] Patients thereby have the opportunity to preoperatively improve their physical fitness and consequently lower their risk of achieving worse postoperative outcomes.

To add preoperative physical fitness as a predictor to our prediction tool, structured measurement of physical fitness should be implemented in clinical practice first. We implemented a preoperative physical therapy screening at the beginning of 2017 in the MUMC+. Here, patients participated in a physical fitness screening, measuring their aerobic capacity, muscle strength, movement control, flexibility and functional status. After data on the first 77 patients were collected, we performed an interim analysis and hereupon analyzed which physical fitness factors were most likely to strengthen accuracy of the prediction tool. We found that aerobic capacity, flexibility and back muscle strength were the best candidate predictors to be added to the model in the context of predicting for short-term (inpatient recovery) and long-term (one to two year pain reduction) outcomes after LSF. This analysis and reasoning shows that adding physical fitness to a prediction model may increase the accuracy of predicted outcomes after LSF. The improvement in prediction accuracy, by adding physical fitness to the prediction tool, should be calculated and validated externally. In turn, providing preoperative exercise therapy may improve preoperative physical fitness of a patient and thereby reduce his or her risk of delayed recovery after LSF. This hypothesis was substantiated pre-experimentally by the results from *chapter 4* of this thesis, as prehabilitation appeared to improve time to functional recovery of patients undergoing LSF. With these results we would recommend preoperatively screening of physical fitness with patients opting for LSF.

Implication for clinical practice V: A preoperative risk screening, including at least aerobic capacity, back muscle strength and flexibility, is advocated for implementation in clinical practice. Results from such a preoperative risk screening probably improve the prediction accuracy of expected results after LSF and thereby support shared decision making of patients and their (in)formal support. Moreover, preoperative screening may

help identify whether or not a patient has low physical fitness and could benefit from participating in preoperative exercise therapy.

III. First steps towards integration of a state-of-the-art real-world data infrastructure

Large amounts of data on a person's functioning is collected 24/7 by persons themselves and by many different stakeholders, like (allied) health professionals. Eliciting the information locked away in this data remains difficult due to lack of data standards and implementation of IT innovations. In *chapters 4 and 6* we focused on standardizing *what* to measure and *how* to measure in the health and healthcare context of patients eligible for LSF. Standardizing data collection (inter)nationally makes it easier to analyze data from different sources. Although this data had been collected in a standardized manner in our clinic, extraction from the many data sources proved to be difficult and was mainly done via 'swivel-chair-integration'; where a researcher manually copies data from the EHR system into a dataset. This is a very time consuming and inefficient way of integrating data from multiple sources. The issue gets exponentially larger when data from more sources and from different lines of care (more heterogeneous) need to be collected and integrated. Achieving the undeniable benefits of P4 medicine will ultimately require the analysis of large amounts of (big) data from multiple sources, not in the least including data on a person's functioning like daily activities, beliefs, social context. These important health modifying factors hold the potential to amplify new knowledge generation, as is done globally for biomedical big data in 'omics' research. Therefore, in *c*hapter 7, we proposed a new 'omics' initiative called 'functionomics'. Here we applied the FAIR (findable, accessible, interoperable and reusable) principles, which are internationally advocated to apply for good data management to data on a person's daily functioning. [16, 49] These principles are already applied successfully to other types of international omics-data, to facilitate new knowledge discovery across many data sources.[50, 51] We operationalized the FAIR principles through Semantic Web technologies.[52] However, data standards – such as ontologies – are lacking for this new functionomics community. In a practical example we showed how such an ontology could be developed, based on the WHO's International Classification of Functioning, Disability and Health (ICF) thesaurus, which is used around the globe by many (allied) healthcare professionals for describing data on functioning.[43] Through application of Semantic Web Technology we were able to make our data machine actionable and have an external party analyze our data without manual interference. Further developing functionomics community standards and spreading these techniques (inter)nationally will lead to multiple FAIR functionomics data silos that can be visited by the so called Personal Health Train (PHT) data infrastructure and thereupon analyzed by anyone (under well-defined terms),[18] most probably leading to exponential increase in value of separately collected and

stored data and increase of new knowledge generation. It is our conviction that this approach will ultimately improve healthcare practices in perioperative care with people undergoing LSF and, when developed further, in all areas of health and healthcare research using functionomics data.

Implication for clinical practice VI: (Allied) healthcare professionals should, to the best of their abilities, try to apply the FAIR principles to their data collected on a person's daily functioning, by using the here proposed technologies. Making this relatively underutilized data machine actionable will likely be a driving force for new knowledge discovery and personalization of perioperative and (allied) healthcare community.

METHODOLOGICAL CONSIDERATIONS & IMPLICATIONS FOR RESEARCH

There are three lines of methodological considerations concerning the research conducted in this thesis, namely: 1) analysis of observational data, 2) handling missing data, and 3) generalizability of results. These topics and accompanying implications for research practice will be discussed in this section.

Ad. 1) Analysis of Observational Data

Results of this thesis rely on the collection and analysis of real-world (observational) data. In essence the conducted research is non- or quasi-experimental, as no experimental research (i.e., randomized controlled trials (RCTs)) were conducted. Historically, the RCT is viewed as the research methodology involving a single study which produces the highest level of evidence in research practice (Figure 3). A view that is still generally accepted today. This view is mainly based on Hill's considerations for causality, which is an application of the counterfactual model from the 1800s.[53, 54] In RCTs, bias due to confounding is considered as highly unlikely to occur, because of the random distribution of possible confounders between groups. Therefore, it is regarded as the highest standard for producing evidence in a single study and evidence produced by cohort, case-control or cross-sectional studies is viewed as weaker. In the last decades RCTs have been the primary source of evidence leading to important scientific findings, changing clinical practice and health(care) policy.[55]

Non- or quasi-experimental observational designs have several advantages in comparison with RCTs. These designs are less costly, less time consuming and less of a burden to patients and professionals.[56] Moreover, the real-world of patients, professionals and (clinical) practice is much more complex than the strictly protocolized interventions and relatively simple causal relations hypothesised and tested on highly selective population

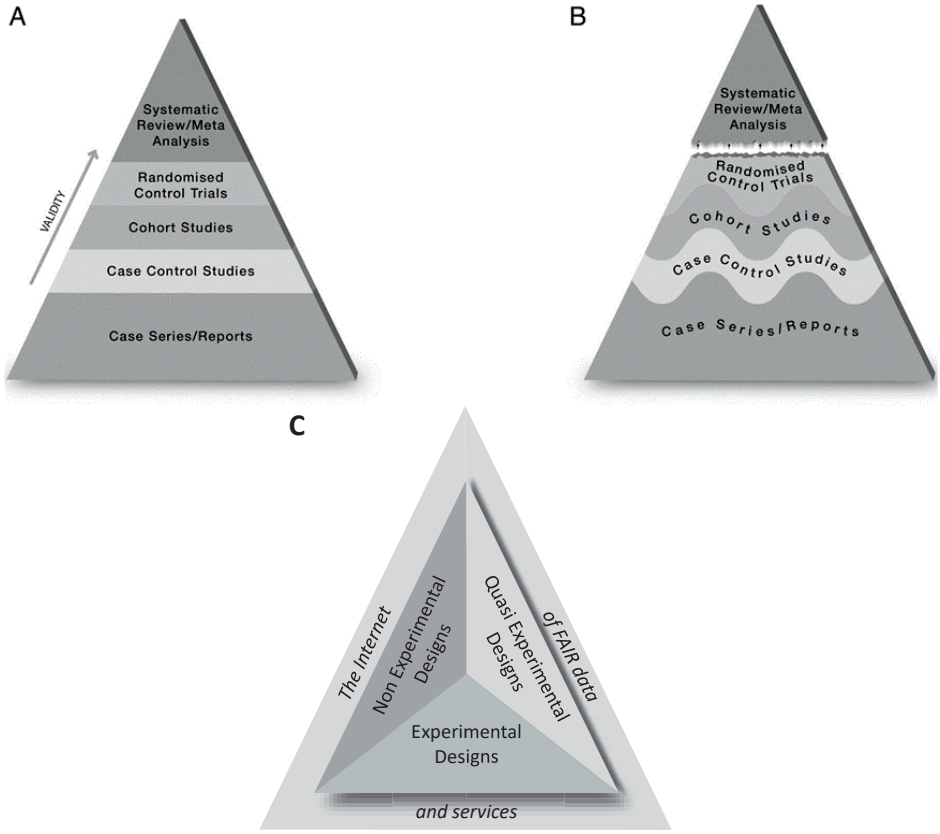
in RCTs. Next to that, observational studies can provide higher resolution data to allow in-depth analyses of intra- and inter-individual variability and context variability.[57-59] Especially, through the application of the FAIR principles, as suggested in *chapter 7*, we will be able to gain more and more detailed data of both the patients and their contexts unveiling the complex dynamics of a person's health. Consequently, observational data and designs become more and more useful for the personalization healthcare, which is one of the aims of this thesis and an important focus in health(care) research for the years to come. Considering the previous, in many cases evidence generated from RCTs and observational studies should be seen as complementary. For example, an intervention may be effective in a highly controlled study setting, but its effect may change once imbedded in the far more dynamic complexity of the real-world. As such, so called design triangulation where results from both observational and experimental studies are combined, could lead to additional insights. For example, in our observational study on risk stratified prehabilitation with patients opting for LSF we found a significant effect on postoperative outcomes. From these outcomes together with the knowledge that preoperative physical fitness is an important contributor to postoperative outcomes we can infer the importance of preoperative risk screening before offering patients the option to participate in a prehabilitation intervention. This insight would be useful to discuss in the light of the findings of the included RCTs in our meta-analysis in *chapter 2*. The included RCTs did not apply a preoperative risk stratification and thereby probably included patients with low and high physical fitness in the experimental and non-experimental arm of the RCT, thereby not targeting those patients that are in need of the intervention. An approach that probably decreased their potential to demonstrate the effectiveness of prehabilitation.

Therefore, we would like to advocate the reconsideration of the classical evidence pyramid (Figure 4A), with the revised pyramid as suggested by Murad et al. as a first step in the right direction (Figure 4B).[60] On top of the suggested revisions, a more egalitarian evidence pyramid integrated with the internet of FAIR data and services, should be considered. In the pyramid in Figure 4C, non-, quasi- and true experimentation are intertwined and evidenced generated from these research types are to be seen as complementary rather than superior and/or inferior. Moreover, evidence generation is supported by the internet of FAIR data and services and is therefore added as a background layer.

Implications for research I: On a case by case basis, observational research should behold the same level of evidence as RCTs. This advocates the use of design triangulation, combining non-, quasi- and true experimental studies.[58, 61] Design triangulation may produce complementary evidence for a certain hypothesis rather than being mutually

exclusive. This approach should be incentivized by both universities, journals and funding bodies alike.

Figure 4. A. classical evidence pyramid showing the hierarchy of research validity, B. revised evidence pyramid [60] and C. design triangulation.



Besides the fact that observational designs have some specific advantages for the personalization of healthcare, advancements in statistics and good data management have made observational data more reliable. For example, in *chapter 4* we used an interrupted time series analysis (ITSA) together with propensity score matching to show a causal relationship between prehabilitation and reduced time to functional recovery. The design is called an ITSA because the intervention is expected to "interrupt" the level and/or trend of the outcome variable—serially measured over time—subsequent to its introduction.[62] However, the validity of this design may be limited by data-driven model specification and lack of explicit control for confounding factors, which do not play a role in RCTs. The limitations of ITSA by confounding can be overcome by finding a control group that is comparable on possible confounders by propensity score match-

ing, as was done in *chapter 4*.[63, 64] Moreover, a priori model specification, based on clinical expertise – here represented by level change model - rather than data alone, decreases the likelihood of overestimation of the effect.

Next to the statistical possibilities, more and more attention is drawn to good data management. Often data (re)usability of any kind (in observational or experimental data collection) is not incentivized, leading to a loss of valuable knowledge and reduced return on invest of public funds. The basis of good data management is proper collection, annotation, and archival of data to produce data of sufficient quality to perform analyses. The FAIR principles have therefore been introduced to promote good data management by making data Findable, Accessible, Interoperable and Reusable. Implementing these principles in research and clinical data management enables the (re)use of these data worldwide, leading to an increased value of any collected data, as was shown in *chapter 7*. For example, by not making data FAIR, annually around €100 billion is estimated to be lost globally, because the information of those data could not be used for innovation and research.[65] Moreover, making data FAIR can also increase productivity of scientists. During the course of this thesis alone, numerous hours have been spent on manually extracting and wrangling data. If these data would have been FAIR at the source, for example within the EHR system used in the research in this thesis, manual data handling would largely had become superfluous. One may read this as a general plea for making data FAIR within the coming decade. Currently, important technical, social, ethical and legal innovations are being developed and validated internationally to make this already partly up and running transition possible.[18]

Implications for research II: Sophisticated statistical methodologies such as an interrupted time series analysis (ITSA) are viable methods for providing causal inference, when randomization is not possible or desirable. In combination with good data management, these innovative "tools" can provide high quality evidence and strong causal inference in observational studies when applied correctly.

Implications for research III: FAIR guiding principles provide guidance on how to apply data management in research practice and should be implemented in all research. We infer that by applying these principles quality and (re)usability of data, publications and their impact on clinical practice and society can be greatly improved.

Ad 2) Handling Missing Data

Inherent to research with real-world (observational) data is the issue of "missing data". Due to the relatively high registration burden perceived by both clinicians as well as patients, who often have to fill in long lists of questionnaires because of obligatory professional administration, we regularly end up with missing or incomplete records.

This may result in reduced study power. To overcome power fallout, we have to consider the use of the many sophisticated imputation techniques which can (up to a certain point) effectively deal with incomplete datasets. In *chapters 2, 5 and 6* we applied multiple imputations (MI), which is in often a superior strategy for handling missing data of independent variables as compared to complete case analysis.[66, 67] In prediction modelling this is a highly preferred method, as it allows the incorporation of extra information from incomplete cases in the model that otherwise would have been omitted. [68] One has to bear in mind that there are different mechanisms of missingness (missing (completely) at random or missing not at random) and in which variable missingness appears (i.e., dependent or independent variable) which need to be considered. MI is a valid and preferable approach for all missing at random (MAR) mechanisms.[69] Though, when data are missing not at random (MNAR), MI may give biased results.[69] Thus, when applying MI one needs to carefully consider the mechanism of missingness, if there are any auxiliary data (data not included in the model) and which data are missing. Evidently, despite all the great possibilities of MI, the best option always is to try to get all data needed.

Implications for research IV: Multiple imputation is often the superior strategy for handling missing data in prediction studies when data are missing at random and should therefore be the preferred method. However, before applying MI one should carefully review the mechanisms of missingness (at random or not) and whether it fits the research goal.

Ad 3) Generalizability of Results

In *chapters 4, 5, 6 and 7* we make use of data collected from patients in the Netherlands, mainly in one academic center. This may prohibit generalizability of our results outside this center or outside the Netherlands. Nonetheless, we aimed to include a population in our research that closely resembles those patients seen in clinical practice. Thus, few inclusion criteria were used, leading to a relatively heterogeneous population included in our studies. This heterogeneity may improve generalizability of our results to other hospitals and help to study the interindividual differences between patients, improving the personalization of healthcare. In *chapter 5* we externally validated our prediction model in a population from a different, non-academic hospital in the Netherlands. The results showed that baseline characteristics were similar and there was little fall out (Δ AUC= -0.06) in the performance of the prediction model. This gives specific presumptive evidence that the population included in our studies is at least generalizable to the Dutch population and probably also to the Western European population of patients eligible for LSF.

Implications for research V: Results of this thesis should be interpreted with the constrained generalizability of the results in mind. Our results will be mainly applicable to Western European healthcare systems and should be ecologically validated in different countries, settings and/or populations.

WHAT IS NEXT

At the start of this thesis, we formulated a central mission: improving the health of people opting for elective lumbar spinal fusion (LSF) by adopting ongoing advancements in healthcare towards an increasingly predictive, preventive, personalized and participatory (P4 medicine) perioperative healthcare approach. For our prospective research we reformulated our mission based on Mazzucato's book "Mission economy: a moonshot guide to changing capitalism" and the National mission driven innovation policy:[70, 71] In 2026 all high-risk patients opting for a LSF in the MUMC+ are provided with state-of-the-art evidence based and evidence generating prophylaxes, care and cure during their entire perioperative journey, thereby preserving and/or improving their health and daily functioning and lowering peri-/postoperative complications with at least 10% and an on average quality of life improvement of 20%. The results of this thesis have already contributed to and will continue to contribute to achieve this mission, through future research endeavors linked to this thesis. We will discuss the most relevant and promising future research prospects here.

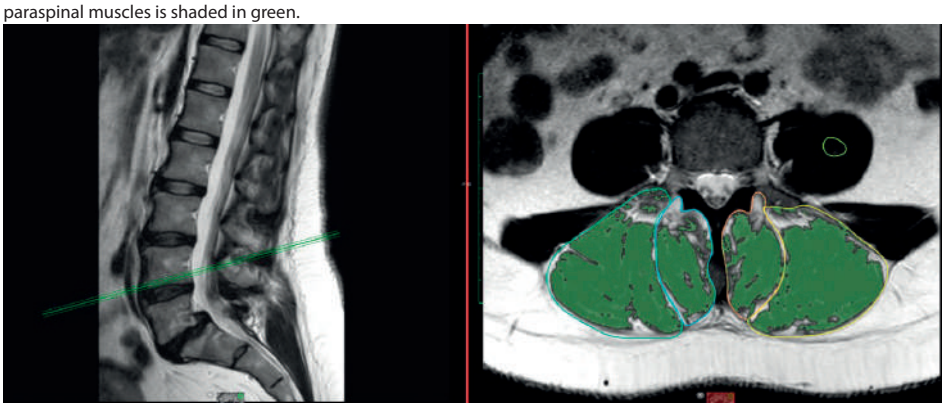
Increasingly Personalized Perioperative Healthcare for Patients Opting for LSF

One of the core objective in this thesis, as it is in the medical field in general, is individualizing care with the patients to better fit their needs.[72] By the activities as described in *chapters 4 and 5*, we developed methods to enable a more personalized and efficient patient journey with patients considering LSF. Moreover, we also acknowledged there is still room for improvement in the accuracy of the prognostic tools, as well as the perioperative care interventions. Due to our growing understanding of what features contribute to health and disease in this population and the complexity of the interaction between these features, continuous optimization of diagnostics, prognostics, monitoring and treatment strategies is attainable and thus ongoing.

We are currently exploring two prospects: I) finding new predictors to further improve prediction accuracy of our prediction tool, and II) moving towards a decision support system throughout the patient journey of patients considering LSF. One of these promising predictive factors is the proportion of fatty infiltrates in the paraspinal muscles.

Through automatic analysis of preoperative MRI imaging, using AI (CoLumbo, SmartSoft healthcare Varna, Bulgaria we are currently able to immediately calculate the proportion of lean muscle versus these fatty infiltrates throughout the lumbar spinal muscles. Figure 5 shows an example of such a measurement of lean muscle tissue on a single sagittal and transverse MRI slide between the 4th and 5th lumbar vertebra. In this figure, the lean muscle tissue is shaded in green and the cross sectional areas of both the right and left m. multifidus and m. erector spinae are delineated in blue and orange. This area of lean muscle tissue is also known in literature as functional cross sectional area (FCSA) and is a well-established predictor of morbidity in patients with diverse types of cancer. [73, 74] Moreover, it is a factor associated with persistent low back pain (OR 9.2; 95% CI 2.0–43.2).[75, 76] However, its predictive value for postoperative outcomes after LSF is still unknown.

Figure 5. Lumbar sagittal (right) and transversal (left) MRI image. In the transversal image the lean muscle tissue of the paraspinal muscles is shaded in green.

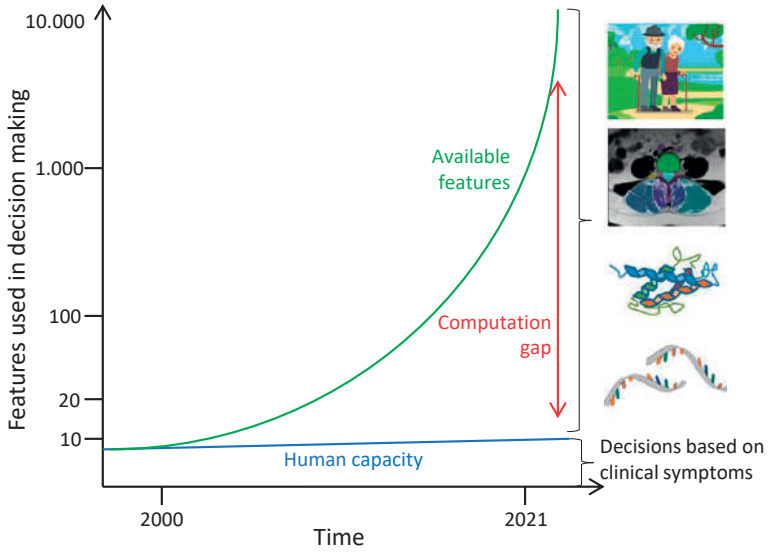


Next to this potential predictive factor, other variables may be of interest. Features that may be of interest and have only sparsely been explored are: diet and use of medication; high resolution features, as used in 'omics' research genes, metabolites, proteins; and features from the full range of the ICF-schema, including often omitted participatory and environmental features (e.g., living environment, societal roles, social support). As low back pain is a complex and multifaceted phenomenon, we believe it is only feasible to improve on prediction when combining features from the whole human exposome, whereas now we limit ourselves mainly to the internal human exposome or biomedical paradigm.[77]

From the latter we can infer, that decision making by the professional(s) preferably relies on a large number of known and relatively or absolute unknown features in order to make the most accurate treatment decision. Moreover, the number of treatment op-

tions is increasing, making it more and more difficult to make the right shared decision with the right patient at the right time.[78] Considering our limited cognitive capacity, we need to rely on prediction models to process the growing amount of features and support the decision making process and bridge this 'computation gap' (Figure 6).[79] By doing so, prediction rules will increasingly play a larger role in shared decision making, be it in clinical practice, in the context of patients or both.

Figure 6. Visualization of the computation gap in decision making. Whilst the blue line represents the number of features humans are able to process whilst making a decision, the number of features available (green line) is growing exponentially. Thus, a 'computation gap' is hypothesized (red arrow) between the amount of information (features) that are available and what we are able to consider as humans whilst making a decision. (Adapted from Abernethy et al. 2010)[80]



Towards the Internet of FAIR Data and Services and Open Science

To incorporate the ever growing amount of data in our decision making, we need to reconsider how we manage data in health and healthcare, which are currently locked away in many different data siloes. Luckily, technologies for acquiring, storing and analyzing real-world big data in the context of health and healthcare are rapidly developing. These technologies are able to help us make better use of our data and that of the many others and bridge the aforementioned computation gap. One of the key developments are the FAIR guiding principles, which are internationally recommended by the G20, European Commission and the European Open Science Cloud. Following these principles would ultimately lead to the transition of the nowadays globally used Internet of things towards the Internet of FAIR data and services. This future internet where data far more divergent than just health and care, can be found, accessed, and (re) used by anyone under prespecified conditions.[15] Consequently, people themselves,

health care professionals and researchers may be granted permission to have access to all features available for decision support.

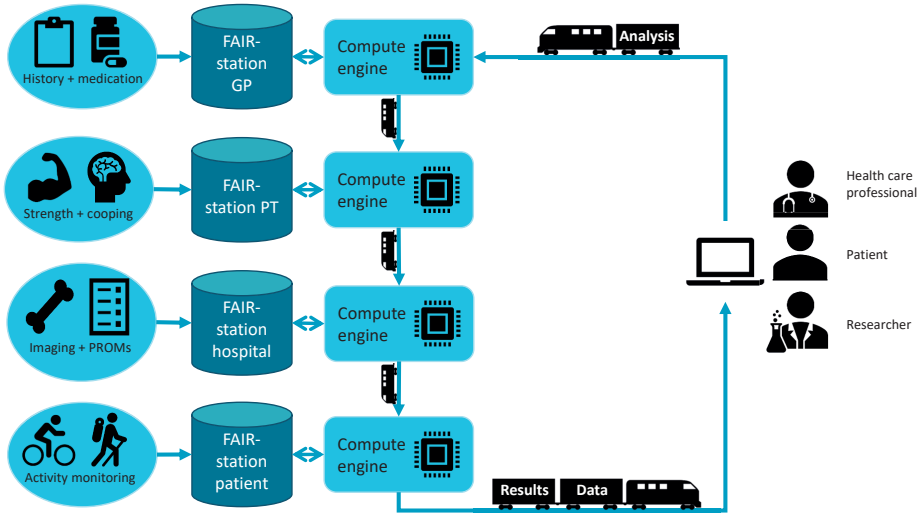
Before the Internet of FAIR data and services can reach its full potential with all, the FAIR principles need to be applied not only in research data, but also in clinical practice and preferably in the "entire exposome". Although this transition is ongoing, we are still at the forefront of FAIRifying real-world data. In *chapter 7* we took a first step in introducing FAIR and underlying digital technologies to (allied) health professionals. The next step in this process is to stimulate the uptake of these technologies, adopt existing and co-develop new community standards and methodologies necessary for their uptake. An important part in this process will be the introduction of functionomics in the 'omics' landscape. We are currently initializing this introduction by building a functionomics learning community and link this community with other important communities and movements within the Netherlands, such as HealthRI, X-Omics and the NL-AI coalition. With the introduction of functionomics, data on person's daily functioning - as can be classified with help of the ICF - become available for high-throughput analysis. As in other 'omics' initiatives, we expect that functionomics will lead to important breakthroughs in personalized prevention as well as in personalized medicine.[50, 81]

Change in social behavior of the current health, healthcare and research systems is just as important as technological developments to achieve the undeniable potential of the internet of FAIR data and services. The current system does not provide much means for sharing knowledge and (research) data. This holds true for the current research culture, as there is for instance much competition in publication, citation, gaining proper funding, et cetera. As a consequence, fear of the loss of research credit makes researchers less inclined to share data.[82] By creating an inhospitable environment for data sharing, valuable knowledge is isolated, leading to reduced return on energy, intelligent and monetary investments of the people providing these data, be it as a patient or a professional, and thereby also a loss of public money put into research. Therefore, governments, funding bodies and society should heavily incentivize FAIR data and knowledge sharing, like for instance Dutch funding bodies as NWO, SIA, ZonMw, Top Sector LSH (Health~Holland) do already for a couple of years. These precautions will increase data sharing practices and thereby facilitate the efficient use of data for increasing the amount of knowledge that's probably always "in there" and resulting from scientific research. Luckily, also initiatives like the European Open Science Cloud and the GoFAIR initiative promotes this way of working and has found endorsement by national and international governing bodies, like G20 and EU.[15] Examples as WODAN may fuel and inspire at the macro level all stakeholders, partners and 'inhabitants of the global research community and also the public at large to adopt these new concepts. In our intended learning community, we will implement at a micro level, as much as possible open science principles in combination with citizen science to enable free – under certi-

fied conditions – use of functionomics data to those that apply to the inherited moral, ethical and juridical rules and regulations.

The implementation of FAIR data is also a first step towards federated learning, which at a first glance takes away most ethical reasons for not sharing privacy sensitive data (Figure 7). Federated learning can, through privacy by design and with established ethical, social and legal policy, enable the analysis of large amounts of FAIR datasets with only aggregated results leaving the data silo. Bear in mind here: the data does not leave the silo, which means people do not have to share any directly traceable data. People just have to consider to provide access of an algorithm to their own data silo and to those data that they are willing to share with the algorithm builder, again: under prespecified conditions. This federated infrastructure, in the context of health and care named the Personal Health Train (PHT), is an example of the application of this technology.[18] We are currently implementing a PHT infrastructure to link data from different hospitals important for our constructed prediction model for patients considering LSF, but also for other orthopedic and physiotherapeutic data. Over time, visiting data silos through these technologies and principles will hopefully assist in building the internet of FAIR data and services and consequently become the norm in our learning community, globally and thereby also in the healthcare settings. This, in our opinion, will facilitate new knowledge discovery and exponentially increase the value of data.

Figure 7. Example of federated learning, sending an algorithm to different FAIR data stations. The algorithm locally computes results, without data leaving the silo. Consecutively, aggregated results are sent back to the person who sent the algorithm.



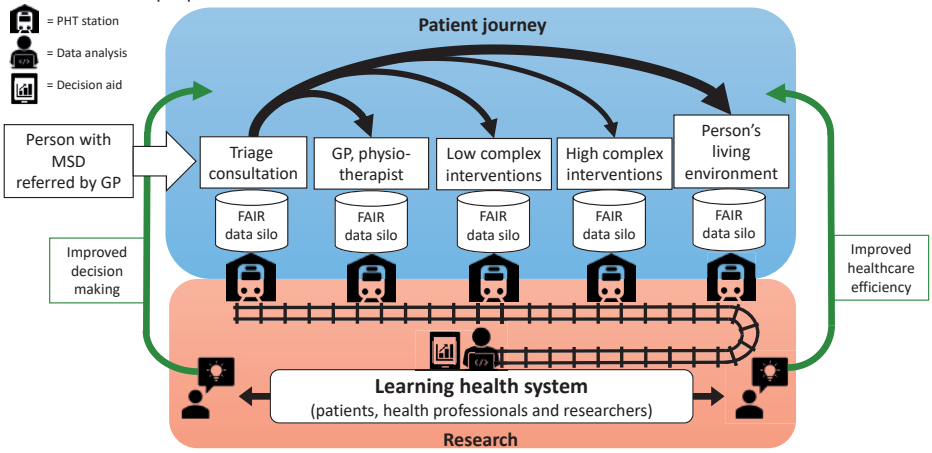
Building a Continuously Learning Health System

Rapid availability of entrance to data and thereby information through the Internet of FAIR data and services, the PHT and consequently the increasing speed of (scientific) discovery poses a problem. Increasing speed of evidence generation implies that rapid uptake of evidence in healthcare practice is important. A transition from a traditional siloed healthcare system towards a regional continuously learning communal health system is a viable solution.[83] A learning health system is defined by the Institute of Medicine as follows: "A learning health system is one in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the care process, patients and families active participants in all elements, and new knowledge captured as an integral by- product of the care experience".[83] Here the technologies introduced in *chapter 7* and discussed in the previous paragraph play a key role, as storing, integrating and analyzing data in silo's from different sources. In turn this feeds the learning health system with much needed information on the functioning of the system. This information can be used to test a hypothesis, which can be translated into (clinical) practice.[84] In the Maastricht-Heuvelland region we are currently building such a system called "Het Beweeghuis" (Figure 8). This system comprises interdisciplinary collaboration between all stakeholders (i.e., people with musculoskeletal disorders and their informal support, healthcare professionals, researchers, healthcare insurance and policy makers) in the health and healthcare process with patients suffering from degenerative musculoskeletal disorders, including those with chronic low back pain eligible for LSF. Here we align people, resources, services, knowledge, technology and reimbursement to achieve the quadruple aim: better outcomes for patients, improved experiences of patients, improved experience of professionals, and at the lowest cost. We do this by focusing on healthy lifestyle changes, and also by investing in best evidence treatment and experimental (de-)implementation of interventions. Moreover, we are currently exploring new ways of outcome based reimbursement of treatment in the system, through bundled payment methods.[85] By transitioning towards a continuously learning health system, we aim to achieve a future savvy health system.

GENERAL CONCLUSION

In this thesis we built upon the many recent advances from a successful world of research in perioperative health and healthcare. We made use of this existing knowledge by translating it to the context of perioperative health and healthcare with people opting for LSF and developed new methods and tools aiding in decision making, risk

Figure 8. The envisioned "Beweeghuis" concept as a continuously learning health system. Not depicted here are the links with data silos from the municipality, healthcare insurers and private parties which collected data that may be relevant as well to the health of people with MSDs.



Abbreviations: FAIR= findable, accessible, interoperable and reusable, MSD= musculoskeletal disorders, GP= general practitioner.

management and good data management that should in turn be ecologically validated in the future.

Building on the background information of current clinical practice and evidence on prehabilitation strategies from *chapters 2 and 3*, we made discoveries and (re)introduced concepts that can help pave the way to truly personalized health and healthcare with people opting for LSF. The importance of preoperative physical fitness as a predictor that can be modified before surgery with patients opting for LSF is highlighted in *chapters 4 and 6*. Thus, adding to the knowledge of existing phenotypes using mainly biomedical features, as used in *chapter 5*. Furthermore, we made a case for the effectiveness of personalized medicine in *chapter 4*, which showed that prehabilitation with a select 'high-risk' subgroup of patients can be effective. We brought together the concepts of personalized medicine and the biopsychosocial approach in *chapter 7* and showed how we can apply both concepts to real-world data by introducing a new 'omics' type called functionomics, potentially improving people's health, using the latest technological advances. With these findings we have moved towards a more and more predictive, preventive, personalized and participatory (P4) perioperative care pathway and thereby provided means for improved health of people opting for elective LSF, now and in the near future.

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Impact paragraph

For this thesis we set a central mission: improving the health of people opting for elective lumbar spinal fusion (LSF) by adopting ongoing advancements in healthcare towards an increasingly predictive, preventive, personalized and participatory (P4 medicine) perioperative healthcare approach. The impact of knowledge gained from this thesis contributes specifically to improving health of people opting for LSF. In a broader sense it contributes to the increasing knowledge on optimal perioperative health and healthcare with patients opting for elective surgery. *Chapter 7* also aids in increasing the value of yet underutilized functionomics data, which can be collected in many contexts, populations and countries, and helps (allied) health professionals apply the FAIR principles. Moreover, the knowledge gained in this thesis also is in line with the motto of the Dutch Top Sector Life Sciences & Health: "Vital functioning citizens in a healthy economy" and invests in the ministry of health missions for the societal challenge of Mission Driven Top Sector and Innovation Policy of the Cabinet: "Health and care".[1]

SCIENTIFIC IMPACT

The results of this thesis contributed to two major shifts in research paradigms: I) combining both the biopsychosocial research paradigm, and II) from closed science towards open science and FAIR data.

I) Considering Functioning in Patients Opting for LSF

Throughout this thesis we focused on functioning of patients opting for LSF. We aimed to incorporate this biopsychosocial view in the social and clinical setting of patients opting for LSF as we believe it contributes to eliciting new scientifically and clinically relevant knowledge on top of the evidence generated from the biomedical paradigm. We did so by establishing a prediction model incorporating patient's perceptions, capable of predicting postoperative outcomes after LSF. Moreover, we found that patients' physical functioning is an important additional predictor capable of improving the predictive power of postoperative outcomes after LSF. This enabled us to identify multifactorial risk profiles that could aid in the personalization of the patient journey. Next, within a community based prehabilitation program we focused on functional exercise training that was tailored to the patients' preferences and involved their social context to accomplish a more participatory exercise regime. This evidence shows that the biopsychosocial approach can contribute to new evidence in the perioperative pathway of patients undergoing LSF.

II) New Data Infrastructure to Stimulate Uptake of Open Science in a New Field

In *chapter 7* we introduced functionomics as a complementary 'omics' initiative. We applied the FAIR and Open Science principles, which are internationally advocated data management principles that already have had been applied successfully in 'omics'-initiatives.[2] Here we wanted to: a) stimulate the adoption of functionomics and Open Science in the field of (allied) health professionals, and b) apply the "FAIR-principles" using the WHO-nomenclature (ICF) to make functionomics data machine actionable. One of the ways functionomics have been brought in action, is by contributing to a book chapter in a Dutch publication on the use of the ICF, in which we have given an introduction on how data science can be applied to the biopsychosocial data.[3] This book is meant for healthcare professionals, students and IT professionals alike. Secondly, we developed an example functionomics ontology and a tutorial to introduce data scientist and healthcare professionals to this concept and published this open access on GitHub; https://github.com/ERCJanssen/Functionomics. To realize FAIR functionomics data, we will initialize a functionomics learning community that serves to get the aforementioned concepts more actionable nationally and internationally. Implementing the FAIR principles is already impacting the way we conduct science and the daily practice of researchers. Moreover, functionomics specifically can include citizens via ways of citizen science in our ambitions and our learning community. Researchers will be able to spend less time curating data from different sources and more time FAIRifying our own data and analyzing data from different FAIR sources. Consequently, a shift in values and attitudes of, amongst others, researchers is inherent to accomplishing the internet of FAIR data and services, on which we want to make our data available as much as possible. Even more so, we want to make data-use more a mutual common ground for all relevant stakeholders. By shifting towards the Open Science principles, functionomics will be operationalized for global use and knowledge generation, as part of the 'omics-family', making use of the Internet of FAIR-data and services in the near future.

National and international knowledge dissemination of the results of this thesis in the scientific community was realized by (inter)national publications, participation in learning communities and conference presentations in the spinal, orthopedic, physiotherapeutic and health technology research community. Moreover, I have had the opportunity to coach several bachelors and master students from various programs (i.e., medicine, physiotherapy sciences, human movement sciences and health sciences) and share and build up our knowledge with them. Through collaboration and knowledge dissemination in the national Better in, Better out (BiBo) community of practice comprising representatives from 14 Dutch hospitals, the local orthopedic science meeting

and FAIR data community, other practitioners and scientists were updated on the latest developments on perioperative care research in the population opting for LSF.

Prehabilitation in general has gained national attention through the parallel Fit4Surgery initiative from the medical specialists initiated recently, where patients from different types of elective surgery are trained before surgery, to optimize postoperative outcomes and reduce complications.

SOCIETAL IMPACT

I) Considering Functioning in Patients Opting for LSF

Impact on patients: On a niche level our results impacted the perioperative patient journey with people opting for LSF in the Maastricht University Medical Center (MUMC+). The patient journey changed, at first through the implementation of a preoperative risk screening and the development and execution of a prediction tool with each and every patient and, a year thereafter, the implementation of a prehabilitation intervention and the scientific evaluation of its preliminary effectiveness. Preoperatively this may have had a positive influence on patient expectations about surgery and postoperative recovery, as well as about their skills in self-management and joint management with their relatives and the formal caregivers. The change towards a more proactive and participatory care pathway means that patients and their social support became more actively involved in their health and care process and get the opportunity to improve their own perceptions, performances (through prehabilitation) and their outcomes. As a result, the functioning of patients in their own living context seems to be impacted in a positive direction and plays a more central role throughout the patient journey.

Impact on healthcare professionals: The results of this thesis have impacted the culture, habits and daily routines of healthcare professionals provided healthcare to patients opting for LSF in the MUMC+. Healthcare professionals have moved towards a more and more P4 based work routine, which emphasizes collaboration with patients and their social support throughout the patient journey.

Monitoring is a central activity in the diagnosis, prognosis and management of all patients and their relatives in a perioperative care pathway and is a substantial part of the workload.[4] During the course of this thesis different methods of standardized professional monitoring throughout the patient journey were implemented. A preoperative risk screening was implemented to diagnose the level of physical fitness with a patient prior to surgery. The resulting prediction tool from *chapter 4* gives patients and surgeons means to better inform each other about on what outcomes to expect before, during

and after surgery. Moreover, early risk screening provides patients, surgeons and physiotherapists with the opportunity to assess the need for interventions like prehabilitation. Frequent monitoring during the patient journey can help quickly identify facilitators and barriers and guide precautions to be jointly considered. The dissemination of our research results also stimulated uptake of standardized preoperative screening and prehabilitation with patients undergoing LSF in two other Dutch hospitals and has also sparked the interest of others.

The implementation of the prehabilitation intervention implies at the same time that outpatient physical therapists are required to update their knowledge on this type of intervention, but also to extend their focus from 'just' the postoperative symptom based therapy towards adding the preoperative prophylactic therapy. We trained outpatient physiotherapists in the region of Maastricht-Heuvelland to implement this innovative vision, culture and professional habits during the accompanying prehabilitation intervention. Next, it requires surgeons and clinical physiotherapists to better inform and support patients and their relatives about the importance of preoperative physical functioning before undergoing major surgery like LSF.

Impact on policy: Due to its low risks (no adverse events registered), estimated low costs (average of €40 per physiotherapy session) and high expected value, national uptake of such prehabilitation interventions is advocated when scientific evaluation is an embedded part of this implementation. A major issue preventing uptake of prehabilitation on a national scale is the need for a trained outpatient physiotherapy network and reimbursement of proactive preoperative prevention strategies such as prehabilitation. Insurance companies need to be convinced to reimburse these novel interventions, because of the favorable results at relatively low cost. Costs are estimated at €240-320 per patient (based on 6-8 preoperative training sessions with a physiotherapist), which compared to LSF surgery (about €17.000) is extremely low. Luckily preoperative interventions, like BiBo, are getting more and more national and also international attention and are likely to become supported by these healthcare insurers, showing their willingness to support this approach that has gained evidence throughout the recent two decades. Here future cost-effectiveness analysis via preferably embedded scientific studies may provide sufficient evidence to enable national implementation.

II) New Data Infrastructure to Stimulate Uptake of Open Science in a New Field

One could argue that it is our civil duty to contribute to advancing health and healthcare research for the greater good. Thereby, we should make 'our' data available to those whose business it is to innovate in health and healthcare.

Impact on patients: The new data infrastructure may have some important consequences for patient. Making data FAIR means these privacy sensitive health data of patients will become available for (re)use in an international research community. FAIR is not equal to Open: The 'A' in FAIR stands for 'Accessible under well-defined conditions'.[5] The question remains however who is the 'owner' of the data and what role patients should have in data usage and consent. For functionomics data this is especially important as these stem from the most important stakeholder that collect such data: the people at large. In general, a more data driven society requires citizens to form an opinion and participate in the policy making on the use of their data in health and healthcare research.

Impact on healthcare professionals: The same issues with regards to the new data infrastructure hold true for healthcare professionals as for patients and their relatives. They can and should play an active role in collecting data and making them available for (re) use to researchers, and in policy making.

Impact on policy: Through innovation and legislation this new way of data use should be embedded in society, where people at large preferably play an active role in data ownership and usage policy. Therefore, we promoted the application of the FAIR principles in a way that enables citizens (in whatever role they have), healthcare professionals and researchers to participate in this transition. Nowadays, from a policy standpoint, exploiting the economic benefits of health, healthcare and research data and its resulting knowledge is emphasized through a strong focus on intellectual property, like invention disclosures, patents, licenses or private party investment. Emphasis on the economic value of data and scientific knowledge alone may hamper the transition towards 'open science' and key scientific values as transparency and sharing of knowledge.[6] Moreover, open science has specific economic and social benefits, by creating higher efficiency of science with important spill over to innovation systems.[7] Especially on the long term, open science may yield high economic and health gain by enabling others to use and reuse scientific data and knowledge.

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Summary

People considering invasive surgery like lumbar spinal fusion (LSF) expect that undergoing such a major life event will ultimately improve their health and daily functioning. For people with low back pain LSF is often seen as a last resort, when conservative treatment modalities have failed to relieve their complaints. There are substantial health risks involved with undergoing LSF, such as (temporary) elongated and worsened deconditioning and pre-, intra- and postoperative complications. Moreover, despite recent advances in surgical and anesthesiological techniques reducing intraoperative stressors, some patients still may not benefit from undergoing LSF. The success rate of LSF described in the literature is variable: on average 56% of patients who opted for LSF experienced a clinically relevant reduction pain reduction two years after surgery. Consequently, there is plenty opportunity for improving preoperative decision making and perioperative care for patients considering LSF.

In this thesis our mission was to improve the health of people opting for elective lumbar spinal fusion (LSF) by adopting ongoing advancements in healthcare towards an increasingly predictive, preventive, personalized and participatory (P4 medicine) perioperative healthcare approach. We achieved this mission, by building on the ongoing transformation and recent discoveries in P4 health and healthcare research in other surgical and technological fields, and adapting these to the context of people opting for elective LSF. We divided this thesis in three themes: I) Preventive and personalized perioperative risk management strategies; II) Innovative methods to guide evidence based shared decision making within the perioperative healthcare pathway, and; III) First steps towards integration of modern real-world perioperative data technology and expanding the 'omics-family' (e.g., genomics, proteomics, metabolomics), by introducing the omic of a person's daily functioning: functionomics.

I) Preventive and Personalized Perioperative Risk Managment Strategies

The perioperative care pathway can contribute to improving perioperative health and daily functioning of patients undergoing LSF. Through prehabilitation interventions, the risks of undergoing major elective surgery can probably be mitigated, as substantiated in populations undergoing cardiac, abdominal and joint replacement surgery. In the systematic review of the current literature with meta-analysis in *chapter 2* we investigated if prehabilitation of any kind was also effective with patients opting for lumbar spine surgery. We discovered that non-risk stratified preoperative cognitive behavioral therapy (CBT) was no more effective than usual care in the pooled results form 13 studies with a total population of 888 patients. The certainty of these findings, based on the grading of recommendations assessment, development and evaluation (GRADE) framework, ranged between very low and low. These low scores could mainly be attributed to the high risk of bias, imprecision of the found effect and small sample size

of the studies. Only two studies (not included in the meta-analysis) described a single non-risk stratified preoperative exercise intervention, which showed a positive effect on short term results (≤6 weeks postoperatively). Due to the uncertainty of the evidence on the effectiveness of preoperative CBT, the results of this systematic review are inconclusive. At the same time we could make several general and specific recommendations to improve future studies in this context, for example by applying preoperative risk stratification, and through that, ensuring the inclusion of patients who are likely to benefit from prehabilitation.

To identify components of the current perioperative care pathway that should be improved, first we intended to describe the current perioperative care pathway. In *chapter 3* we performed a nationwide survey study to determine the current state of expert perioperative physiotherapy care for patients opting for LSF in 2014. Twenty-eight (82% of all invited therapists/hospitals) expert clinical physiotherapists from individual hospitals completed our survey. In six hospitals (21%) they provided preoperative physiotherapy care services to patients opting for LSF. The preoperative services mainly consisted of group-based information sessions (100%) and preoperative assessment (67%). Postoperatively most patients participated in inpatient physiotherapy as part of standard care (79%), sometimes only when the patient required such care (14%) and in two hospitals it was unclear which patients received postoperative inpatient physiotherapy. Postoperative physiotherapy focused on safe functioning and information provision (82-96%). The content of postoperative information on the resumption of daily activities was extremely variable between respondents. A minority of physiotherapists used any type of measurement instrument to monitor patient's (functional) recovery (4-18%). Postoperative outpatient physiotherapy was mostly prescribed if deemed necessary. However, it was unknown on what assumptions necessity of providing postoperative outpatient physiotherapy care services was based. Conclusively, we envisage that there is substantial room for improvement in the perioperative care of physiotherapists towards a more evidence and at the same time P4 based perioperative physiotherapy care pathway with patients opting for LSF.

In 2017 we started to transform the perioperative care pathway in the MUMC+. Firstly by implementing an evidence based preoperative risk assessment, evaluating the preoperative physical fitness with patients opting for LSF. Secondly, from November 2018 onwards, patients that were identified as being at high risk for delayed postoperative recovery were offered a prehabilitation intervention. The prehabilitation intervention comprised a community based functional high-intensity interval training (*f*-HIIT) program, combining the high-intensity interval training principles with functional training, where patients together with their therapist decide on exercises that best fit the patient's individual physical functioning needs in their context. In *chapter 4* we determined the feasibility, safety and preliminary effectiveness of this preoperative

f-HIIT program with people undergoing LSF that were identified as being at high risk for delayed postoperative recovery. From February 2017 till February 2020, 135 patients opting for LSF participated in the preoperative screening. From this population 46 patients were identified as high risk (34%). Of the 23 high-risk patients screened after November 2018, 11 (48%) participated in the *f*-HITT program. None of these participants experienced adverse events from the training and only one patient missed one training session of a total of 74 training sessions. All patients participating in the *f*-HITT program improved their preoperative fitness, on average with 21.2%, and obtained postoperative in-hospital functional recovery faster (measured with the modified Iowa Level of Assistance Scale) compared to propensity score matched untrained high-risk patients (median 4.5 vs. 7.5 days; P= 0.013). Therefore, we concluded that the *f*-HITT program provides high-risk patients opting for LSF feasible and potentially effective means for improvement of their preoperative fitness and in-hospital functional recovery time.

II) Innovative Methods to Guide Evidence Based Shared Decision Making Within the Perioperative Healthcare Pathway

Prediction tools can help patients and surgeons in the difficult process of shared decision making before opting for LSF and can help guide the personalized perioperative care pathway. They do so by calculating the probability of a certain outcome for an individual patient, based on a set of variables from that patient. We developed and externally validated a clinical prediction tool able to predict the probability of achieving a clinically relevant pain reduction one to two years after LSF in *chapter 5*. This prediction tool was developed using preoperative patient characteristics and patient reported outcome measures (PROMs) of 202 patients, expected to have prognostic value by orthopedic- and neurosurgeons. We used logistic regression with backward elimination to develop the prediction algorithm. The final model showed patients had a higher probability (odds ratio [95% confidence interval]) of achieving a clinically relevant pain reduction if they were non-smoking patients (0.41 [0.19-0.87]) with lower BMI (0.93 [0.85-1.01]), short pain duration (0.49 [0.20-1.19]), low educational level (0.46 [0.19-1.12]), less comorbidities (4.82 [1.35-17.25]), higher predominant pain scores (1.05 [1.02-1.08]), better functioning (0.96 [0.93-1.00]) and better mental health (1.03 [0.10-1.06]). This algorithm was then externally validated on data of 251 patients of another hospital, and yielded an area under the curve (AUC) of 0.68. To easily implement this model in clinical practice we transformed the algorithm into a nomogram, which can be filled in by patients and surgeons during the decision making for LSF to estimate their chance of achieving a clinically relevant pain reduction and use this information in their decision.

The AUC of 0.68 of the externally validated prediction model means there is still a proportion of variability in postoperative outcomes after LSF which cannot be explained by the variables in the model. To improve the AUC we should try to identify new predic-

tors able to improve the AUC and thereby the prediction accuracy. Therefore, in *chapter 6*, we explored if preoperative physical fitness, as measured in the preoperative risk assessment, could contribute to predicting postoperative outcomes after LSF. In the preoperative risk assessment aerobic capacity, back muscle strength, flexibility, motor control and functional capacity were measured. We used a machine learning variable selection algorithm, called random forest, to try to identify stable associations between these preoperative physical fitness variables and short- and long-term postoperative outcomes in 77 patients undergoing LSF. We found that three physical fitness factors showed consistent associations with outcomes (i.e. in-hospital functional recovery, length of hospital stay and change in pain) after LSF: aerobic capacity, flexibility and muscle strength (Z-scores ranged between 2.8-13.5). Due to the strong associations of these factors with postoperative outcomes after LSF, these could probably improve the predictive accuracy of a prediction tool. As such, these parameters could aid in the preoperative shared decision making process before undergoing LSF. Moreover, physical fitness is a factor that can preoperatively be improved by implementing an exercise prehabilitation intervention, as proposed in *chapter 4*. Thus by adding physical fitness measurements to a preoperative risk assessment patients and surgeons may be able to make better informed decisions for or against LSF and when a patient's physical fitness is low they could improve their success probability by participating in a prehabilitation intervention.

III) First Steps Towards Integration of a State-of-the-art Real World Data Infrastructure

In this thesis alone we collected a large variety of data on person's functioning of over 600 patients and using a labor intensive process of manually copying these data into structured datasets so that they could be analyzed. The amount of data collected by and on a person's functioning worldwide is exponentially larger – multiple terabytes – and will only continue to grow. Within the fields of oncology, radiology and genetics, computerized analysis of high-throughput data or big data, is often referred to as 'omics' research and has already shown benefits for the personalization and optimization of healthcare, for example by eliciting new knowledge on tumor phenotypes and prediction models of cancer survival. Historically, these omics initiatives focus mainly on biomedical factors (e.g., genes, metabolites) or the internal exposome. However, health is heavily impacted by our daily functioning, personal and environmental factors (specific and general external exposome), as can be concluded from this thesis. The problem is that these data on daily functioning are often not machine actionable or openly available. Therefore, important information on people's health and its interaction with daily functioning remains hidden, potentially leading to suboptimal health, prevention and care.

Deriving the information currently locked away in these data can revolutionize personalized prevention and healthcare, improving health and life expectancy of not only patients opting for LSF but of all citizens. Therefore, we introduced functionomics as a new 'omics'-initiative defined as 'the analysis of high-throughput data on people's daily functioning' in *chapter 7*. Moreover, we showed how to apply the FAIR (Findable, Accessible, Interoperable and Reusable) principles operationalized through Semantic Web technology to make these data machine actionable in a use case of perioperative care with patients opting for LSF. We built a functionomics ontology, based on the International Classification of Functioning, Disability and Health (ICF) framework and constructed a federated data infrastructure that enabled outsiders to analyze our data. We advocate the investment in the proposed IT solutions for making functionomics actionable and to achieve more and more P4 based medicine leading to improved health of citizens, when and where needed assisted by likewise improved healthcare provided by professionals.

DISCUSSION & CONCLUSION

The general discussion (*chapter 8*) reflects on the findings of this thesis and their implications for clinical practice, methodological considerations, and future research prospects that build on the findings in this thesis. In general, we can assume that an increasingly P4 based approach shows a clear potential to improve the health and functioning of patients opting for LSF. Specifically, we have developed tools and services that are implemented in the perioperative care pathway of patients opting for LSF in the MUMC+ to move from a rather reactive one-size-fits-all approach, towards a more and more proactive personalized approach. These solutions have shown or can potentially improve the health of patients opting for LSF and are mostly ready to be implemented on a national scale. Moreover, we have proposed how to approach the integration of real-world data collection in standard perioperative care to make them (re)usable for research in a machine actionable way, by following the FAIR principles. If we continue on this path via the in the discussion recommended future research prospects, there is in our opinion great potential to achieve a future savvy perioperative care pathway with patients opting for LSF, not only improving surgical outcomes but improving their health in general.

S

Samenvatting

Mensen die een invasieve operatie overwegen, zoals een lumbale spondylodese, verwachten dat het ondergaan van zo'n groot life event op de lange termijn leidt tot een betere gezondheid en functioneren. Voor mensen met lage rugklachten wordt het verkiezen van een lumbale spondylodese vaak gezien als een laatste redmiddel, als andere conservatieve behandelingen geen uitweg bieden. Het ondergaan van een lumbale spondylodese gaat gepaard met substantiële risico's voor de gezondheid, zoals (tijdelijk) verslechterde conditie, vertraagd herstel en pre-, per en postoperatieve complicaties. Ondanks de recente vooruitgangen in operatie en anesthesiologische technieken die de intra-operatieve stressoren reduceren, heeft niet iedere patiënt baat bij een lumbale spondylodese. De succeskans na een lumbale spondylodese wordt in de literatuur beschreven als variabel: gemiddeld ervaren 56% van de mensen die een lumbale spondylodese hebben ondergaan een klinisch relevante pijnreductie twee jaar na de operatie. Er is dus nog voldoende ruimte om de preoperatieve besluitvorming en perioperatieve zorg van mensen die een lumbale spondylodese overwegen te verbeteren.

Onze missie tijdens dit proefschrift was het verbeteren van de gezondheid en het dagelijks functioneren van mensen die een lumbale spondylodese verkiezen door een in toenemende mate predictief, preventief, gepersonaliseerd en participatoir (P4) perioperatief zorgpad te adopteren. Deze missie werd geoperationaliseerd, door voort te bouwen op de recente voortschrijdende innovaties in P4 gezondheid en gezondheidszorg onderzoek in chirurgische en technologische onderzoeksvelden en deze te vertalen naar de context van perioperatieve zorg met mensen die een lumbale spondylodese verkiezen. Dit proefschrift is onderverdeeld in drie thema's: I) Preventieve en gepersonaliseerde risico management strategieën; II) Innovatieve methoden voor evidence based gezamenlijke besluitvoering tijdens het perioperatieve zorgpad, en; III) De eerste stappen richting integratie van moderne real-world data technologie in de perioperatieve context en het toevoegen van een nieuwe 'omics' (zoals genomics, proteomics, metabolomics), door het introduceren van de omic van het dagelijks functioneren: functionomics.

I) Preventieve en Gepersonaliseerde Risico Management Strategieën

Het perioperatieve zorgproces kan bijdragen aan het verbeteren van de perioperatieve gezondheid en het dagelijks functioneren van patiënten die een lumbale spondylodese verkiezen. Prevalidatie kan de risico's van het ondergaan van een grote electieve operatie waarschijnlijk reduceren, zoals gesubstantieerd werd in onderzoek met mensen die cardiale, abdominale en gewrichtsvervangende operaties hebben ondergaan. In het systematische literatuur onderzoek met meta-analyse in *hoofdstuk 2* hebben we onderzocht of prevalidatie ook effectief is bij mensen die een lage rugoperatie verkiezen. We vonden dat niet risico-gestratificeerde cognitieve gedragstherapie (CGT) niet effectiever

was dan standaard zorg in de resultaten van 13 gepoolde studies met in het totaal 888 patiënten. De zekerheid van deze resultaten, zoals beoordeeld met 'the grading of recommendations assessment, development and evaluation' (GRADE), varieerde tussen zeer laag en laag. Deze lage score werd veroorzaakt door het hoge risico op bias, de onnauwkeurigheid van de resultaten en de kleine groepsgrootte in de studies. Er waren slechts twee onderzoeken (die niet meegenomen zijn in de meta-analyse) die een enkele niet risico-gestratificeerde oefentherapie interventie beschreven en positieve resultaten lieten zien op korte termijn uitkomsten (≤6 weken postoperatief). Door de grote onzekerheid over de resultaten van deze systematische review, waarbij de effectiviteit van CGT werd onderzocht, zijn de conclusies niet onweerlegbaar. Wel konden we algemene en specifieke aanbevelingen doen om vervolgonderzoek in deze context te verbeteren, bijvoorbeeld door een preoperatieve risico stratificatie uit te voeren vóór inclusie in een prevalidatie interventie, en daarmee vooral patiënten te includeren bij wie een groot effect te verwachten is.

Om componenten te identificeren in het huidige perioperatieve zorgpad die verbeterd dienen te worden hebben we eerst het huidige zorgpad geschetst. In *hoofdstuk 3* hebben we nationale vragenlijst uitgezet om de huidige stand van expert fysiotherapeutische zorg, van patiënten die een lumbale spondylodese verkiezen, in 2014 te beschrijven. Achtentwintig (82% van alle benaderde fysiotherapeuten/ziekenhuizen) expert klinische fysiotherapeuten van verschillende ziekenhuizen hadden deze vragenlijst ingevuld. In zes ziekenhuizen (21%) werden preoperatieve fysiotherapeutische diensten aangeboden aan patiënten die een lumbale spondylodese verkiezen. Deze preoperatieve diensten bestonden voornamelijk uit groepsgebonden informatie sessies (100%) en preoperatieve testen (67%). De meeste patiënten kregen standaard postoperatieve ziekenhuis fysiotherapie aangeboden (79%), soms werd postoperatieve ziekenhuis fysiotherapie alleen aangeboden als dit nodig werd geacht (14%) en bij twee ziekenhuizen was het onduidelijk of en wanneer patiënten postoperatieve ziekenhuis fysiotherapie kregen. Postoperatieve fysiotherapie concentreerde zich vooral op veilig functioneren en informatie voorziening (82-96%). De inhoud de postoperatieve informatie over het hervatten van dagelijkse activiteiten was extreem variabel tussen respondenten. Slechts een klein deel van de fysiotherapeuten maakte gebruik van klinimetrie om het (functioneel) herstel van patiënten te monitoren (4-18%). Er werd in de meeste gevallen alleen doorverwezen naar postoperatieve eerstelijns fysiotherapie indien dit nodig geacht werd. Het was echter niet bekend op basis van welke redenering er werd doorverwezen. Deze resultaten bieden, naar onze mening, veel ruimte voor het verbeteren van het perioperatieve fysiotherapeutische zorgpad richting een meer evidence based en P4 gebaseerd perioperatief zorgpad van mensen die een lumbale spondylodese verkiezen.

In 2017 zijn we begonnen het perioperatieve zorgpad in het MUMC+ te transformeren. Ten eerste hebben we een evidence based preoperatieve risicoscreening

geïmplementeerd, welke de fysieke fitheid met patiënten die een lumbale spondylodese verkiezen objectiveert. Ten tweede, hebben we vanaf november 2018 alle patiënten die geïdentificeerd konden worden als hoog-risico voor vertraagd postoperatief herstel een prevalidatie interventie aangeboden. Deze prevalidatie interventie omvatte een functionele hoog-intensieve intervaltraining (*f*-HIIT) in de thuiscontext, welke de principes van hoog-intensieve intervaltraining combineert met functionele training, waarbij wordt gekeken naar oefeningen die het beste passen bij de behoeftes van de patiënt in zijn eigen context. In *hoofdstuk 4* hebben we de haalbaarheid, veiligheid en voorlopige effectiviteit van dit preoperatieve *f*-HITT programma onderzocht met patiënten die een lumbale spondylodese verkiezen en die geïdentificeerd konden worden als hoog-risico voor vertraagd postoperatief herstel. Van februari 2017 tot februari 2020 werden er 135 patiënten die een lumbale spondylodese verkozen gescreend. Van deze populatie konden 46 patiënten geïdentificeerd worden als hoog-risico (34%). Van de 23 hoog-risico patiënten die gescreend waren na november 2018 participeerde er 11 (48%) in het *f*-HITT programma. Er waren geen complicaties tijdens het trainen en slechts één patiënt had één trainingssessie gemist van de in het totaal 74 trainingssessies. Alle patiënten die participeerden in het *f*-HITT programma verbeterden hun fysieke fitheid met gemiddeld 21.2% en waren postoperatief sneller functioneel hersteld (gemeten met de modified Iowa Level of Assistance Scale) in vergelijk met niet getrainde propensity score gematchte hoog-risico patiënten (mediaan 4.5 t.o.v. 7.5 dagen; P= 0.013). Het *f*-HITT programma is dus een haalbaar en potentieel effectieve interventie voor het verbeteren van tijd tot functioneel herstel voor hoog-risico patiënten die een lumbale spondylodese verkiezen.

II) Innovatieve Methoden voor Gezamenlijke Besluitvoering Tijdens het Perioperatieve Zorgpad

Predictiemodellen kunnen patiënten en chirurgen ondersteunen in het moeilijke proces van gezamenlijke besluitvorming voor een lumbale spondylodese en kan de personalisatie van het perioperatieve zorgpad ondersteunen. Dit doen ze door de kans op een uitkomst van de individuele patiënt te voorspellen, gebaseerd op de kenmerken van die patiënt. In *hoofdstuk 5* hebben we een predictiemodel ontwikkeld en extern gevalideerd, welke de kans op een klinisch relevante pijnreductie één tot twee jaar na een lumbale spondylodese kan voorspellen. Dit model werd ontwikkeld aan de hand van preoperatieve patiëntkarakteristieken en patiënt gerapporteerde uitkomsten (PROMs) van 202 patiënten, welke door neuro- en orthopedisch chirurgen waren geïdentificeerd als mogelijke voorspellers. Middels logistische regressie met achterwaartse eliminatie hebben we het predictie algoritme ontwikkeld. Het uiteindelijk model toonde aan dat patiënten een hogere kans (odds ratio [95% betrouwbaarheidsinterval]) hadden op het behalen van een klinisch relevante pijnreductie indien ze niet rookten 0.41 [0.19-0.87]),

een lagere BMI (0.93 [0.85-1.01]), korte pijnduur (0.49 [0.20-1.19]), laag opleidingsniveau (0.46 [0.19-1.12]), minder comorbiditeiten (4.82 [1.35-17.25]), hogere predominante pijnscore (1.05 [1.02-1.08]), beter functioneren (0.96 [0.93-1.00]) en betere mentale gezondheid (1.03 [0.10-1.06]) hadden. Het algoritme werd vervolgens extern gevalideerd op de data van 251 patiënten van een ander ziekenhuis en had een area under the curve (AUC) van 0.68. Om het algoritme eenvoudig te kunnen implementeren in de klinische praktijk hebben we het algoritme vertaald naar een nomogram, welke ingevuld kan worden door patiënten en chirurgen tijdens het gezamenlijke besluitvormingsmoment voor een lumbale spondylodese, om zo de kans op het behalen van een klinisch relevante pijnreductie mee te laten wegen.

De AUC van 0.68 van het extern gevalideerde predictiemodel laat zien dat er een deel van de variabiliteit in de uitkomsten na een lumbale spondylodese niet verklaard kan worden door de variabelen in het model. Om deze AUC te verbeteren moeten er nieuwe voorspellers geïdentificeerd worden die de accuraatheid van het predictiemodel kunnen verbeteren. Daarom hebben we in *hoofdstuk 6* de voorspellende waarde van fysieke fitheid, zoals gemeten tijdens de preoperatieve screening, voor postoperatieve uitkomsten na een lumbale spondylodese onderzocht. Tijdens de preoperatieve screening werden aerobe capaciteit, rugspierkracht, flexibiliteit, coördinatie en functionele capaciteit gemeten. Middels een variabelen selectie algoritme, genaamd random forest, hebben we stabiele associaties tussen preoperatieve fysieke fitheid en korte- en lange termijn uitkomsten in 77 patiënten die een lumbale spondylodese verkiezen onderzocht. Stabiele associaties met uitkomsten werden gevonden in drie variabelen: aerobe capaciteit, flexibiliteit en rugspierkracht (Z-scores varieerde tussen 2.8-13.5). Omdat deze variabelen een sterke associatie hebben met uitkomsten na een lumbale spondylodese kunnen ze waarschijnlijk de accuraatheid van een voorspellend model vergroten. Daarmee kunnen ze ondersteunen in de gezamenlijke besluitvorming voor een lumbale spondylodese. Daarnaast is fysieke fitheid voor een lumbale spondylodese te verbeteren middels prevalidatie, zoals aangetoond in hoofdstuk 4. Als er dus een lage fysieke fitheid wordt geconstateerd tijdens de preoperatieve screening kunnen patiënten hun postoperatieve succeskans mogelijk vergroten door te participeren in een prevalidatie programma.

III) Eerste Stappen Richting de Integratie van Moderne Real-world Data Technologie

Alleen al in dit proefschrift hebben we een grote variabiliteit aan data van meer dan 600 mensen hun dagelijks functioneren verzameld en middels een tijdrovend proces van handmatig kopiëren omgezet in gestructureerde datasets, zodat deze geanalyseerd konden worden. De hoeveel data die wereldwijd verzameld wordt over het dagelijks functioneren van mensen is nog vele male groter – meerdere terabytes – en zal de

komende jaren alleen nog maar groeien. In oncologische, radiologische en genetische onderzoeksvelden wordt geautomatiseerde analyse van grote hoeveelheden data ook wel 'omics' onderzoek genoemd en heeft door de jaren al grote meerwaarde laten zien voor het personaliseren en optimaliseren van gezondheidszorg, bijvoorbeeld door het ontsluiten van nieuwe kennis over tumor fenotypes en predictiemodellen voor overlevingskans bij kanker. Van oorsprong focussen deze omics initiatieven zich vooral op biomedische factoren (bijv., genen en eiwitten) ook wel het interne exposome genoemd. Echter, onze gezondheid wordt sterk beïnvloed door ons dagelijks functioneren, persoonlijke en omgevingsfactoren (specifieke en generale externe exposome), zoals ook blijkt uit dit proefschrift. Het probleem is echter dat deze data over het dagelijks functioneren van personen niet machineleesbaar zijn of vrij te gebruiken. Hierdoor blijf belangrijke informatie over de gezondheid van mensen en hun interactie met het dagelijks functioneren buiten beschouwing bij velen onderzoeken, wat mogelijk leidt tot suboptimale gezondheid, preventie en zorg.

Het bruikbaar maken van deze informatie die nu versleuteld is kan een belangrijke revolutie in het personaliseren van preventie en zorg teweegbrengen, waardoor gezondheid en levensduur van niet alleen van mensen die een lumbale spondylodese verkiezen verbeterd kan worden, maar van alle burgers. Daarom introduceren we in *hoofdstuk 7* een nieuw omics initiatief genaamd functionomics, welke gedefinieerd wordt als 'de analyse van big data over mensen hun dagelijks functioneren'. We laten daarbij zien hoe functionomics geoperationaliseerd kan worden door het toepassen van de FAIR (Findable, Accessible, Interoperable and Reusable) principes middels Semantische Web technologie in een "use case" in de perioperatieve zorg met mensen die een lumbale spondylodese verkiezen. We hebben daarvoor een functionomics ontology gebouwd, gebaseerd op de internationaal toegepaste International Classification of Functioning, Disability and Health (ICF) en hebben aan de hand daarvan een gefedereerde data infrastructuur gebouwd welke het mogelijk maakt voor externe onderzoekers om gebruik te maken van deze data. Hiermee willen we investering in de beschreven IT technieken stimuleren, om functionomics operabel te maken en daarmee een meer en meer P4 gebaseerde gezondheidszorg, wat zal leiden tot verbeterde gezondheid van burgers.

DISCUSSIE & CONCLUSIE

In de discussie (*hoofdstuk 8*) wordt gereflecteerd op de bevindingen van dit proefschrift en hun implicaties voor de klinische praktijk, methodologische overwegingen, en toekomstige onderzoeksperspectieven die voorbouwen op deze bevindingen. Over het algemeen kunnen we stellen dat een steeds meer P4 gebaseerd perioperatief zorgpad veel potentie laat zien om de gezondheid en het dagelijks functioneren van mensen die

een lumbale spondylodese verkiezen te verbeteren. Specifieker hebben we middelen en diensten ontwikkeld die geïmplementeerd zijn in het perioperatieve zorgpad van mensen die een lumbale spondylodese verkiezen in het MUMC+ om van een reactief one-size-fits-all aanpak, naar een meer en meer proactieve en gepersonaliseerde aanpak. Deze puntoplossingen hebben hun effect laten zien of kunnen potentieel bijdragen aan verbeterde gezondheid van mensen die een lumbale spondylodese verkiezen en zijn grotendeels klaar om nationaal geïmplementeerd te worden. Daarnaast hebben we een voorstel gedaan om naar een nieuwe data infrastructuur toe te werken welke de bruikbaarheid van standaard zorgdata in het perioperatieve zorgproces vergroot en ze toegankelijk maakt voor wetenschappelijk onderzoek, door de FAIR principes te volgen. Door te continueren op dit pad, middels de in de discussie benoemde onderzoeksprojecten, kunnen we een toekomstbehendig perioperatief zorgpad ontwikkelen met mensen die een lumbale sponylodese verkiezen, waardoor niet alleen operatieve uitkomsten verbeten, maar ook de gezondheid van deze mensen in zijn geheel.

Cv

Cirriculum vitae

CIRRUCULUM VITAE

Esther Rosa Catharina Janssen was born in Venlo, the Netherlands, on the 11th of March 1992. After graduating from high school in 2011 (VWO, Valuas College, Venlo), she studied Physiotherapy at the University of applied sciences Zuyd, Heerlen. She started working as a physiotherapist in 2014 in a private practice in Duisburg, Germany. Her interest in research promted her to concurrently start her pre-master Clinical Health Sciences at Utrecht University. In 2015 she started her Research Master Health Sciences at Maastricht University. Her master internship at the department of orthopaedics in the Maastricht UMC+ led to a PhD trajectory after receiving a grant from EUROSPINE, which eventually resulted in this dissertation. Esther is a registered physiotherapists and epidemiologist and continues to work at the department of orthopeadics in the Maastricht UMC+ and VieCuri MC.

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