Multimorbid degenerative lumbar spinal stenosis with knee or hip osteoarthritis: prevalence and associated characteristics

Young, James

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PhD Thesis

Multimorbid degenerative lumbar spinal stenosis with knee or hip osteoarthritis: prevalence and associated characteristics

James J. Young
Center for Muscle and Joint Health
Department of Sports Science and Clinical Biomechanics
Faculty of Health Science
University of Southern Denmark

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Supervisors

Jan Hartvigsen
Professor
Center for Muscle and Joint Health, Department of Sports Science and Clinical Biomechanics,
University of Southern Denmark

Ewa M. Roos
Professor
Center for Muscle and Joint Health, Department of Sports Science and Clinical Biomechanics,
University of Southern Denmark

Rikke Krüger Jensen
Associate Professor
Center for Muscle and Joint Health, Department of Sports Science and Clinical Biomechanics,
University of Southern Denmark

Carlo Ammendolia
Assistant Professor
Institute of Health Policy, Management and Evaluation
University of Toronto

Assessment committee

Karen Andersen-Randberg (Chair)
Associate Professor
Epidemiology, Biostatistics and Biodemography
University of Southern Denmark

Inger Mechlenberg
Professor
Department of Clinical Medicine – Orthopedic Surgery
Aarhus University

Jeremy Fairbank
Professor
Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences
University of Oxford

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Table of Contents

1 Preface

This PhD project was conducted at the Center for Muscle and Joint Health, Department of Sports Science and Clinical Biomechanics, Faculty of Health Science, University of Southern Denmark.

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1.1 List of thesis-related publications

Paper I:

Young JJ, Hartvigsen J, Jensen RK, Roos EM, Ammendolia C, Juhl CB. Prevalence of multimorbid degenerative lumbar spinal stenosis with knee and/or hip osteoarthritis: protocol for a systematic review and meta-analysis. Systematic Reviews. 2020;9:232.

Paper II:

Young JJ, Jensen RK, Hartvigsen J, Roos EM, Ammendolia C, Juhl CB. Prevalence of multimorbid degenerative lumbar spinal stenosis with knee or hip osteoarthritis: a systematic review and meta-analysis. BMC Musculoskeletal Disorders. 2022:23:177.

Paper III:

Young JJ, Hartvigsen J, Roos EM, Ammendolia C, Kongsted A, Skou ST, Grønne DT, Jensen RK. Symptoms of lumbar spinal stenosis in people with knee or hip osteoarthritis or low back pain: a cross-sectional study of 10,234 participants in primary care. Osteoarthritis and Cartilage. 2021:29(11):1515-1520.

Paper IV:

Young JJ, Kongsted A, Jensen RK, Roos EM, Ammendolia C, Skou ST, Grønne DT, Hartvigsen J. Characteristics associated with comorbid lumbar spinal stenosis symptoms in people with knee or hip osteoarthritis: an analysis of 9,136 Good Life with osteoArthritis in Denmark (GLA:D®) participants. In review.

1.2 Other PhD activities

Additional publications

Berg LS, Young JJ, Hurwitz E, Kopansky-Giles D, Eberspaecher S, Outerbridge G, Hartvigsen J. Musculoskeletal conditions in persons living with HIV/AIDS: a scoping review. Current Medical Science. 2022. 42(1):17-25.

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arrest the global disability burden: empirical development of prioritised components for a global strategy for improving musculoskeletal health. BMJ Global Health. 2021;6:e006045.

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Young JJ, Važić O, Cregg A. Management of knee and hip osteoarthritis: an opportunity for the Canadian chiropractic profession. Journal of the Canadian Chiropractic Association. 2021;65(1):6-13.

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Huckel Schneider C, Parambath S, Young JJ, Mishrra S, Slater H, Sharma S, Kopansky-Giles D, March L, Briggs AM. From local action to global policy: a systematic comparative policy content analysis of national policies to address musculoskeletal health to inform global policy development.

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Yu H, Cancelliere C, Mior S, Pereira P, Nordin M, Brunton G, Wong JJ, Shearer HH, Connell G, Verville L, Rezai M, Myrtos D, Wang D, Marchand A, Romanelli A, Germann D, To D, Young JJ, Southerst D, Tailor-Vasey A, Candelaria H, Hogg-Johnson, S, Côté P. Effectiveness of postsurgical rehabilitation in adults treated surgically for lumbar disc herniation: a systematic review.

Knowledge dissemination activities

The Hip-Spine Syndrome. Invited Lecture. Science in Action; Research Unit for Musculoskeletal Function and Physiotherapy; University of Southern Denmark. 01 December 2021.

Young JJ, Jensen RK, Hartvigsen J, Roos EM, Ammendolia C, Juhl CB. Prevalence of multimorbid degenerative lumbar spinal stenosis with knee or hip osteoarthritis: a systematic review and meta-analysis. Platform Presentation. Back and Neck Pain Forum. Online Conference. 12 November 2021.

Knee and hip osteoarthritis: an opportunity for the Canadian chiropractic profession. Invited Lecture. Canadian Chiropractic Association Master Class Series. Online event. 03 June 2021. https://www.youtube.com/watch?v=BHLo8qZgJKU

Young JJ, Hartvigsen J, Roos EM, Ammendolia C, Kongsted A, Skou ST, Grønne DT, Jensen RK. Prevalence of lumbar spinal stenosis symptoms in patients from primary care treated for knee or hip osteoarthritis or low back pain. Poster Presentation. OARSI World Congress. Online Conference. 29 April 2021.

Young JJ, Hartvigsen J, Jensen RK, Roos EM, Ammendolia C, Juhl CB. Prevalence of multimorbid degenerative lumbar spinal stenosis with knee and/or hip osteoarthritis: protocol for a systematic review and meta-analysis. Poster Presentation. CARLoquium. Online Conference. 02 March 2021

Hip-Spine Syndrome. Invited Lecture. Canadian Memorial Chiropractic College Graduate Department Rounds. 16 October 2020.

Young JJ, Skou ST, Koes BW, Grønne DT, Roos EM. Comparison of clinical criteria for hip osteoarthritis in primary care: a cross sectional study from Good Life with osteoArthritis in Denmark (GLA:D). Poster Presentation. OARSI World Congress. Vienna, Austria. 01 May 2020.

Special topics in clinical science. Guest Lecture. Chiropractic Clinical Sciences Graduate program, Canadian Memorial Chiropractic College. 04 October 2019.

Young JJ, Ammendolia C, Côté P, Schneider M, Rampersaud R, Hawker G. Predictors of improved walking distance following non-operative care for lumbar spinal stenosis. Poster Presentation. SpineFEST (University of Toronto, Faculty of Medicine). Toronto, Canada. 10 June 2019.

Young JJ, Ammendolia C, Côté P, Schneider M, Rampersaud R, Hawker G. Does duration of symptoms affect walking outcomes in patients receiving non-surgical care for lumbar spinal stenosis? Poster Presentation. SpineFEST. Toronto, Canada. 10 June 2019.

1.3 Thesis overview

Study	Aims	Methods	Findings
I. Prevalence of multimorbid degenerative lumbar spinal stenosis with knee or hip osteoarthritis: a systematic review and meta-analysis	1. To estimate the prevalence of multimorbid LSS with knee or hip OA based on clinical and/or imaging case definitions. 2. To investigate factors associated with the prevalence of multimorbid LSS with knee or hip OA.	A systematic review and meta-analysis of studies estimating the prevalence of multimorbid LSS with knee OA and meta-regression analyses of factors associated with prevalence estimates. 10 studies included.	The prevalence of multimorbid LSS with knee OA ranged from 5-54% and from 0-35% for multimorbid LSS with hip OA. Prevalence estimates varied by case definitions used. Included studies were from surgical settings and at a high risk of bias. Meta-regression analyses were not possible to conduct.
II. Symptoms of lumbar spinal stenosis in people with knee or hip osteoarthritis or low back pain: a cross-sectional study of 10,234 participants in primary care	1. To report the proportion of people self-reporting LSS symptoms in a structured education and exercise primary care program for knee or hip OA. 2. To estimate the prevalence of self-reported clinical LSS in people with knee or hip OA.	Descriptive registry study reporting the proportion of GLA:D® participants self-reporting 11 symptoms of LSS and fulfilling two sets of adapted clinical criteria for LSS. 6,541 participants with knee OA and 2,595 with hip OA were included.	The prevalence of LSS symptoms ranged from 8-40% in people with knee OA and from 11-50% in people with hip OA. The prevalence of clinical LSS ranged from 2-3% in people with knee OA and from 3-4% in people with hip OA.
III. Characteristics associated with comorbid lumbar spinal stenosis symptoms in people with knee or hip osteoarthritis: an analysis of 9,136 Good Life with osteoArthritis in Denmark (GLA:D®) participants	1. To investigate characteristics associated with comorbid symptoms of LSS in the same primary care cohorts of people with knee or hip OA.	GLA:D® registry study using multiple multivariable logistic regression models to determine association estimates between participant characteristics and comorbid LSS symptoms. 6,541 participants with knee OA and 2,595 with hip OA were included.	Both in people with knee or hip OA, characteristics such as sick leave in the past year, back pain in the last month, and a symptom duration greater than two years were associated with comorbid LSS symptoms. These characteristics were associated irrespective of LSS symptom definition or model building procedure.

1.4 Summary in English

The overall aim of this PhD thesis was to provide foundational data to help answer the questions of how often multimorbid lumbar spinal stenosis (LSS) with knee or hip osteoarthritis (OA) occurs and what characteristics are associated with this multimorbid presentation. To answer these questions, three studies were conducted:

Study I was a systematic review with the primary objective of investigating the prevalence of multimorbid LSS with knee or hip OA based on varying case definitions. This review found there is an overall lack of available literature with sufficient data to estimate the multimorbid prevalence, but that published studies suggest 5-54% of people may have coexisting LSS and knee OA and 0-35% of people may have coexisting LSS and hip OA. The majority of estimates are derived from samples of people with LSS and prevalence estimates are highly dependent on the case definitions used for both LSS and OA. The secondary objective was to investigate factors associated with multimorbid prevalence estimates, but the dearth of published literature using similar case definitions for LSS and OA prevented the conduct of meta-regression analyses. The study protocol has been published in *Systematic Reviews* (DOI:10.1186/s13643-020-01478-4) and the final study has been accepted for publication in *BMC Musculoskeletal Disorders* (DOI:10.1186/s12891-022-05104-3).

Study II was based on data from the Good Life with osteoArthritis in Denmark (GLA:D®) database including people seeking treatment for knee or hip OA. Participants completed 11 self-report questions on symptoms commonly associated with LSS. We found that 8-40% of participants with knee OA self-reported LSS symptoms, depending on the specific symptom. Likewise, 11-50% of people with hip OA self-reported the different LSS symptoms. Using these symptoms to operationalize adapted versions of two published clinical criteria for symptomatic LSS, less than 3% and 5% of people with knee and hip OA were considered to have clinical LSS, respectively. This study has been published in *Osteoarthritis and Cartilage* (DOI:10.1016/j.joca.2021.07.012).

Study III was based on the same GLA:D® cohort of people seeking care for knee or hip OA. Here, we aimed to identify characteristics associated with comorbid LSS symptoms. We performed multiple multivariable logistic regression analyses in each cohort independently, using comorbid LSS symptom status as the dependent variable. We also conducted sensitivity analyses to ensure our findings were robust to a different definition of comorbid LSS symptoms and different model building procedures. In both cohorts, we found consistent evidence across models and sensitivity models that sick leave in the past year, back pain in the last month, and knee or hip symptom duration greater than 2 years, were associated with comorbid LSS symptoms. We also found a similar pattern of other associated characteristics between cohorts, but these characteristics did not show consistent associations across all models and sensitivity models. This study is currently in review for publication.

Overall, this thesis found a significant proportion of people may experience multimorbid LSS with knee or hip OA and has uncovered patient characteristics associated with multimorbid presentations. Future studies accounting for the methodological limitations uncovered in this thesis are needed to better inform the clinical care of people with multimorbid LSS with knee or hip OA.

1.5 Summary in Danish

De overordnede formål med denne PhD-afhandling var at besvare spørgsmålene om, hvor ofte lumbal spinal stenose (LSS) forekommer sammen med knæ eller hofteartrose (OA), og hvilke karakteristika der er forbundet med denne form for multimorbiditet. For at besvare disse spørgsmål blev de følgende tre studier gennemført:

Studie I var et systematisk litteraturstudie med det primære formål at undersøge forekomsten af multimorbid LSS med knæ- eller hofte-OA baseret på forskellige diagnosekriterier. Litteraturgennemgangen fandt, at der er mangel på tilgængelige studier til at estimere forekomsten, men at hidtidige studier sammenfattet tyder på, at 5-54% af befolkningen kan have sameksisterende LSS og knæ OA, og at 0-35% kan have sameksisterende LSS og hofte OA. Størstedelen af estimaterne er afledt fra befolkningsgrupper med LSS, og er generelt afhængige af, hvilke diagnosekriterier der anvendes for både LSS og OA. Det sekundære formål var at undersøge hvilke faktorer der er forbundet med sameksisterende LSS og OA, men manglen på publiceret litteratur med sammenlignelige diagnosekriterier for LSS og OA forhindrede udførelsen af metaanalyse. Studieprotokollen er blevet offentliggjort i *Systematic Reviews* (DOI:10.1186/s13643-020-01478-4), og det endelige studie er blevet accepteret til at blive publiceret i *BMC Musculoskeletal Disorders* (DOI:10.1186/s12891-022-05104-3).

Studie II var baseret på data fra Godt Liv med Artrose i Danmark (GLA:D®), som inkluderer personer i behandling for knæ- eller hofte-OA. Deltagerne udfyldte 11 spørgsmål om symptomer, der er forbundet med LSS. Vi fandt, at 8-40% af deltagerne med knæ OA selvrapporterede LSS-symptomer, afhængigt af det specifikke symptom. Ligeledes rapporterede 11-50% af personer med hofte-OA at de havde LSS-symptomer. Når vi anvendte disse symptomer til at operationalisere tidligere offentliggjorte diagnosekriterier, blev mindre end 3% og 5% af personer med henholdsvis knæ og hofte-OA anset for at have klinisk LSS. Dette studie er blevet publiceret i *Osteoarthritis and Cartilage* (DOI:10.1016/j.joca.2021.07.012).

Studie III var baseret på den samme GLA:D®-kohorte som studie II. Her var formålet at identificere karakteristika forbundet med sameksisterende LSS symptomer. Vi udførte flere multivariable logistiske regressionsanalyser i hver af kohorterne (hofte og knæ OA) separat ved at bruge LSS symptomstatus som den afhængige variabel. Vi udførte også sensitivitetsanalyser for at sikre, at vores resultater var robuste over for andre definitioner af sameksisterende LSS symptomer og forskellige opbygninger af analysemodeller. På tværs af begge kohorter fandt vi konsistente indikationer for at sygefravær inden for det seneste år, rygsmerter inden for den sidste måned og varighed af knæ eller hoftesymptomer på mere end to år, var forbundet med sameksisterende LSS symptomer. Vi fandt lignende mønstre for andre associerede karakteristika mellem kohorter, men disse karakteristika viste ikke konsistente associationer på tværs af alle modeller og følsomhedskriterier. Dette studie er under revision forud for publicering.

Samlet set fandt denne PhD-afhandling, at en betydelig andel af befolkningen oplever sameksisterende LSS med OA i knæ eller hofte. Derudover blev patientkarakteristika forbundet med sameksisterende symptomer afdækket. Fremtidige, metodisk optimerede, studier er nødvendige for bedre at informere behandling af mennesker med multimorbid LSS med knæ eller hofte OA.

1.6 List of abbreviations

LSS	Lumbar spinal stenosis
OA	Osteoarthritis
MSK	Musculoskeletal
CAD	Canadian dollar
DKK	Danish krone
BMI	Body mass index
LBP	Low back pain
GLA:D®	Good Life with osteoArthritis in Denmark
PROSPERO	International Prospective Register of Systematic Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
CI	Confidence interval
STROBE	STrengthening the Reporting of Observational studies in Epidemiology
KOOS-12	Knee injury and Osteoarthritis Outcome Score 12-item version
HOOS-12	Hip disability and Osteoarthritis Outcome Score 12-item version
ASES	Arthritis Self-Efficacy Scale
UCLA	University of California and Los Angeles Activity Score

1.7 List of tables

1.8 List of figures

2 Background

This thesis was developed around the general hypothesis that degenerative lumbar spinal stenosis (LSS) and knee and hip osteoarthritis (OA) may be more similar conditions than not, perhaps indicating that they should not be considered explicitly distinct. There is growing recognition that overall, different musculoskeletal (MSK) disorders share many attributes and commonly co-occur. This is especially true in multi-joint OA, where the coexistence of spinal OA is increasingly recognized. Degenerative LSS can be conceived as lumbar spine OA with the potential for neurological symptoms, supporting the idea that LSS, knee OA, and hip OA are similar disorders. Similar risk factors, physiological processes, and diagnostic and management approaches for degenerative LSS and knee and hip OA strengthen this hypothesis.

If these three conditions are similar entities, coexistence may be expected, which is termed multimorbidity. Clinical reports of coexistence in the hip-spine syndrome literature and lesser-known knee-spine syndrome literature, as well as the multi-joint OA literature, suggest these multimorbid presentations may be an underrecognized phenomenon with important clinical implications, such as altered response to current management approaches or the need for tailored interventions. However, little is known about how often LSS, knee OA, and hip OA co-occur, or characteristics associated with this specific multimorbidity. Therefore, the overarching purpose of this thesis was to conduct preliminary investigations aimed at exploring the prevalence of multimorbid degenerative LSS with knee or hip OA and associated characteristics.

2.1 OA, LSS, and multimorbidity

To better understand how and why LSS and knee or hip OA may coexist in some people, we must first clarify what is meant by the terms OA, LSS, and multimorbidity. Important similarities and differences in terminology exist across these research fields.

2.1.1 What is OA?

OA of the knee and hip are considered diseases of the whole joint organ,[1,2] meaning more than just the articular cartilage is affected. Changes to the synovial capsule and synovium, menisci,

subchondral bone, ligaments, and muscles also occur.[3] Clinically, the person with knee or hip OA can experience various symptoms such as stiffness, reduced joint range of motion, muscle weakness, and reduced walking ability or other functional abilities,[1,2,4] with pain being the primary symptom leading to care-seeking.[5] However, there is variability in how people experience OA symptoms and progression.[6–9] Some individuals experience intermittent symptoms or flares,[10] while others may develop a chronic or persistent pain pattern.[6] Likewise, the location of pain is inconsistent, with some individuals reporting localized joint pain, some variable pain locations, and others diffuse pain presentations.[11–13]

2.1.1.1 OA epidemiology

Global Burden of Disease data estimates that over 300 million people have knee or hip OA.[14] OA is a major cause of global disability[15,16] and is especially burdensome in older adults.[1,17] There is a significant health systems and societal cost associated with OA, but individual patients also bear large personal cost.[18] OA was the 8th leading cause of healthcare spending in 2016 in the United States[19] and over 1.4 billion CAD is spent on knee and hip replacement surgeries alone in Canada.[20] From a societal perspective, OA can cost upwards of 2.5% of gross domestic product.[21] For example, the 2010 cost of OA to the Danish society was 6.8 billion DKK.[22] Alarmingly, the prevalence of OA and attributed disability have steadily risen in the past 30 years and continue to increase,[14–16] meaning the cost of OA will continue to grow in the future.

2.1.1.2 Defining OA

The prevalence of OA varies by the case definition used.[23] Typically, OA is defined as radiographic or symptomatic, although self-report and clinical definitions are also used.[23–25] Therefore, the generic term OA can be used to mean radiographic or clinical findings. Radiographic definitions rely on changes in the joint structure visualized on imaging, with the most common scoring criteria being the Kellgren-Lawrence scale.[23,25,26] Symptomatic definitions require the presence of joint-related symptoms in addition to imaging changes.[23,25] In general, the radiographic prevalence of OA is greater than the symptomatic prevalence (minimum 2.5 times greater in both knee and hip OA).[23] The presence of symptoms alone can also be used to

define OA clinically,[4,27–29] but relatively fewer prevalence estimates using these definitions are available.

2.1.2 What is degenerative LSS?

Degenerative LSS results from age-related OA changes to structures of the functional spinal unit (or motion segment), leading to narrowing of the central or lateral spinal canals.[30–33] Affected structures may include the facet joints, intervertebral disc, ligamentum flavum, and other boney and ligamentous structures.[30,31,33] This anatomical narrowing can lead to compression and ischemia of the neurovascular structures, resulting in the clinical syndromes of LSS.[30,31] Typically, three clinical syndromes associated with LSS are described in the literature.[30,34] The most commonly referenced clinical LSS syndrome is neurogenic claudication, which is a result of central canal stenosis and is described as bilateral or unilateral buttocks and leg pain, weakness, or heaviness, typically aggravated by walking and standing and relieved with sitting and forward bending.[32,35–37] The second clinical presentation is radicular pain/radiculopathy resulting from lateral canal stenosis, and the third is mixed or combined type, resulting from mixed central and lateral canal stenosis.[30,34]

The clinical symptoms of LSS overlap those from knee and hip OA.[34,38–41] The major difference is the potential for neurological symptoms in severe cases of LSS, but in most cases, the neurological examination is unremarkable.[31] Otherwise, like OA, pain in the buttocks and lower extremities are the most common feature of LSS.[30–32] Likewise, walking limitations are a dominant functional impairment in LSS, knee OA, and hip OA.[42] Back pain may be present, but is not a key feature of LSS,[43–45] and is also experienced by people with knee and hip OA.[46,47] Finally, the symptomatic nature of LSS is variable and different symptom trajectories exist, which are similar to those seen in people with OA. Some individuals with LSS remain in an intermittent symptom pattern, some develop a chronic persistent pain pattern, and some experience symptom resolution.[48,49] Overall, the symptomatic profile of LSS, knee OA, and hip OA have considerable overlap.

2.1.2.1 LSS epidemiology

There is no specific Global Burden of Disease estimate for the prevalence of LSS or associated disability. A recent review of prevalence estimates found 11% of the general population has symptomatic LSS.[50] Like OA, LSS is especially burdensome in older adults,[50–52] where it is the leading reason for spinal surgery.[53] Surgery for LSS is costly to health systems[54,55] and the number of LSS surgeries around the world are quickly increasing.[53,55–57] Similar to projections for knee and hip OA, the LSS prevalence, burden, and cost is expected to continue to grow.[30,51]

2.1.2.2 Defining LSS

Much like OA, the prevalence of LSS depends on the selected case definition.[50] For example, the prevalence of radiographic LSS is 38% in the general population compared to only 11% when using a clinical case definition.[50] Radiographic definitions are based only on anatomical narrowing of the central and/or lateral spinal canals.[50,58,59] Magnetic resonance (MRI) or computed tomography (CT) images are used to define radiographic LSS, but exact criteria to define the presence of LSS do not currently exist.[50,58–60] Clinical case definitions of LSS are based on reported symptoms, such as reduced walking capacity, or increased/decreased pain with different body positions.[43,45,50] Similarly, there is no agreed-upon definition of what constitutes clinical LSS.[34,43–45,61–63] Finally, the term symptomatic LSS (radiographic findings plus clinical symptoms) appears in the literature,[32] but is not often used compared to symptomatic OA, despite the combination of clinical and imaging findings often being needed to confirm the diagnosis.[30,31,34,45,64] As such, LSS and OA can be largely defined in a similar manner, although variations in terminology exist within the respective fields.

There is one key difference in the terminology related to the definition of LSS compared to OA. The term OA can be used to mean both the structural (imaging) changes and/or clinical symptoms. However, the terminology used in the literature for degenerative LSS can create confusion. LSS is used to describe the structural spinal (imaging) changes, but both LSS and neurogenic claudication are used interchangeably when speaking about the clinical symptom presentation.[31,34,65,66] In this thesis, we have used the term LSS with appropriate descriptors

based on the case definition (e.g. radiographic, clinical, symptoms). This approach was selected to best match the terminology in the OA field and allow for a common method of description across LSS and OA.

2.1.3 What are multimorbidity and comorbidity?

The terms multimorbidity and comorbidity, while similar, represent meaningfully different constructs.[67] Multimorbidity is the presence of two or more conditions without specification of a primary or index condition.[68,69] Comorbidity refers to the presence of additional conditions (one or more) in a person with a specified index condition.[69] An example using LSS and knee OA can help to illustrate the difference. If interested in determining the prevalence of LSS and knee OA in people from the general population, neither condition is of greater importance or focus, and therefore the term multimorbidity is used. Alternatively, if interested in the prevalence of knee OA in a sample of people treated for LSS, LSS is the index condition and therefore knee OA represents the comorbid condition.

This thesis explored multimorbid LSS with knee or hip OA, but to do so, we were required to look at both LSS with comorbid knee and hip OA and the alternative, knee or hip OA with comorbid LSS. Additionally, alternative definitions for multimorbidity may include: a greater number of conditions; the weighting of included conditions; or symptoms and/or risk factors for disease.[70–72] For this thesis, only LSS, knee OA, and hip OA were of interest. Therefore, no other conditions, symptoms, risk factors, or weighting of conditions were included in the definition of multimorbid LSS with knee or hip OA.

2.2 Multimorbid LSS with knee or hip OA

Both LSS and knee or hip OA are related to age-related or degenerative changes in the functional joint unit.[1,2,30,31] There is evidence from basic science studies suggesting the physiological processes giving rise to these changes are similar in the spine, knee, and hip.[73–76] This includes common mechanisms of degenerative change,[73,74] inflammatory biomarkers,[75] and genetic variants.[76] Therefore, LSS may be conceived as lumbar spine OA with the potential

for neurological symptoms.[77,78] Moreover, there are similar factors, such as increasing age, female sex, and increasing body mass index (BMI), that may increase the risk of developing LSS and knee or hip OA.[1,2,31,52,79] Finally, there is a range of published literature that suggests LSS and knee or hip OA may coexist. Studies on general MSK multimorbidity, multi-joint OA, and the hip-spine syndrome all provide indirect evidence for multimorbid LSS with knee or hip OA (Figure 1).

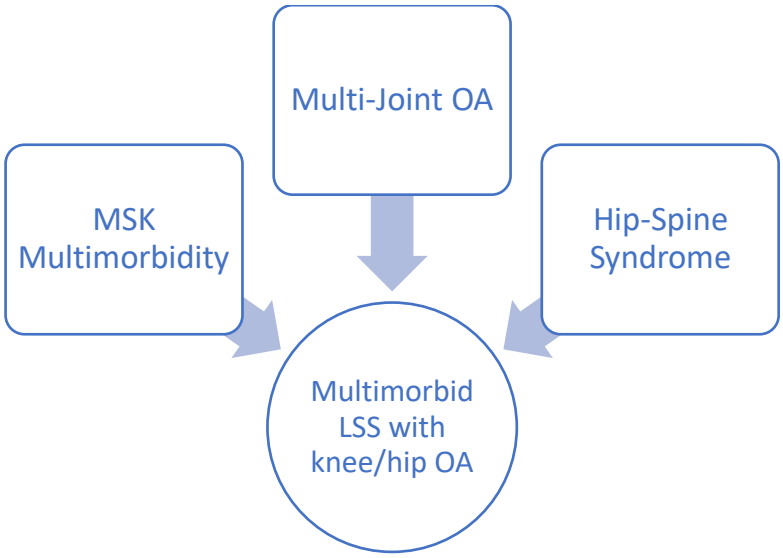


Figure 1. **Evidence for multimorbid LSS with knee or hip OA**

2.2.1 MSK multimorbidity

MSK multimorbidity is a growing area of interest for overall MSK health.[80,81] Individuals often experience multiple MSK disorders and/or pain sites,[77,82–92] termed MSK multimorbidity. Regardless of the precise definition used, having MSK multimorbidity is associated with worse health status and response to treatment,[77,82,83,85,87–90,92–94] and even mortality.[95] Multiple MSK conditions are so common and impactful that a shift in the management approach away from single conditions or body areas has been proposed.[96]

People with OA frequently experience multimorbidity, including additional MSK conditions.[2,46,47] For example, the prevalence of low back pain (LBP) ranges from 33 to 56% in people with knee and hip OA.[46,47] In the Good Life with osteoArthritis in Denmark (GLA:D®)

program, LBP is reported by 67% and 75% of people with knee and hip OA, respectively.[97] There is comparatively less literature on comorbidities in people with LSS, but available data also shows comorbidities are common and associated with worsened health states.[93,98] Although these data sources have not looked at comorbid OA specifically, comorbid arthritis is common.[93,98]

2.2.2 Multi-joint OA

Multi-joint OA, also called generalized OA,[99] is a specific subset within MSK multimorbidity.[100] Although no standardized definition exists yet, it appears multi-joint presentations are more common than having a single-affected joint.[92,101–103] Multiple joint involvement is also associated with worsened patient health status and response to treatment.[92,103–105] However, the lumbar spine has not been included in most multi-joint OA definitions.[77,102] Data from the Johnston County OA project has shown that people with radiographic lumbar OA are more likely also to have radiographic knee OA, but no relationship with hip OA was found.[106] Conversely, in a cadaveric study, hip OA was a stronger predictor than knee OA for having spine OA.[107] Since LSS is a result of lumbar spine OA,[77,78] it could be part of the multi-joint OA profile. It is crucial to understand how often LSS and OA in other joints coexist since having additional symptomatic joints, including the hip and knee, reduces the likelihood of attaining a clinically meaningful improvement following surgery for LSS.[77]

2.2.3 Hip-spine syndrome

Finally, the body of literature on the hip-spine syndrome[108–113] and less-developed body of literature on the knee-spine syndrome[114,115] also suggests that co-occurring LSS with knee or hip OA could be an important clinical consideration. The term hip-spine syndrome has grown to include various links between the hip and the spine,[108] but originally described co-occurring LSS and hip OA.[116] Other clinical reports[109,117] have also found these conditions coexist, but the prevalence of hip-spine syndrome is unknown. However, the mechanism underlying hip-spine syndrome is not known, but alterations in structural alignment and joint-loading are thought to play a role.[108] The knee-spine syndrome, which has emerged from interest in the hip-spine

syndrome, has primarily focused on structural alignment relationships with no explicit linkages made between LSS and knee OA.[114,115]

Numerous studies have looked at the influence of hip-spine syndrome (i.e. all relationships between LBP and hip disorders) on treatment response,[108] but few studies have specifically examined the impact of multimorbid LSS with knee or hip OA. There is evidence that having knee or hip OA reduces the likelihood of a clinically meaningful improvement in function following lumbar decompression surgery for LSS, but not for post-operative symptoms.[118] Therefore, how often LSS co-occurs with knee or hip OA and the consequences for clinical care require further investigation.

2.3 Summary and knowledge gaps

Overall, LSS, knee OA, and hip OA are more similar than not. Definitions for LSS and OA, including the descriptive terminology, are largely the same. Evidence across different research areas suggests that multimorbid LSS with knee or hip OA may exist and could have a substantial impact on the health and care of people traditionally thought to have only one of LSS, knee OA, or hip OA. However, very few studies, if any, have specifically examined multimorbid LSS with knee or hip OA. Therefore, there is a need to understand the scope of this potential problem; namely how often multimorbid LSS with knee or hip OA occurs and which individuals might be at risk.

3 Aims

The thesis aimed to answer two overall questions (Figure 2):

1. How often does multimorbid LSS with knee or hip OA occur?
2. What characteristics are associated with multimorbid LSS with knee or hip OA?

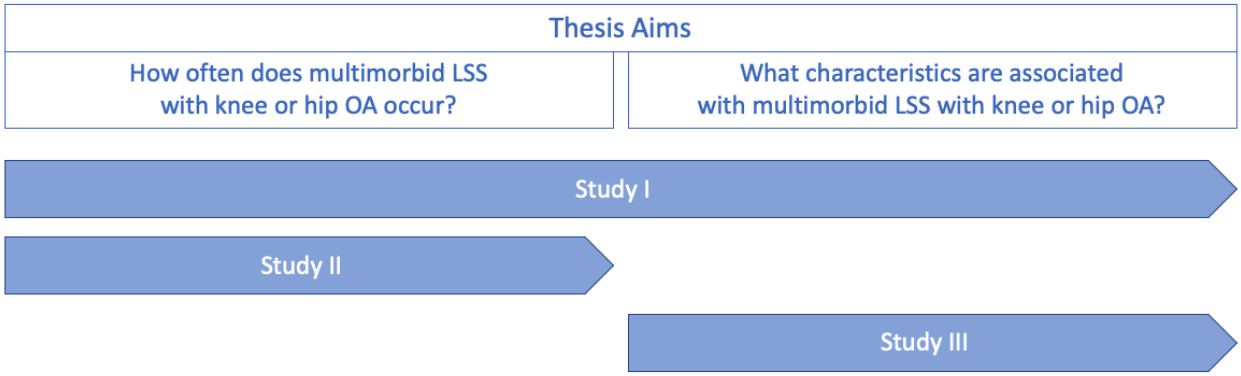


Figure 2. **Thesis aims and studies**

3.1 Objectives

The overall aims of this thesis were operationalized in five study-specific objectives:

1. To estimate the prevalence of multimorbid LSS with knee or hip OA based on clinical and/or imaging case definitions (Study I)
2. To investigate factors associated with the prevalence of multimorbid LSS with knee or hip OA (Study I)
3. To report the proportion of people self-reporting LSS symptoms in a structured education and exercise primary care program for knee or hip OA (Study II)
4. To estimate the prevalence of self-reported clinical LSS in people with knee or hip OA (Study II)
5. To investigate characteristics associated with comorbid symptoms of LSS in the same primary care cohorts of people with knee or hip OA. (Study III)

4 Methods

4.1 Study I

4.1.1 Objectives

The primary aim of this study was to estimate the prevalence of multimorbid LSS with knee or hip OA based on various case definitions. Four specific objectives were investigated:

1. to estimate the prevalence of index LSS with comorbid knee OA based on imaging, clinical, and combined case definitions;
2. to estimate the prevalence of index LSS with comorbid hip OA based on imaging, clinical, and combined case definitions;
3. to estimate the prevalence of index knee OA with comorbid LSS based on imaging, clinical, and combined case definitions; and
4. to estimate the prevalence of index hip OA with comorbid LSS based on imaging, clinical, and combined case definitions.

The secondary aim was to identify factors associated with the prevalence of multimorbid LSS with knee or hip OA.

4.1.2 Study design

This study was a systematic review and meta-analysis of prevalence data. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020177759) and published (paper I).[119] This review was performed following the Cochrane Handbook[120] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[121]

4.1.3 Search strategy

An electronic database search was performed on 03 May 2021. The following databases were searched with no publication date or language restrictions: MEDLINE, EMBASE, CENTRAL, and CINAHL. The search strategy was developed in collaboration with a health sciences librarian. Search strategies for each database are available in Appendix 1 (Table A 1). Three search

domains were created to cover LSS, knee OA, and hip OA, based on search terms used in previous Cochrane reviews.[65,122,123] Search terms related to LBP were included in the LSS domain to increase the sensitivity of the search.

Reference lists of included studies were screened for additional studies and forward citation tracking was performed in Web of Science. The reference list from a recently published review on LSS prevalence[50] was also screened and PROSPERO was searched for related ongoing or completed systematic reviews. Conference abstracts presented between 2018 and 2020 at the Osteoarthritis Research Society International World Congress and International Forum for Back and Neck Pain Research in Primary Care were also screened to identify potentially relevant publications. Finally, content experts known to the author group were contacted to identify known publications with data relevant to this review. All references were managed using Endnote X9 (Clarivate Analytics, Philadelphia, USA) and Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

4.1.4 Eligibility criteria

Studies were included if they met the eligibility criteria in Table 1.

Table 1. **Study I eligibility criteria**

Inclusion criteria	Exclusion criteria
Cross-sectional, cohort, case-control, or randomized controlled trials	Included individuals with low back, knee, or hip pain due to other origins (e.g., fracture, tumour, inflammatory disease, infection, lumbar disc herniation)
Adults 18 years or older	Laboratory or cadaveric studies, or conference abstracts
Assessed the prevalence of co-occurring LSS with knee and/or hip OA or presented sufficient cross-sectional data for estimating prevalence	Included congenital or non-degenerative forms of LSS, without separate data on degenerative LSS
Full-text paper published in English in peer-reviewed journal	Provided aggregate prevalence data for knee and hip OA

4.1.5 Case definitions

All case definitions for degenerative LSS and knee and hip OA were included in this review. Case definitions were classified into three categories: imaging, clinical, and combined (imaging plus clinical) definitions. Criteria for each case definition are described below. Case definitions were also assigned as the index condition based on participant inclusion criteria (study population) in the study. As an example, in a study including participants undergoing surgery for LSS who were evaluated for knee OA by radiographs, LSS was the index condition (combined case definition) and knee OA was the comorbid condition (imaging case definition).

4.1.5.1 Imaging definitions

All diagnoses based on radiographic, magnetic imaging resonance, or computerized tomography for the lumbar spine, knee, and hip were included in the imaging definition category.

4.1.5.2 Clinical definitions

Diagnoses based on signs and symptoms of LSS, knee OA, or hip OA were classified as a clinical case definition. All clinical manifestations of LSS, including neurogenic claudication, radicular type, and mixed types, were included as they represent central, lateral, and combined central and lateral lumbar canal stenosis.[34] Unless explicitly stated otherwise, patient self-report and medical chart reviews, including International Classification of Disease codes, were classified as clinical diagnosis for both LSS and OA.

4.1.5.3 Combined definitions

Studies including a definition of LSS or knee or hip OA that satisfied both the imaging and clinical definitions described above were classified as a combined case definition. Studies on surgical samples for LSS or OA that did not provide explicit case definitions were considered combined diagnoses since it is unlikely surgical interventions are performed based on imaging or clinical findings alone.

4.1.6 Study selection

A two-phase article selection process was conducted by two reviewers. In phase one, titles and abstracts were independently screened using a sensitive approach where articles were moved to full-text review if mentioning any of the following:

1. LSS in isolation;
2. knee or hip OA and comorbidities;
3. knee or hip OA and LBP; or
4. prevalence of multiple musculoskeletal conditions

This approach was used reduce the probability of excluding relevant studies due to a lack of reporting in study abstracts. Discrepancies were resolved through discussion.

In the second phase, full-text versions of the studies identified in phase-one were independently screened against study eligibility criteria (Table 1). Discrepancies were resolved through discussion or review by a third reviewer when necessary.

4.1.7 Data extraction

Study data were extracted independently by two reviewers using a standardized data extraction form. The following information was extracted: first author, publication year, country, study design, population (LSS, knee OA, or hip OA), inclusion criteria, study setting, age, sex, case definition LSS and knee and/or hip OA, numerator and denominator for prevalence calculation, and items used in the risk of bias assessment. Disagreements were resolved through consensus discussion.

4.1.8 Risk of bias assessment

Risk of bias assessment was performed independently by two reviewers on all included studies using a modified version of the Risk of Bias Tool for Prevalence Studies.[124] Modifications to the tool were made for the purposes of this study. All items making specific reference to LBP were altered to LSS or knee or hip OA, where applicable. Specific modifications were made to items 1, 5, 6, 7, and 9. The wording of item 1 was changed from “a close representation of the

national population" to "a close representation of the target population" because this review was not concerned with national populations. Item 5 was completely removed as clinical and imaging information can only be collected directly from participants. Items 6 (acceptability of case definition) and 7 (validity/reliability of study instruments) were each split into two questions to allow independent ratings of LSS and OA definitions and measurement properties. An additional response option (irrelevant) was included for item 9 because studies using imaging-only case definitions are not impacted by recall bias. The modifications for this study followed the approach used in two recent systematic reviews using the same risk of bias tool.[50,82] The entire modified risk of bias tool is presented in Appendix 1 (Table A 2).

Individual items were rated as "Yes" for low of bias and "No" for high risk of bias or if insufficient information was reported to render a judgement. A judgement on the overall risk of bias (low, moderate, high) was made independently by the two reviewers. Disagreements were resolved through consensus discussion. No quantitative thresholds were used to judge the overall risk of bias.

4.1.9 Evidence synthesis

Study and participant characteristics were reported descriptively. Pooled prevalence estimates with 95% confidence intervals (CI) were calculated using a random effects model for each case definition combination of LSS with knee or hip OA where sufficient comparable studies were available. Due to the low number of studies using comparable case definitions for LSS and knee and/or hip OA, only pooled estimates for combined LSS and comorbid i) clinical knee OA, ii) imaging knee OA, iii) clinical hip OA, and iv) imaging hip OA were calculated. One study reporting a multimorbid prevalence of 0% was artificially given a numerator of 0.001 to allow for inclusion in the meta-analysis. The low number of studies in each pooled estimate prevented the calculation of heterogeneity statistics. All statistical analyses were performed in Stata 16.1 (StataCorp LLC, College Station, USA).

4.1.10 Meta-regression analyses

Pre-planned meta-regression analyses investigating the impact of various factors on multimorbid prevalence estimates were not conducted due to the low number of included studies. Planned meta-regression analyses included: participant age, sex, LSS clinical presentations (neurogenic claudication, radicular type, mixed type); LSS pain severity, LSS disability level, healthcare setting (hospital, community), and study risk of bias.

4.2 Study II

4.2.1 Objectives

The primary aim of this study was to report the proportion of people in a primary care treatment program for knee or hip OA who self-report symptoms associated with LSS. The secondary aim was to estimate the prevalence of self-reported clinical LSS in these primary care cohorts.

4.2.2 Study design

This was a cross-sectional analysis of baseline registry data from the GLA:D® for knee and hip OA primary care treatment program[125] reported according to the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist for cross-sectional studies.[126] Ethics approval was not required per the Health Research Ethics Committee of the North Denmark Region. All participants provided informed consent to report data in the GLA:D® registry. GLA:D® has been approved by the Danish Data Protection Agency (SDU; 10.084).

4.2.3 Participants

Participants enrolled in GLA:D® between January 2019 and February 2020 with available baseline data were included in both studies. GLA:D® for knee and hip OA is a national primary care treatment program in Denmark.[125,127] GLA:D® has been implemented in 300 clinics (majority physiotherapy) across Denmark and enrols around 10,000 people with knee or hip OA annually.[127] The GLA:D® treatment program consists of two group-based patient education sessions on knee and hip OA and 12 sessions of group-based, standardized and individualized,

exercise sessions delivered over 6-8 weeks.[127] Participants can access GLA:D® through referral from a general practitioner or specialist or self-referral to a GLA:D® clinic.[127] Eligibility criteria for enrolment in GLA:D®[125] are listed in Table 2. No specific diagnostic criteria for knee or hip OA, including diagnostic imaging, are required to participate in GLA:D®.

Two cohorts were identified at baseline according to the participant-reported primary joint complaint (knee or hip). These same knee OA and hip OA cohorts were used for studies II and III. Participants answering the baseline self-report LSS primary symptom item were included in both analyses.

Table 2. **Eligibility criteria for GLA:D® for knee and hip OA**

1.	Understand Danish
2.	Pain and/or functional limitations in the knee or hip joint
3.	Do not have another condition with more severe symptoms than OA (e.g. fibromyalgia, chronic generalized pain, serious pathology)
4.	Do not have another condition responsible for their joint symptoms (e.g. inflammatory joint disease, patellar tendinopathy)

4.2.4 Baseline characteristics

Participant baseline characteristics in the GLA:D® registry were collected via a combination of electronic questionnaires administered to participants and clinicians. Baseline characteristics were classified according to three domains: social demographics, clinical characteristics, and health status measures. A detailed description of the GLA:D® registry collection for each selected baseline characteristic is available in Appendix 1 (Table A 3).

4.2.4.1 Sociodemographics

Age strata (<50, 50-59, 60-69, 70-79, ≥80), sex (male/female), body mass index (BMI; categories: underweight normal weight, overweight, obese), highest level of education attained (categories: primary school, secondary school, short-term education, middle-term education, long-term education), current employment status (categories: employed/student, full-time sick leave, part-time sick leave, retired, unemployed, self-imposed early retirement, early

retirement due to low workability), and sick leave within the past year (yes/no) were included in the baseline sociodemographics domain.

4.2.4.2 Clinical characteristics

Symptom duration (categories: <3 months, 3-12 months, 13-24months, >24 months), presence of bilateral joint symptoms (yes/no), comorbid hip symptoms (yes/no; knee cohort only), comorbid knee symptoms (yes/no; hip cohort only), comorbid back pain in the last month (yes/no), number of comorbidities (categories: 0, 1, 2, ≥3), current use of pain medication (yes/no), current use of opioids (yes/no), and fear of movement (yes/no) were included in the baseline clinical characteristics domain.

4.2.4.3 Health status measures

The Knee injury and Osteoarthritis Outcome Score 12-item version (KOOS-12; knee cohort only) or Hip disability and Osteoarthritis Outcome Score 12-item version (HOOS-12; hip cohort only) pain, function, and quality of life subscales (0-100, worst-best),[128,129] Arthritis Self-Efficacy Scale (ASES) pain and other symptoms subscales (10-100, worst-best),[130] University of California and Los Angeles (UCLA) Activity Score (1-10, worst-best),[131] 30-second chair stand test (number of repetitions completed),[132] and the 40 meter fast-paced walk test (seconds)[132] were included in the baseline health status measures domain.

4.2.5 Self-report LSS symptom items

Eleven self-report LSS symptom questions (response options yes/no) were administered electronically at baseline as part of the GLA:D® registry data collection. English-language versions of these questions are presented in

Table 3. LSS symptom items were selected based on a previous review of self-report diagnostic screening questions for LSS.[44] The majority of these items adequately differentiate LSS from other sources of back-related leg pain.[44] All participants answered the LSS primary symptom item (item 1). Participants answering “yes” to the primary item were asked to answer the remaining ten symptom items. Participants answering “no” to the primary item were assigned

an answer of “no” on the remaining ten symptom items, as the remaining items are irrelevant if participants do not report the presence of leg pain or numbness. This data collection approach was implemented to reduce respondent burden in the already large GLA:D® registry. Importantly, participants were instructed to answer the LSS symptom items in reference to symptoms unrelated to their knee or hip complaint (see item 1 in

Table 3).

Table 3. **Self-report LSS symptom items**

Item number	Question
1 (primary symptom item)	Do you sometimes have pain or numbness in one or both legs or the buttock? (other symptoms than related to knee or hip)
The next questions concern how you feel your pain and numbness symptoms (examples). Please mark if you had the symptom during the last month.	
2	Do you have pain or numbness in both legs or the buttocks?
3	Do you have numbness under both feet?
The next questions concern what can worsen your pain or numbness (examples). Please mark if you felt worsening during the following activities within the last month.	
4	Is your pain or numbness in one or both legs or in the buttock worsening when you are walking?
5	Is your pain or numbness in one or both legs or in the buttock worsening when you have been standing for a while?
The next questions concern what can reduce your pain or numbness (examples). Please mark if you had relief of symptoms during the following activities within the last month.	
6	Is your pain or numbness in one or both legs or in the buttock relieved when you are bending forwards?
7	Is your pain or numbness in one or both legs or in the buttock relieved when you are sitting?
8	Is your pain or numbness in one or both legs or in the buttock relieved when you are riding a bicycle?
9	Is your pain or numbness in one or both legs or in the buttock relieved when you are bending over the shopping cart?
The next questions concern what happens when you are walking. Please mark if you had experienced the following during the last month.	
10	Do you bend forwards while walking?

11	Do you have the feeling of weakness in your legs while walking?

4.2.6 Adapted LSS clinical criteria

LSS symptom items were used to operationalize adapted versions of published clinical criteria for LSS.[43,61] There is currently no consensus criteria for diagnosing or classifying LSS.[30,31,44,45,62] Likewise, no valid or reliable screening questionnaires for LSS are currently available.[44] Therefore, two sets of clinical criteria were chosen to better estimate the prevalence of clinical LSS.

4.2.6.1 Tomkins-Lane criteria

The first set of clinical criteria included were adapted from the published criteria by Tomkins-Lane et al.[43] These items and their operationalization are presented in Appendix 1 (Table A 4). This set of clinical criteria for LSS has not been validated, but the original Tomkins-Lane publication found that expert clinician participants are 86% certain in the diagnosis of LSS after asking six questions.[43]

Two modifications to the original criteria were made. “Presence of normal foot pulses” was not evaluated in the GLA:D® registry and therefore not included in this study. “Lower extremity weakness” was also excluded from this study because the corresponding LSS symptom (item 11: feeling weakness in legs while walking) was already used to operationalize the Tomkins-Lane item “motor or sensory disturbance while walking”.

4.2.6.2 Genevay criteria

The classification criteria for neurogenic claudication published by Genevay et al.,[61] were also adapted for this study. Items, scoring, and operationalization are presented in Appendix 1 (Table A 5). Final scores on the original classification criteria could range from 0-19 with a score of ≥11 indicating neurogenic claudication due to LSS. Compared to expert clinical diagnosis, this cut point had a specificity of 92% and sensitivity of 82% in the development sample.[61] This set of criteria has not been validated in an external sample.

This set of criteria was also modified since neither physical examination test (30 second extension and straight leg raise) are evaluated in the GLA:D® registry. Therefore, the scoring was adjusted for the adapted Genevay criteria. A maximum total score of 13 was possible on the adapted criteria, but the cut point to indicate neurogenic claudication due to LSS was held at ≥11, representing a conservative approach to prevalence estimation. Due to the scoring weights of the remaining four items in the adapted criteria, a total score of ≥11 was possible only if all items were satisfied (i.e., any combination of three or less items could not reach the ≥11 cut point). Therefore, participants needed to satisfy all four items in the adapted criteria to be classified as having clinical LSS.

4.2.7 Statistical analysis

Descriptive baseline characteristics for both cohorts were reported as means and 95% CI (continuous data) and proportions and 95% CI (categorical and binary data). Participants with missing data on the self-reported LSS primary symptom item were compared to participants with complete data using summary statistics on age, sex, BMI, symptom duration, current use of pain medication, and current use of opioids (this data is not patient self-reported).

The proportion and 95% CI of participants self-reporting each LSS symptom item was calculated in both the knee and hip cohorts. Additionally, the proportion and 95% CI of participants fulfilling each set of adapted LSS clinical criteria was calculated, as well as the proportion (95% CI) satisfying both sets of criteria. No statistical comparison of LSS symptom item or clinical criteria endorsement between cohorts was conducted. All statistical analyses in both studies were performed in Stata 17.0 (StataCorp LLC, College Station, USA).

4.3 Study III

4.3.1 Objective

The aim of this study was to investigate characteristics associated with comorbid symptoms of LSS in the same GLA:D® primary care cohorts of people with knee or hip OA.

4.3.2 Study design

Like study II, this was a cross-sectional analysis of baseline registry data from the GLA:D® for knee and hip OA primary care treatment program.[125] This study was also reported according to the STROBE checklist for cross-sectional studies.[126] Similarly, ethics approval was not required per the Health Research Ethics Committee of the North Denmark Region. All participants provided informed consent to report data in the GLA:D® registry. GLA:D® has been approved by the Danish Data Protection Agency (SDU; 10.084).

4.3.3 Participants

The same sample of participants included in study II was used in this study. Like in study II, participants were divided into a separate knee and hip cohort based on self-reported primary joint complaint.

4.3.4 Comorbid LSS symptoms definition

A definition of comorbid LSS symptoms was constructed using the self-report LSS symptom items included in study II (Table 3). A participant was classified as having comorbid LSS symptoms if they answered "yes" to the primary symptom item plus yes to any of the following items: worsening when walking; worsening when standing; relieved when bending forwards; relieved when sitting; relieved when riding a bicycle; relieved when bending over a shopping cart; bending forward while walking; or feeling weakness in the legs while walking (Table 4). This definition was chosen due to the lack of consensus diagnostic criteria for LSS [30,31,44,45,62] and the low prevalence of individuals fulfilling the adapted LSS clinical criteria in study II.

Table 4. **Comorbid LSS symptom definition and alternate definition**

Comorbid LSS symptoms definition	Alternate comorbid LSS symptoms definition
Participants answering "yes" to: 1. Do you sometimes have pain or numbness in one or both legs or the buttock? (other symptoms than related to knee or hip); **Plus "yes" to at least one of items:** 4. Is your pain or numbness in one or both legs or in the buttock worsening when you are walking? 5. Is your pain or numbness in one or both legs or in the buttock worsening when you have been standing for a while? 6. Is your pain or numbness in one or both legs or in the buttock relieved when you are bending forwards? 7. Is your pain or numbness in one or both legs or in the buttock relieved when you are sitting? 8. Is your pain or numbness in one or both legs or in the buttock relieved when you are riding a bicycle? 9. Is your pain or numbness in one or both legs or in the buttock relieved when you are bending over the shopping cart? 10. Do you bend forwards while walking? 11. Do you have the feeling of weakness in your legs while walking?	**Participants answering "yes" to:** 1. Do you sometimes have pain or numbness in one or both legs or the buttock? (other symptoms than related to knee or hip); **Plus "yes" to at least one of worsening items:** 4. Is your pain or numbness in one or both legs or in the buttock worsening when you are walking? 5. Is your pain or numbness in one or both legs or in the buttock worsening when you have been standing for a while?; **Plus "yes" to at least one of relieving items:** 6. Is your pain or numbness in one or both legs or in the buttock relieved when you are bending forwards? 7. Is your pain or numbness in one or both legs or in the buttock relieved when you are sitting? 8. Is your pain or numbness in one or both legs or in the buttock relieved when you are riding a bicycle? 9. Is your pain or numbness in one or both legs or in the buttock relieved when you are bending over the shopping cart?

4.3.5 Baseline characteristics

The same baseline characteristics in study II were included in this study. Similar to study II, baseline characteristics were divided into three domains: sociodemographics; clinical characteristics; and health status measures (section 4.2.4).

4.3.6 Statistical analysis

The same sample descriptive characteristics reported for study II (section 4.2.7) were included in this study. Additionally, differences in baseline characteristics between participants answering with and without comorbid LSS symptoms were compared within the knee and hip cohorts, respectively.

Four multivariable logistic regression models (three domain-specific models, one overall model) were built in both the knee and hip cohorts, respectively, to evaluate the association of

baseline characteristics (22 total) with the primary LSS symptom definition (binary outcome: yes/no). First, all baseline characteristics in each of the sociodemographics, clinical characteristics, and health status measures domains were entered into separate domain-specific models. Second, all baseline characteristics from each of the three domains were entered into one overall model. Each baseline characteristic was therefore evaluated in two multivariable models (domain-specific and overall models) in each cohort. This modelling approach was selected due to the dependence of association estimates on the specific covariates included in multivariable models.[133,134] This four-model strategy allowed for the estimation and comparison of association estimates for potentially important characteristics across a range of included covariates. Associations between each baseline characteristic and LSS symptoms were reported as odds ratios (OR) and 95% CI. All statistical analyses in both studies were performed in Stata 17.0 (StataCorp LLC, College Station, USA).

4.3.7 Sensitivity analyses

Two sensitivity analyses were conducted. The purpose of the first sensitivity analysis was to evaluate the robustness of the study findings to an alternative model building procedure. In this analysis, all baseline characteristics with a p-value <0.2 in the domain-specific models were entered into one overall reduced model, using the comorbid LSS symptom definition from the primary analysis. This reduced model allowed for an additional comparison of association estimates in the presence of a different combination of covariates in the multivariable model.

The purpose of the second sensitivity analysis was to evaluate the robustness of the study findings to an alternate definition of comorbid LSS symptoms. In this analysis, participants were classified as having comorbid LSS symptoms if they answered “yes” to the primary symptom item; plus “yes” to any of the symptom worsening items: worsening when walking; or worsening when standing; plus “yes” to at least one of the symptom relieving items: relieved when bending forwards; relieved when sitting; relieved when riding a bicycle; or relieved when bending over a shopping cart (Table 4). This definition is a more specific operationalization of comorbid LSS symptoms. In this analysis, the overall multivariable logistic regression model was

repeated in each cohort using this alternate comorbid LSS symptom definition as the independent variable.

5 Results

5.1 Study I

5.1.1 Study selection

The study selection flow diagram is presented in Appendix 2 (Figure A 1). A total of 3,891 records were identified through database searching and other sources. 2,891 titles and abstracts were screened after the removal of duplicate records and 517 full-text articles were screened. Ten studies satisfied the eligibility criteria.[41,135–143]

5.1.2 Study characteristics and risk of bias

No studies with the objective of investigating the prevalence of multimorbid LSS with knee or hip OA were identified. All included studies provided secondary data that could be used to calculate prevalence estimates.

Across all included studies, sample sizes ranged from 44 to 2,857,999 and mean age from 61 to 73 years. One study [138] was rated as moderate risk of bias and all other studies were rated as high risk of bias. Risk of bias ratings for all included studies are presented in Appendix 2 (Table A 6).

5.1.3 Prevalence of multimorbid LSS with knee or hip OA

The prevalence of multimorbid LSS with knee OA across all case definitions ranged from 5 to 54%,[135–142] and from 0 to 35% across all case definitions of multimorbid LSS with hip OA.[41,135,137,139,140,143]

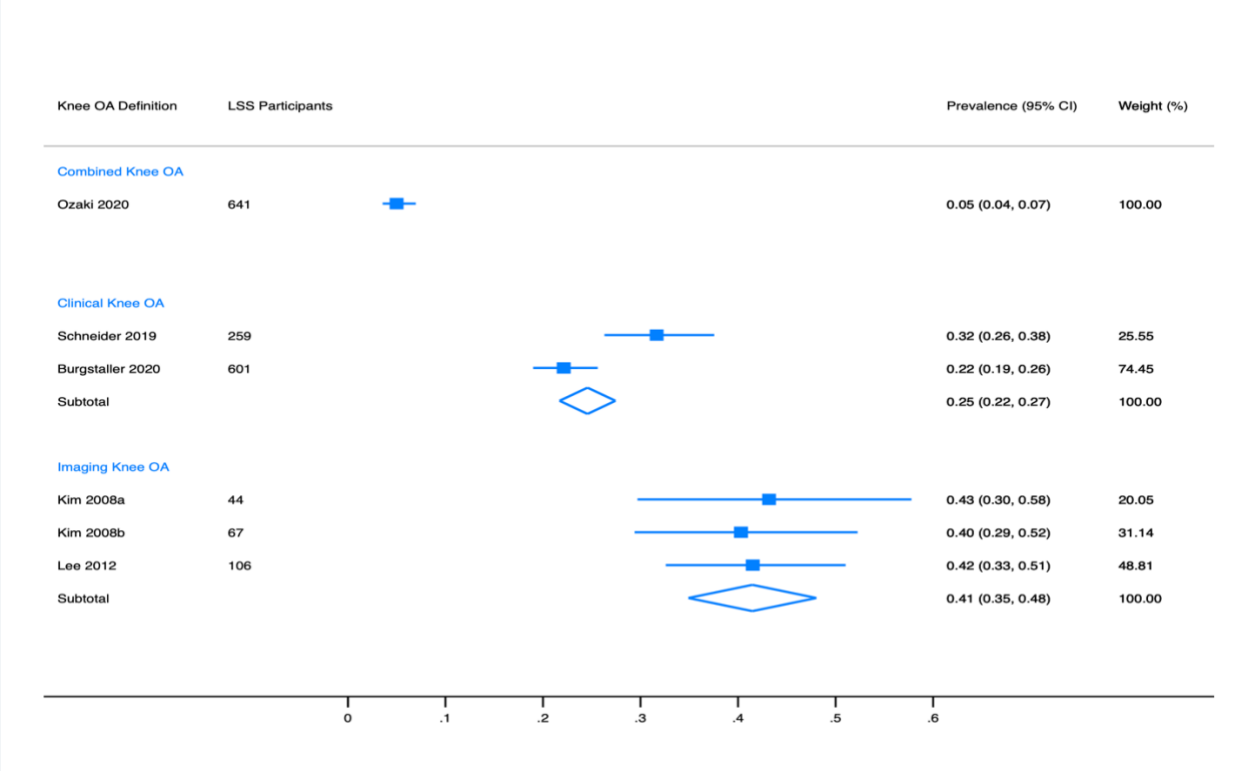
5.1.3.1 LSS and comorbid knee OA

Six studies provided data to calculate the prevalence of index LSS with comorbid knee OA.[135–137,139–141] Characteristics of the included studies are presented in Appendix 2 (Table A 7. Study characteristics of included studies for LSS with comorbid knee OATable A 7). All but one study enrolled participants from surgical care settings. The single study by Schneider et al.,[139]

included a mixed sample of community and primary and secondary care participants. Index LSS was defined using a combined case definition in all studies. One, two, and three studies defined comorbid knee OA using a combined,[141] clinical,[139,140] and imaging[135–137] case definition, respectively.

Prevalence estimates by case definition are presented in
Figure 3. The prevalence of index combined LSS with comorbid combined knee OA (one study; n=641) was 5% (95% CI 4-7%).[141] The pooled prevalence of index combined LSS with comorbid clinical knee OA (two studies; n=860) was 25% (95% CI 22-27%).[139,140] The pooled prevalence of index combined LSS with comorbid imaging knee OA (three studies; n=217) was 41% (95%CI 35-48%).

(A)



(B)

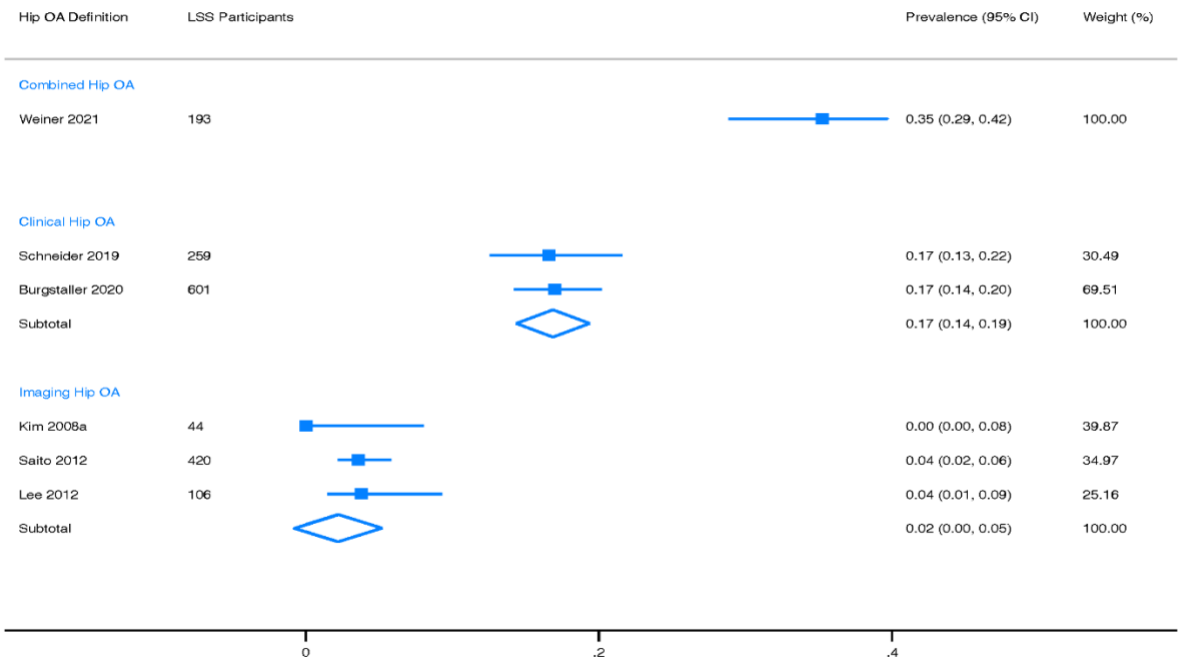


Figure 3. **Prevalence estimates for combined LSS with comorbid (A) knee OA and (B) hip OA**

5.1.3.2 LSS and comorbid hip OA

Six studies provided data to calculate the prevalence of index LSS with comorbid hip OA.[41,135,137,139,140,143] Study characteristics are presented in Appendix 2 (Table A 8). Five studies enrolled participants from surgical care settings.[41,135,137,140,143] One study enrolled a mixed sample of participants from community, primary, and secondary care settings.[139] Index LSS was defined using a combined case definition in all studies. One, two, and three studies defined comorbid hip OA using a combined,[143] clinical,[139,140] and imaging[41,135,137] case definition, respectively.

Prevalence estimates by case definition are presented in
Figure 3. The prevalence of index combined LSS with comorbid combined hip OA (one study; n=193) was 35% (95% CI 29-42%).[143] The pooled prevalence of index combined LSS with comorbid clinical hip OA (two studies; n=860) was 17% (95% CI 14-19%).[139,140] The pooled prevalence of index combined LSS with comorbid imaging hip OA (three studies; n=570) was 2% (95% CI 0-5%).[41,135,137]

5.1.3.3 Knee OA and comorbid LSS

Two studies provided data to calculate the prevalence of index knee OA with comorbid LSS.[138,142] Study characteristics are presented in Appendix 2 (Table A 9). Index OA was defined using a combined case definition in both studies and one study each defined comorbid LSS using a combined[142] and clinical[138] case definition.

No pooled prevalence estimates were calculated. The prevalence of index combined knee OA with comorbid combined LSS (one study; n=200) was 54% (95% CI 47-61%).[142] The prevalence of index combined knee OA with comorbid clinical LSS (one study; n=2,857,999) was 17% (95% CI 17-17%).[138]

5.1.3.4 Hip OA and comorbid LSS

No studies evaluating the prevalence of index hip OA with comorbid LSS were identified.

5.1.4 Factors associated with multimorbid prevalence

No meta-regression analyses were conducted due to the low number of included studies.

5.2 Study II

5.2.1 Sample characteristics

The study flow diagram is presented in Appendix 2 (Figure A 2). Included in the analysis were 6,541 participants with a primary knee complaint and 2,595 participants with a primary hip complaint (overall response rate 82%). Sample baseline characteristics for the knee (Table A 10) and hip (Table A 11) cohorts are presented in Appendix 2. In the knee cohort, participants had a mean age of 65.5 years and a mean BMI of 29.0 kg/m^2. In the hip cohort, participants were slightly older (mean age of 66.7 years) and had a lower mean BMI (27.2 kg/m^2). In both cohorts, 69% of the participants were female.

5.2.2 Excluded participants

Comparison of the GLA:D® participants during the study period excluded from the analysis due to missing baseline LSS symptom item data (n=1,989) is presented in Appendix 2 (Table A 12). Excluded participants were generally older, more likely to be male, and were more likely to be using any pain medication and opioids specifically.

5.2.3 Prevalence of LSS symptoms

The proportion of participants endorsing each self-report LSS symptom item in both the knee and hip cohorts is presented in Table 5. The prevalence of individual symptoms varied greatly within both cohorts, with a range from 11 to 50% in the hip cohort and from 8 to 40% in the knee cohort. In both cohorts, the LSS primary symptom item was most often reported. The least common symptom in the hip cohort was “numbness in the soles of both feet”, whereas “relieved leg/buttock pain with forward bending” was the least common in the knee cohort.

Between the cohorts, LSS symptoms were more often reported by participants with hip OA than with knee OA. This pattern was observed for all symptom items.

Table 5. **Prevalence of self-reported LSS symptoms in the knee and hip cohorts**

LSS symptom item	Knee cohort (n=6,541)	Hip cohort (n=2,595)
1. Sometimes pain or numbness in one/both legs or buttocks†	39.6 (38.4, 40.8)	50.4 (48.5, 52.4)
2. Pain or numbness in both legs or buttocks§	18.4 (17.4, 19.3)	20.8 (19.3, 22.4)
3. Numbness in the soles of both feet	10.2 (9.5, 11.0)	10.9 (9.8, 12.2)
4. Worsened leg/buttock pain when walking	21.7 (20.7, 22.8)	29.9 (28.2)
5. Worsened leg/buttock pain when standing	28.8 (27.7, 29.9)	37.2 (35.3, 39.1)
6. Relieved leg/buttock pain with forward bending	8.2 (7.6, 8.9)	12.6 (11.4, 14.0)
7. Relieved leg/buttock pain with sitting	18.5 (17.6, 19.5)	23.0 (21.4, 24.7)
8. Relieved leg/buttock pain with biking	13.6 (12.8, 14.4)	16.1 (14.8, 17.6)
9. Relieved leg/buttock pain when using shopping cart	13.5 (12.7, 14.3)	19.4 (17.9, 21.0)
10. Bend forwards while walking	12.7 (11.9, 13.5)	19.9 (18.4, 21.5)
11. Weakness in legs while walking	23.8 (22.7, 24.8)	29.7 (28.0, 31.5)

Reported as % (95% CI); † = LSS primary symptom item.

5.2.4 Prevalence of clinical LSS

The proportion of participants in the knee and hip cohorts satisfying the adapted Tomkins-Lane and Genevay criteria for self-reported clinical LSS are presented in Table 6. Few participants in both cohorts fulfilled either set of criteria, with the largest estimate of clinical LSS being 4.3% in the hip cohort according to the adapted Tomkins-Lane criteria. Likewise, only 1.0% of participants with hip OA fulfilled both sets of clinical LSS criteria and only 0.8% with knee OA.

Table 6. **Prevalence of clinical LSS in the knee and hip cohorts**

	Knee cohort (n=6,541)	Hip cohort (n=2,595)
Adapted Tomkins-Lane criteria	**2.7 (2.3, 3.1)**	**4.3 (3.5, 5.1)**
Back pain	66.0 (64.8, 67.1)	75.0 (73.3, 76.7)
4. Worsened leg/buttock pain when walking	21.7 (20.7, 22.8)	29.9 (28.2, 31.7)
6. Relieved leg/buttock pain with forward bending	8.2 (7.6, 8.9)	12.6 (11.4, 14.0)
8. Relieved leg/buttock pain with biking	13.6 (12.8, 14.4)	16.1 (14.8, 17.6)
9. Relieved leg/buttock pain when using shopping cart	13.5 (12.7, 14.3)	19.4 (17.9, 21.0)
11. Weakness in legs while walking	23.8 (22.7, 24.8)	29.7 (28.0, 31.5)
Adapted Genevay criteria	**1.8 (1.5, 2.2)**	**2.7 (2.1, 3.4)**
Age >60	73.8 (72.7, 74.9)	78.5 (76.8, 80.0)
2. Pain or numbness in both legs or buttocks	18.4 (17.4, 19.3)	20.8 (19.3, 22.4)
6. Relieved leg/buttock pain with forward bending	8.2 (7.6, 8.9)	12.6 (11.4, 14.0)
7. Relieved leg/buttock pain with sitting	18.5 (17.6, 19.5)	23.0 (21.4, 24.7)
Both sets of adapted criteria	**0.8 (0.6, 1.1)**	**1.0 (0.7, 1.6)**

Reported as % (95% CI).

5.3 Study III

5.3.1 Sample characteristics

Sample characteristics for the overall knee cohort and by comorbid LSS symptom status are presented in Appendix 2 (Table A 10). Sample characteristics for the overall hip cohort and by comorbid LSS symptom status are presented in Appendix 2 (Table A 11).

In the knee cohort, 37% of participants fulfilled the comorbid LSS symptom definition (24% alternate definition), while 48% of participants in the hip cohort fulfilled the comorbid LSS symptom definition (32% alternate definition).

5.3.2 Missing data

Since the same participant sample was included in studies II and III, those excluded from this analysis due to missing LSS data were older, more likely to be male, and were more likely to be using pain medication and opioids specifically (Table A 12). Among included participants, there was very little missing data for the other baseline variables, except for the 30-second chair-stand test and 40 meter fast-paced walk test. Missing data on either of the 30-second chair-stand test (knee cohort χ^2=1.38, p=0.24; hip cohort χ^2=0.09, p=0.77) or 40 meter fast-paced walk test (knee cohort χ^2=0.15, p=0.70; hip cohort χ^2=0.49, p=0.49) was not associated with reporting comorbid LSS symptoms.

5.3.3 Characteristics associated with comorbid LSS symptoms

Associations for each baseline characteristic across all models in the knee cohort are presented in Table 7. Associations for each baseline characteristic across all models in the hip cohort are presented in Table 8.

5.3.3.1 Sociodemographics

Sick leave in the past year was the only sociodemographic item that was significantly associated with reporting comorbid LSS symptoms in both the knee and hip cohort, regardless of the model-building procedure or LSS outcome definition. The ORs ranged from 1.29 to 1.41 in the knee cohort and from 1.48 to 1.90 in the hip cohort.

Overweight, obesity, and early retirement due to low workability were significantly associated with LSS symptoms in most models in the knee cohort, but never in the hip cohort. Conversely, being 80 years of age or older was significantly associated with not having LSS symptoms in most models in the hip cohort, but never in the knee cohort.

5.3.3.2 Clinical characteristics

In both cohorts, having a symptom duration >24 months and back pain in the last month were both associated with having LSS symptoms, regardless of the model-building procedure or LSS

outcome definition. The ORs for symptom duration >24 months ranged from 1.32 to 1.61 in the knee cohort and from 1.75 to 2.05 in the hip cohort, while the ORs for back pain in the last ranged from 1.85 to 2.07 in the knee cohort and 1.42 to 1.74 in the hip cohort. In most models across both cohorts, bilateral knee or hip symptoms, ≥3 medical comorbidities, and pain medication use were associated with LSS symptoms.

In the hip cohort, all symptom duration categories ≥3 months were associated with LSS symptoms in all models, but only inconsistently associated in the knee cohort. In the knee cohort, having comorbid hip symptoms was always associated with LSS symptoms, but having comorbid knee symptoms was not associated with LSS symptoms in the hip cohort.

5.3.3.3 Health status measures

In both cohorts, having better functional levels (measured by the KOOS-12 and HOOS-12 function subscales) was consistently associated with slightly reduced odds of LSS symptoms. The ORs for these associations were always 0.99 in both cohorts, indicating this association is unlikely to be clinically relevant.

In the knee cohort, being less able to manage other symptoms related to knee OA (measured by the ASES other symptoms subscale) was consistently associated with slightly greater odds of LSS symptoms, but was inconsistently associated in the hip cohort. The OR for all associations in both cohorts was 0.99 in all models, again indicating that this relationship is unlikely to be clinically relevant.

Table 7. **Association of characteristics with comorbid LSS in the knee OA cohort**

	Domain-specific models	Overall model	Reduced model	Alternate LSS symptom model
Sociodemographics				
Age				
<50	---	---	---	---
50-59	0.98 (76.9-1.24)	1.03 (0.79-1.34)	1.03 (0.79-1.34)	1.22 (0.91-1.64)
60-69	0.79 (61.6-1.02)†	0.85 (0.64-1.12)	0.85 (0.64-1.12)	0.97 (0.71-1.32)
70-79	74.9 (0.56-1.00)*	0.83 (0.60-1.14)	0.82 (0.60-1.13)	0.92 (0.64-1.32)
≥80	0.85 (0.60-1.20)	0.97 (0.66-1.42)	0.96 (0.65-1.41)	1.06 (0.79-1.64)
Female	1.09 (0.97-1.22)†	0.99 (0.87-1.12)	0.98 (0.86-1.11)	0.97 (0.84-1.12)
Body mass index				
Underweight	1.77 (0.85-3.70)†	2.25 (1.00-5.06)*	2.24 (0.99-5.02)	2.18 (0.90-5.26)
Healthy weight	---	---	---	---
Overweight	1.34 (1.17-1.54)***	1.24 (1.07-1.44)**	1.23 (1.06-1.43)**	1.12 (0.94-1.34)
Obese	1.52 (1.32-1.75)***	1.18 (1.00-1.39)*	1.17 (0.99-1.37)	1.32 (1.10-1.58)**
Education				
Primary school	---	---	---	---
Secondary school	0.89 (0.73-1.08)	0.94 (0.76-1.16)	0.93 (0.76-1.15)	0.83 (0.65-1.05)
Short-term	0.86 (0.73-1.01)†	0.92 (0.77-1.11)	0.92 (0.77-1.11)	0.96 (0.79-1.18)
Middle-term	0.91 (0.78-1.05)†	0.98 (0.84-1.56)	0.99 (0.84-1.16)	0.97 (0.81-1.15)
Long-term	0.73 (0.60-0.89)**	0.82 (0.66-1.02)	0.83 (0.67-1.04)	0.82 (0.64-1.06)
Employment				
Employed/student	---	---	---	---
Sick leave full-time	1.50 (1.08-2.07)*	0.98 (0.68-1.40)	0.96 (0.67-1.37)	0.84 (0.57-1.24)
Sick leave part-time	1.38 (1.00-1.89)*	0.95 (0.67-1.34)	0.93 (0.66-1.32)	0.93 (0.64-1.34)
Retired	1.17 (0.98-1.39)†	1.10 (0.91-1.34)	1.09 (0.90-1.32)	1.21 (0.97-1.51)
Unemployed	1.73 (1.22-2.46)**	1.48 (1.01-2.17)*	1.47 (1.00-2.15)*	1.44 (0.97-2.14)
Self-imposed early retirement	1.18 (0.89-1.57)	1.20 (0.88-1.62)	1.20 (0.88-1.62)	1.15 (0.81-1.63)
Early retirement due to low workability	2.33 (1.66-3.27)***	1.55 (1.07-2.25)*	1.52 (1.05-2.21)*	1.22 (0.83-1.79)
Sick leave in past year	1.41 (1.19-1.67)***	1.33 (1.10-1.60)**	1.31 (1.09-1.58)**	1.29 (1.06-1.58)*

Clinical characteristics				
Symptom duration				
<3 months	---	---	---	---
3-12 months	1.23 (1.00-1.50)*	1.23 (0.99-1.52)	1.22 (0.98-1.51)	1.60 (1.22-2.08)**
13-24 months	1.30 (1.04-1.63)*	1.23 (0.96-1.57)	1.22 (0.96-1.56)	1.69 (1.26-2.27)***
>24 months	1.35 (1.09-1.66)**	1.32 (1.05-1.65)*	1.32 (1.05-1.65)*	1.61 (1.22-2.12)**
Bilateral knee symptoms	1.43 (1.29-1.60)***	1.40 (1.25-1.57)***	1.39 (1.24-1.56)***	1.27 (1.11-1.45)***
Comorbid hip symptoms	1.54 (1.34-1.76)***	1.54 (1.33-1.78)***	1.54 (1.33-1.78)***	1.46 (1.24-1.70)***
Back pain in last month	2.07 (1.84-2.33)***	1.86 (1.64-2.11)***	1.85 (1.63-2.10)***	1.94 (1.67-2.26)***
Number of comorbidities				
0	---	---	---	---
1	1.12 (0.99-1.27)†	1.06 (0.92-1.21)	1.05 (0.92-1.21)	1.04 (0.89-1.22)
2	1.35 (1.16-1.57)***	1.30 (1.10-1.53)**	1.29 (1.09-1.52)**	1.13 (0.94-1.37)
≥3	1.82 (1.51-2.19)***	1.60 (1.30-1.97)***	1.59 (1.29-1.95)***	1.52 (1.22-1.89)***
Pain medication use	1.41 (1.27-1.58)***	1.13 (1.00-1.28)*	1.12 (0.99-1.27)	1.27 (1.10-1.46)**
Opioid use	1.41 (1.10-1.80)**	1.23 (0.94-1.60)	1.22 (0.94-1.59)	1.22 (0.93-1.59)
Fear of movement	1.36 (1.18-1.57)***	1.15 (0.98-1.35)	1.15 (0.99-1.35)	1.16 (0.98-1.38)
Health status measures				
KOOS-12 pain subscale	0.99 (0.99-1.00)*	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
KOOS-12 function subscale	0.99 (0.98-0.99)***	0.99 (0.98-0.99)***	0.99 (0.99-1.00)***	0.99 (0.98-0.99)***
KOOS-12 quality of life subscale	0.99 (0.99-1.00)**	1.00 (0.99-1.00)	1.00 (0.99-1.00)	0.99 (0.99-1.00)*
ASES pain subscale	1.00 (1.00-1.00)	1.00 (1.00-1.00)	Removed	1.00 (1.00-1.01)
ASES other symptoms subscale	0.99 (0.98-0.99)***	0.99 (0.99-1.00)***	0.99 (0.99-0.99)***	0.99 (0.99-1.00)*
UCLA Activity Score	1.03 (1.00-1.06)†	1.05 (1.01-1.08)**	1.05 (1.02-1.09)**	1.07 (1.03-1.11)***

30-second chair stand test	1.01 (0.99-1.03)	1.02 (1.01-1.04)**	Removed	1.01 (0.99-1.03)
40 meter fast-paced walk test	1.00 (1.00-1.01)†	1.00 (1.00-1.01)	1.00 (0.99-1.01)	1.01 (1.00-1.01)

All results reported as OR (95% CI); --- = reference category; † = statistical significance at p<0.2 (domain-specific models only); * = statistical significance at p<0.05, ** = statistical significance at p<0.01; *** = statistical significance at p<0.001; all KOOS-12 subscales scored 0(worst) to 100(best); all ASES subscales scored 10(worst) to 100(best); UCLA Activity Score scored 1(inactive) to 10(active); 30-second chair-stand test scored as number of repetitions completed; 40-meter fast-paced walk test scored in seconds.

Table 8. **Association of characteristics with comorbid LSS in the hip OA cohort**

	Domain-specific models	Overall model	Reduced model	Alternate LSS symptom model
Sociodemographics				
Age				
<50	---	---	---	---
50-59	1.04 (0.68-1.59)	1.04 (0.65-1.64)	1.04 (0.66-1.64)	1.17 (0.73-1.90)
60-69	0.77 (0.50-1.18)	0.75 (0.47-1.20)	0.76 (0.48-1.21)	1.02 (0.62-1.67)
70-79	0.64 (0.40-1.03)†	0.63 (0.37-1.06)	0.64 (0.38-1.08)	0.74 (0.43-1.29)
≥80	0.56 (0.32-0.98)*	0.47 (0.25-0.88)*	0.48 (0.26-0.90)*	0.62 (0.31-1.22)
Female	0.96 (0.81-1.15)	0.93 (0.77-1.13)	Removed	0.94 (0.76-1.15)
Body mass index				
Underweight	0.58 (0.22-1.55)	0.61 (0.22-1.72)	0.60 (0.21-1.70)	1.07 (0.36-3.18)
Healthy weight	---	---	---	---
Overweight	1.06 (0.88-1.28)	0.98 (0.80-1.20)	1.00 (0.82-1.22)	1.08 (0.86-1.34)
Obese	1.18 (0.96-1.46)†	0.93 (0.73-1.19)	0.94 (0.74-1.20)	1.09 (0.84-1.40)
Education				
Primary school	---	---	---	---
Secondary school	0.87 (0.64-1.17)	0.96 (0.69-1.33)	0.96 (0.69-1.32)	1.21 (0.86-1.70)
Short-term	0.97 (0.75-1.25)	1.10 (0.83-1.46)	1.09 (0.83-1.45)	1.06 (0.78-1.43)
Middle-term	0.90 (0.72-1.13)	1.12 (0.87-1.44)	1.12 (0.87-1.44)	1.21 (0.93-1.59)
Long-term	0.81 (0.59-1.09)†	0.99 (0.70-1.39)	0.99 (0.71-1.40)	1.00 (0.68-1.45)
Employment				
Employed/student	---	---	---	---
Sick leave full-time	0.79 (0.41-1.52)	0.78 (0.37-1.62)	0.79 (0.38-1.64)	0.75 (0.36-1.57)
Sick leave part-time	1.73 (0.95-3.15)†	1.15 (0.60-2.21)	1.15 (0.60-2.22)	0.93 (0.51-1.70)
Retired	1.06 (0.81-1.39)	0.95 (0.71-1.27)	0.93 (0.70-1.25)	1.04 (0.76-1.42)
Unemployed	1.77 (0.84-3.75)	1.20 (0.53-2.69)	1.19 (0.53-2.68)	1.09 (0.49-2.42)
Self-imposed early retirement	1.06 (0.66-1.69)	1.01 (0.60-1.68)	0.99 (0.60-1.65)	1.01 (0.58-1.74)
Early retirement due to low workability	1.01 (0.60-1.71)	0.60 (0.34-1.07)	0.60 (0.34-1.07)	0.72 (0.39-1.30)
Sick leave in past year	1.90 (1.34-2.72)***	1.48 (1.01-2.17)*	1.48 (1.01-2.17)*	1.51 (1.04-2.18)*

Clinical characteristics				
Symptom duration				
<3 months	---	---	---	---
3-12 months	1.80 (1.23-2.63)**	1.85 (1.22-2.79)**	1.86 (1.23-2.80)**	1.86 (1.16-3.00)*
13-24 months	1.99 (1.33-2.98)**	2.01 (1.30-3.12)**	2.02 (1.30-3.13)**	1.92 (1.16-3.17)*
>24 months	2.05 (1.38-3.03)***	2.00 (1.30-3.08)**	1.99 (1.30-3.06)**	1.75 (1.07-2.87)*
Bilateral hip symptoms	1.41 (1.17-1.70)***	1.27 (1.04-1.55)*	1.26 (1.03-1.54)*	1.10 (0.89-1.36)
Comorbid knee symptoms	1.22 (1.03-1.44)*	1.14 (0.95-1.37)	1.13 (0.94-1.36)	1.14 (0.94-1.39)
Back pain in last month	1.74 (1.44-2.10)***	1.42 (1.15-1.74)**	1.42 (1.15-1.73)***	1.55 (1.23-1.96)***
Number of comorbidities				
0	---	---	---	---
1	1.03 (0.85-1.24)	1.09 (0.88-1.33)	1.08 (0.88-1.33)	1.00 (0.79-1.25)
2	1.18 (0.94-1.48)†	1.25 (0.97-1.62)	1.26 (0.98-1.62)	1.26 (0.97-1.65)
≥3	1.57 (1.17-2.11)**	1.62 (1.16-2.28)**	1.63 (1.17-2.29)**	1.38 (0.97-1.94)
Pain medication use	1.41 (1.19-1.68)***	1.26 (1.04-1.53)*	1.26 (1.04-1.53)*	1.21 (0.98-1.49)
Opioid use	1.48 (1.06-2.06)*	1.24 (0.86-1.77)	1.24 (0.86-1.77)	0.98 (0.68-1.40)
Fear of movement	1.58 (1.21-2.05)**	1.30 (0.97-1.73)	1.30 (0.97-1.73)	1.01 (0.75-1.37)
Health status measures				
HOOS-12 pain subscale	0.99 (0.99-1.00)†	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.00 (0.99-1.01)
HOOS-12 function subscale	0.99 (0.98-1.00)**	0.99 (0.98-1.00)**	0.99 (0.98-1.00)**	0.99 (0.98-0.99)***
HOOS-12 quality of life subscale	0.99 (0.98-1.00)*	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.98-1.00)*
ASES pain subscale	0.99 (0.99-1.00)†	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.01)
ASES other symptoms subscale	0.99 (0.99-1.00)*	0.99 (0.99-1.00)	0.99 (0.99-1.00)	0.99 (0.98-1.00)*
UCLA Activity Score	1.05 (1.00-1.10)†	1.04 (0.99-1.10)	1.05 (0.99-1.10)	1.01 (0.96-1.07)

30-second chair stand test	0.99 (0.97-1.02)	1.00 (0.98-1.03)	Removed	1.01 (0.98-1.04)
40 meter fast-paced walk test	0.99 (0.98-1.00)†	1.00 (0.99-1.02)	1.00 (0.99-1.01)	1.01 (0.99-1.02)

All results reported as OR (95% CI); --- = reference category; † = statistical significance at p<0.2 (domain-specific models only); * = statistical significance at p<0.05, ** = statistical significance at p<0.01; *** = statistical significance at p<0.001; all HOOS-12 subscales scored 0(worst) to 100(best); all ASES subscales scored 10(worst) to 100(best); UCLA Activity Score scored 1(inactive) to 10(active); 30-second chair-stand test scored as number of repetitions completed; 40-meter fast-paced walk test scored in seconds.

6 Discussion

Below, the findings for each of the aims are discussed. Methodological issues uncovered while studying each of these objectives are also discussed. Finally, considering the findings of our studies and methodological concerns, the clinical implications and directions for future research are presented.

6.1 Overview of findings

6.1.1 Prevalence of multimorbid LSS with knee or hip OA

We provided a range of estimates for the prevalence of multimorbid LSS with knee or hip OA (study 1). Most importantly, we did not find a single study that had the objective of estimating the prevalence of co-occurring LSS with knee or hip. Therefore, we had to calculate prevalence estimates based on data reported in the studies. We found the prevalence of multimorbid LSS with knee OA ranged from 5 to 54% and the prevalence of multimorbid LSS with hip OA from 0 to 35%, but that prevalence estimates varied depending on the case definitions for LSS and OA used. Most of these estimates examined comorbid knee or hip OA in people with LSS, almost exclusively in secondary care settings.

Almost all included studies in study I were at a high risk of bias and heterogenous case definitions were used, making our results uncertain and difficult to compare. This was most prominently observed in the opposite prevalence patterns in comorbid knee OA versus hip OA in people with LSS (Figure 3). We suspected that definitions using imaging-only case definitions would have the highest prevalence, but that was not the case for LSS with comorbid hip OA. These specific estimates appear to be at odds with prevalence estimates for LSS-alone or OA-alone,[23,50] where imaging-only definitions result in a greater prevalence than estimates based on symptomatic definitions. Unfortunately, sufficient data to investigate these differences was not available. It is therefore unclear what might be responsible for these obviously different patterns.

There were no prevalence estimates explicitly from primary care or community settings in study I and only two studies of comorbid LSS in people with knee or hip OA. Fortunately, we were able to provide the first estimates of comorbid LSS symptoms in people with knee or hip OA in primary care (study II). We found symptoms of LSS are common in people with knee (up to 40%) and hip (up to 50%) OA, but a clinical diagnosis of LSS is much less common (less than 5% regardless of clinical criteria used or index condition). Interestingly, the prevalence of LSS symptoms (and to some extent clinical LSS) in these GLA:D® cohorts is higher in people with hip OA compared to knee OA, opposite to the findings of our prevalence review (study I). This raises questions about the role of the study setting (primary versus secondary care) in the prevalence of multimorbid LSS with knee or hip OA. However, it is important to note that in study II we used self-report LSS symptom questions that have not been validated in knee or hip OA populations and are not likely useful for LSS diagnosis, although they can differentiate LSS-related leg pain from other low back causes.[44] Therefore, the differences in LSS case definitions (symptoms versus diagnosis) also limit comparisons of findings in studies I and II.

6.1.2 Characteristics associated with multimorbid LSS with knee or hip OA

Unfortunately, we were unable to find any data in the prevalence review (study I) to help answer this aim. We were, however, able to provide the first estimates of characteristics associated with comorbid LSS symptoms in patients with OA in the primary care GLA:D® program (study III). The associated characteristics identified in this thesis may help to clinically identify people with multimorbid LSS with knee or hip OA and people at risk of developing this multimorbidity.

In the prevalence review (study I), we were interested in exploring if factors such as case definition (including clinical LSS presentations), healthcare setting, disease severity (pain and disability), age and sex, and study risk of bias would alter prevalence estimates. However, we were unable to perform meta-regression analyses because of the small number of studies with comparable case definitions and the lack of studies that explicitly investigated prevalence. Since no study investigated the prevalence, there was no data available that could be used to

compare those with and without multimorbidity, even informally. Therefore, it was impossible to estimate the impact of various clinical or methodological factors that might have influenced the prevalence estimates. We suspect that all these factors will influence any future prevalence estimates.

We had hoped to inform our selection of potentially important characteristics associated with multimorbid presentations in study III based on the findings of study I, but this was not possible. Instead, we conducted an exploratory analysis relying on theory to investigate associated characteristics.

In study III, we found a similar pattern of characteristics associated with comorbid LSS in people with knee or hip OA in a primary care treatment program. In general, we found most sociodemographic items were not associated with reporting comorbid LSS symptoms, except for having been on sick leave in the past year. This finding matches the general trend of worse work outcomes observed in people with multiple MSK disorders.[80,82] Scores on health status measures also generally did not help identify participants with comorbid LSS symptoms. Although higher levels of function on the KOOS-12 and HOOS-12 function subscales were significantly associated with reduced odds of LSS symptoms, the strength of these associations were so small that this relationship is not clinically relevant.

Our results in study III indicate that several clinical characteristics may be help identify patients with knee or hip OA and comorbid LSS. Back pain was associated with comorbid LSS symptoms, which is not surprising given that individuals with LSS can experience back pain.[30,31,144] However, because many people with LSS do not experience back pain, it is not a diagnostic necessity for LSS.[43,45,61–63] Therefore, there should be increased suspicion of comorbid LSS in people with knee or hip OA who report LBP, but also the recognition that comorbid LSS symptoms may be present without LBP.

A greater number of symptomatic knee and hip joints was associated with comorbid LSS symptoms. Bilateral knee symptoms and comorbid hip symptoms in people with knee OA, and bilateral hip symptoms in people with hip OA seem to increase the likelihood of having comorbid LSS symptoms. This pattern fits with the trends observed in the multi-joint OA literature, where multiple joint presentations may be more common than single-joint presentations.[92,102] Considering LSS as lumbar spine OA,[77,78] it is logical that people with greater numbers of joints with OA may be at risk of multimorbid LSS with knee or hip OA. Finally, we observed that people with longer knee or hip symptom durations are more likely to have comorbid LSS symptoms. This finding is also not surprising, given that OA in a single weight-bearing joint may cause biomechanical joint loading changes at other joints over time, resulting in the development of OA.[108] However, this association may also be explained by the development of a widespread pain profile or central sensitization; well-known phenomena in people with OA.[145,145,146]

6.2 Methodological considerations

6.2.1 LSS and OA case definitions

All studies in this thesis were limited by the lack of consensus, valid case definitions for LSS and OA. Study I found heterogenous LSS case definitions across the included studies when reported. Additionally, most OA case definitions were imaging-only definitions. In studies II and III, the LSS symptom items and constructed LSS case definitions have unknown validity. Therefore, our prevalence estimates are limited and specific to the case definitions used. This is a well-known limitation of the entire LSS[50] and OA prevalence literature,[23] where prevalence estimates vary based on the case definitions employed.

Ideally, our studies would have employed a definition known to be valid for LSS symptoms/diagnosis, but no such definition exists.[43–45,61,62] For example, in the review of LSS prevalence estimates,[50] a diagnostic support tool for LSS[147,148] was often used to define LSS, but it is unclear if this tool has been validated across different populations. We overcame this limitation in study I by including all LSS and OA definitions, recognizing that this approach also

considers the dependency of the prevalence estimates on the specific case definition used. Prevalence estimates derived from definitions including clinical symptoms (clinical-only and combined clinical plus imaging) are the most informative, since symptoms and disability are not solely related to imaging findings of OA or LSS.[1,30] However, it was important that we provided prevalence data for all published case definitions in this first comprehensive review.

In study II, we chose to first report the prevalence of LSS symptoms, and then clinical LSS based on adapted versions of previously published criteria. In study III, we constructed multiple LSS symptom definitions (primary analysis and sensitivity analysis). These definitions are also limited, and therefore our prevalence estimates (study II) and characteristics associated with comorbid LSS symptoms in people with OA (study III) may not be valid or generalizable to other populations. However, the symptom items we used have been shown to identify LSS from other spinal causes of leg pain.[44] Moreover, using an alternate LSS symptom definition in the sensitivity analysis in study III increases our confidence in the findings.

Therefore, the approach in this thesis is the best that is currently available to provide foundational data, especially considering that costly imaging procedures were not needed for participants. Future studies should consider using case definitions for LSS and OA that include both clinical symptoms and imaging changes. Finally, until the field arrives at a consensus valid and reliable definition for LSS and its clinical consequences, and to a lesser extent knee and hip OA, all future prevalence estimates will remain limited and challenging to compare.

6.2.2 Co-occurring disorders versus symptomatic overlap

It is not possible to determine the extent to which studies in this thesis have identified true co-occurring disease or symptomatic overlap. The clinical differentiation of LSS versus hip OA is complex and potential for misdiagnosis exists, due to the high degree of symptomatic overlap in LSS, hip OA, and knee OA.[34,38–42,108] While certain signs and symptoms favour one diagnosis over the others,[34,39] these findings are not definitive of a specific disease and overlap still exists.[40] The development of widespread pain in OA conditions[145,146,149] over time can further

complicate the diagnostic picture. In the worst-case scenario, complete misdiagnosis is possible. For example, someone diagnosed with hip OA and comorbid LSS symptoms may in truth only have LSS. It is unlikely that any case definitions relying on clinical symptoms and/or imaging can differentiate these conditions, given the vast amount of symptomatic overlap[39,41] and discordance between imaging findings and symptoms.[1,30]

6.2.3 Multimorbidity definitions

Similar to LSS and OA definitions, there is little agreement on how best to define multimorbidity.[70–72,150] A prevalence definition for multimorbidity can include the number of diseases, symptoms, and risk factors. Definitions can also be simple counts of these domains or involve weighting of different aspects. Even in the simplest multimorbidity definitions where only the presence of conditions are counted, different cut points for the number of conditions required (≥2, ≥3, 4+) alter prevalence estimates,[70–72] including in MSK multimorbidity estimates.[151]

Since our studies aimed to provide the foundational data, we selected the most practical definitions of multimorbid LSS with knee or hip OA: the co-existence of these conditions (or LSS symptoms in study II) in an individual. We did not include risk factors or other conditions in our multimorbid definition. This is a reductionistic approach that does not account for the complex interactions between symptoms and risk factors for OA and LSS,[70] nor their relation with other health conditions.[80,152] However, we were explicitly interested in only co-occurring LSS and OA and counting the presence of conditions is the most commonly used multimorbidity definition.[71] Since LSS and OA diagnoses are typically based on a collection of symptoms, multimorbidity definitions including symptoms could offer greater insight into the relationship between co-occurring LSS and OA.

In our prevalence review (study I), it was also challenging to identify studies reporting data to estimate the multimorbid prevalence of LSS and OA. Since no studies have explicitly investigated this prevalence, it is difficult to design a literature search strategy to capture all

relevant articles. We used an overly sensitive screening process to decrease the chance of excluding an article with relevant data for our research question. The use of multimorbidity or comorbidity as key words to tag these studies will help to capture studies in future reviews. The lack of a specific search term for multimorbidity in bibliographic databases has been cited as a limitation in other prevalence reviews.[70] Finally, the wider multimorbidity epidemiological literature suffers from inadequate tools to measure the risk of bias. A tool specifically designed to evaluate the risk of bias in prevalence studies for multiple MSK conditions would improve this area of research.[82]

6.2.4 Healthcare setting impact on prevalence

The study setting influences multimorbid LSS and OA prevalence estimates. We were unable to explicitly investigate this in our prevalence review (study I). We were only able to find prevalence estimates from secondary care settings and estimate the prevalence of LSS symptoms and clinical LSS in the GLA:D® primary care program (study II). More studies are needed before we can judge the effect study setting has on prevalence estimates. However, it is known that the prevalence of LSS alone is greater in secondary care compared to primary care samples.[31] This is also the case for the prevalence of OA alone[23] and multimorbidity in general.[71] Therefore, the study setting and population should be explicitly defined when estimating the prevalence of multimorbid LSS and OA.

The healthcare setting also needs to be considered when studying characteristics associated with multimorbid presentations and subsequent risk factor studies. For example, in study III, we found that the older a person with hip OA is, the less likely they are to have comorbid LSS symptoms. This finding is counterintuitive since increasing age is a risk factor for LSS, OA, and multimorbidity, but could be explained by a selection bias in the primary care GLA:D® program. Older individuals with more severe LSS may not participate in GLA:D®, therefore reducing the association with age. Likewise, the eligibility criteria in GLA:D® precludes individuals from participating if they have more severe symptoms from a different condition (such as LSS) compared to their hip or knee joint. This will also alter the relationship between participant

characteristics and multimorbid presentations. Therefore, the study setting must be well defined to facilitate useful comparisons of characteristics associated with multimorbid LSS and OA.

6.2.5 Study strengths

In study I, we provided a comprehensive overview of prevalence estimates for multimorbid LSS with knee or hip OA, including all case definitions for LSS and OA and care settings. The rigorous search strategy and screening process reduced the chance we missed any articles with relevant information. In studies II and III, we provided the first original data on comorbid LSS in people with knee or hip OA in a primary care treatment program. The specific LSS symptoms and case definitions used were a cost-efficient approach to estimate prevalence and associated characteristics, especially considering there are no obviously superior definitions of symptomatic LSS. Moreover, the large sample size in the knee and hip OA cohorts and differing operationalizations of comorbid LSS symptoms increases our confidence in the thesis findings. Overall, the methods employed in these thesis studies provide a strong foundation for future research.

6.3 Clinical considerations

The findings of this thesis suggest that practicing clinicians should be aware a significant proportion of patients with LSS or knee or hip OA can have co-occurrence. We did not specifically investigate treatment aspects for multimorbid LSS with knee or hip OA, but our findings likely have important clinical implications. For instance, single condition approaches recommended in treatment guidelines do not adequately manage multimorbid presentations.[153] This is also the case for musculoskeletal conditions,[83,96] including OA and LSS. The healthcare setting, where the typical interventions employed for this patient population and the amount of literature to guide intervention selection for multimorbid LSS with knee or hip OA differs, is also an essential element in shared decision-making. However, it remains unclear which individuals may benefit from a surgical versus non-surgical approach to care for

OA or LSS alone,[154–165] but ongoing trials should help to clarify appropriate intervention selection.[166–168]

6.3.1 Primary care management

There is currently no evidence examining the utility of common primary care interventions for multimorbid LSS with knee or hip OA. Therefore, care for people with multimorbid LSS and OA should be based on a balance of interventions recommended in condition-specific guidelines[27,169–175] and multimorbidity care guidelines.[176] However, there is limited evidence on what constitutes effective primary care for multimorbidity. While it is difficult to improve outcomes in people with multimorbidity and more high-quality studies are needed,[177] interventions aimed at improving functional limitations are the most likely to improve health outcomes.[178]

In the specific case of multimorbid LSS and OA, we can extract commonalities in condition-specific clinical practice guidelines to inform treatment decisions. In both conditions, non-pharmacological care such as education, self-management strategies, physical activity, and exercise should be prioritized.[169–172] Therefore, a primary care treatment approach incorporating these elements is likely best for people with multimorbid LSS and OA. A similar approach is evident in treatment guidelines across MSK disorders[179] and both exercise and lifestyle behavioural interventions have shown beneficial effects on outcomes in people with multimorbidity.[180,181] It may also be that tailored treatment approaches aimed at both the spine and knee or hip could increase benefit to patients, but there is no data to support this approach.

Other adjunct interventions for MSK conditions, such as manual therapy or injectables, may not be as appropriate as a sole treatment modality for people with multimorbid LSS and OA, due to the single-joint nature of these interventions. Analgesic medication may be another readily available option with a non-joint-specific mechanism, but the potential benefits should be weighed against the potential for adverse events, especially in people with other co-occurring

chronic health conditions. However, it must be recognized there is no available data on how to best manage people with multimorbid LSS and OA in the primary care setting, nor to draw conclusions on the impact of multimorbid presentations on currently recommended single-condition interventions.

6.3.2 Secondary care management

In contrast to primary care interventions, there is more available data to assess the impact of multimorbid LSS and OA on surgical outcomes. For LSS and OA independently, surgery should be reserved for people who do not achieve adequate symptomatic control with recommended primary care interventions.[1,31] These surgeries are generally effective for most patients with OA or LSS, but a significant proportion do not experience improved outcomes.[182–184] Comorbid medical conditions, including co-occurring musculoskeletal disorders, have been recognized as a cause for lack of improvement in both LSS and OA surgeries.[185–188] For example, a recent study found the odds for not attaining a clinically significant improvement with LSS surgery are 32% greater with each additional symptomatic joint.[77] In this study, 33% and 41% of participants had symptomatic knee and hip joints, respectively.[77]

Numerous clinical reports have identified the impact of co-occurring LSS and OA on surgical outcomes, but do not provide sufficient data to critically evaluate these claims.[108] In Study I of this thesis, we identified just one study each investigating the impact of knee OA and hip OA on LSS surgical outcomes.[141,143] Comorbid knee OA was associated with poorer LSS surgical outcomes,[141] but comorbid hip OA was not.[143] We found no evidence to guide decision-making on management for people undergoing knee or hip surgery who have comorbid LSS.

There are other studies that have examined the impact of multimorbid degenerative spinal conditions with knee or hip OA on surgical outcomes, but the case definitions used in these studies did not satisfy the eligibility criteria of our review. These studies have found inconsistent associations between multimorbid presentations in people undergoing total knee replacement,[189,190] total hip replacement,[191–193] and lumbar decompression surgeries.[194–196]

Further studies of multimorbid LSS and OA presentations and surgical impact are needed for knee, hip, and spine surgeries to better inform clinical decision-making and patient expectations. It may be that a tailored surgical intervention or mixed surgical and non-surgical interventions are required for people with differing multimorbid LSS and OA presentations.

6.3.3 Other management considerations

While this thesis has limited the definition of multimorbidity to two MSK disorders, the probability of additional chronic non-communicable diseases in people with MSK disorders[152] warrants consideration in care decisions.[81] All studies included in our multimorbid prevalence review (study I) included individuals with many additional comorbidities. As an example, US patients being treated for LSS had on average over four comorbidities (not including knee or hip OA).[139] In studies II and III, hypertension (39%) and diabetes (7%) were reported by GLA:D® participants, among additional comorbidities.[197] Multimorbidity care requires more than a simple shift away from managing single conditions in isolation, but rather a whole-person perspective that accounts for factors such as the social determinants of health.[198–201] This broader health perspective is also advocated for in OA, LBP, and general MSK care.[202–205] Therefore, while the presence of multimorbid LSS and OA is an important management consideration, it should not be viewed in isolation from other medical comorbidities or the psychosocial factors experienced by the individual.

6.4 Future research directions

We have provided the first overview of existing knowledge and contributed original data to the overall thesis aims, but the questions of how often they coexist and associated characteristics still largely remain. New questions have also arisen throughout this thesis: why might they coexist and what is the impact on treatment? Each of these questions are discussed below with recommendations made for future studies. Studies aimed at answering these questions should all be conducted with recognition of the methodological considerations outlined above (section 6.2).

6.4.1 How often do they coexist?

We have shown that the prevalence of LSS with knee or hip OA is based on few studies, mainly including people with an index condition of LSS in secondary care settings. The prevalence of comorbid LSS in people with knee or hip OA has hardly been investigated, and except for study II in this thesis, has not been studied in primary care settings. There is a clear need for more studies investigating multimorbid LSS with knee or hip OA, in both people sampled based on LSS status and knee or hip OA status and in various care settings. This data will help to understand the opposite prevalence patterns of comorbid knee versus hip OA in people with LSS that we observed in study I. It is also necessary to investigate the co-occurrence pattern of LSS and knee OA and hip OA, since all three conditions are likely to occur [77,92,102] and many participants in the GLA:D® program report symptomatic knee and hip joints.[197]

Future research should explore available data sources that have collected information on LSS and OA, such as surgical registers with diagnostic codes for LSS and OA, which will serve as an inexpensive approach to generating more prevalence data. However, these data sources likely suffer from the same case definition limitations in this thesis. Therefore, prospective studies using appropriate case definitions for LSS and OA are needed to best understand the prevalence of multimorbid LSS with knee or hip OA.

6.4.2 Who is at risk?

We were only able to provide data on characteristics associated with co-occurrence in people with knee or hip OA and comorbid LSS symptoms in a primary care setting. We found no data in secondary care settings, or when looking at people with an index condition of LSS and comorbid knee or hip OA. Different factors are likely associated with this multimorbid presentation depending on whether participants are sampled based on an index condition of LSS or knee or hip OA, and on the study setting (community versus primary care versus secondary care). Fortunately, if enough explicit multimorbid LSS and OA prevalence studies are performed (as described in section 6.4.1), there will be an opportunity to evaluate the impact different clinical and methodological factors (case definitions, healthcare setting, level of disability) have on

prevalence estimates. From here, prospective studies could be conducted to investigate risk factors that may lead to a multimorbid LSS and OA presentation.

6.4.3 Why might they coexist?

It is unknown why LSS and knee or hip OA coexist, but many potential mechanisms could offer an explanation. There is evidence that lumbar spine OA/LSS and knee and hip OA have a similar physiological cause.[73–76] Systemic inflammation has been put forward as a mechanism for multi-joint OA[102,206,207] and may also contribute to LSS.[77] Other sources suggest the relationship may be due to biomechanical factors, such as altered joint loading patterns in the presence of one joint condition that may lead to development of symptoms in other joints.[108,114,115] Co-occurrence may also be a function of the high prevalence of both conditions alone[80] and increases in prevalence with age,[39] meaning that a certain proportion of people will have multimorbid conditions simply by chance. However, it is still largely unknown why LSS or OA occur in isolation, and it is therefore not surprising little is known about why these conditions coexist. A complex interplay of multiple mechanisms is most likely responsible for co-occurring LSS and knee and hip OA. For example, there is evidence that structural causes and systemic metabolic changes can simultaneously contribute to co-occurrence.[107] Future research spanning the basic and clinical sciences should explore how each of these mechanisms might be related to the multimorbid LSS and OA presentation. A better mechanistic understanding could help identify individuals at risk of multimorbid LSS and OA and aid in the clinical differentiation of symptoms arising from the spine versus hip versus knee.

6.4.4 What is the impact on treatment?

Having multimorbid LSS with knee or hip OA is only important if it has a negative effect on treatment prognosis. There is an indication that multimorbid LSS with knee or hip OA has a negative impact on outcomes after surgery for each of these conditions,[118,141,143] but there are few studies to draw conclusions from. The different case definitions for LSS and OA and the variety of clinical outcomes measured in these studies also make it difficult to draw an overall conclusion. For all other treatments, there is virtually no data available to estimate the impact

of multimorbid LSS with knee or hip OA on outcomes. This is especially problematic since most people with OA or LSS should be managed non-surgically.[1,2,31]

There is a need to investigate the impact of multimorbid LSS and OA on primary care interventions such as education and exercise and surgical interventions for each condition. In a subsequent study, we plan to assess the impact of LSS symptoms on outcomes following the GLA:D® program. Some of the currently available data sources discussed in section 6.4.1 may also provide an opportunity to efficiently evaluate the response to a range of treatments. It is preferable to asses clinical outcomes on measures that can capture the disease experience associated with LSS and knee and hip OA, but it is unlikely that such a tool currently exists outside of general quality of life or function measures.

7 Conclusion

This thesis provided the foundational data indicating that a significant proportion of people may experience multimorbid LSS with knee or hip OA and has uncovered patient characteristics associated with multimorbid presentations. However, there is limited data available to define the magnitude of this multimorbid presentation or who may be at risk. Regardless, this thesis has shown that further investigations into multimorbid LSS with knee or hip OA are needed, but that significant methodological limitations must be considered. Future research using robust methods in pursuit of these questions should be conducted to inform the clinical care of people with multimorbid LSS with knee or hip OA.

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9 Appendix 1 – Additional methods

9.1 Study I

Table A 1. Electronic database search terms and results

MEDLINE (Ovid)

#	Searches	Results
1	exp Spinal Stenosis/	6382
2	(spin* adj5 stenosung*).mp.	9802
3	(lumbar adj5 stenos*).mp.	4710
4	(neuro* adj2 claud*).mp.	956
5	lumbar radicular pain.mp.	239
6	exp Cauda Equina/	3293
7	cauda equina.mp.	6060
8	exp Spinal Osteophytosis/	4058
9	spinal osteophytosis.mp.	3398
10	exp Spondylosis/	7767
11	spondylos*.mp.	5177
12	exp Spondylolisthesis/	4834
13	spondylolisthesis.mp.	6968
14	exp Low Back Pain/	22861
15	(low* adj5 back adj5 pain).mp.	40389
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	66246
17	exp Osteoarthritis/	66232
18	osteoarthr*.mp.	100798
19	(degenerative adj2 arthritis).mp.	1464
20	arthros*.mp.	46209
21	17 or 18 or 19 or 20	140482
22	exp Knee/	14766
23	exp Knee Joint/	62935
24	knee.mp.	175832
25	22 or 23 or 24	177753
26	exp Hip/	12172
27	exp Hip Joint/	28142
28	hip.mp.	169451
29	26 or 27 or 28	169452
30	(25 or 29) and 21	71219
31	16 and 30	670

EMBASE (Ovid)

#	Searches	Results
1	exp vertebral canal stenosis/	13529
2	(spin* adj5 stenos*).mp.	11245

3	(lumbar adj5 stenos*).mp.	7165
4	(neuro* adj2 claud*).mp.	1398
5	lumbar radicular pain.mp.	367
6	exp cauda equina/	4742
7	cauda equina.mp.	9184
8	spinal osteophytosis.mp.	70
9	exp spondylosis/	9980
10	spondylos*.mp.	11747
11	exp spondylolisthesis/	10186
12	spondylolisthesis.mp.	11100
13	exp low back pain/	63789
14	(low* adj5 back adj5 pain).mp.	74828
15	1 or 2 or 3 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	111736
16	exp osteoarthritis/	147402
17	osteoarthr*.mp.	169104
18	(degenerative adj2 arthritis).mp.	2173
19	arthros*.mp.	65727
20	16 or 17 or 18 or 19	229398
21	exp knee/	82399
22	knee joint.mp.	32436
23	knee.mp.	261803
24	21 or 22 or 23	261870
25	exp hip/	129178
26	hip joint.mp.	18591
27	hip.mp.	252822
28	25 or 26 or 27	302389
29	(24 or 28) and 20	112068
30	15 and 29	2576

CENTRAL

#	Searches	Results
1	MeSH descriptor: [Spinal Stenosis] explode all trees	431
2	spin* near/5 stenos*	1289
3	lumbar near/5 stenos*	903
4	neuro* near/2 claud*	244
5	lumbar radicular pain	555
6	MeSH descriptor: [Cauda Equina] explode all trees	14
7	cauda equina	170
8	MeSH descriptor: [Spinal Osteophytosis] explode all trees	87
9	spinal osteophytosis	108
10	MeSH descriptor: [Spondylosis] explode all trees	382
11	spondylosis	936

12	MeSH descriptor: [Spondylolisthesis] explode all trees	221
13	spondylolisthesis	800
14	MeSH descriptor: [Low Back Pain] explode all trees	3984
15	low* near/5 back near/5 pain	11401
16	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	13852
17	MeSH descriptor: [Osteoarthritis] explode all trees	7790
18	osteoarth*	19529
19	degenerative near/2 arthritis	152
20	arthros*	6497
21	#17 or #18 or #19 or #20	24696
22	MeSH descriptor: [Knee] explode all trees	822
23	MeSH descriptor: [Knee Joint] explode all trees	3380
24	knee	31703
25	#22 or #23 or #24	31728
26	MeSH descriptor: [Hip] explode all trees	425
27	MeSH descriptor: [Hip Joint] explode all trees	1006
28	hip	24567
29	#26 or #27 or #28	24567
30	(#25 or #29) and #21	18007
31	#16 and #30	273

CINAHL

#	Query	Results
1	(MH "Spinal Stenosis")	2844
2	TI spin* n5 stenos* OR ABspin* n5 stenos* OR TW spin* n5 stenos*	2825
3	TI spin* n5 stenos* OR ABspin* n5 stenos* OR TW spin* n5 stenos*	2825
4	TI neuro* n5 claud* OR AB neuro* n5 claud* ORTW neuro* n5 claud*	367
5	TI lumbar radicular painOR AB lumbar radicularpain OR TW lumbar radicular pain	222
6	(MH "Cauda Equina")	371
7	TI cauda equina OR ABcauda equina OR TW cauda equina	962
8	(MH "Spinal Osteophytosis+")	515
9	TI spinal osteophytosisOR AB spinal osteophytosis OR TW spinal osteophytosis	4
10	(MH "Spondylosis+")	2687
11	TI spondylos* OR ABspondylos* OR TW spondylos*	714
12	(MH "Spondylolisthesis")	1493
13	TI spondylolisthesis OR AB spondylolisthesis ORTW spondylolisthesis	1715
14	(MH "Low Back Pain")	20607
15	TI low* n5 back n5 pain OR AB low* n5 back n5 pain OR TW low* n5 backn5 pain	20085
16	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 ORS14 OR S15	33785
17	(MH "Osteoarthritis+")	29655
18	TI osteoarthr* OR ABosteoarthr* OR TW osteoarthr*	30628

19	TI degenerative n2 arthritis OR AB degenerative n2 arthritisOR TW degenerative n2 arthritis	348
20	TI arthros* OR AB arthros* OR TW arthros*	15082
21	S17 OR S18 OR S19 OR S20	53825
22	(MH "Knee")	9654
23	(MH "Knee Joint+")	20223
24	TI knee OR AB knee OR TW knee	66186
25	S22 OR S23 OR S24	72389
26	(MH "Hip")	6834
27	(MH "Hip Joint")	8641
28	TI hip OR AB hip OR TW hip	58232
29	S26 OR S27 OR S28	61291
30	(S25 OR S29) AND S21	29504
31	S16 AND S30	372

Table A 2. Modified Risk of Bias Tool for Prevalence Studies

Item	Answer criteria	Additional notes
External validity		
1. Was the study's population a close representation of the target population in relation to relevant variables, (e.g. age, sex, occupation)?	Yes (LOW RISK): The study's target population was a close representation of the target population. No (HIGH RISK): The study's target population was clearly NOT representative of the target population.	The target population refers to the group of people or entities to which the results of the study will be generalized. Examples: The study was a national health survey of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: Yes (LOW RISK). The study was conducted in one province only, and it is not clear if this was representative of the national population. The answer is: No (HIGH RISK). The study was undertaken in one village only and it is clear this was not representative of the national population. The answer is: No (HIGH RISK).
2. Was the sampling frame a true or close representation of the target population?	Yes (LOW RISK): The sampling frame was a true or close representation of the target population. No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	The sampling frame is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: The sampling frame was a list of almost every individual within the target population. The answer is: Yes (LOW RISK). The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: Yes (LOW RISK). The sampling frame was a list of just one particular ethnic group within the overall target population, which comprised many groups. The answer is: No (HIGH RISK).
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps to minimize study bias. Examples: The sample was selected using simple random sampling. The answer is: Yes (LOW RISK). The target population was the village and every person in the village was sampled. The answer is: Yes (LOW RISK). The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: No (HIGH RISK).

	to select the sample.	
4. Was the likelihood of non-response bias minimal?	Yes (LOW RISK): The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders. No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	Examples: The response rate was 68%; however, the researchers did an analysis and found no significant difference between responders and non-responders in terms of age, sex, occupation and socioeconomic status. The answer is: Yes (LOW RISK). The response rate was 65% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics between responders and non-responders. The answer is: No (HIGH RISK). The response rate was 69% and the researchers did an analysis and found a significant difference in age, sex and socio-economic status between responders and non-responders. The answer is: No (HIGH RISK).
5. Removed		
Internal validity		
6a. Was an acceptable case definition of lumbar spinal stenosis used in the study?	Yes (LOW RISK): An acceptable case definition of lumbar spinal stenosis was used. No (HIGH RISK): An acceptable case definition of lumbar spinal stenosis was <u>NOT</u> used.	For a study on LSS, the following two case definitions were used: 1. Clinical symptoms of LSS could include: neurogenic claudication, reduced waking distance due to leg pain relieved when sitting or flexing the spine. Time frame, frequency, duration and severity are not applicable to LSS and can be absent in the description. The answer is: Yes (LOW RISK). 2. Radiological LSS could include: narrowing of the central, lateral (recess) or foraminal canal; decreased visible fluid around nerve structures. The answer is: Yes (LOW RISK)
6b. Was an acceptable case definition of knee and hip osteoarthritis used in the study?	Yes (LOW RISK): An acceptable case definition of osteoarthritis was used. No (HIGH RISK): An acceptable case definition of osteoarthritis	For a study on osteoarthritis, the following two case definitions were used: 1. Clinical symptoms of osteoarthritis could include: joint pain, stiffness, crepitus, swelling, reduced range of motion, instability, swelling, etc. Time frame, frequency, duration and severity are not applicable to osteoarthritis and can be absent in the description. The answer is: Yes (LOW RISK).

	was NOT used.	2. Radiological osteoarthritis could include: reduced joint space, osteophytes, subchondral cyst, bone marrow edema, intraarticular swelling, etc. The answer is: Yes (LOW RISK)
7a. Was the study instrument that measured the parameter of interest (e.g. prevalence of lumbar spinal stenosis) shown to have reliability and validity (if necessary)?	Yes (LOW RISK): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-retest, piloting, validation in a previous study, etc. No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	Examples: The authors used a questionnaire, which had previously been validated. They also tested the inter-rater reliability of the questionnaire. The answer is: Yes (LOW RISK). The authors developed their own questionnaire and did not test this for validity or reliability. The answer is: No (HIGH RISK).
7b. Was the study instrument that measured the parameter of interest (e.g. prevalence of knee or hip osteoarthritis) shown to have reliability and validity (if necessary)?	Yes (LOW RISK): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-retest, piloting, validation in a previous study, etc. No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	Examples: The authors used a questionnaire, which had previously been validated. They also tested the inter-rater reliability of the questionnaire. The answer is: Yes (LOW RISK). The authors developed their own questionnaire and did not test this for validity or reliability. The answer is: No (HIGH RISK).
8. Was the same mode of data collection used for all subjects?	Yes (LOW RISK): The same mode of data collection was used for all subjects. No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. The most common modes are face-to-face interviews, telephone interviews and self-administered questionnaires. Examples: All eligible subjects had a face-to-face interview. The answer is: Yes (LOW RISK). Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: No (HIGH RISK).

9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes (LOW RISK): The shortest prevalence period for the parameter of interest was appropriate (e.g. point prevalence, one-week prevalence, one-year prevalence). No (HIGH RISK): The shortest prevalence period for the parameter of interest was not appropriate (e.g. lifetime prevalence). Irrelevant: This item is irrelevant for imaging studies.	The prevalence period is the period that the subject is asked about e.g. "Have you experienced lumbar spinal stenosis or knee or hip osteoarthritis over the previous year?" In this example, the prevalence period is one year. The longer the prevalence period, the greater the likelihood of the subject forgetting if they experienced the symptom of interest (e.g. lumbar spinal stenosis or knee and hip osteoarthritis). Examples: Subjects were asked about pain over the past week. The answer is: Yes (LOW RISK). Subjects were only asked about pain over the past three years. The answer is: No (HIGH RISK).
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes (LOW RISK): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence multisite pain in people with low back pain). No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of lumbar spinal stenosis and knee or hip osteoarthritis. The answer is: Yes (LOW RISK). In reporting the overall prevalence of multimorbid lumbar spinal stenosis and knee or hip osteoarthritis (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: No (HIGH RISK).

Overall Risk of Bias

LOW RISK OF BIAS: Further research is very unlikely to change our confidence in the estimate.
MODERATE RISK OF BIAS: Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.
HIGH RISK OF BIAS: Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

9.2 Study II and III

Table A 3. Overview of included variables collected in GLA:D® registry

Variable	Data source	Question (English translation)	Response options	Changes for analysis
Age strata	CPR number	Calculated from CPR number and date of first visit	Current age in years	Categorized into strata: <50, 50-59, 60-69, 70-79, ≥80
Sex	CPR number	Calculated from CPR number	Male/Female	
Body mass index	Clinician-reported	Calculated from height and weight variables	Kg/m^2	Categorized into: underweight (<18.5), health weight (18.5-24.9), overweight (25.0-29.9), obese (≥30.0)
Highest level of education attained	Patient-reported	What is the highest level of education that you have completed?	1. Primary school 2. Secondary school 3. Short-term education (under 3 years after secondary school) 4. Middle-term education (3-4 years after secondary school) 5. Long-term education (at least 5 years after secondary school)	
Current employment	Patient-reported	What is your current employment?	1. Employed/student 2. On sick leave full time 3. On sick leave part time 4. Retired 5. Unemployed 6. Self-imposed early retirement 7. Early retirement due to low workability	

Sick leave in past year	Patient-reported	Have you been on sick leave because of knee/hip during last year?	Yes/No	
Symptom duration	Clinician-reported	How long has the patient had the symptom in the most painful joint?	Months	Categorized into: <3 months, 3-12 months, >12 months
Bilateral joint symptoms	Patient-reported	Calculated from questions about presence of symptoms in knee or hip joints	Yes/No	
Comorbid hip or knee symptoms	Patient-reported	Calculated from questions about presence of symptoms in knee and hip joints	Yes/No	
Comorbid back pain in past month	Patient-reported	Did you have pain in your back within the last month (highest level of pain)?	0 no pain – 10 worst pain	Dichotomized into yes/no using cut point of yes = ≥1
Number of comorbidities	Patient-reported	14 questions on presence of medical comorbidities (high blood pressure, high cholesterol, heart disease, ulcers in stomach or other stomach disease, chronic lung disease, diabetes type I, diabetes type II, kidney or liver disease, anemia or other blood disease, cancer, depression, rheumatoid arthritis, neurological disease, other medical disease)	Yes/No	Categorized into: 0, 1, 2, ≥3
Current use of pain medication	Clinician-reported	Does the patient take any pain medications including herbal or dietary supplements? (Yes to at least one of the following: Paracetamol/Acetaminophen, Non-steroidal anti-inflammatory drugs/NSAID, Topical NSAID cream, Morphine, Tramadol, Codeine)	Yes/No	
Current use of opioids	Clinician-reported	Calculated from current use of pain medication question if yes to one of following: Morphine, Tramadol, Codeine	Yes/No	
Fear of movement	Patient-reported	Are you afraid that your joints will be damaged from physical activity and exercise?	Yes/No	

KOOS-12 pain subscale	Patient-reported	Calculated from four KOOS-12 pain items	0 worst – 100 best
KOOS-12 function subscale	Patient-reported	Calculated from four KOOS-12 function items	0 worst – 100 best
KOOS-12 quality of life subscale	Patient-reported	Calculated from four KOOS-12 quality of life items	0 worst – 100 best
HOOS-12 pain subscale	Patient-reported	Calculated from four HOOS-12 pain items	0 worst – 100 best
HOOS-12 function subscale	Patient-reported	Calculated from four HOOS-12 function items	0 worst – 100 best
HOOS-12 quality of life subscale	Patient-reported	Calculated from four HOOS-12 quality of life items	0 worst – 100 best
ASES pain subscale	Patient-reported	Calculated from five ASES pain items	10 worst – 100 best
ASES other symptoms subscale	Patient-reported	Calculated from six ASES other symptoms items	10 worst – 100 best
UCLA Activity Score	Patient-reported	What is your current activity level? Consider your activity level during the last 4 weeks.	1 worst – 10 best
30-second chair stand test	Clinician-reported	Not applicable	Number of repetitions completed
40 meter fast-paced walk test	Clinician-reported	Not applicable	Seconds

CPR = Danish Det Centrale Personregister; KOOS: Knee injury and Osteoarthritis Outcome Score; HOOS: Hip disability and Osteoarthritis Outcome Score; ASES: Arthritis Self-Efficacy Scale; UCLA: University of California and Los Angeles.

Table A 4. Operationalization of Tomkins-Lane clinical criteria

Original criteria item	Item operationalization
Does the patient have back pain?	Participant baseline questionnaire: Have you had pain in your back within the last month (highest level of pain, 0 no pain – 10 worst pain)? Dichotomized into yes/no using cut point of ≥1
Does the patient have leg or buttock pain while walking?	LSS symptom item 4: Is your pain or numbness in one or both legs or in the buttock worsening when you are walking?
Does the patient flex forward to relieve symptoms?	LSS symptom item 6: Is your pain or numbness in one or both legs or in the buttock relieved when you are bending forwards?
Does the patient feel relief when using a shopping cart or bicycle?	LSS symptom item 8: Is your pain or numbness in one or both legs or in the buttock relieved when you are riding a bicycle? Or LSS symptom item 9: Is your pain or numbness in one or both legs or in the buttock relieved when you are bending over the shopping cart?
Does the patient have motor or sensory disturbance while walking?	LSS symptom item 11: Do you have the feeling of weakness in your legs while walking?
Are the pulses in the foot present and symmetric?	Not included
Does the patient have lower extremity weakness?	Not included

*Participants answering yes to the LSS symptom items were considered to satisfy the original criteria item.

Table A 5. Operationalization of Genevay clinical criteria

Original criteria item	Scoring weight	Item operationalization
Patient age over 60 years	4	Calculated from Danish Det Centrale Personregister (CPR) number. Dichotomized into yes/no using cut point of ≥60
Pain in both legs	3	LSS symptom item 2: Do you have pain or numbness in both legs or the buttocks?
Leg pain decreased by leaning forward or flexing the spine	3	LSS symptom item 6: Is your pain or numbness in one or both legs or in the buttock relieved when you are bending forwards?
Leg pain relieved by sitting	3	LSS symptom item 7: Is your pain or numbness in one or both legs or in the buttock relieved when you are sitting?
Positive 30 second extension test	4	Not included

Negative straight leg raises test at 60°	2	Not included

*Participants answering yes to the LSS symptom items were considered to satisfy the original criteria item.

10 Appendix 2 – Additional results

10.1 Study I

Figure A 1. **Study selection flow diagram**

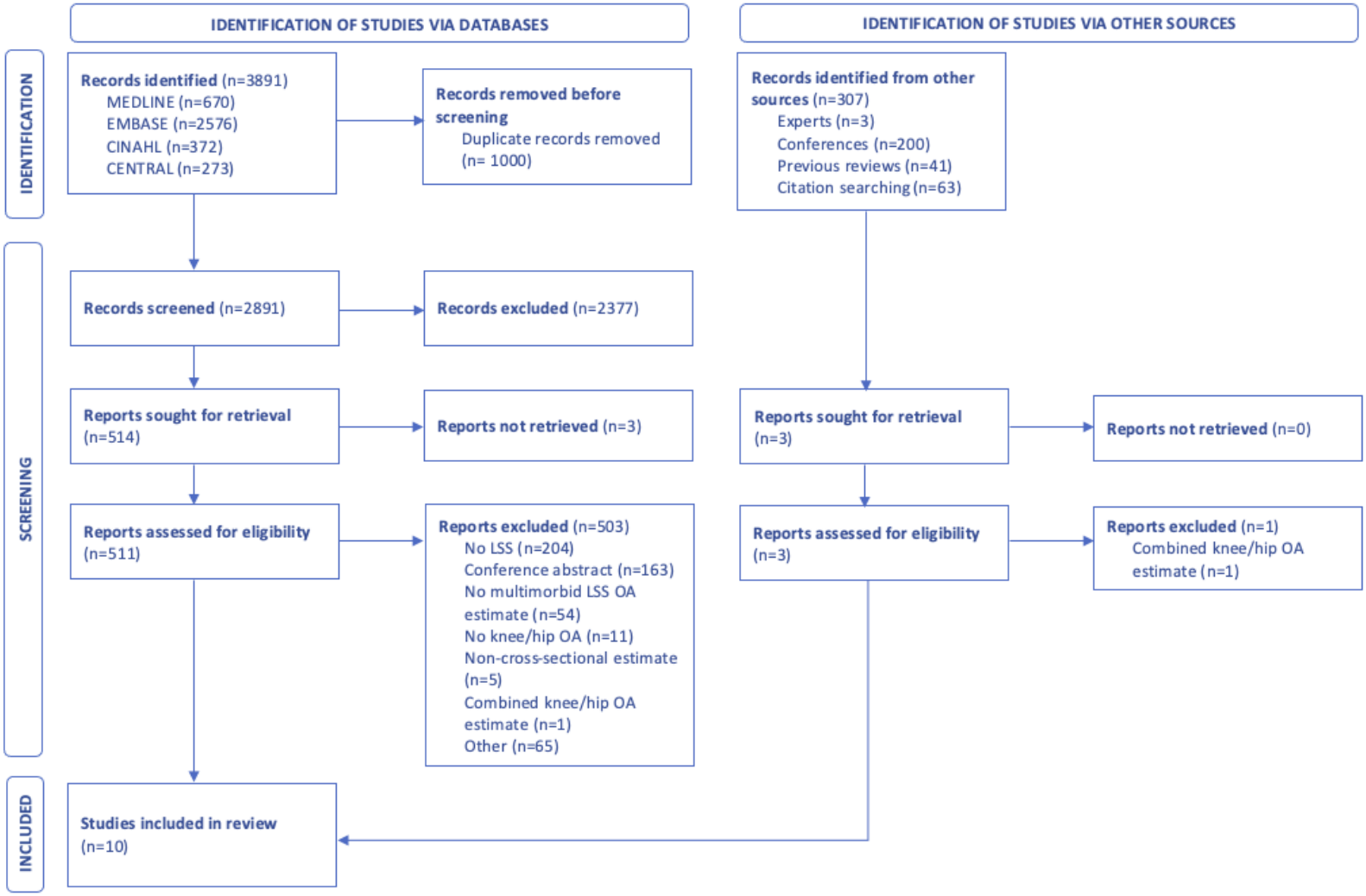

Table A 6. Risk of bias of included studies

Author, year	External validity				Internal validity							Overall risk of bias
	Item 1	Item 2	Item 3	Item 4	Item 6a	Item 6b	Item 7a	Item 7b	Item 8	Item 9	Item 10	
Kim, 2008a	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Kim, 2008b	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Saito, 2012	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	High
Lee, 2012	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Cho, 2019	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Schneider, 2019	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	High
Burgstaller, 2020	No	No	No	No	Yes	Yes	No	No	No	Yes	Yes	High
Ozaki, 2020	No	No	No	No	Yes	Yes	No	Yes	No	No	Yes	High
Londhe, 2020	No	No	No	No	No	Yes	No	Yes	No	Yes	Yes	High
Weiner, 2021	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	High

Yes = low risk of bias; No = high risk of bias.
Item 1 = Study population is a close representation of the target population
Item 2 = Sampling frame is a close representation of the target population
Item 3 = Random selection of sample or census
Item 4 = Likelihood of non-response bias is minimal
Item 6a = Acceptable case definition of lumbar spinal stenosis
Item 6b = Acceptable case definition of knee and/or hip osteoarthritis
Item 7a = Instrument used to measure lumbar spinal stenosis is valid and reliable
Item 7b = Instrument used to measure knee and/or hip osteoarthritis is valid and reliable
Item 8 = Same mode of data collection for all subjects
Item 9 = Appropriate length of shortest prevalence period

Table A 7. Study characteristics of included studies for LSS with comorbid knee OA

Author, year	Study design	Country: setting	Age, mean (SD)	Female	LSS definition	LSS sample size	Knee OA definition	Knee OA sample size	Prevalence
Kim, 2008a	Cohort	Korea: surgical department	61 (NR)	100%	Combined: undergoing surgery	44	Imaging: K/L grade 2-4	19	43%
Kim, 2008b	Cross-sectional	Korea: surgical department	67 (7.0)	100%	Combined: neurogenic claudication + MRI	67	Imaging: K/L grade 2-4	27	40%
Lee, 2012	Cross-sectional	Korea: surgical department	66 (8.4)	100%	Combined: neurogenic claudication + MRI	106	Imaging: K/L grade 2-4	44	42%
Schneider, 2019	RCT	USA: mixed community/primary/secondary care	72 (7.8)	52%	Combined: clinical examination + MRI/CT	259	Clinical: ACR criteria	82	32%
Burgstaller, 2020	Cohort	Switzerland: eight rheumatology and surgical departments	73 (8.5)	52%	Combined: neurogenic claudication + MRI/CT	601	Clinical: self-reported	133	22%
Ozaki, 2020	Case-control	Japan: surgical department	69 (8.3)*	71%*	Combined: neurogenic claudication + MRI/myelography	641	Combined: medical history + K/L grade 2-4	32	5%

* = estimates for knee OA group only; LSS = lumbar spinal stenosis; OA = osteoarthritis; NR = not reported; Combined = clinical and imaging findings of LSS or knee OA; ACR = American College of Rheumatology; MRI = magnetic resonance imaging; CT = computed tomography; K/L = Kellgren-Lawrence.

Table A 8. Study characteristics of included studies for LSS with comorbid hip OA

Author, year	Study design	Country: setting	Age, mean (SD)	Female	LSS definition	LSS sample size	Knee OA definition	Knee OA sample size	Prevalence
Kim, 2008a	Cohort	Korea: surgical department	61 (NR)	100%	Combined: undergoing surgery	44	Imaging: K/L grade 2-4	0	0%
Saito, 2012	Cohort	Japan: surgical department	NR	NR	Combined: low back and leg pain + MRI/myelography/CT	420	Imaging: not described	15	4%
Lee, 2012	Cross-sectional	Korea: surgical department	66 (8.4)	100%	Combined: neurogenic claudication + MRI	106	Imaging: K/L grade 2-4	4	4%
Schneider, 2019	RCT	USA: mixed community/primary/secondary care	72 (7.8)	52%	Combined: clinical examination + MRI/CT	259	Clinical: ACR criteria	43	17%
Burgstaller, 2020	Cohort	Switzerland: eight rheumatology and surgical departments	73 (8.5)	52%	Combined: neurogenic claudication + MRI/CT	601	Clinical: self-reported	102	17%
Weiner, 2021	Cohort	USA: military veterans surgical department	66 (9.7)	3%	Combined: neurogenic claudication + MRI	193	Combined: ACR clinical + radiographic criteria	68	35%

LSS = lumbar spinal stenosis; OA = osteoarthritis; NR = not reported; Combined = clinical and imaging findings of LSS or knee OA; ACR = American College of Rheumatology; MRI = magnetic resonance imaging; CT = computed tomography; K/L = Kellgren-Lawrence.

Table A 9. Study characteristics of included studies for knee OA with comorbid LSS

Author, year	Study design	Country: setting	Age, mean (SD)	Female	Knee OA definition	Knee OA sample size	LSS definition	LSS sample size	Prevalence
Cho, 2019	Cross-sectional	Korea: national insurance claims	64 (9.8)	62%	Combined: ICD-10 codes for diagnosis and imaging	2,857,999	Clinical: ICD-10 codes	479,311	17%
Londe, 2020	Cohort	India: surgical department	66 (14.8)	82%	Combined: undergoing surgery	200	Combined: symptoms + MRI/CT	108	54%

LSS = lumbar spinal stenosis; OA = osteoarthritis; NR = not reported; Combined = clinical and imaging findings of LSS or knee OA; MRI = magnetic resonance imaging; CT = computed tomography; ICD-10 = International Classification of Diseases 10th revision.

10.2 Study II and III

Figure A 2. Study II and III flow diagram

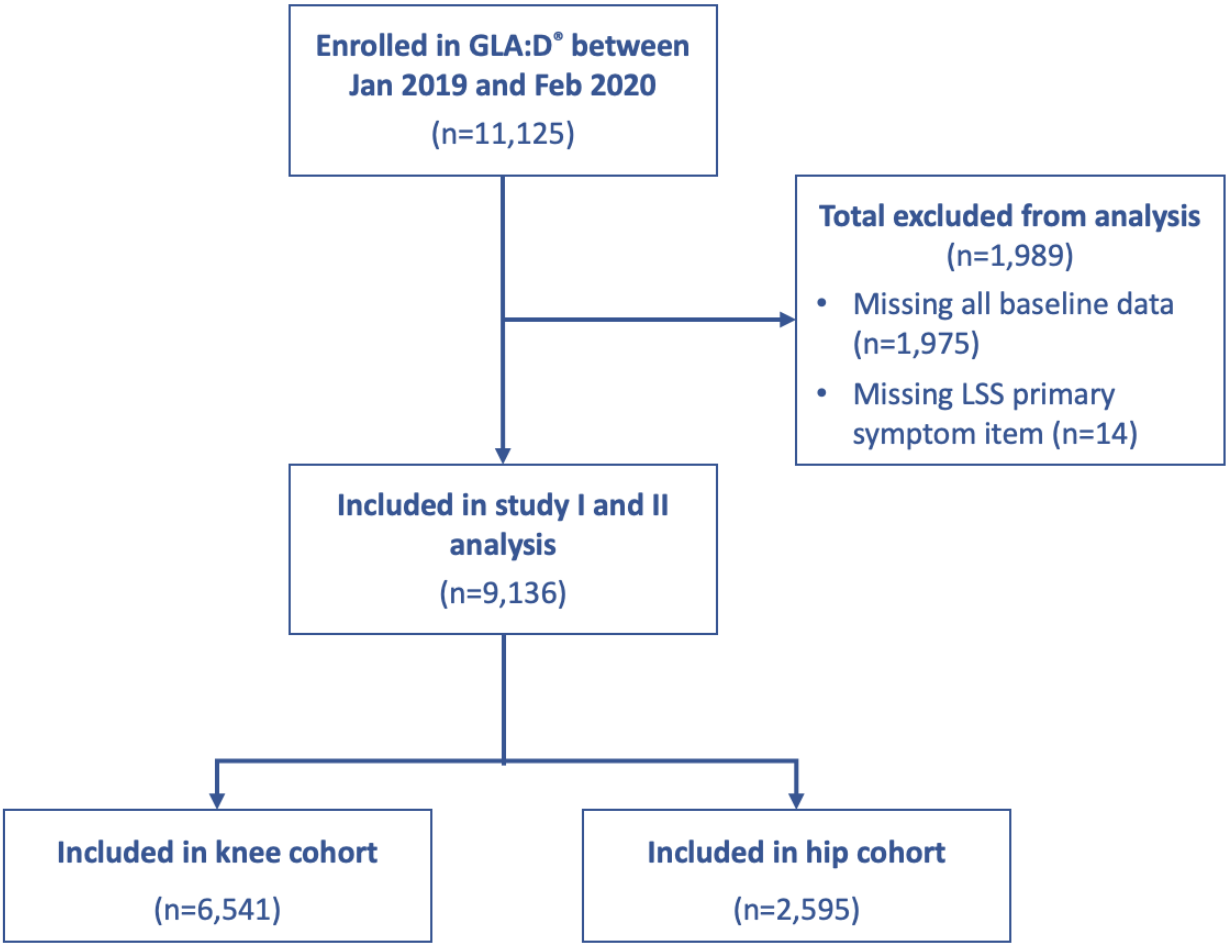

Table A 10. Overall knee cohort sample characteristics and by LSS symptom status

	Knee cohort (n=6,541)	Comorbid LSS symptoms (n=2,435)	No LSS symptoms (n=4,106)
Sociodemographics			
Age, % (95% CI)			
<50	5.4 (4.9-6.0)	6.4 (5.5-7.5)	4.8 (4.2-5.5)
50-59	20.8 (19.8-21.8)	23.6 (21.9-25.3)	19.1 (17.9-20.3)
60-69	36.7 (35.6-37.9)	35.6 (33.7-37.6)	37.4 (35.9-38.9)
70-79	31.0 (29.9-32.1)	28.5 (26.7-30.3)	32.5 (31.1-33.9)
≥80	6.1 (5.5 6.7)	5.9 (5.0-6.9)	6.2 (5.5-7.0)
Missing, n	0	0	0
Female, % (95% CI)	68.9 (67.8-70.0)	70.3 (68.4-72.1)	68.1 (66.7-69.6)
Missing, n	0	0	0
Body mass index, % (95% CI)			
Underweight	0.5 (0.3-0.7)	0.5 (0.3-0.9)	0.4 (0.2-0.7)
Healthy weight	24.2 (23.1-25.2)	19.4 (17.9-21.1)	26.6 (25.3-28.0)
Overweight	38.9 (37.7-40.1)	38.5 (36.6-40.5)	38.6 (37.1-40.1)
Obese	36.5 (35.3-37.7)	41.0 (39.1-43.0)	33.3 (31.9-34.8)
Missing, n	54	12	42
Education level, % (95% CI)			
Primary school	18.2 (17.3-19.2)	19.8 (18.3-21.5)	17.2 (16.1-18.4)
Secondary school	11.0 (10.3-11.8)	11.2 (9.9-12.5)	10.9 (10.0-11.9)
Short-term education	20.2 (19.2-21.2)	20.5 (18.9-22.1)	19.9 (18.7-21.2)
Middle-term education	39.2 (38.0-40.4)	39.4 (37.4-41.4)	39.0 (37.5-40.5)
Long-term education	11.4 (10.7-12.2)	9.3 (8.2-10.5)	12.7 (11.7-13.7)
Missing, n	9	0	9
Current employment, % (95% CI)			
Employed/student	32.3 (31.1-33.4)	31.8 (30.0-33.7)	32.5 (31.1-34.0)
Sick leave full-time	2.6 (2.2-3.0)	3.5 (2.8-4.3)	2.0 (1.6-2.4)
Sick leave part-time	2.7 (2.3-3.1)	3.5 (2.8-4.3)	2.2 (1.8-2.7)
Retired	53.6 (52.4-54.8)	50.2 (48.2-52.2)	55.7 (54.1-57.2)
Unemployed	2.1 (1.8-2.5)	3.0 (2.3-3.7)	1.6 (1.2-2.0)
Self-imposed early retirement	4.4 (3.9-4.9)	4.3 (3.5-5.2)	4.4 (3.8-5.1)

Early retirement due to low workability	2.4 (2.1-2.8)	3.7 (3.0-4.5)	1.7 (1.3-2.1)
Missing, n	0	0	0
Sick leave in past year, % (95% CI)	11.5 (10.8-12.3)	14.9 (13.5-16.3)	9.5 (8.6-10.5)
Missing, n	1	0	1
Clinical characteristics			
Symptom duration, % (95%CI)			
<3 months	8.7 (8.1-9.4)	7.0 (6.0-8.1)	9.7 (8.9-10.7)
3-12 months	46.0 (44.8-47.2)	44.1 (42.1-46.1)	47.2 (45.6-48.7)
13-24 months	15.4 (14.5-16.3)	16.0 (14.5-17.5)	15.0 (13.9-16.1)
>24 months	29.9 (28.8-31.0)	32.9 (31.1-34.8)	28.1 (26.7-29.5)
Missing, n	2	0	2
Bilateral knee symptoms, % (95% CI)	43.7 (42.5-45.0)	49.6 (47.6-51.6)	40.3 (38.8-41.8)
Missing, n	1	0	1
Comorbid hip symptoms, % (95% CI)	18.6 (17.7-19.6)	23.7 (22.1-25.5)	15.6 (14.5-16.7)
Missing, n	3	0	3
Back pain in last month, % (95% CI)	66.0 (64.8-67.1)	77.9 (76.2-79.5)	58.9 (57.4-60.4)
Missing, n	0	0	0
Number of comorbidities, % (95% CI)			
None	35.9 (34.7-37.1)	30.9 (29.1-32.8)	38.8 (37.3-40.3)
One	36.4 (35.3-37.6)	35.1 (33.2-37.0)	37.2 (35.8-38.7)
Two	17.9 (17.0-18.9)	20.4 (18.8-22.1)	16.4 (15.3-17.6)
Three or more	9.7 (9.0-10.5)	13.6 (12.3-15.0)	7.4 (6.6-8.3)
Missing, n	3	0	3
Pain medication use, % (95% CI)	59.3 (58.1-60.4)	66.6 (64.7-68.5)	54.9 (53.4-56.5)
Missing, n	0	0	0
Opioid use, % (95% CI)	4.6 (4.1-5.1)	6.7 (5.7-7.8)	3.3 (2.8-3.9)
Missing, n	1	0	1
Fear of movement, % (95% CI)	15.3 (14.5-16.2)	18.0 (16.4-19.6)	13.7 (12.7-14.8)
Missing, n	0	0	0

Health status measures			
K)OS-12 pain subscale, mean (95% CI)	50.3 (49.9-50.7)	46.1 (45.5-46.7)	52.8 (52.2-53.3)
Missing, n	0	0	0
KOOS-12 function subscale, mean (95% CI)	56.9 (56.4-57.3)	51.6 (50.9-52.3)	60.0 (59.4-60.5)
Missing, n	0	0	0
KOOS-12 quality of life subscale, mean (95% CI)	46.0 (45.6-46.4)	42.0 (41.4-42.6)	48.3 (47.8-48.8)
Missing, n	0	0	0
ASES pain subscale, mean (95% CI)	64.8 (64.3-65.3)	60.6 (59.8-61.4)	67.2 (66.6-67.9)
Missing, n	10	0	10
ASES other symptoms subscale, mean (95% CI)	69.1 (68.7-69.6)	64.5 (63.8-65.3)	71.8 (71.2-72.4)
Missing, n	10	1	9
UCLA Activity Score, mean (95% CI)	5.5 (5.4-5.5)	5.4 (5.3-5.5)	5.5 (5.5-5.6)
Missing, n	0	0	0
30-second chair-stand test, mean (95% CI)	11.9 (11.8-12.0)	11.6 (11.4-11.8)	12.1 (12.0-12.2)
Missing, n	339	116	223
40-meter fast-paced walk test, mean (95%)	29.0 (28.7-29.2)	29.8 (29.4-30.2)	28.5 (28.2-28.8)
Missing, n	421	153	268

All KOOS-12 subscales scored 0(worst) to 100(best); all ASES subscales scored 10(worst) to 100(best); UCLA Activity Score scored 1(inactive) to 10(active); 30-second chair-stand test scored as number of repetitions completed; 40-meter fast-paced walk test scored in seconds.

Table A 11. Overall hip cohort sample characteristics and by LSS symptom status

	Hip cohort (n=2,595)	Comorbid LSS symptoms (n=1,253)	No LSS symptoms (n=1,342)
Sociodemographics			
Age, % (95% CI)			
<50	4.3 (3.6-5.2)	5.1 (4.0-6.5)	3.6 (2.6-4.7)
50-59	17.2 (15.8-18.7)	20.6 (18.4-22.9)	14.1 (12.3-16.1)
60-69	35.7 (33.9-37.6)	36.2 (33.6-39.0)	35.2 (32.7-37.9)
70-79	36.5 (34.7-38.4)	32.9 (30.3-35.6)	39.9 (37.3-42.6)
≥80	6.2 (5.3-7.2)	5.2 (4.0-6.6)	7.2 (5.8-8.7)
Missing, n	0	0	0
Female, % (95% CI)	68.9 (67.0-70.7)	68.3 (65.7-70.9)	69.4 (66.9-71.9)
Missing, n	0	0	0
Body mass index, % (95% CI)			
Underweight	0.7 (4.7-1.2)	0.5 (0.2-1.0)	1.0 (0.5-1.7)
Healthy weight	35.6 (33.7-37.4)	33.4 (30.8-36.0)	37.0 (34.4-39.7)
Overweight	38.7 (36.9-40.6)	38.1 (35.4-40.8)	38.7 (36.1-41.4)
Obese	25.0 (23.3-26.7)	27.0 (24.5-29.5)	22.7 (20.4-25.0)
Missing, n	22	14	8
Education level, % (95% CI)			
Primary school	17.8 (16.4-19.3)	18.0 (15.9-20.3)	17.5 (15.5-19.7)
Secondary school	11.7 (10.5-13.0)	11.3 (9.6-13.2)	11.9 (10.2-13.8)
Short-term education	20.4 (18.9-22.0)	21.5 (19.2-23.8)	19.4 (17.3-21.6)
Middle-term education	38.7 (36.8-40.6)	38.5 (35.8-41.2)	38.7 (36.1-41.4)
Long-term education	11.4 (10.3-12.7)	10.5 (8.9-12.4)	12.2 (10.5-14.1)
Missing, n	5	2	3
Current employment, % (95% CI)			
Employed/student	29.7 (27.9-31.5)	32.4 (29.8-35.1)	27.1 (24.8-29.6)
Sick leave full-time	1.5 (1.1-2.1)	1.7 (1.0-2.6)	1.4 (0.9-2.2)
Sick leave part-time	2.2 (1.7-2.9)	3.2 (2.4-4.4)	1.3 (0.7-2.0)
Retired	59.3 (57.4-61.2)	54.7 (51.9-57.5)	63.6 (61.0-66.2)
Unemployed	1.3 (1.0-1.9)	1.9 (1.2-2.8)	0.8 (0.4-1.5)
Self-imposed early retirement	3.4 (2.8-4.2)	3.4 (2.5-4.6)	3.4 (2.5-4.5)

Early retirement due to low workability	2.4 (1.9-3.1)	2.6 (1.8-3.6)	2.3 (1.6-3.3)
Missing, n	0	0	0
Sick leave in past year, % (95% CI)	6.6 (5.7-7.7)	9.3 (7.7-11.0)	4.2 (3.2-5.4)
Missing, n	0	0	0
Clinical characteristics			
Symptom duration, % (95%CI)			
<3 months	5.4 (4.6, 6.4)	3.7 (3.7-4.9)	7.1 (5.8-8.6)
3-12 months	47.6 (45.7-49.5)	46.4 (43.7-49.3)	48.7 (46.0-51.4)
13-24 months	19.7 (18.2-21.3)	20.4 (18.2-22.7)	19.1 (17.1-21.4)
>24 months	27.2 (25.5-29.0)	29.5 (27.0-32.1)	25.1 (22.8-27.5)
Missing, n	0	0	0
Bilateral hip symptoms, % (95% CI)	24.6 (23.0-26.3)	28.3 (25.8-30.8)	21.2 (19.0-23.4)
Missing, n	0	0	0
Comorbid knee symptoms, % (95% CI)	35.1 (33.3-37.0)	38.1 (35.4-40.9)	32.3 (29.7-34.8)
Missing, n	0	0	0
Back pain in last month, % (95% CI)	75.0 (73.3-76.7)	81.6 (79.4-83.6)	68.9 (66.3-71.3)
Missing, n	0	0	0
Number of comorbidities, % (95% CI)			
None	34.9 (33.1-36.8)	32.3 (29.7-35.0)	37.3 (34.7-40.0)
One	36.1 (34.2-38.0)	34.4 (31.8-37.1)	37.7 (35.1-40.4)
Two	19.2 (17.7-20.8)	20.9 (18.7-23.3)	17.6 (15.6-19.7)
Three or more	9.7 (8.6-10.9)	12.2 (10.4-14.2)	7.4 (6.0-8.9)
Missing, n	2	2	0
Pain medication use, % (95% CI)	65.5 (63.7-67.4)	70.9 (68.3-73.4)	60.6 (57.9-63.2)
Missing, n	0	0	0
Opioid use, % (95% CI)	6.7 (5.8-7.7)	8.7 (7.3-10.5)	4.8 (3.7-6.0)
Missing, n	0	0	0
Fear of movement, % (95% CI)	10.3 (9.1-11.5)	12.3 (10.5-14.2)	8.3 (6.9-10.0)
Missing, n	0	0	0

Health status measures			
HOOS-12 pain subscale, mean (95% CI)	49.3 (48.7-49.9)	46.2 (45.4-47.1)	52.2 (51.3-53.1)
Missing, n	0	0	0
HOOS-12 function subscale, mean (95% CI)	59.4 (58.6-60.1)	55.4 (54.3-56.5)	63.1 (62.1-64.2)
Missing, n	0	0	0
HOOS-12 quality of life subscale, mean (95% CI)	48.8 (48.1-49.4)	45.7 (44.8-46.6)	51.7 (50.8-52.6)
Missing, n	0	0	0
ASES pain subscale, mean (95% CI)	61.2 (60.4-62.0)	57.8 (56.6-58.9)	64.5 (63.3-65.6)
Missing, n	5	2	3
ASES other symptoms subscale, mean (95% CI)	67.0 (66.3-67.7)	63.5 (62.4-64.5)	70.3 (69.3-71.3)
Missing, n	5	2	3
UCLA Activity Score, mean (95% CI)	5.6 (5.5-5.7)	5.5 (5.4-5.7)	5.6 (5.5-5.7)
Missing, n	0	0	0
30-second chair-stand test, mean (95% CI)	12.2 (12.0-12.3)	11.9 (11.7-12.2)	12.4 (12.2-12.6)
Missing, n	123	61	62
40-meter fast-paced walk test, mean (95%)	28.8 (28.4-29.1)	29.0 (28.5-29.5)	28.5 (28.1-28.9)
Missing, n	167	85	82

All HOOS-12 subscales scored 0(worst) to 100(best); all ASES subscales scored 10(worst) to 100(best); UCLA Activity Score scored 1(inactive) to 10(active); 30-second chair-stand test scored as number of repetitions completed; 40-meter fast-paced walk test scored in seconds.

Table A 12. Comparison of GLA:D® participants with missing LSS symptom item data

	Complete LSS symptom data (n=9,136)	**Missing LSS symptom data (n=1,989)**
Age, %		
<50	5.1 (4.7-5.6)	6.9 (5.9-8.1)
50-59	19.8 (19.0-20.6)	19.4 (17.7-21.2)
60-69	36.4 (35.5-37.4)	27.8 (25.9-29.8)
70-79	32.6 (31.6-33.5)	33.0 (31.0-35.1)
≥80	6.1 (5.6-6.6)	12.9 (11.5-14.5)
Missing, n	0	0
Female, %	68.9 (68.0-69.9)	65.7 (63.6-67.8)
Missing, n	0	0
Body mass index, %		
Underweight	0.5 (0.4-0.7)	0.6 (0.3-1.1)
Normal weight	27.2 (26.3-28.1)	24.6 (22.8-26.6)
Overweight	38.5 (37.5-39.5)	38.3 (36.1-40.4)
Obese	32.9 (32.0-33.9)	33.8 (31.8-36.0)
Missing, n	76	53
Symptom duration, %		
<3 months	7.8 (7.2-8.4)	8.5 (7.4-9.9)
3-12 months	46.5 (45.4-47.5)	48.0 (45.7-50.2)
13-24 months	16.6 (15.8-17.4)	16.1 (14.5-17.8)
>24 months	29.1 (28.2-30.1)	27.3 (25.4-29.3)
Missing, n	2	1
Pain medication use, % (95% CI)	61.1 (60.1-62.1)	66.8 (64.7-68.9)
Missing, n	0	0
Opioid use, % (95% CI)	5.2 (4.7-5.7)	6.7 (5.6-7.9)
Missing, n	1	1

11 Appendix 3 – Published papers

Paper I