Depression as a Prognostic Factor for Lumbar Spinal Stenosis Outcomes

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Physical Therapy
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Abstract
A systematic review was conducted to examine the literature regarding the prognostic value of depression for LSS outcomes. Findings suggest small to moderate prognostic value of depressive symptoms for post-operative outcomes in patients with LSS, with strong evidence for disability. Next, a prospective cohort study was conducted to investigate two objectives. The first objective was to investigate the prognostic value of depression for LSS related disability and physical function outcomes. While the second objective was to investigate social support as a modifier of the relationship between depression and outcomes of LSS related disability and physical function. Results showed that baseline depressive symptoms score was significantly associated with greater disability (β=0.3, P<0.001) and physical function (β= 0.03, P<0.001) at follow-up. Additionally, social support did not appear to modify this relationship. Therefore, more research investigating other outcomes and possible interventions for depression in patients with LSS is needed.

Keywords
Lumbar spinal stenosis, depression, depressive symptoms, disability, social support
Summary for Lay Audience

Lumbar spinal stenosis (LSS) is a common spinal condition associated with symptoms of lower quality of life and increased disability. Psychological factors such as depression have been found to be associated with poorer symptoms in patients with LSS. We conducted a systematic review of all the literature on depression as a predictive factor for outcomes in patients with LSS. There were 22 articles included, and nine different outcomes (e.g. pain, physical function, etc.) were studied. The review identified gaps in the current literature and found a small to moderate prognostic value of depressive symptoms in patients with LSS undergoing nonsurgical treatment. We then conducted a study to address these gaps by investigating LSS individuals who were primarily under nonsurgical treatment. This study confirmed that depression had some predictive value for greater disability in individuals with LSS that did not undergo surgical treatment. Additionally, this study looked at social support as a potential modifier for the association between depressive symptoms and disability outcomes. While no association was found, the analysis was limited by a small sample. Future research should investigate other outcomes and look at possible interventions for depression in patients with LSS that could promote better outcomes.
Co-Authorship Statement

The thesis question and study designs were formulated by Ariel Morales with the assistance of his co-supervisors, Dr. Michele Battie and Dr. Alison Rushton. Co-investigators were recruited when additional expertise would be beneficial to the project. Specific roles of individuals are listed below.

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Laura Gibbons - statistical guidance and critical revisions of statistical methods
Acknowledgements

I would like to start with thanking my co-supervisors, Michele C. Battè and Alison Rushton, for their support throughout my MSc program. They both have provided a lot of guidance, given my great amounts of input and have been extremely patient with me.

I also want to thank Swati Mehta who is on my advisory committee, who provided me with instant and impactful feedback whenever asked. Also, I am very grateful to Laura Gibbons who has assisted me with the statistical analyses and gave me confidence in my statistical methods.

I would like to thank everyone of The Common Spinal Disorders lab and the CanSpine members for all the input I have gotten throughout my MSc, not just with projects but with everything else as well.

I would like to thank the administrative staff and professors at the Health and Rehabilitation Science program at Western University. I appreciate the assistance you have given me throughout my MSc.

Lastly, I would like to thank my mom, dad and two brothers for their love and support. Thank you for always being there for me my entire MSc journey.
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List of Abbreviations

AMSTAR-2: Assessment of multiple systematic reviews
β: Beta coefficient
BDI: Beck Depression Inventory
CES-D: Center for Epidemiologic Studies Depression Scale
CI: Confidence interval
CT: Computed tomography
EQ-5D: EuroQol Group-5 Dimension
GRADE: Grading quality of evidence and strength of recommendations
GSI: Global Severity Index
HADS: Hospital Anxiety and Depression scale
HDRS: Hamilton Depression Rating Scale
HRQoL: Health-related Quality of Life
ICD: International Classification of Diseases
JOA: Japanese Orthopaedic Association
LBP: Low back pain
LSS: Lumbar Spinal Stenosis
MCAR: Missing completely at random
MICE: Multiple Imputation by chained equations
MMPI: Multiphasic Personality Inventory
MOS: Medical Outcome Study
MRI: Magnetic resonance imaging
NRS: Numerical Rating Scale
NSAIDS: Non-steroidal anti-inflammatory medicines
ODI: Oswestery Disability Index
OR: Odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International prospective register of systematic reviews
PSQI: Pittsburgh Sleep Quality Index
QUIPS: Quality in Prognostic Studies tool
SCL-90-R: Symptom Checklist-90-Revised
SD: Standard Deviation
SF-12: Short Form Health Survey
SSSQ: Swiss Spinal Stenosis Questionnaire
TENS: Transcutaneous electrical nerve stimulation
VAS: Visual Analogue Scale
WHO: World Health Organization
ZDS: Zung Depression Scale
Chapter 1

1.0 Introduction

The focus of this thesis is the prognostic value of depression with lumbar spinal stenosis (LSS) outcomes. This thesis begins with a systematic review of the literature investigating the evidence regarding the prognostic value of depression for LSS outcomes. Following the systematic review, a prospective cohort study was conducted using data from the Alberta Lumbar Spinal Stenosis Study [1,2] to investigate depression as a prognostic factor for LSS disability and physical function outcomes, and social support as a potential modifier of the relationship between depression outcomes in individuals with LSS.

1.1 Lumbar Spinal Stenosis

Lumbar spinal stenosis is a degenerative condition characterized by the narrowing of the spinal canal caused by anatomical changes in discs, ligamentum flavum or facet joints, disturbing the neural and vascular structures within [3,4]. The common clinical presentation of LSS includes back pain, leg pain and walking disability [5]. Furthermore, the cardinal symptom associated with LSS is neurogenic intermittent claudication that can be defined as diffused buttock and leg pain, paresthesia and cramping of lower extremities caused by walking [6]. However, older persons who show the anatomical changes mentioned may not always present symptoms, despite the fact that the anatomical condition is a prerequisite for the clinical syndrome of LSS [7]. Therefore, it would seem that anatomical stenosis might be necessary but insufficient for the clinical syndrome of LSS.

1.2 Prognosis

Prognosis can be defined as the probability or risk of a future outcome based on the individual’s health condition or disease [8]. These outcomes may include specific events such as death or other complications, disease progression, and changes in pain or quality of life [9]. Prognostic factor research aims to investigate factors that have the possibility of modification for interventions to improve outcomes and provide the building blocks for prognostic models [10]. Multiple predictors are used in prognostic models to estimate a patient’s prognosis, meaning there needs to be a consideration for a multivariable approach to account for different
combinations of predictors and explain variability in the outcomes [9]. While the design and analysis of etiologic research are similar to those of prognostic research, they differ when it comes to explaining the prediction of outcomes. Etiologic research aims to explain whether an outcome can reliably be attributed to a particular risk factor with adjustment for confounders. Conversely prognostic research aims to use variables to predict accurately the risk of a future outcome in individuals with disease or health conditions [8]. This thesis focuses on the prognostic value of depression with LSS outcomes.

1.3 Natural History of LSS
The natural history of a disease or condition can be defined as the progression of the disease in an individual without treatment or intervention from the time of onset until an outcome, such as recovery, chronic symptoms, or death, has occurred [11]. Knowing the natural history of a disease or condition gives patients and clinicians insight of the expected course, timing, and outcome. This information is essential in patients’ decision to seek medical care and clinicians’ decision regarding interventions. Furthermore, understanding the natural history of a condition allows researchers and clinicians to investigate the different stages of a disease and attempt to alter the course of the disease to promote better outcomes [11]. The patient can be informed about potential health problems that might occur and future therapies or interventions that might aid in the disease's natural progression by being aware of the disease's natural history.

An early study by Porter et. al, (1984) attempted to explain the natural history of LSS. In this study 249 patients had severe symptoms from “entrapment of the lumbar root within the root canal”. Aside from clinical consultation, 81% of the 249 patients received no "active treatment," while 14% received one or more steroid epidural injections and 10% received surgical decompression [12]. Among the patients who received surgery (n=24) only three had recovered fully at 1-year follow-up, 15 moderately improved and six patients experienced no changes. A mailed questionnaire was used to assess the 225 patients who were treated without surgery, and at the 3-year follow-up 78% of respondents had some leg pain that was not severe enough to seek surgical treatment [12].
A study by Johnsson et al. (1991) compared the clinical course of central LSS in 44 surgically treated patients and 19 conservatively treated patients. There was a mean follow-up of 3-years in the nonsurgical group and 4-years in the surgical group. In the nonsurgical group most patients improved or did not change, and only 10% got worse as compared to 20% in the surgical group [13]. Overall, the proportion of improved patients was similar between groups at 3-year follow-up regarding outcomes of pain, working capacity and neurophysiologic changes. However, there was a greater increase in walking capacity found among those patients in the surgical group.

Herno and colleagues reported the natural course of 91 non-surgically treated patients in a retrospective study with a mean follow-up of 8 ± 3 years at the annual meeting of the International Society for the Study of the Lumbar Spine in 1996 [14]. According to radiologic findings, patients were divided into four groups: 11 had a complete block, 40 had moderate stenosis (anterior-posterior diameter 10 mm), 18 had mild stenosis (10-12 mm), and 22 had lateral stenosis [14]. The Oswestry questionnaire was used to assess outcomes, and a visual analogue scale was used to assess pain severity in the back and leg after walking on a treadmill [14]. At the end of the study, 27 patients remained unchanged, 41 improved, and 23 worsened. The authors concluded from these findings that the natural course was benign in all 91 patients and that there was remarkable stability in the physical and subjective manifestations [14]. Herno and colleagues used a matched-pair design in another study to compare outcomes in surgically and conservatively treated LSS patients [15]. They were able to form 54 matched pairs using the matching criteria of sex, age, symptom duration, and myelographic findings [15]. The main outcomes were neurogenic claudication, leg pain and mixed symptoms and were based on the Oswestry score and on an estimation of the functional status by clinical examination. Overall, the mean Oswestry score was similar between patients treated with and without surgery at a follow-up time of approximately 5 years. Additionally, the mean Oswestry score was similar among women with and without surgery, but the Oswestry score in surgically treated men was significantly better compared to men who were treated conservatively [15]. In 1997 at the annual meeting of the International Society for the Study of the Lumbar Spine Herno and associates presented a longitudinal analysis of 38 patients with LSS who were treated conservatively [16]. Of the 38 patients there were 19 men and 19 women examined in 1989 and 1995. In addition, radiologic examination revealed that 27 patients had central stenosis and 11 patients had lateral
stenosis [16]. The overall change in the patients' condition was assessed using four criteria: physical condition, ability to perform daily tasks, treadmill walking capacity, and pain severity after the treadmill test [16]. The findings indicated that the patients' overall condition remained unchanged, with the exception of patients with a complete block on myelography whose condition worsened. According to the authors, patients with block stenosis require surgical decompression [16].

Hurri et al. (1998) conducted a longitudinal study on the long-term prognosis of LSS [17]. There were 75 patients with LSS diagnosed by myelography who were evaluated by telephone interview after a 12-year follow-up [17], including 57 who had received spine surgery and 18 who had not. At the 12-year follow-up, 11% of the conservatively treated patients had worsened conditions, 45% remained unchanged, and 44% had improved. In contrast, 18% of surgically treated patients had worsened conditions, 19% remained unchanged, and 63% improved [17].

According to the studies reviewed, conservatively treated patients with LSS generally had good results, meaning their conditions remained stable or improved over time. Furthermore, when compared to conservative treatment, surgically treated patients had better overall results that remained stable over time [18]. Moreover, studies found that surgery performed after failure of conservative treatment produced comparable results to patients who had surgery earlier [18]. According to the findings of these studies, patients with severe baseline symptoms, block stenosis, and degenerative spondylolisthesis may benefit from surgical decompression, however, patients should not be treated solely on the basis of pathoanatomical stenosis severity [18].

Both Benoist (2002) and Kreiner et al. (2013) acknowledge that the current literature has limitations. Furthermore, Benoist (2002) emphasizes the limitations in outcome evaluation, and Kriener et al. (2003) discuss how the authors were unable to define the natural history of LSS due to limitations in the literature [18,19]. Nonetheless, studies that investigate the natural history of LSS are important for researchers and clinicians to help investigate interventions to alter the course of disease and for patients to be well informed about their condition, possible outcomes, and treatment options.
1.4 Treatment of LSS
The management of LSS includes non-surgical options and if ineffective surgical options are recommended. Non-surgical management options include drugs, physiotherapy, rehabilitation and lifestyle changes. Drugs include over the counter and prescription drugs for treatment of LSS. However, there is limited evidence to guide individuals on which drug to use. Small trials with low to very low quality of evidence suggest prostaglandins, gabapentin and vitamin B1 improve pain and walking distance [3]. Non-steroidal anti-inflammatory medicines (NSAIDs) are helpful in LSS, despite the fact that the literature indicates they are not any more effective than acetaminophen [20-23]. Opioids and muscle relaxants are also prescribed for LSS, even though there is no proof to suggest they are any more effective than acetaminophen or NSAIDs at relieving pain [24,25]. Physiotherapy and rehabilitation are other non-surgical management options for individuals with LSS. Exercise, weight supported walking, muscular coordination training, braces or corsets, pain-relieving therapies (such as heat, ice, massage), and spinal manipulation are only a few examples of treatments [3]. A systematic review by Temporiti et al. (2022) aimed to determine the efficacy of various rehabilitation approaches used in the treatment of LSS outcomes [26]. The authors investigated various physiotherapy approaches, such as weight-supported walking, aquatic exercises, cycling, manual therapy, transcutaneous electrical nerve stimulation (TENS) and ultrasounds. Findings of this review suggest that three weeks of weight-supported walking improve pain and disability, while 8 weeks of aquatic exercises improve pain and walking tolerance with a very low quality evidence rated by the Grading quality of evidence and strength of recommendations tool (GRADE) [26-30]. Furthermore, six weeks of cycling reduced disability compared to weight-supported walking based on low quality evidence [26,29]. Six weeks of manual therapy plus exercise or supervised exercises improved pain, walking tolerance, disability and quality of life based on moderate to low quality evidence [26,31-34]. Lastly, 2 weeks of TENS and ultrasounds showed no effects [26,35,36]. As for lifestyle changes, a study by Tomkins-Lane, et al. (2015) investigated the use of a spinal stenosis pedometer and nutrition lifestyle intervention in overweight individuals with LSS [37]. Each individual was given pedometer, a personalized consultation with a dietitian and an exercise physiologist. At 13-week follow-up there were significant improvements in symptom severity, a 50% increase in walking capacity, a 60% increase in quality of life and a mean increase in 15%
of maximum continuous activity measured by accelerometry [37]. There were no significant improvements found for the outcomes of pain and disability [37].

Surgical management options may include but are not limited to decompression surgery, spinal fusion and interspinous spacer devices. Decompression surgery has the primary goal to free the neural structures that are being disturbed, hopefully resulting in symptom relief and improvement in function [3]. There is variation in the surgical approach which depends on the location of the stenosis, number of segments affected, associated deformity, spinal instability, history of previous surgery and the surgeon’s preferences [38]. Additionally, these approaches include traditional laminectomy, bilateral laminotomies, bilateral decompression through unilateral laminotomy and different forms of laminoplasty [38]. However, there is limited evidence comparing the effectiveness of these surgical approaches. Regardless, LSS symptoms related to the legs are typically improved by decompression of the neural structures more than LSS symptoms related to the back, despite some relief in back pain [39]. Spinal fusion is typically recommended for spinal stenosis associated with degenerative spondylolisthesis, recurrent stenosis after previous decompression, instability or scoliosis. However, research found that in the absence of these conditions lumbar fusion has not been shown to improve outcomes [38]. An alternative method of treating spinal stenosis uses interspinous spacers, which are designed to separate the spinous processes at the stenotic level to prevent narrowing brought on by lumbar extension and stress [3].

1.5 Depression

For simplicity, the term "depression" is used to refer to both clinical depression and depressive symptoms. The screening for depression typically involves a variety of questions from an established self-reported questionnaire measuring depressive symptoms. There are several tests that can be used to screen for depression, such as the Beck Depression Inventory (BDI), Hospital Anxiety and Depression scale (HADS), Zung Depression Scale (ZDS), Hamilton Depression Rating Scale (HDRS) and the Center for Epidemiologic Studies Depression Scale (CES-D). All these questionnaires have shown to have acceptable validity and reliability for the screening of depression among the general and older adult population [40-44]. The cause for depression is not fully understood but involve a complex interaction between social, biological, and psychological
factors. Depression is the leading cause of disability and can be long-lasting or recurrent, greatly affecting an individual’s quality of life [45]. Both terms of depressive symptoms and clinical depression share similar definitions and differ mostly in how each are measured. For example, depressive symptoms include persistent sadness, loss of appetite, tiredness and poor concentration. While clinical depression is classified as a mood or affective disorder that includes depressive symptoms previously mentioned [45]. In this thesis, depressive symptoms are considered a continuous variable and measured using an established measure such as the CES-D. (i.e. a score ranging from 0-60). In contrast, clinical depression is considered a dichotomized variable and measured using a cut-off point on the CES-D to characterize clinical depression.

Understanding the difference between depressive symptoms and clinical depression is important because there are different implications for each. Such that findings for depressive symptoms may indicate that for every point increase in the continuous measurement there is an association with the outcome of interest. While clinical depression implies that an individual has surpassed a meaningful threshold of depressive symptoms for a major depressive disorder which is associated with the outcome of interest. Such a state may have a different prognostic value than variations that can occur anywhere on the spectrum of depressive symptoms. Also, as depression screening in the clinical setting often aims to identify the presence of a major depressive disorder, further research investigating the prognostic value of such could have important clinical implications.

1.6 Association of Depression with Spinal Conditions
A typical medical model of disease views that illness is caused by physical pathology with symptoms being directly related and that any psychological element is relatively unimportant or secondary to the physical disease [46]. However, a medical model cannot explain the rationale for this association of depression with spinal conditions and is better explained by a biopsychosocial model of illness. The biopsychosocial model emphasizes human illness rather than disease and explains how psychological and social influences may contribute to an individual’s perception of and response to a disease [46]. The gate control theory of pain provided the physiologic basis for the biopsychosocial model stating that pain can no longer be
regarded as only a physical sensation of disease but there needs to be consideration for the mental, emotional and sensory mechanisms of pain [46]. Although, pain is used in this example, similar statements can be applied to disability outcomes and the same considerations need to be taken. Furthermore, it is common for depression to be associated with outcomes related to spinal conditions and thus possibly increasing the severity of symptoms in patients [47-50]. Prior literature has focused on a variety of spinal conditions and mainly low back pain, rather than specifically LSS, apart from McKillop et al. (2014) and Aalto et al. (2006) [48,49]. However, LSS is known to be a sub-population of individuals with low back pain.

1.7 Social Support
There is reason to believe that social support may be a potential modifier of the association of depression with LSS outcomes and therefore could help improve outcomes in individuals with LSS. A previous study found that overall social support was associated with recovery from depression in individuals with chronic low back pain [2]. This supports the idea that if depression is a prognostic factor for LSS outcomes then modification with an intervention such as social support may have an effect on the relationship between depression and LSS-related outcomes. There have been consistent associations between social support and health outcomes in chronic and acute disease; however, there are still some concerns limiting the confidence in these results [52,53]. Specifically, the need for more data on the stage of disease that is potentially impacted by social support and a universally agreed definition of social support is needed due to the complexity of the construct [52,53]. Social support has been defined by Cohen (2004) as “a social network's provision of psychological and material resources intended to benefit an individual's ability to cope with stress” [54]. Social support is multidimensional and includes a combination of different types of support including emotional, instrumental, appraisal and informational support [55]. Emotional support involves the feeling of being loved, cared for and connectedness to people. Instrumental support includes tangible elements such as housing, transportation and money. Appraisal support includes personal feedback concerning attitudes and behaviours. Lastly, informational support usually involves guidance with issues and receiving advice [56]. Social support can be formal or informal and sources of social support may vary but most commonly involve family, romantic partners, friends, pets, and community members [57].
Formal support includes community services, drop-in centers or self-help groups. While informal support includes sources from family, friends, co-workers and neighbours [56].

Social support as a modifying factor of the association of depression with LSS outcomes can be viewed in two ways; a direct method and an indirect method [58]. The direct method links social support to illness either through influence on behavioural patterns for disease or through effects on biological responses that influence disease [58]. While the indirect method of social support can be described using a stress-buffering model, the stress buffering model insists social support works by preventing behavioural and biological responses to stress that would result in disease [58]. Stress buffering is the concept that social support is only helpful during stressful situations [59,60].

1.8 Research Gaps in the current knowledge
The current literature reports that depressive symptoms have some prognostic value in LSS outcomes but there is a need for a systematic review to synthesize and update the current knowledge as the last review on this topic was from almost a decade ago [24]. Furthermore, the current literature is limited to a small number of cohorts causing a concern for possible publication bias because the majority of the literature is composed of the same group of authors using the same cohort in multiple studies. Additionally, the current literature has been focused on the post-surgical outcomes of individuals with LSS and has neglected individuals who have been treated by non-surgical strategies. This limitation makes the current knowledge difficult to generalize to the entire LSS population and is biased towards individuals who elect surgery. Lastly, clinical depression as a prognostic factor has been under researched as the current literature mostly measures depressive symptoms. Clinical depression may prove to have a different prognostic value as it typically represents when an individual has exceeded an important number of points on a depression scale. Meeting this threshold implies that the level of depression functionally impairs their ability to engage in activities of daily living.

1.9 Future Directions
A new systematic review will clearly establish limitations previously mentioned and also identify solutions. Furthermore, observational studies need to be conducted to examine the prognostic value of both depressive symptoms and clinical depression. Additionally, observational studies
using unique cohorts not limited to surgical treatment are needed to generalize future studies to the entire LSS population.

1.9.1 Thesis Objectives

The objectives of this thesis are to:

1) Update and synthesize the evidence on the prognostic value of depression in patients with LSS
2) Investigate depression as a prognostic factor for LSS disability and physical function, and to examine social support as a potential modifier.
1.9.2 References


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Chapter 2: Depressive Symptoms as a Prognostic Factor for Lumbar Spinal Stenosis Outcomes. A Systematic Review.

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2.1 Introduction

Lumbar spinal stenosis (LSS) is primarily a degenerative condition affecting older adults and is characterized by narrowing of the spinal canal or neural foramina [1]. The clinical syndrome of LSS includes features such as low back pain (LBP) and lower extremity symptoms, including neurogenic intermittent claudication, that limit activity. These symptoms and related disabilities can lead to further adverse health effects, such as obesity, physical deterioration, cardiovascular complications, and other health problems [2]. It has been estimated that spinal stenosis based on imaging findings is present in approximately 47% of individuals over 60 years of age and that by the year 2030, 30% of the 73 million people in the United States over the age of 65 will have symptoms of LSS [3].

In addition to experiencing symptoms of pain and disability, individuals with LSS have been found to have increased levels of psychological distress, including elevated symptoms of depression, anxiety, and hopelessness [6,7]. With respect to low back pain, psychological factors, such as depression, have been associated with poorer health-related outcomes, including worse pain and disability [8-10]. Following an early review of related literature, Pincus et al. (2002) concluded that depressive symptoms and depression might increase the risk of persisting symptoms and disability, as well as the overall cost of healthcare [11]. Supporting the latter, a study by Welch et al. (2009) found that patients with depression had higher annual non-mental health-related costs in the 11 diseases studied, one of which was back pain [12].

Specific to LSS, two previous systematic reviews evaluated the prognostic value of depression in patients with LSS who underwent spine surgery [6,13]. In the most recent review from nearly a decade ago, McKillop et al. concluded that evidence supported an association between preoperative depression and postoperative disability and symptom severity. However, effect sizes ranged from no effect to moderate effect, and it was noted that findings were based on inadequate evidence to confidently express the prognostic value of preoperative depression for
these postoperative outcomes [6]. Furthermore, little evidence was available for other outcomes, such as walking capacity and patient satisfaction, or for patients with LSS who manage their conditions conservatively.

The aim of the present study was to update and synthesize the evidence on the prognostic value of depression, both depressive symptoms and clinical depression, for a range of outcomes and follow-up times in patients with LSS treated surgically or conservatively.

2.2 Methods
2.2.1 Design
A systematic review and narrative synthesis were conducted according to a predefined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14], which was registered with PROSPERO, the International Prospective Register of Systematic Reviews, on March 18, 2021 (registration number-CRD42021235227). The Cochrane handbook was used to aid the writing process of the protocol and review [15].

2.2.2 Eligibility Criteria
The inclusion criteria were: 1) prospective longitudinal studies that investigated clinical depression or depressive symptoms as a prognostic factor for LSS health-related outcomes (of physical or mental health), and 2) used established measurement methods for clinical depression or depressive symptoms. No restrictions were applied to the participants' age or sex. Case reports, editorials, abstract-only papers, opinion papers, and studies that could not be effectively translated into English were excluded.

2.2.3 Search Strategy
Searches were conducted using MEDLINE, Web of Science, Scopus, Nursing and Allied Health, CINAHL, EMBASE and PsycInfo databases. Each database was searched using terms and synonyms related to depression and LSS (Supplementary file). In addition, Boolean operators were used to combine keywords. The search strategy was created with the help of an experienced health sciences librarian. Full searches from each database were imported into Covidence, where the web-based software automatically removed duplicates and assisted with organizing studies for screening. Each database was searched on March 9, 2022.
2.2.4 Selection Process
Applying inclusion and exclusion criteria to the title and abstract screening, two reviewers independently selected potentially relevant studies for full-text screening. Two reviewers then independently conducted full-text screening to determine eligibility for inclusion, and a third reviewer was available to resolve any disagreements.

2.2.5 Data Items and Extraction
Two reviewers independently extracted relevant data from the selected studies and recorded the information in a table prepared for this purpose, using the data extraction table by McKillop et al. (2014) as a guide [6]. The extracted information included sample size and characteristics, the depression measurement tool or scale used, the follow-up period or time point at which the outcome was measured, the outcome measure(s) (LSS outcome domain and measurement tool), and results of univariable and multivariable analyses (including effect estimates, significance levels and confidence intervals, and other variables adjusted for in the multivariable model). In some studies, the prognostic factor was measured both as a continuous and categorical variable; depressive symptoms are referred to when measured on a continuous scale. Otherwise, clinical depression is referred to when the measurement uses a cut-off score and dichotomizes the presence or absence of clinical depression (yes/no). Effect estimates were recorded for both measurements, including odds ratios (OR) and Beta coefficients (β). The extracted data were then carefully reviewed, and any discrepancies were resolved through discussion between the two reviewers. A third reviewer was available to resolve conflicts if an agreement could not be reached.

2.2.6 Risk of Bias Assessment
Two authors assessed the risk of bias independently using the Quality in Prognostic Studies tool (QUIPS) [16] for each included study and recorded. QUIPS consists of 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, statistical analysis, and reporting. The overall ratings of low, moderate or high risk of bias were reached using a combination of the original QUIPS article and supporting studies [16,17]. The formula used to determine overall ratings can be found in the supplementary file.
2.2.7 GRADE Assessment of Evidence

To assess the cumulative evidence gathered in this systematic review, two authors independently used an adapted version of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool [18]. Important features adapted to the GRADE framework for prognostic reviews included the phase of investigation, with phase 2 and 3 investigations starting at high quality of evidence (i.e. confirmatory studies) and phase 1 investigations (i.e. exploratory studies) starting at moderate quality of evidence. The study design was not considered to affect the quality of evidence since only prospective longitudinal designs were included and deemed an acceptable study design for prognostic reviews. The last adaptation to the modified GRADE framework for prognostic studies was to omit plausible confounding in rating the quality of evidence since assumptions cannot be made about the impact of confounders in prognostic studies [18,19].

2.2.8 Data Synthesis

Data were not pooled to conduct meta-analyses due to insufficient data relating to a lack of unique cohorts for each outcome, varying follow-up times, and differences in measurements for both prognostic factors and outcomes. Instead, a narrative synthesis summarized the included studies, highlighted similarities and differences, and provided possible explanations of conflicting findings. Additionally, the effect estimates from all the studies, both univariable and multivariable results, were tabulated (Table 1). Studies were then grouped by the outcome and analyzed using the GRADE tool [18,20]. Finally, summary statements were made concerning the association of clinical depression or depressive symptoms as a prognostic factor for each LSS outcome domain and evaluated using GRADE.

2.3 Results

2.3.1 Search Results

The search strategy identified 16,733 potentially relevant articles from databases and reference lists. After removing duplicates, 7,574 articles remained for title and abstract screening. Of these, 7,495 articles were ineligible, leaving 79 articles for full-text screening. After the full-text screening, 23 articles were included in the review and were used in data extraction (Figure 1).
2.3.2 Study Characteristics
All studies, with the exception of one [38], investigated patients undergoing LSS surgery. There was a total of 10 unique cohorts studied, with 13 of the 23 articles using the same cohort [22-30,33,35,39,29,40]. Follow-up times varied from 3-months to 10-years, and studies were conducted in several different countries, including Italy, Finland, the United States, Japan, Mexico and South Korea.

2.3.3 Measurement of Depressive Symptoms
Most studies used the Beck Depression Inventory (BDI) [22-30,33,35,37,39,40] to measure depression; 3 studies used the Zung Self-rating Depression Scale (ZDS) [31,32,41,43]. Other studies used either the Hospital Anxiety and Depression Scale (HADS) [34], the Minnesota Multiphasic Personality Inventory (MMPI) [36], the Hamilton Depression Rating Scale (HDRS) [38] or a 3-item depression scale from the Rand Health Insurance study [42]. Also, “Depressive burden” was measured as a continuous variable calculated using the sum of BDI scores obtained at 3- and 6-month preoperatively and as a dichotomized (yes/no) variable calculated using the median preoperative BDI score [24,26,29,30,33,35,39].

2.3.4 Risk of Bias in Studies
Eighteen of the 23 studies scored an overall “low risk of bias” rating using QUIPS. One study scored a “moderate risk of bias” [38], and four studies had an overall “high risk of bias” related to the statistical analysis domain [21,36,37,43], the domains of both confounding and statistical analysis [21], or due to a “moderate risk of bias” in several domains [36]. The ratings for all six domains and the overall rating for each study are detailed in Table 2.

2.3.5 Association of Depressive symptoms with LSS outcomes
Pain was investigated as a post-surgical outcome using a Visual Analogue Scale (VAS) in two studies at 1-year follow-up (n=151) [29,37]. One study using univariable analysis found no association between depressive symptoms and pain outcomes at 1-year follow-up [29]. The other study [37] found that at 1-year follow-up, the clinical outcomes of 15 patients with postoperative persistent depressive symptoms were worse than those of 43 patients without persistent depressive symptoms in terms of severe disability (53% vs. 9.3%), severe back pain (20% vs. 0%), and severe leg pain (40% vs. 2.3%) [37]. One could argue, however, that the presence or
absence of persistent depressive symptoms cannot be viewed as a prognostic factor, as knowledge of depressive symptoms at the time of outcome was needed to determine persistence.

There was a high risk of bias in 1 of the 2 studies using QUIPS [37] and, as determined by GRADE, there was very low quality of evidence for any association between depressive symptoms and pain outcomes at 1-year follow-up using univariable analyses (Table 3).

Disability, as measured using the Oswestry Disability Index (ODI), was investigated as a postsurgical outcome at follow-up times of 1 year in 2 cohorts (n=120) [21,29] and at 2 years in 2 cohorts (n=120) [25,26,28,30,31,41]. In multivariable analysis, one study found that a high baseline BDI score was associated with greater disability at 1-year follow-up (OR=1.15) [29]. In the other study, using univariable analysis, patients characterized by depression defined as one standard deviation above the mean were more likely to have severe disability (ODI>40%, p=0.029) 1 year after surgery [21]. Worse baseline depression was also associated with greater ODI scores at 2-year follow-up, with reported ORs ranging from 1.18 to 2.94 [25,26,28,30], and with low-back specific disability with statistically significant reported coefficients ranging from -1.67 to 0.67 from multivariable analysis [31,41].

While there was a low risk of bias in the studies of 2-year follow-up, as indicated by QUIPS, there was a high risk of bias in 1 of the 2 studies at 1-year [21]. Overall, using GRADE, there was low quality of evidence supporting the association of depressive symptoms with greater disability outcomes at 1-year follow-up; and moderate quality of evidence supporting an association of depression with greater disability outcomes at a 2-year follow-up using multivariable analyses (Table 3).

Measurements of symptom severity included questions regarding pain, numbness or tingling, weakness, and balance [44]. Symptom severity was investigated in multivariable analyses as a post-surgical outcome in 2 cohorts across 3 studies at a follow-up time of 2-year (n=295) [25,26,42]. The results showed that depressive symptoms were associated with greater symptom severity at 2-year follow-up with odds ratios of 1.16 [25] and 1.20 [26], both analyzed using the
same cohort. The study of the other cohort also found that lower depressive symptom scores predicted less severe LSS symptom severity ($\beta=2.3$, $P=0.02$) [42].

There was a low risk of bias using QUIPS in the study results related to symptom severity. Overall, using GRADE, there was moderate quality of evidence that depressive symptoms are associated with greater symptom severity at 2-year follow-up in multivariable analyses (Table 3).

Walking capacity was investigated as a post-surgical outcome in 2 unique cohorts across 3 studies at a 2-year follow-up time ($n=295$) [25,26,42]. No significant associations were found between depressive symptoms and 2-year walking capacity in the multivariable analyses.

There was a low risk of bias using QUIPS for these studies. Overall, using GRADE, there was moderate quality of evidence that depressive symptoms are not associated with walking capacity at 2-year follow-up using multivariable analyses (Table 3).

Patient satisfaction was investigated as a post-surgical outcome in 2 unique cohorts at a 2-year follow-up time ($n=223$) [31,42]. Depressive symptoms measured with the BDI score were not associated with patient satisfaction at 2-year follow-up in a multivariable analysis [31]. However, lower depressive symptom scores predicted greater patient satisfaction ($\beta=1.9$, $P=0.05$) in a different cohort in multivariable analysis [42].

There was a low risk of bias using QUIPS for the results related to patient satisfaction. Overall, using GRADE there was a moderate quality rating. However, it is unclear if depressive symptoms are associated with patient satisfaction at 2-year follow-up given the inconsistent findings (Table 3).

Four other outcomes looked at among the included articles in this systematic review, including life satisfaction [23,24,39], sense of coherence [27], sleep disturbance [38], falling [34] and a surgical outcome score [36], reflecting back and leg pain relief, return to work, restriction of activities and analgesic use. There were significant associations found with the outcomes of sense of coherence, sleep disturbance and falling. However, these outcomes were not included in the GRADE synthesis because each outcome was investigated in only one cohort.
2.4 Discussion

This review provides an updated evidence synthesis on depressive symptoms and clinical depression as prognostic factors for outcomes in patients with LSS and expands the population of interest by including those who received either surgical or conservative care. Furthermore, contemporary tools for judging the risk of bias of prognostic studies and quality of overall evidence were used to provide more confidence in the synthesized findings and to indicate methodological shortcomings that require more attention [18].

The previous review by McKillop et al., nearly a decade ago, concluded that "preoperative depression is likely a prognostic factor for postoperative LSS-related symptom severity and disability at various follow-up points.” The current review provides further evidence supporting and strengthening this conclusion, particularly for 2-year outcomes. Effect estimates for disability and symptom severity continue to be in the small to moderate range, with odds ratios ranging from 1.16 to 2.94 [46]. For example, the OR of 1.16 indicated that for every 10-point increase on a 63-point depressive symptoms scale increased the odds of disability by 160%.

The moderate level of evidence that preoperative depressive symptoms are prognostic of disability and symptom severity two years postoperatively remained in multivariable analyses adjusting for confounding factors, supporting the possibility of a direct or causal effect. If so, modifying or treating depression in LSS patients may lead to better disability and symptom severity outcomes. However, to our knowledge, there have been no studies conducted on the effects of treating depression on LSS disability and symptom severity to test this hypothesis. Such research could provide clinically valuable insights.

McKillop et al further concluded, “The prognostic value of depression on the outcomes of pain and walking capacity is less clear” [6,13]. Evidence of depressive symptoms as a prognostic factor for postoperative pain remains conflicting and inconclusive, with a very low GRADE rating providing little confidence in the effect estimate [18]. This highlights the methodological deficits needing attention, which may have led to the inconsistencies in results. Future research would be strengthened by more confirmatory studies of additional cohorts, more consistent use
of standardized measurements of depression and outcomes of interest, and more consistency in reporting of univariable and multivariable analyses.

With respect to walking capacity, however, currently available evidence of moderate quality suggests that preoperative depressive symptoms are not prognostic of postoperative walking capacity measured at 2-year follow-up [25,26,42], although the association was inconsistent for one of the cohorts measured at 3- and 12-month follow-up [22,29].

The prognostic value of depressive symptoms for other outcomes remains uncertain. The evidence for the outcome of patient satisfaction at 2-year follow-up was rated as moderate, but there were inconsistencies noted in the results. These inconsistencies may be attributed, in part, to the use of different questionnaires to measure post-surgical patient satisfaction. A dichotomized patient satisfaction measure created by the authors was used in one study [31], and in the other study a more in-depth scale was used to measure patient satisfaction on a scale from 0-100 [42]. The scale assessed items such as satisfaction with surgery outcomes related to pain improvement, relief of numbness and tingling, and ability to perform physical activities and found a significant association in the multivariable analysis [42]. Also, dichotomizing a continuous variable can simplify results for interpretation, but at the cost of lost precision that can be seen in wider confidence intervals and lower statistical power [45]. Additional outcomes investigated in single studies, such as life satisfaction, sense of coherence, sleep disturbance and falling, await confirmatory studies of additional cohorts [23,24,27,34,38,39].

The evidence that was gathered on at least two cohorts related to the outcomes of pain, disability, symptom severity, walking capacity, and patient satisfaction, assessed using GRADE, all investigated the prognostic factor of depressive symptoms. Only two studies [21,28] investigated clinical depression as a prognostic factor for disability at 1- and 2-year follow-up [21,28] and pain at the 2-year follow-up [28]. Thus, further research investigating its prognostic value is warranted.
Furthermore, a striking finding of this review was the almost complete neglect of related research on patients with LSS who manage their condition conservatively. There was only a single study that investigated depressive symptoms in a non-surgical LSS population, and only sleep outcomes were investigated [38], stressing the need for more prognostic research in this population, as results related to post-operative outcomes may not be generalizable to LSS patients managing their symptoms through conservative care.

Strengths of this review include use of an established protocol registered on PROSPERO and standardized methodology, including screening of articles, data extraction, and risk of bias and quality assessment of individual studies using QUIPS, by two independent reviewers to minimize potential biases. Furthermore, the use of a modified GRADE for prognostic studies provided an overall judgement of the strength of the body of evidence for each association of interest, along with a transparent methodology [18]. A methodological limitation of the review involves the database search. While no articles were excluded based on inability to translate into English, the databases used were primarily English Databases. Thus, there is the possibility that some relevant non-English articles were missed in this systematic review that may have been picked up through investigating foreign databases.

2.5 Conclusion

In conclusion, the strongest evidence, of moderate quality, supports the prognostic value of preoperative depressive symptoms for postoperative disability and symptom severity, particularly measured at two-year follow-up. Similarly, moderate quality evidence suggests depressive symptoms are of no prognostic value for postoperative walking capacity. Single studies investigated other LSS patient outcomes, such as falling, sleep disturbance, and sense of coherence, and await confirmatory studies. Further research on additional cohorts using standardized measurements for all outcomes is needed to strengthen effect estimates and conclusions. Clinical depression as a prognostic factor also requires more attention, as do patients with LSS managing their condition conservatively, who have been neglected in related research.
2.6 References


20. Popay, J., et al., Guidance on the conduct of narrative synthesis in systematic reviews: A product from the ESRC Methods Programme. 2006


stenosis: A two-year prospective study comparing two age groups. Disability And Rehabilitation, 32(6), 462-468. doi: 10.3109/09638280903171477


Table 1: Data extraction of the 23 Included studies

<table>
<thead>
<tr>
<th>Study Citation</th>
<th>Sample Characteristics</th>
<th>Depression Prognostic Measure</th>
<th>Follow-up timepoint</th>
<th>Outcome Measure (Measurement type)</th>
<th>Univariable analysis findings</th>
<th>Multivariable analysis (adjusted) findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobran et al. (2018) [21]</td>
<td>n=25 patients</td>
<td>SCL-90-R (Dichotomized)</td>
<td>1-year</td>
<td>Disability: ODI (Dichotomized)</td>
<td>Patients characterized by depression (SCL-90-R score higher than +1 SD), have a higher correlation with a severe disability (ODI &gt; 40%, p= 0.029) 1-year after surgery.</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>Patients underwent decompressive laminectomy</td>
<td>90-item questionnaire</td>
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<tr>
<td></td>
<td></td>
<td>GSI (Continuous)</td>
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<tr>
<td>Sinikallio et al. (2007) [22]</td>
<td>n=102 patients</td>
<td>Finish BDI (Continuous)</td>
<td>3-month</td>
<td>Disability: ODI (Dichotomized)</td>
<td>After adjusting for age, sex, marital status, somatic comorbidity, previous lumbar spine operation, ODI, VAS and symptoms severity. BDI score was associated with ODI (OR=1.19, 95% CI [1.05,1.36], p=0.01), VAS (OR 1.13, 95% CI [1.00,1.27], p=0.05) and symptom severity (OR=1.16, 95% CI [1.02, 1.31], p=0.05).</td>
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<tr>
<td>Finland</td>
<td>At 3-month follow-up n=99</td>
<td>21-item questionnaire</td>
<td></td>
<td>Pain: VAS (Dichotomized)</td>
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<tr>
<td></td>
<td>Selected for surgical treatment</td>
<td>(Scale of 0-63)</td>
<td></td>
<td>Symptom severity: Stucki severity score (Dichotomized)</td>
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<tr>
<td>Sinikallio et al. (2007)</td>
<td>n=102 patients</td>
<td>Finnish BDI (Continuous)</td>
<td>3-month</td>
<td>Life satisfaction: 4-item (Continuous)</td>
<td>At 3-month follow-up n=98</td>
<td>Finland</td>
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<tr>
<td>Sinikallio et al. (2009)</td>
<td>n=102 patients</td>
<td>Finish BDI (Continuous)</td>
<td>2-year</td>
<td>Life satisfaction: 4-item self-reported scale (Continuous)</td>
<td>At 2-year follow-up n=96</td>
<td>Finland</td>
</tr>
</tbody>
</table>
After adjusting for age, sex, marital status, preoperative somatic comorbidity, 3-month pain drawings and 3-month VAS. BDI score at 3-months was associated with an increase in ODI (OR=1.18, [95% CI 1.04, 1.34], p<0.05) and symptom severity (OR=1.16, [95% CI 1.02, 1.31], p<0.05) at a 2-year follow-up.

No significant association found between 3-month BDI score and walking capacity.

After adjusting for age, sex, marital status, somatic comorbidity, previous lumbar spine operation, ODI, symptom severity and BDI. Preoperative BDI score was independently associated with symptom severity (OR= 1.20, p<0.01, 95%CI [1.06,1.35]) and ODI (OR=1.17, p<0.01, 95% CI [1.05,1.30]).

Depressive burden (Continuous) was independently associated with postoperative ODI (OR= 1.09, p<0.001, 95% CI [1.04,1.15]), symptom severity (OR= 1.08, p<0.01, 95% CI [1.03,1.14]), and poorer walking capacity (OR= 1.04, p<0.05, 95% CI [1.01,1.08]).

Depressive burden (Dichotomized) was independently associated with postoperative ODI (OR= 19.69, p<0.001, 95% CI
| Sinikallio et al. | n=102 patients | Finnish BDI (Continuous) | 1-year Sense of coherence (SOC): 13-item scale | After adjusting for adjusting for age, sex, and preoperative self-reported walking capacity, ODI and VAS, preoperative baseline BDI predicted a low SOC score on 1-year follow up (OR=1.19, 95% CI [1.05,1.36], p<0.01). After adjusting for 3-month self-reported walking capacity, ODI and VAS, BDI score at 3 months predicted a low SOC score (OR=1.44, 95% CI [1.19,1.75], p<0.001) |
| Finland | | | | |
| Sinikallio et al. | n=102 patients | Finnish BDI (Dichotomized) | 2-year Disability: ODI (Dichotomized) | Preoperative BDI score predicted greater ODI (OR=5.42, 95% CI [2.23,13.16], p<0.001). After adjusting for age, sex, marital status, symptom severity and disability scores, 3-month BDI score predicted less improvement in ODI (OR=2.94, 95% CI [1.06,8.12], p=0.04), 6-month BDI score predicted less improvement in ODI (OR=4.94, 95% CI [1.35,18.09], p=0.02) and 3-month BDI was associated with less improvement in VAS (OR=3.33, 95% CI, p=0.03 [1.13,9.79]). |
| Finland | | | | |
| | At 1-year follow-up n=97 | | | |
| | At 2-year follow-up n=96 | | | |
| | Selected for surgical treatment | | | |
| | | | | |
6-month BDI score predicted 2-year ODI (OR=11.04, 
p<0.001, 95% CI [2.99,40.74]), < 30% 
decrease in ODI (OR=8.82, 
p<0.001, 95% CI [3.01,25.86]), 2-year pain 
(OR=3.43, p<0.05, 95% CI [1.24,9.48]) and < 30% 
decrease in VAS (OR=2.81, 
p<0.05, 95% CI [1.04,7.59]).

1-year BDI score predicted 2-year ODI (OR=5.94, 
p<0.001, 95% CI [2.27,15.55]), < 30% 
decrease in ODI (OR=4.84, 
p<0.01, 95% CI [1.92,12.15]).

Preoperative BDI score was associated with 
ODI (OR=1.15, 95%CI [1.03,1.29], p<0.05), 
symptom severity (OR=1.15, 95%CI 
[1.03,1.29], p<0.05), walking capacity 
(OR=1.19, 95%CI [1.05,1.35], p<0.05).

An independent association was found 
between the depressive burden (Continuous) 
and ODI (OR=1.13, p<0.01, 95% CI 
[1.04,1.21]), symptom severity (OR=1.08, 
p<0.05, 95% CI [1.01,1.14]), poorer walking
Walking capacity: Self-reported in meters (Dichotomized)

An independent association was found between the depressive burden (Dichotomized) and ODI (OR=17.31, p<0.001, 95% CI [4.03,74.37]), VAS (OR=3.84, 95% CI [1.22,12.04], p<0.05), Stucki-severity (OR=6.13, p<0.01, 95% CI [1.83,20.57]), poorer walking capacity (OR=12.13, p<0.001, 95% CI [3.26,45.11]).

Among elder age group (≥62 years). After adjusting for age, sex, marital status, preoperative somatic comorbidity, preoperative ODI and preoperative VAS, there was an association between baseline BDI score and ODI (OR=1.20, 95% CI [1.02, 1.23], p<0.05). Depressive burden (Continuous) showed an association with ODI (OR=1.12, p<0.05, 95% CI [1.02,1.23]). Depressive burden (Dichotomized) showed an association with ODI (OR=15.22, p<0.01, 95% CI [2.13,108.76]).

Among younger age group (<62 years) Depressive burden (Continuous) showed an association with ODI (OR=1.07, p<0.05, 95% CI [1.00,1.14]). Depressive burden (Dichotomized) showed an independent with ODI (OR=13.21, p<0.01, 95% CI [30] Sinikallio et al. (2010) Finland

<table>
<thead>
<tr>
<th>Study Parameters</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=102 patients</td>
<td>Finnish BDI (Continuous)</td>
</tr>
<tr>
<td>At the 2-year follow up n=96</td>
<td>Depressive burden (Continuous and Dichotomized)</td>
</tr>
<tr>
<td>Selected for surgical treatment</td>
<td>Dichotomized</td>
</tr>
<tr>
<td>Disability: ODI (Dichotomized)</td>
<td>Pain: VAS (Dichotomized)</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Adogwa et al. (2014)</td>
<td>United States</td>
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<tr>
<td>Katz et al. (1995) [32]</td>
<td>United States</td>
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</table>

[2.05,85.18]), VAS (OR= 4.98, 95% CI [1.06,23.48], p<0.05).
Patients underwent surgical treatment not significantly associated with patient satisfaction.

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment</th>
<th>Country</th>
<th>Follow-up</th>
<th>Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuomainen et al. (2018) [33]</td>
<td>102 enrolled</td>
<td>Finland</td>
<td>10-year</td>
<td>Patients with a higher preoperatively BDI score had higher mean ODI and VAS (ODI=34.46, VAS=44.24, p&lt;0.005).</td>
<td>Higher preoperative BDI scores were significantly associated with a greater ODI (ODI=1.74, p&lt;0.001, 95% CI [1.30, 2.18]) and increased VAS (VAS=2.34, p&lt;0.001, 95% CI [1.67, 3.01]).</td>
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<tr>
<td>Finland</td>
<td>Depressive burden</td>
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<tr>
<td>Wada et al. (2020) [34]</td>
<td>n=82 patients</td>
<td>Japan</td>
<td>12-month</td>
<td>Fallers had a significantly higher preoperative HADS-depression score (HADS-depression= 7.0, p=0.007) compared to non-fallers (HADS-depression=5.0, p=0.007).</td>
<td>Depressive burden was associated with ODI (ODI= 0.25, SD=0.04, p&lt;0.001 95% CI [0.18, 0.33]) and VAS (VAS=0.19, SD= 0.06, p&lt;0.005, 95%CI [0.07, 0.31]).</td>
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<td>After adjusting for age, sex, previous fall history, JOA score, muscle weakness in the tibialis anterior, walking speed and low muscle mass, there was a significant association between HADS score and falls 12 months after surgery (OR=1.19, 95% CI [0.98, 1.44], p=0.079).</td>
</tr>
<tr>
<td>Pakarinen et al. (2014) [35]</td>
<td>n=102 patients</td>
<td>Finland</td>
<td>5-year</td>
<td>Preoperative BDI showed no significant correlation with the change in ODI (r=0.017, p=.904), VAS (r=0.065, p=0.609) or walking distance (r=0.065, p=0.234).</td>
<td>A high BDI score at the 5-year follow-up was independently associated with greater ODI (β=0.57, SE=0.26, t=2.21, p&lt;.05).</td>
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<td>Depressive burden (Categorical) was independently associated with increased ODI (β= 9.37, p&lt;0.05).</td>
</tr>
</tbody>
</table>

Patients underwent surgical treatment (Continuous and Categorical) Walking capacity: Self-reported in meters (Continuous)
Patients with a high depressive burden had higher mean ODI (ODI=32.00, SD=16.2, p<0.01) compared to those with a low depressive burden (ODI=18.90, p<0.01).

Walking distance was shorter among the high depressive burden group (2313.46m, p<0.01) compared to the low depressive burden group (4294.57m, p<0.01). No significant association between VAS and depressive burden.

Depressive burden (continuous) was independently associated with increased ODI (β=0.14, p<0.05).

---

**Herron et al. (1986) [36]**

United States

n=57 patients

At 1-year follow-up n=51

Patients underwent surgical treatment

Surgical outcome: surgical rating scale consisted of good, fair or poor (Dichotomized)

Depression was not associated with surgical outcome in LSS patients.
Urban-Baeza et al. (2015) [37]

**Mexico**

- **n=58 patients**
- **Patients underwent surgical treatment**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Continuous</th>
<th>1-year</th>
<th>Back and leg pain intensity: VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spanish BDI</td>
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<tr>
<td>Disability: ODI</td>
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<tr>
<td>Global effectiveness of surgery: Likert Scale</td>
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</tbody>
</table>

Persistent depression group had moderate ODI (47%), severe back pain (20%), severe leg pain (40%) and severe disability (53%).

Persistent depression was associated with lumbar pain (p=0.00), leg pain (p=0.05) and ODI (p=0.00). 33% of patients with persistent depression thought that the "surgery helped a lot" (p=0.001).

In the original group with depression only leg pain outcomes (p=0.05) were associated with depression.

Patients with persistent depression had less expectations of improvement in back pain, leg pain, walking capacity, independence (p=0.01), physical duties (p=0.05) and social activities (p=0.001).
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Outcome Measure</th>
<th>Follow-up</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Kim et al. (2020) [38]</td>
<td>n=201 patients</td>
<td>HDS (Continuous)</td>
<td>6-month</td>
<td>Sleep disturbance: PSQI (Continuous)</td>
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<tr>
<td>Korea</td>
<td>147 conservative treatments</td>
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<td>HDS score was found to be associated with less sleep improvement (increase in PSQI score ≥ 3, mean=11.0 +/- 7.6 or increase &lt; 3, mean= 14.2 +/- 9.2, with a p=0.022).</td>
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<td>54 surgical treatments</td>
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<td>Pakarinen et al. (2016) [39]</td>
<td>n=102 patients</td>
<td>Finnish BDI (Continuous)</td>
<td>10-year</td>
<td>Life satisfaction: 4-item scale (Continuous).</td>
</tr>
<tr>
<td>Finland</td>
<td>At-10 year follow-up n=72</td>
<td>Depressive burden (Continuous)</td>
<td></td>
<td>After adjusting for age, sex, marital status, preoperative ODI, preoperative VAS and preoperative walking distance, preoperative BDI was associated with greater life dissatisfaction (OR=1.27, p&lt;0.01, 95% CI [1.07,1.50]).</td>
</tr>
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<td>Patients underwent surgical treatment</td>
<td></td>
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<td>Depressive burden was associated with greater life dissatisfaction (OR=1.04, p&lt;0.05, 95% CI [1.01,1.08]).</td>
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<td>Pakarinen et al. (2017) [40]</td>
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<td>Finnish BDI (Continuous)</td>
<td>5-year</td>
<td>Sense of Coherence: 13-item scale (Continuous)</td>
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<td>At the 5-year follow-up n=74</td>
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<td>After adjusting for age and gender, 3-month BDI score was significantly associated with a lower 5-year SOC score (β= -1.31, SE=0.30, p&lt;0.01).</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Patients</td>
<td>ZDS (Continuous, 20-item questionnaire)</td>
<td>Disability: ODI (Continuous)</td>
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<td>ZDS (Continuous, 20-item questionnaire)</td>
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<td>3-item depression scale from the Rand Health Insurance study (Continuous) [48]</td>
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<td>n=257</td>
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<td>At 6-month follow up n=228</td>
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Records identified from Databases
Total: (n= 16721)
MEDLINE: (n= 2154)
EMBASE: (n= 5487)
Web of Science Search: (n= 1591)
Scopus: (n= 4250)
Nursing and Allied Health: (n= 3020)
CINAHL: (n= 79)
PsycInfo: (n= 140)

Records removed before screening:
Duplicate records removed (n= 9159)

Records identified from:
Reference lists (n= 12)

Records excluded by Covidence (n= 7495)

Records sought for retrieval (n= 67)

Reports excluded (n= 46):
No full-text available (n= 9)
No depression tool reported (n= 1)
Study design (n= 15)
Patient population (not LSS) (n= 12)
Depression as an outcome (n= 4)
Depression with other mental illness...

Reports not retrieved (n= 0)

Reports not retrieved (n= 0)

Reports not retrieved (n= 0)

Reports assessed for eligibility (n= 12)

Reports assessed for eligibility (n= 12)

Reports assessed for eligibility (n= 12)

Studies included in review (n= 23)

Figure 1: PRISMA flow diagram of the article search and selection
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Participation</th>
<th>Study Attrition</th>
<th>Prognostic factor measurement</th>
<th>Outcome measurement</th>
<th>Study Confounding</th>
<th>Statistical analysis and reporting</th>
<th>Overall risk of bias</th>
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<td>Outcome</td>
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<td>Risk of Bias</td>
<td>Inconsistency</td>
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<td>RoB</td>
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</table>
Studies included for each outcome: Pain [29,37], Disability at 1-year [21,29] and at 2-year [25,26,28,20,31,41], Walking capacity [25,26,42], symptom severity [25,26,42] and patient satisfaction [31,42].

Overall quality: ++++ High quality of evidence, +++ Moderate quality of evidence, ++ Low quality of evidence, + Very low quality of evidence

X: not present for moderate/large effect size or exposure-gradient effect
Chapter 3: Depression as a prognostic factor for disability and physical function in lumbar spinal stenosis

3.1 Background

Lumbar spinal stenosis (LSS) is a common spinal condition in older adults associated with significant disability and diminished health-related quality of life [1], which is increasing in prevalence and related economic burden as the mean age of the population rises [2-8]. In addition to pain and disability, individuals with LSS also experience elevated levels of psychological distress, including symptoms of depression, anxiety, and hopelessness [9,10].

Previous research found that psychological factors, such as depression, were associated with poorer health-related outcomes, including the severity of pain and disability, in patients with spinal conditions [11,12,13]. A related review by Burton, Vogel & Field (2002) suggested that depressive mood may increase the risk of persistent symptoms and disability in patients with lower back pain (LBP) while increasing the cost of healthcare [14]. Specific to LSS, a systematic review published in 2014 suggested that individuals who underwent surgery for LSS and had higher levels of pre-operative depression had poorer health related outcomes, including post-operative disability and symptom severity [9]. However, the authors noted several limitations and gaps in the literature that limited conclusions [9].

Chapter 2 details a systematic review to update current knowledge on depression as a prognostic factor for LSS outcomes, revealing several remaining literature gaps. First, there was a lack of unique cohorts studied. For example, even though depressive symptoms have been studied as a prognostic factor for disability at two-time points in LSS, only two unique cohorts were used to investigate this outcome at each time point [15-22]. Additionally, the literature had focused mainly on depressive symptoms as a prognostic factor, and further research investigating clinical depression is needed. Another gap in the literature was that investigations of LSS outcomes were conducted almost exclusively in patients undergoing surgery, as opposed to patients receiving conservative or non-surgical care. Finally, as revealed using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, the overall
evidence for the association between depressive symptoms and disability ranged from low to moderate, depending on the follow-up time, necessitating further research.

While it has not yet been studied, there is reason to believe that social support may be a modifier of the effects of depression on LSS outcomes. Social support has been defined by Cohen (2004) as "a social network's provision of psychological and material resources intended to benefit an individual's ability to cope with stress" [23]. Social support has been postulated to be protective against mental health conditions directly, such as through relationships, or indirectly by buffering properties in stressful situations [24-26]. A study by McKillop et al. (2016) looked at social support as a prognostic factor for depression in spinal pain and found that emotional/informational, functional, and tangible social support, as well as the overall social support score, were all strongly associated with depression recovery, which may help individuals with low back pain cope [27].

3.2 Objectives
The primary objective of this study was to investigate depression as a prognostic factor for LSS disability and physical function. A secondary objective was to examine social support as a potential modifier of the association of depression with LSS disability.

3.3 Methods
3.3.1 Sources of data
This prospective cohort study was part of the Alberta Lumbar Spinal Stenosis Study, which examined prognostic factors and outcomes in an inception cohort of patients with lumbar spinal stenosis, recruited at the time of diagnostic imaging [27]. The baseline data were collected through a telephone interview that included demographic data, comorbid conditions, disability, social support, and depressive symptoms. Follow-up data were collected through telephone interview that included a reassessment of disability and physical function. Initially, follow-up was to occur at 3 and 6 months after baseline measurements and then annually, but it was soon apparent that precisely timed telephone interviews was not feasible, and follow-up occurred at variable times over the subsequent two years.
3.3.2 Participants
Participants in the Alberta Lumbar Spinal Stenosis Study were patients referred by general practitioners or specialists for a lumbar MRI or CT scan from May 2004 to April 2005 at one of four adult imaging centers serving the Calgary Health Region of Alberta Health Services in Canada, a public health care system. Participants in the Alberta Lumbar Spinal Stenosis Study were adult patients who gave consent for their scans to be utilized in future research and to be contacted about possible involvement in a further study depending on the results of their imaging. There were 2,296 (72.5%) patients of those imaged who gave their consent. Of those, 1,178 (51%) were determined to have some form of LSS (central canal, lateral recess or foraminal) on imaging, as reported by a clinical radiologist, and no exclusion criteria of spinal malignancies, infections, inflammatory conditions, or fractures; and no active cancer for which metastases were suspected. A phone call was made to invite those who met the inclusion criteria to participate, and 800 (68%) were successfully reached and volunteered to take part in the study.

As radiological findings of lumbar stenosis are sometimes incidental, findings and not always associated with symptoms [53], and the current study therefore included a subset of the Alberta Lumbar Spinal Stenosis Study. Participants with a clinical diagnosis of LSS who were of a minimum age of 40 years old at baseline were included. The clinical diagnosis of LSS was determined by a referral for lumbar spine imaging based on a suspicion of LSS, which was confirmed by imaging findings of stenosis at one or more levels indicated on a clinical radiological report. The diagnosis of LSS was confirmed by a consulting spine surgeon and noted on a participant’s medical chart after imaging, or from ICD 9 codes indicating spinal stenosis in the administrative health data accessible for two five years after baseline measurements. Lastly, individuals with a follow-up period between 3-22 months were included to minimize loss to follow-up. Of the 800 Alberta Lumbar Spinal Stenosis Study participants, 288 met the subset criteria for inclusion in the current study.

3.3.3 Prognostic factors of interest
Clinical depression or major depressive disorder can affect the emotional and physical well-being of individuals. Clinical depression was represented by a dichotomous variable signifying presence or absence of major depressive disorder [29]. Depressive symptoms, defined as any
symptoms that affect how individuals feel, think, and perform activities [28], were measured as a continuous variable with a range of possible scores.

Clinical depression and depressive symptoms were measured at baseline using the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a 20-item, self-report questionnaire that measures how often individuals have experienced symptoms associated with depression over the past week, such as restless sleep, poor appetite and feeling lonely. Each item is rated from 0 to 3 (0= rarely or none of the time, 1= some or little of the time, 2= moderately or much of the time, 3=most or almost all the time). The overall score can range from 0 to 60, with higher scores indicating greater depressive symptoms.

The CES-D has been used across a wide age range, is sensitive to differences between groups, to changes in depressive symptoms after interventions [30] and has high internal consistency, acceptable test-retest stability, and good concurrent and construct validity [31]. The CES-D has shown to be a reliable measure for assessing the number, types, and duration of depressive symptoms across race, sex, and age [31]. High internal consistency was demonstrated with Cronbach’s alpha coefficient ranging from 0.85 to 0.90 across studies [31]. Although, many studies have used a cut-off score of 16, Turk et al. (1994) argued that a higher cut-off score may reduce the number of false positives within individuals with chronic pain conditions [29]. They found that in a chronic pain sample the mean CES-D score for patients who were not depressed was 18.32, thus incorrectly classifying those patients as depressed. Therefore, a higher cut-off score was advised for populations with chronic pain conditions to avoid false positives [29]. In this study we used a validated cut-off score of 19 as recommended by Turk et al (1994), with 19 or greater indicating clinical depression [29].

3.3.4 LSS outcomes of interest (Disability and Physical Function)
Disability was defined by the World Health Organization (WHO) as the temporary, prolonged, or permanent reduction or absence of the ability to perform certain activities of daily living [32]. Physical function was defined as the ability to perform both basic and instrumental activities of daily living [52]. Disability was measured using the Oswestry Disability Index (ODI) and
physical function was measured using the Swiss Spinal Stenosis Questionnaire (SSSQ) Physical Function Subscale. Both disability and physical function were continuous variables.

The ODI is a continuous measure that uses summary scores ranging from 0-100, with greater scores indicating more disability [33]. The ODI has been shown to have good construct validity, internal consistency, good test-retest reliability, and high responsiveness [34]. The SSSQ physical function subscale quantifies physical function characteristics specifically of patients with LSS by asking questions about their walking capacity and ambulation in the past month (distance, walking outdoors, indoors, etc.). The physical function subscale contains 5 questions that use a 4-point ordinal scale scored from 1 to 4 (maximum score of 20), with greater scores indicating less physical function. The SSSQ physical function subscale has demonstrated excellent internal consistency, reliability, ability to detect change, and good convergent and discriminant validity regarding the subscales and total SSSQ physical function subscale score [35].

3.3.5 Modifying factor (Social Support)
Social support was investigated as a possible modifier of the relationship between depression and LSS outcomes. Social support is conceptualized as “a social network's provision of psychological and material resources intended to benefit an individual's ability to cope with stress” [23]. Social support was measured as a continuous variable using the Medical Outcome Study (MOS) Social Support Survey. The choice of domains by the developers of the MOS survey was guided by current theory as to the most important dimensions of social support [36]. The MOS Social Support Survey measures the availability of social support using 19-items assessed by a 5-point Likert scale that represents the four dimensions of emotional/informational (“e.g., someone to share your most private worries and fears with”), tangible (e.g., “someone to take you to the doctor if you needed it”), affectionate (e.g., “someone who hugs you”) and positive social interaction (e.g., “someone to have a good time with”). The scale also provides an overall index of social support, where scales are transformed so that the lowest possible score is 0 and the highest possible score is 100, indicating more frequent availability of different types of support. The overall functional social support index was calculated using the average scores from each subscale. A single item from the emotional/informational subscale was missing
leaving 7 out of the 8 items. However, the internal consistency of this subscale is very high with a Cronbach's alpha of 0.96 [27]. All four social support subscales and the overall social support index have high internal consistency, with Cronbach’s alpha coefficients greater than 0.91, and were found to be stable over a one-year interval [36]. The MOS survey is also easily administered to chronically ill patients, since items are short, simple, and easy to understand.

3.3.6 Possible Confounders
There are multiple variables to consider as possible confounders of the relationship between depression and LSS outcomes of disability or function [37]. We considered co-morbidity, education level as a surrogate of socioeconomic status, sex, surgery status, age and follow-up time.

*Co-morbidity* has been associated with both the prognostic factor and the outcome of interest. The risk of having a somatic disease is approximately twice as high for persons with severe mental illness, such as affective disorders including clinical depression, then for people without mental disorders [38]. Co-morbidity has been found to increase the burden of LSS outcomes [39]. To identify co-morbidities, patients were asked to report any of the following conditions derived from Statistics Canada’s Canadian Community Health Survey, including asthma, chronic bronchitis or emphysema, high blood pressure, heart disease, diabetes, cancer, effects of stroke, migraine headaches, Alzheimer’s disease or any other dementia, urinary incontinence, bowel disorder, thyroid condition or “any other long-term condition [1].

Education level was included as a surrogate of *socio-economic status*. Low socio-economic status has been found to be associated with a higher prevalence of depression. Also, in some cases individuals with a low socio-economic status may not be able to afford resources to manage LSS outcomes as well as someone of higher socioeconomic status. There is evidence that low socio-economic status may predict and influence LSS outcomes in patients undergoing spinal surgery, as well [40]. Thus, socio-economic status may confound the relationship of depression and LSS outcomes.

Education level was recorded using an ordinal list of 8 response options to the question: What is your highest level of education completed? The possible responses were: 1. No Schooling, 2.

Sex was also considered, as female patients with LSS have been found to report worse preoperative pain, disability and HRQoL [41], and greater low back pain and leg pain than men with LSS [42]. However, the prevalence of depression has been found to be similar in males and females over 55 years old [43].

In addition, whether spine surgery was received and, if so, the date of surgery (to calculate the time from baseline and follow-up measures), as well as age, were included as possible confounders and to further characterize the study sample of patients with LSS. Subjects with follow-up data gathered within 3 months immediately following surgery were excluded from the study sample, as recovery from surgery may have influenced the outcomes within this period.

Lastly, the effects of variation in follow-up time (3-22 months) on the relation of depression to disability and physical function were examined through statistical analyses and scatter plots.

3.3.7 Statistical Analysis
Descriptive statistics for continuous variables (e.g. age, CES-D score for depressive symptoms, MOS score, SSSQ physical function score, ODI score and time to follow-up) included means and standard deviations, and for categorical variables (e.g. sex, presence or absence of clinical depression, presence or absence of surgery and education level) frequencies and percentages were calculated. Lastly, two separate univariate analyses based on surgery status were conducted for additional information.

The primary objective of investigating baseline clinical depression and depressive symptoms as prognostic factors for disability (ODI score) or physical function (SSSQ score) in LSS patients was achieved through use of linear regression models. Number of comorbidities, education level, sex, age, as well as surgery and follow-up time were examined as possible confounders and adjusted in multivariable models as appropriate. Identification of possible confounding factors
was based on prior literature and the magnitude of change in the estimate of the variable of interest. A magnitude of greater than 20% change in the coefficient estimate would indicate the variable as confounding [54]. Overfitting was avoided by following guidelines by Babyak (2004) recommending at least 10 events per variable in the model [44]. Scatterplots were used to examine the association of follow-up time with disability and physical function outcomes.

The secondary study objective to investigate social support as a potential modifier of the relationship between depression/depressive symptoms and outcomes of disability or physical function was achieved through the addition of an interaction term of social support with both depression and depressive symptoms in a multivariable linear regression analyses. An interaction occurs when an independent variable (depression) has a different effect on the outcome (disability) depending on the values of another independent variable (social support) [55].

Missing values were imputed using multiple imputation by chained equations (MICE) method (Azur, Stuart, Frangakis & Leaf, 2011). Multiple imputations by linear regression were used for continuous missing data and by logistic regression for binary missing data. Multiple imputation was chosen because the missing data were greater than 5%. Imputation was supported by Little’s test of data missing completely at random (p<0.05) [45].

All statistical analyses, including imputations, met statistical assumptions (Appendix 2), and were performed using Stata (StataCorp LLC, version 17.0), with p-values <0.05 considered statistically significant and 95% confidence intervals reported.

3.4 Results
There were 288 participants who met the inclusion criteria for the diagnosis of LSS. However, a total of 41 participants were excluded from this group due to having no follow-up data between 3 to 22 months (n=22), surgery before the baseline interview (n=13) or a follow-up interview less than 3 months after surgery (n=6). The final study sample, therefore, consisted of 247 participants whose follow-up time ranged from 3 to 22 (Figure 1). Appendix 1 shows the total number of missing observations for both the primary independent and dependent variables used in this study, ranging from 8% for physical function score to 11% for baseline MOS scores,
which were determined to be missing completely at random (MCAR) using Little’s MCAR test [45]. Lastly, the magnitude of each potential confounding variable mentioned in the methods section were assessed and no evidence of confounding was found. However, the variable of surgery closely approached the threshold established for confounding in the association between clinical depression and physical function (0.20).

3.4.1 Baseline Characteristics
The study sample (n=247) had a mean age of 64.3 years (SD= 12.5), 59.0% were women and 14.2% had undergone surgery. Disability among these participants was moderate [34,46] at baseline, with a mean ODI score of 27.2 (SD=8.4) and 39.0% were deemed to have clinical depression according to the CES-D cut off score of 19. The mean CES-D score was 19.3 (SD=6.7) and the mean MOS overall score was 71.6 (SD=15.1). Other baseline characteristics were recorded in Table 1.

3.4.2 Univariate Associations
Baseline depressive symptoms and depression were associated with higher disability measured with the ODI and physical function measured with a subscale of the SSSQ at follow-up, in a univariate analysis (Table 2).

The sample was also separated into two groups based on surgery status: a surgical (n=35) and a nonsurgical group (n=212). The nonsurgical group found that depressive symptoms and depression were associated with higher disability and physical function. In contrast, the surgical group found only depressive symptoms associated with higher disability (Table 3).

3.4.3 Multivariable Regression Analysis
CES-D scores remained significantly associated with the outcomes of disability (ODI) and physical function (SSSQ) while adjusted for age, sex, social support, comorbidity, education level, surgery and follow-up time (Table 3). Those clinically depressed (CES-D score ≥19) were more likely to score higher on the ODI and physical function scales. Similarly, those who had higher depressive symptoms (baseline CES-D scores) were more likely to have higher ODI and physical function scores (Table 4). The additional multivariable analysis investigating the interaction between CES-D scores and social support revealed no such interaction for either
outcome of disability or physical function (Table 5). Multivariable analyses conducted without
imputation yielded similar findings (Appendix 2).

3.4.4 Consideration of variable follow-up time and surgery available
The coefficients remained statistically similar, with overlapping confidence intervals in the
additional multivariable analysis also adjusting for follow-up time (3-22 months) suggesting the
difference in effect estimates is insignificant (Table 4) [56]. Additionally, the scatterplots of
follow-up times with depressive symptoms and LSS outcomes showed no apparent relationship
(Figures 3, 4 & 5). Lastly, when calculating the magnitude of confounding by follow-up time,
there was no evidence of confounding. Additional investigations of the effect of surgery status
included the regression model adjusting for age, sex, social support, comorbidity, education
level, follow-up time and surgery. As well as a second model not adjusting for surgery, both of
which had similar coefficients (Table 4). Last, the magnitude of confounding was calculated, and
no evidence of surgery status confounding was discovered. However, clinical depression and
physical function surgery were close to passing the threshold but not considered confounders.

3.5 Discussion
We found that depression was a prognostic factor for disability and physical function outcomes
in individuals with LSS, both in the univariable and multivariable analysis, which is expected
because the factors adjusted for were found not to be confounding factors. Concerning the
estimates of the association, every point 10-point increase in the CES-D scale was associated
with a 3.0-point increase on the ODI scale and a 0.3-point increase on the SSSQ scale (Table 4).
Compared to the prior literature, there were a few critical differences in the measurement of
depressive symptoms, focus on primarily a surgical LSS population and stricter follow-up times
[15,47-50,16,17]. Despite these differences, this study still found that depressive symptoms and
clinical depression were predictive of poorer disability and physical function outcomes.
Additionally, similar results mean that the prognostic value of clinical depression and depressive
symptoms can be generalized to the entire population of LSS regardless of treatment and follow-
up time. With these findings, future research can focus on interventions tailored for individuals
with LSS to promote better outcomes. In addition to investigating the magnitude of confounders,
the results of different multivariable models (Table 4) give us confidence that the association
between CES-D scores and outcomes of disability and physical function are not confounded by
follow-up time. Furthermore, prior literature used stricter follow-up times; this study uses a follow-up period with high variability. Even so, this study still found that depressive symptoms are prognostic of outcomes of disability and physical function in individuals with LSS. This type of analysis has yet to typically be done compared to prior literature, as most studies have a strict follow-up time. This study may open the way for new studies with large sample sizes regardless of variation in follow-up times to obtain similar results.

When looking at the nonsurgical population of our study (Table 3), results showed significant associations between depressive symptoms and clinical depression with outcomes of disability and physical function. The estimates remained statistically similar to that of the multivariate model (Table 4), although the majority of the study sample was the nonsurgical group (n=212). However, these findings may suggest that the relationship between CES-D score and disability or physical function is not affected by the presence of surgery. Prior literature is almost exclusively focused on the surgical LSS population, and this study primarily consists of a nonsurgical LSS population (n=212). However, these results are similar as both show depressive symptoms and clinical depression to be predictive of disability and physical function in individuals with LSS. Currently, this is the only study that used a primarily nonsurgical LSS population to investigate the prognostic value of depressive symptoms and clinical depression with outcomes of disability and physical function. Because this is the only study to use a nonsurgical population of LSS individuals, it has added necessary research to the literature by investigating a once-ignored sub-population of LSS. By looking at the nonsurgical population of LSS, researchers can be more confident that the prognostic value of depressive symptoms and clinical depression is generalizable to the entire LSS population. "After adjusting for multiple confounders, clinical depression and depressive symptoms continued to be associated with worse disability and physical function outcomes in individuals with LSS, supporting the possibility that depression may be a prognostic determinant for disability and physical function outcomes [57]." Prior literature adjusted for similar confounding variables, except for adjustment for follow-up time and the presence of surgery. Additionally, these methods and results show that the prognostic value of depressive symptoms with the outcomes of disability and physical function are not confounded by factors such as follow-up time or the presence of surgery. However, the presence of surgery was borderline not a confounder in the relation between clinical depression with
disability and physical function outcomes. So, research looking at each group of the surgical and nonsurgical LSS population may be of interest. Knowing this should guide future research to further investigate nonsurgical LSS and modifying depression as there is a possibility to obtain a better outcome of disability and physical function.

There was no evidence to suggest that baseline social support modifies the association between baseline depression and disability or physical function at 3-22-month follow-up. This may be due to insufficient sample size, as regression models with an interaction term require greater sample sizes [51]. Also, baseline CES-D and MOS variables were moderately correlated (r=-0.37), which could explain that significant associations were found when these predictors were analyzed separately. Once they are involved in an interaction, the overall model fit decreases and no significant association is found. However, prior literature in combination with our findings of this study, only stresses the need for further research on social support as a potential modifier of prognostic depressive symptoms in the LSS population [24-27].

3.5.1 Strengths and Limitations
A strength of this study is that this study sample is primarily made up of a nonsurgical population (n=212) which is much different as the prior literature was almost exclusively looking at a surgical population. Therefore, findings in this study suggest that depressive symptoms are also a prognostic factor for LSS outcomes of disability or function in patients receiving nonsurgical care. Additionally, to our knowledge, it is one of the only studies that investigated the interaction of social support with clinical depression or depressive symptoms with LSS outcomes of disability and function. All prior literature had investigated depressive symptoms as a prognostic factor on various LSS outcomes but had never looked at modifying it. Another strength of this study is the statistical analysis; multiple imputations were used to avoid discarding data, and multivariable linear regression models were used to investigate our objectives while considering other variables in the association. Additionally, there were similar findings in multivariable analyses conducted without imputation (Appendix 2). Therefore, the imputed values were not significantly different from the actual values and there can be more confidence that the findings are not biased by the use of imputations.
There are limitations to this study as well. First, the available data lacked some variables that may have been informative for our study objectives. For example, it would have been interesting if stress data had been collected because of the stress buffering hypothesis mentioned previously. Another limitation of this study was that there was more than 10% missing data associated with both predictor and outcome variables. However, data were determined to be missing at random and multiple imputations by chained regression methods were used to avoid discarding subjects’ data. Another limitation was that individuals in the study sample had great variation in their follow-up times, resulting in the loss of some potential study subjects. However, analyses were conducted to investigate the possible effect of variable follow-up times between 3 and 22 months, and no such effects were apparent. Finally, the sample size was another limitation. First, there were not enough participants in this study to obtain a sufficiently powered surgical group, which limits the analyses and conclusions that can be made. Secondly, the sample size was also limited for investigating interactions. For example, when involving an interaction in a regression model, the sample size required is greater than the sample size used in a regression model without an interaction [51]. Therefore, with an underpowered analysis, there was not a sufficient sample size to answer the question of “social support as a potential modifier.”

3.6 Conclusion
Depressive symptoms and clinical depression have prognostic value for the outcome of disability and physical function in LSS patients. This study is unique as it looked at a primarily non-surgical population and can be generalized as such. There was no indication that social support was a modifier of the relation of baseline depression with disability or physical function at follow-up, although sample size was a limitation.
3.7 References


<table>
<thead>
<tr>
<th>Step</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original participants recruited</td>
<td>Adult patients who came in for lumbar MRI or CT scan</td>
</tr>
<tr>
<td>n= 2296</td>
<td></td>
</tr>
<tr>
<td>Participants with some form of LSS</td>
<td>Some form of lumbar spinal stenosis noted on clinical imaging</td>
</tr>
<tr>
<td>n= 1178</td>
<td></td>
</tr>
<tr>
<td>Successfully contacted</td>
<td>Successfully contacted for participation in Alberta Lumbar Spinal Stenosis Study</td>
</tr>
<tr>
<td>n= 800</td>
<td></td>
</tr>
<tr>
<td>Received LSS diagnosis</td>
<td>Met inclusion criteria for the clinical diagnosis of LSS</td>
</tr>
<tr>
<td>n= 288</td>
<td></td>
</tr>
<tr>
<td>Follow-up between 3-22 months</td>
<td>Excluded 41 participants (16 had no follow-up data, 6 did not fall within the specified follow-up period, 13 had less than 3-months after surgery and 6 had surgery before baseline)</td>
</tr>
<tr>
<td>n= 247</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Study sample recruitment and inclusion flowchart
Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Sample Size (n= 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex: n (%), Female</strong></td>
<td>145 (59.0%)</td>
</tr>
<tr>
<td><strong>Age (years): mean (SD)</strong></td>
<td>64.3 (12.5)</td>
</tr>
<tr>
<td><strong>ODI: mean (SD)</strong></td>
<td>27.2 (8.4)</td>
</tr>
<tr>
<td><strong>SSSQ Physical function: Mean (SD)</strong></td>
<td>2.2 (0.8)</td>
</tr>
<tr>
<td><strong>CES-D Scores</strong></td>
<td></td>
</tr>
<tr>
<td>• Depressive symptoms (CES-D 0-60): mean (SD)</td>
<td>19.3 (6.7)</td>
</tr>
<tr>
<td>• Depression ≥19 (Dichotomous): n (%)</td>
<td>96 (39.0%)</td>
</tr>
<tr>
<td><strong>MOS Overall Score: mean (SD)</strong></td>
<td>71.6 (15.1)</td>
</tr>
<tr>
<td><strong>Co-morbidity: mean count (SD)</strong></td>
<td>1.9 (1.8)</td>
</tr>
<tr>
<td><strong>Education level n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>• Junior high or less</td>
<td>25 (10.1%)</td>
</tr>
<tr>
<td>• High School</td>
<td>83 (33.6%)</td>
</tr>
<tr>
<td>• Non-University Degree</td>
<td>67 (27.1%)</td>
</tr>
<tr>
<td>• Partial University Degree</td>
<td>18 (7.3%)</td>
</tr>
<tr>
<td>• Undergraduate degree</td>
<td>36 (14.6%)</td>
</tr>
<tr>
<td>• Graduate Degree</td>
<td>17 (6.9%)</td>
</tr>
<tr>
<td><strong>Surgery: n (%), Yes</strong></td>
<td>35 (14.2%)</td>
</tr>
<tr>
<td><strong>Follow-up (Months): mean (SD)</strong></td>
<td>8.0 (5.2)</td>
</tr>
</tbody>
</table>

SD: standard deviation; ODI: Oswestry Disability Index; SSSQ: Swiss Spinal Stenosis Questionnaire; CES-D: Centre for Epidemiologic Studies Depression Scale; MOS: Medical Outcomes Study Social Support Survey
Table 2: Univariable Linear Regression Analyses of independent variables at baseline and their associations with follow-up disability and physical function scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Disability (ODI)</th>
<th>Physical Function (SSSQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Coeff [95% CI])</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Baseline CES-D Scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Depressive symptoms 0-60</td>
<td>0.4 [0.3, 0.6]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(Continuous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clinical Depression &gt;19</td>
<td>5.5 [3.1, 7.9]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(Dichotomous)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; ODI: Oswestry Disability Index; SSSQ: Swiss Spinal Stenosis Questionnaire; CES-D: Centre for Epidemiologic Studies Depression Scale; MOS: Medical Outcomes Study Social Support Survey; CI: Confidence Interval
Table 3: Univariate regression models of surgical and nonsurgical groups.

<table>
<thead>
<tr>
<th></th>
<th>Nonsurgical Group (n=212)</th>
<th>Surgical Group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeff [95% CI]</td>
<td>P-value</td>
</tr>
<tr>
<td>Disability (ODI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms 0-60</td>
<td>0.5 [0.3,0.6]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(Continuous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Depression &gt;19</td>
<td>5.7 [3.1,8.4]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(Dichotomous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Function (SSSQ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms 0-60</td>
<td>0.04 [0.02,0.05]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(Continuous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Depression &gt;19</td>
<td>0.5 [0.2,0.8]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(Dichotomous)</td>
<td></td>
<td></td>
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</table>

SD: standard deviation; ODI: Oswestry Disability Index; SSSQ: Swiss Spinal Stenosis Questionnaire; CES-D: Centre for Epidemiologic Studies Depression Scale; MOS: Medical Outcomes Study Social Support Survey; CI: Confidence Interval
Table 4: Multivariable Linear Regression Analyses models for outcome of follow-up disability and physical function scores, with two parameterizations of CES-D

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>Coef [95% CI]</th>
<th>P-value</th>
<th>Coef [95% CI]</th>
<th>P-value</th>
<th>Coef [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adjusted for age, sex, education, MOS, comorbidity, surgery and follow-up time</td>
<td>0.3 [0.2,0.5]</td>
<td>&lt;0.001*</td>
<td>0.3 [0.2,0.5]</td>
<td>&lt;0.001*</td>
<td>0.3 [0.2,0.5]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>2</td>
<td>No adjustment follow-up time. Adjusted for age, sex, education, MOS, comorbidity and surgery.</td>
<td>3.5 [0.9,6.0]</td>
<td>0.008*</td>
<td>3.4 [0.9,6.0]</td>
<td>0.009*</td>
<td>3.4 [0.9,5.9]</td>
<td>0.008*</td>
</tr>
<tr>
<td>3</td>
<td>No adjustment for surgery. Adjusted for age, sex, education, MOS, comorbidity, and follow-up time</td>
<td>0.03 [0.01,0.04]</td>
<td>0.001*</td>
<td>0.03 [0.01,0.04]</td>
<td>0.001*</td>
<td>0.02 [0.009,0.04]</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

SD: standard deviation; ODI: Oswestry Disability Index; SSSQ: Swiss Spinal Stenosis Questionnaire; CES-D: Centre for Epidemiologic Studies Depression Scale; MOS: Medical Outcomes Study Social Support Survey; CI: Confidence Interval
Table 5: Multivariable Linear Regression Analyses for **follow-up disability and physical function scores** with **interactions of CES-D scores with social support**, adjusted for age, sex, education level, comorbidity, presence of surgery and follow-up time.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Variable</th>
<th>Coeff [95% CI]</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disability (ODI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depressive symptoms 0-60</td>
<td>0.4 [-0.2,0.9]</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>(Continuous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Depression &gt;19 (Dichotomous)</td>
<td>7.2 [-3.5,17.9]</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>MOS score</td>
<td>-0.07 [-0.3,0.1]</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>CESD scores#MOS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depressive symptoms 0-60</td>
<td>-0.0003 [-0.06,0.1]</td>
<td>0.93</td>
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<tr>
<td></td>
<td>(Continuous)</td>
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ODI: Oswestry Disability Index; SSSQ: Swiss Spinal Stenosis Questionnaire; CES-D: Centre for Epidemiologic Studies Depression Scale; MOS: Medical Outcomes Study Social Support Survey; CI: Confidence Interval; # means interaction
Figure 2: Scatter plot of the physical function score and follow-up period (3-22 months)
Figure 3: Scatterplot of ODI scores and follow-up period (3-22 months)
Figure 4: Scatterplot of Depressive symptoms and follow-up period (3-22 months)
Chapter 4: Discussion & Conclusion

4.1 Overview of thesis findings

In chapter 2, the systematic review synthesized the current evidence on the prognostic value of depression for individuals with LSS. This review concluded that there is moderate quality of evidence for depressive symptoms as a prognostic factor for postoperative LSS-related symptom severity and disability at the 2-year follow-up [1-7]. Additionally, the prognostic value of depressive symptoms with pain outcomes remains inconsistent, and no confident statement can be made. Lastly, the prognostic value of depression for several other outcomes including life satisfaction, sense of coherence, sleep disturbance, falling and a surgical outcome score remain unknown and awaits new studies using unique cohorts. In chapter 3, the cohort study aimed to investigate depression as a prognostic factor for LSS disability and to examine social support as a potential modifier. The prospective cohort study found that depression was prognostic for disability and physical function outcomes in individuals with LSS regardless of follow-up time from 3-22 months or whether surgical or nonsurgical treatment was received. This suggests that screening for depression in individuals with LSS may help improve outcomes regarding disability and physical function. Furthermore, there was no evidence that social support was a modifier of the relation between depression and social support with disability and physical function outcomes. However, we cannot confidently say that social support is not a modifier in this relationship. In order to upgrade the literature, future research should aim to collect a variety of variables that may have an effect on social support (i.e. stress) and obtain a large enough sample size to provide enough power to analyze the interaction of social support. The prospective cohort study addresses the gaps identified in the systematic review by investigating the prognostic value of depressive symptoms and clinical depression among a unique cohort that consists of individuals with LSS who have been treated both surgically and conservatively. The results of the prospective cohort study have strengthened the current literature by addressing these limitations. However, the variation in follow-up time complicates the possibility of adding this study to the GRADE table in chapter 2 as outcomes were grouped by specific follow-up times and it is uncertain how it would change the GRADE conclusions.
4.2 Strengths and limitations
The strength of this thesis is the production of two high quality studies that provide a review of the current literature and further strengthen evidence, as well as outlining the next steps for future research. The quality of the systematic review was critically appraised using AMSTAR-2 to give readers confidence that the systematic review had appropriate methodology [16]. Furthermore, after using AMSTAR-2 there were no critical weaknesses identified in the systematic review, which indicates a high-quality review (Appendix 3). Another strength is that the prospective cohort study was critically appraised using QUIPS [17], indicating there was an overall low risk of bias in the prospective cohort study (Appendix 3).

However, apart from specific limitations of the individual studies mentioned earlier, the overall thesis had a limitations, as well. Despite the systematic review being rated high quality by AMSTAR-2 and the prospective cohort study being high rated quality by QUIPS each assessment was done by a single reviewer, myself. An assessment outside the authors involved in each study may give others greater confidence in these assessments.

4.3 Implications
The systematic review can serve as a guide for future research in this area so that studies address the literature gaps. The cohort study for this thesis addressed the gaps in the literature. However, more research with unique cohorts is needed to strengthen the confidence in our findings. Findings from the cohort study indicate that screening for depression may aid management strategies for LSS disability or physical function by providing a better understanding that may lead to better outcomes. Additionally, screening for depression can be done through self-report measures, providing less of a burden on the clinicians [11-15]. Lastly, the cohort study found that clinical depression was a prognostic factor for LSS disability and physical function. Therefore, screening for clinical depression can help clinicians identify patients who may benefit from psychotherapy in both surgical and nonsurgical patients with LSS.

4.4 Conclusion
This thesis provided a high-quality systematic review that not only synthesized and updated the current literature but also identified several gaps in the literature, including the lack of unique
cohorts, the focus on depressive symptoms as a prognostic factor, while neglecting the prognostic value of clinical depression, and a dearth of prognostic research in patients receiving non-surgical treatment for LSS, and low to moderate evidence for the association between depressive symptoms and disability. We addressed several of these gaps by conducting a prospective cohort study to investigate both depressive symptoms and clinical depression as a prognostic factor for LSS disability and physical function. From this we learned that there is prognostic value in depressive symptoms and clinical depression for patients with LSS with disability outcomes regardless of the treatment they receive. This thesis also takes the next step in research, which should be to investigate the use of potential modifiers of depression in the hopes of better LSS-related outcomes. The prospective cohort study investigated the use of social support as a potential modifier for depression and, to our knowledge, is the only study to do so. However, we found no significant associations of social support as a modifier for the association of depression with LSS disability and physical function. Nonetheless, future research should focus on the prognostic value of depression in relation to other LSS outcomes that require confirmatory studies, as well as the use of interventions as potential modifiers.
4.5 References


Appendix 1: Chapter 2

Search strategy and results

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QUIPS Judgment formula

To determine an overall judgement the following formula was followed: A low overall RoB was if all domains were rated as “low” or up to one “moderate”, a high overall RoB was if one or more domains were classified as having a “high” RoB or 3+ “moderate”, a moderate overall RoB if 2 domains are “moderate” and 4 domains are rated as “low”.
Appendix 2: Chapter 3

Ethics Approval Notice
Western University, London, ON

Date: 3 May 2022
To: Professor Michele Batté
Project ID: 120534
Study Title: Depression as a prognostic factor for disability/function in patients with lumbar spinal stenosis.
Application Type: HSREB Initial Application
Review Type: Delegated
Full Board Reporting Date: 24 May 2022
Date Approval Issued: 03 May 2022
REB Approval Expiry Date: 03 May 2022

Dear Professor Michele Batté,

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study.

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No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP), Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions. Sincerely,

Ms. Runamooz Subendran, Ethics Coordinator on behalf of Dr. Philip Jones, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Table 1: Missing variables in study sample

<table>
<thead>
<tr>
<th></th>
<th>Number of missing observations</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CESD</td>
<td>25/247</td>
<td>10%</td>
</tr>
<tr>
<td>Baseline MOS</td>
<td>28/247</td>
<td>11%</td>
</tr>
<tr>
<td>ODI</td>
<td>21/247</td>
<td>8.5%</td>
</tr>
<tr>
<td>SSSQ - Physical function</td>
<td>20/247</td>
<td>8%</td>
</tr>
</tbody>
</table>

Tests for Assumptions for Multivariable regression

Figure 1: Histogram of residuals
swilk(res)

| Variable | Obs | W     | V     | z     | Prob>|z|
|----------|-----|-------|-------|-------|-----|
| res      | 186 | 0.98921 | 1.512 | 0.948 | 0.17166 |

Figure 2: Shapiro-Wilk test for normality

Figure 3: Scatter plot to show linearity between baseline CES-D and Disability

Figure 4: Scatter plot to show linearity between baseline CES-D and Physical Function
Figure 5: Test of multicollinearity with depressive symptoms and disability outcome
. regress odc baseDepress baseMos age0 female ib1.educvar baseComorbid surgery Months

<table>
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<td>334.31897</td>
<td>F(10, 175) = 5.86</td>
</tr>
<tr>
<td>Residual</td>
<td>9977.4391</td>
<td>175</td>
<td>57.033937</td>
<td>R-squared = 0.2510</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adj R-squared = 0.2082</td>
</tr>
<tr>
<td>Total</td>
<td>13320.7581</td>
<td>185</td>
<td>72.8040976</td>
<td>Root MSE = 7.5588</td>
</tr>
</tbody>
</table>

|          | Coef. | Std. Err. | t     | P>|t| | 95% Conf. Interval |
|----------|-------|-----------|-------|-----|-------------------|
| baseDepress | 3.818548 | 1.30177 | 2.93 | 0.004 | 1.241358 | 6.379738 |
| baseMos    | -0.1106303 | 0.401872 | -2.75 | 0.007 | -0.8099443 | -0.313164 |
| age0       | -0.0173528 | 0.050002 | -0.35 | 0.729 | -0.1160374 | 0.0813317 |
| female     | 2.036448 | 1.185628 | 2.39 | 0.018 | .4964779 | 5.276419 |
| educvar    | -1.904772 | 2.409527 | -0.79 | 0.430 | 6.60244 | 2.859699 |
| surgery    | -1.79561 | 2.379549 | -0.72 | 0.474 | -4.01918 | 2.999098 |
| Months     | -4.091629 | 2.50564 | -1.63 | 0.104 | 9.03692 | -4.855339 |
| baseComorbid | 0.7643251 | 0.3538211 | 2.17 | 0.031 | 0.099666 | 1.456684 |
| surgery    | 1.132473 | 1.747256 | 0.65 | 0.518 | -4.58088 | 2.315934 |
| Months     | 0.519122 | 0.336796 | 1.57 | 0.120 | 1.2290225 | 0.328469 |
| baseComorbid | 31.78452 | 5.922316 | 5.35 | 0.000 | 20.61616 | 43.9288 |

. vif

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<td>0.737954</td>
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<tr>
<td>baseMos</td>
<td>1.24</td>
<td>0.807012</td>
</tr>
<tr>
<td>age0</td>
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<td>0.854229</td>
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<tr>
<td>female</td>
<td>1.12</td>
<td>0.892455</td>
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<td>educvar</td>
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<td>4.14</td>
</tr>
<tr>
<td>3</td>
<td>4.40</td>
<td>0.227040</td>
</tr>
<tr>
<td>4</td>
<td>3.46</td>
<td>0.289230</td>
</tr>
<tr>
<td>baseComorbid</td>
<td>1.26</td>
<td>0.756449</td>
</tr>
<tr>
<td>surgery</td>
<td>1.12</td>
<td>0.893417</td>
</tr>
<tr>
<td>Months</td>
<td>1.14</td>
<td>0.873958</td>
</tr>
</tbody>
</table>

| Mean VIF | 2.04 |

Figure 6: Test of multicollinearity with clinical depression disability outcome
Figure 7: Test of multicollinearity with depressive symptoms and physical function outcome
. regress sssfs baseDepress baseMos age0 female ib1.educvar baseComorbid surgery Months

<table>
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<tbody>
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<td>27.4221749</td>
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<td>2.74221749</td>
<td>F(10, 175) = 4.97</td>
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<tr>
<td>Residual</td>
<td>96.4910836</td>
<td>175</td>
<td>0.551381735</td>
<td>Prob &gt; F = 0.0000</td>
</tr>
<tr>
<td>Total</td>
<td>123.913978</td>
<td>185</td>
<td>.669805280</td>
<td>R-squared = 0.2213</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adj R-squared = 0.1760</td>
</tr>
</tbody>
</table>

| sssfs       | Coef.  | Std. Err. | t     | P>|t| | [95% Conf. Interval] |
|-------------|--------|-----------|-------|-----|---------------------|
| baseDepress | 0.3284646 | 0.1274794 | 2.58  | 0.011 | 0.076857 | .580496 |
| baseMos     | -0.0058845 | 0.003969 | -1.48 | 0.140 | -0.057018 | .045235 |
| age0        | -0.00625 | 0.004126 | -0.13 | 0.897 | -0.05223 | .043772 |
| female      | 0.1142799 | 0.1169982 | 0.98  | 0.330 | -0.116629 | .345189 |
| educvar      |        |          |       |     |         |         |
| 2           | -0.4046352 | 0.231826 | -2.10 | 0.037 | -0.948591 | .8235893 |
| 3           | -0.5870539 | 0.2200791 | -2.57 | 0.011 | -0.837194 | .169142 |
| 4           | -0.5431947 | 0.2352519 | -2.27 | 0.024 | -0.813535 | -.0710041 |
| baseComorbid | 0.1129075 | 0.0343977 | 3.28  | 0.001 | 0.045058 | .1807953 |
| surgery     | -0.3553809 | 0.1677528 | -2.12 | 0.036 | -0.806459 | .094019 |
| Months      | 0.0158287 | 0.0135712 | 1.17  | 0.245 | -0.080556 | .047131 |
| _cons       | 2.486275 | 0.5790856 | 4.16 | 0.000 | 1.263543 | 3.549088 |

. vif

<table>
<thead>
<tr>
<th>Variable</th>
<th>VIF</th>
<th>1/VIF</th>
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</thead>
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<td>0.740011</td>
</tr>
<tr>
<td>baseMos</td>
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<td>0.807043</td>
</tr>
<tr>
<td>age0</td>
<td>1.17</td>
<td>0.852705</td>
</tr>
<tr>
<td>female</td>
<td>1.13</td>
<td>0.886331</td>
</tr>
<tr>
<td>educvar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.86</td>
<td>0.258025</td>
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<tr>
<td>3</td>
<td>4.16</td>
<td>0.248091</td>
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<td>4</td>
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<td>0.296259</td>
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<td>baseComorbid</td>
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<td>0.783105</td>
</tr>
<tr>
<td>surgery</td>
<td>1.10</td>
<td>0.905441</td>
</tr>
<tr>
<td>Months</td>
<td>1.14</td>
<td>0.873458</td>
</tr>
</tbody>
</table>

Mean VIF 1.98

Figure 8: Test of multicollinearity with clinical depression and physical function outcome

. estat hettest

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity
Ho: Constant variance
Variables: fitted values of odq

\[
\text{chi}^2(1) = 1.85 \\
\text{Prob} > \text{chi}^2 = 0.1743
\]

Figure 9: Test of Homoscedasticity
### Figure 10: Multivariable regression analyses of depressive symptoms with disability without multiple imputations (n=186)

<table>
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<td>9334.57536</td>
<td>175</td>
<td>53.3404360</td>
<td>Prob &gt; F = 0.0000</td>
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<tr>
<td>Total</td>
<td>13320.7581</td>
<td>185</td>
<td>72.0040976</td>
<td>R-squared = 0.2992</td>
</tr>
</tbody>
</table>

| Coef. | Std. Err. | t | P>|t| | [95% Conf. Interval] |
|-------|-----------|---|-----|--------------------------|
| baseCESD | 0.3862145 | 0.0838992 | 4.61 | 0.000 | 0.2207089 | 0.55172 |
| baseMos | -0.006652 | 0.0393656 | -2.05 | 0.042 | -0.1583576 | -0.0029727 |
| age0 | 0.0388784 | 0.0506136 | 0.77 | 0.443 | -0.0610133 | 0.1387701 |
| female | 2.614207 | 1.14632 | 2.28 | 0.024 | 0.3510163 | 4.876598 |
| educvar | 2 | 4830875 | 2.407623 | 2.02 | 0.841 | -4.268628 | 5.234803 |
| 3 | 0.2697205 | 2.358825 | 0.11 | 0.999 | -4.385291 | 4.024732 |
| 4 | -1.79349 | 2.486509 | -0.72 | 0.472 | -6.704841 | 3.117862 |
| baseComorbid | 0.701065 | 0.3407258 | 2.06 | 0.041 | 0.0285458 | 1.373467 |
| surgery | -1.750181 | 1.68088 | -1.05 | 0.297 | -5.075007 | 1.555664 |
| Months | 0.168066 | 0.1341198 | 0.13 | 0.900 | -0.2478999 | 0.231501 |
| _cons | 18.94283 | 6.749184 | 2.81 | 0.006 | 5.6222558 | 32.26311 |

### Figure 11: Multivariable regression analyses of clinical depression with disability without multiple imputations (n=186)

<table>
<thead>
<tr>
<th>Source</th>
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<tbody>
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<td>Model</td>
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<td>334.3331897</td>
<td>F(10, 175) = 5.86</td>
</tr>
<tr>
<td>Residual</td>
<td>9977.4391</td>
<td>175</td>
<td>57.0139377</td>
<td>Prob &gt; F = 0.0000</td>
</tr>
<tr>
<td>Total</td>
<td>13320.7581</td>
<td>185</td>
<td>72.0040976</td>
<td>R-squared = 0.2510</td>
</tr>
</tbody>
</table>

| Coef. | Std. Err. | t | P>|t| | [95% Conf. Interval] |
|-------|-----------|---|-----|--------------------------|
| baseDepress | 3.810548 | 1.30177 | 2.93 | 0.004 | 1.241358 | 6.379738 |
| baseMos | -0.1106303 | 0.040172 | -2.75 | 0.007 | -0.1929443 | -0.0283164 |
| age0 | -0.0175328 | 0.0506002 | -0.35 | 0.729 | -0.1168374 | 0.081317 |
| female | 2.836448 | 1.185628 | 2.39 | 0.018 | 0.4964779 | 5.176419 |
| educvar | 2 | -1.904772 | 2.409527 | -0.79 | 0.430 | -6.660244 | 2.858099 |
| 3 | -1.78561 | 2.379549 | -0.72 | 0.474 | -6.481918 | 2.906988 |
| 4 | -0.091629 | 2.50564 | -0.33 | 0.739 | -9.036792 | 8.535339 |
| baseComorbid | 0.7643251 | 0.3518211 | 2.17 | 0.031 | 0.059666 | 1.458684 |
| surgery | -1.132473 | 1.747256 | -0.65 | 0.518 | -4.58888 | 2.3235934 |
| Months | 0.0519122 | 0.1347986 | 0.37 | 0.709 | -2.220225 | 0.3258469 |
| _cons | 31.79452 | 5.922316 | 5.35 | 0.000 | 20.01616 | 43.39288 |

99
Figure 12: Multivariable regression analyses of depressive symptoms with physical function without multiple imputations (n=186)

. regress sssf baseCESD baseMos age0 female ib1.educvar baseComorbid surgery Months

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<thead>
<tr>
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<td>2.97826136</td>
<td>Adj R-squared = 0.1969</td>
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<tr>
<td>Residual</td>
<td>94.133649</td>
<td>175</td>
<td>.537893514</td>
<td>Root MSE = .73341</td>
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<tr>
<td>Total</td>
<td>123.913978</td>
<td>185</td>
<td>.669805289</td>
<td></td>
</tr>
</tbody>
</table>

| sssf | Coef. | Std. Err. | t | P>|t| | [95% Conf. Interval] |
|------|-------|-----------|---|-------|----------------------|
| baseCESD | .027751 | .0082945 | 3.35 | .001 | .0113888 | .0441212 |
| baseMos | -.0043474 | .0039688 | -1.19 | .275 | -.0121803 | .0034854 |
| age0 | .0028785 | .0049688 | .08 | .563 | -.0069279 | .0126849 |
| female | .1896042 | .1152431 | 1.63 | .105 | -.0634897 | .4427381 |
| educvar | 2 | -.2976543 | .2382265 | -1.25 | .213 | .7678211 | .1725124 |
| | 3 | -.4334614 | .2328156 | -1.86 | .064 | .8929492 | .0260263 |
| | 4 | -.3687954 | .2452821 | -1.47 | .143 | .8447293 | .1231386 |
| baseComorbid | .1803594 | .0340437 | 5.30 | .000 | .0938043 | .3669146 |
| surgery | -.383167 | .1652256 | -2.32 | .022 | -.7091979 | -.0570545 |
| Months | .0126793 | .0133744 | 0.95 | .344 | -.0137165 | .0390752 |
| _cons | 1.57672 | .6742399 | 2.34 | .020 | .2468315 | 2.907408 |

Figure 13: Multivariable regression analyses of clinical depression with physical function without multiple imputations (n=186)

. regress sssf baseDepress baseMos age0 female ib1.educvar baseComorbid surgery Months

<table>
<thead>
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<td>2.74221749</td>
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<td>96.4918036</td>
<td>175</td>
<td>.551381735</td>
<td>Root MSE = .74255</td>
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<td>Total</td>
<td>123.913978</td>
<td>185</td>
<td>.669805289</td>
<td></td>
</tr>
</tbody>
</table>

| sssf | Coef. | Std. Err. | t | P>|t| | [95% Conf. Interval] |
|------|-------|-----------|---|-------|----------------------|
| baseDepress | .3284646 | .1274794 | 2.58 | .011 | .0768697 | .5800596 |
| baseMos | -.0058845 | .003969 | -1.48 | .140 | -.0137178 | .0019489 |
| age0 | -.006625 | .0048126 | -0.13 | .897 | -.0101232 | .0008732 |
| female | .1142799 | .1169882 | 0.98 | .330 | -.1166292 | .345189 |
| educvar | 2 | -.4846352 | .2310282 | -.210 | .037 | -.940591 | -.0286793 |
| | 3 | -.5870539 | .2280791 | -.257 | .011 | -.1.837194 | -.1369142 |
| | 4 | -.5431947 | .2392519 | -.227 | .024 | -.1.015385 | -.0710461 |
| baseComorbid | .1129675 | .0343977 | 3.28 | .001 | .0450198 | .1.807953 |
| surgery | -.3553809 | .1677528 | -.212 | .036 | -.6864599 | -.0243019 |
| Months | .0158287 | .0135712 | 1.17 | .245 | -.0109556 | .0426131 |
| _cons | 2.486275 | .5790856 | 4.16 | .000 | 1.263543 | 3.749008 |

100
Appendix 3: Chapter 4

Depression as a Prognostic Factor for LSS Outcomes is a Moderate quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO? Yes Yes Yes Yes Yes Yes Yes

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Yes Yes Yes Yes Yes Yes Yes

3. Did the review authors explain their selection of the study designs for inclusion in the review? Yes Yes

4. Did the review authors use a comprehensive literature search strategy? Partial Yes Yes Yes Yes Yes

5. Did the review authors perform study selection in duplicate? Yes Yes

6. Did the review authors perform data extraction in duplicate? Yes Yes

7. Did the review authors provide a list of excluded studies and justify the exclusions? Yes Yes

8. Did the review authors describe the included studies in adequate detail? Partial Yes Yes Yes Yes Yes

Figure 1: AMSTAR-2 of Systematic Review
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<th>RCT</th>
<th>NRSI</th>
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<tr>
<td>9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>10. Did the review authors report on the sources of funding for the studies included in the review?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?</td>
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<td>0</td>
</tr>
<tr>
<td>12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?</td>
<td>No</td>
<td></td>
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</table>

To cite this tool: Shea BJJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.
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<th>Outcome</th>
<th>Study</th>
<th>Statistical analysis and reporting</th>
<th>Overall risk of bias</th>
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<td>Low</td>
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</tr>
</tbody>
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Curriculum Vitae

Name: Ariel Morales, BSc.

Faculty of Health and Rehabilitation Sciences, School of Physical Therapy
Western University, London, Ontario, Canada

Post-secondary education and Degrees

BSc. of Medical Sciences (Honours) Sept 2016 – April 2020
MSc. of Physical Therapy September 2020 – Present

Related Work Experience

Volunteering: Brock-Niagara Centre for Health & Well-Being, St. Catharines, ON, (Dec 2019 – April 2020)

• Helped the members at a rehabilitation centre with physical activities. These included weightlifting, walking and supervision during exercises

Professional Experience: Teaching Assistantship, Faculty of Health Sciences, UWO

• Course: HS4320- Human Embryology (Winter 2021)
• Course: HS4120- Social Media and Health (Winter 2021, Winter 2022)

Presentations

London Health Research Day (May 2022)

• Poster presentation: Depression as a prognostic factor for Lumbar Spinal Stenosis outcomes. A Systematic Review

Joint Mental Health Research and Innovation Day (October 2022)

• Oral Presentation: Depression as a prognostic factor for outcome of disability and physical function in individuals with Lumbar Spinal Stenosis