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Growing up with pediatric hip disease– a companion for life

Exploring the multifaceted experiences throughout life, with special attention to Legg-Calvé Perthes disease

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Abstract

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Pediatric hip diseases such as developmental dysplasia of the hip, Legg-Calvé-Perthes disease, and slipped capital femoral epiphysis can lead to lasting hip deformities and early-onset osteoarthritis. This thesis explores the long-term impacts of these conditions, combining patient experiences with large-scale data.

Study I used data from the Swedish Pediatric Orthopedic Quality Register to examine the incidence, demographics, and risk factors for containment surgery in patients with unilateral Legg-Calvé-Perthes disease. 309 patients registered between 2015 and 2024. The study found a national yearly incidence of 4.2 per 100,000 children aged 2–12 years, somewhat lower than previously reported in Sweden. The disease was more common in boys (77%), with an average diagnosis age of 6 years. Notably, 30% of patients were overweight or obese at diagnosis, increasing to around 40% at the 2-year follow-up. The study also found that older age, a positive Trendelenburg sign, and limited hip abduction at diagnosis increased the likelihood of surgical intervention.

Study II focused on the long-term impact of Legg-Calvé-Perthes disease as experienced by patients through qualitative interviews. Themes that emerged included self-reinvention, concerns about future health, surgical interventions, and challenges with physical activities leading to sedentary lifestyles. The study also highlighted patients' sense of disconnection during the transition from pediatric to adult care and emphasized the need for continuous, age-appropriate information and structured healthcare transitions.

Study III explored whether individuals with a history of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis are at increased risk of receiving prescriptions for pain or antidepressant medications in adulthood. The study, which included 1,292 Legg-Calvé-Perthes disease patients and 1,613 slipped capital femoral epiphysis patients, found a higher risk of analgesic prescriptions in both groups compared to matched controls. Additionally, slipped capital femoral epiphysis patients had a slightly higher risk of antidepressant prescriptions. The findings underscore the need for long-term pain management and health support.

Study IV investigated mortality risks after total hip arthroplasty in patients with a history of pediatric hip disease. Among 4,043 patients identified from the Swedish Hip Arthroplasty Register, the study found no increased 90-day mortality risk compared to the general population. These patients' overall mortality risk was lower, suggesting that total hip arthroplasty does not increase mortality risks despite their pre-existing conditions.

In conclusion, this thesis provides a comprehensive view of the long-term impacts of pediatric hip diseases, highlighting the need for improved, continuous, and age-appropriate care strategies to enhance patient outcomes.

Keywords: Ortopedics, pediatric hip disease, demographics, life impact, mortality, chronic disease, chronic pain, Legg-Calvé-Perthes disease, developmental dysplasia of the hip, slipped capital femoral epiphysis

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To Philip, Diana, Eleonora, and Andreas

List of Papers

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Wadström MG, Hailer NP, Hailer YD. (2024) Demographics and risk for containment surgery in patients with unilateral Legg–Calvé–Perthes disease: a national population-based cohort study of 309 patients from the Swedish Pediatric Orthopedic Quality Register. *Acta Orthopaedica*. 2024 Jun 18;95:333-339.

II. Wadström MG, Röding AJ, Milner J, Hailer YD. (2024) Chronic diseases in childhood: Not just a condition but a companion for life. Submitted.

III. Wadström MG, Hailer YD. (2022) Pediatric Hip Disease Increases the Risk for Opioid Use in Adulthood: Long-term Burden of Pain and Depression. *Pain Physician*. 2022 Oct;25(7):E1153-E1160.

IV. Wadström MG, Hailer NP, Hailer YD. (2021) No increased mortality after total hip arthroplasty in patients with a history of pediatric hip disease: a matched, population-based cohort study on 4,043 patients. *Acta Orthopaedica*. 2021 Dec;92(6):673-677.

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Abbreviations

BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
DDH	Developmental dysplasia of the hip
HR	Hazard Ratio
LCPD	Legg-Calvé-Perthes disease
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OR	Odds Ratio
PROM	Patient-reported outcome measure
SCFE	Slipped capital femoral epiphysis
SNRI	Serotonin and norepinephrine reuptake inhibitors
SPOQ	Swedish Pediatric Quality Register
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
THA	Total hip arthroplasty

Introduction

Developmental dysplasia of the hip, Legg-Calvé-Perthes disease, and slipped capital femoral epiphysis (Figure 1) are pediatric hip diseases that pediatric orthopedic surgeons regularly encounter and treat. Although these hip diagnoses have different etiologies and characteristics, they all affect the hip joints of children and carry a risk of permanent hip deformities. These deformities, in turn, are linked to an increased risk of early secondary osteoarthritis development [56, 112], and more often necessitate total hip arthroplasty surgery at a younger age than patients who undergo surgery because of primary hip osteoarthritis [32, 155].

Most research on pediatric hip disease focuses on improving methods for diagnosis and treatment in the active phase of the disease in childhood. Less attention is given to understanding the long-term impacts of these conditions on patients' lives. There is limited knowledge about whether these diagnoses should be regarded as isolated disease episodes in childhood, or if they should be considered as lifelong conditions, and what impact they carry later in adulthood.

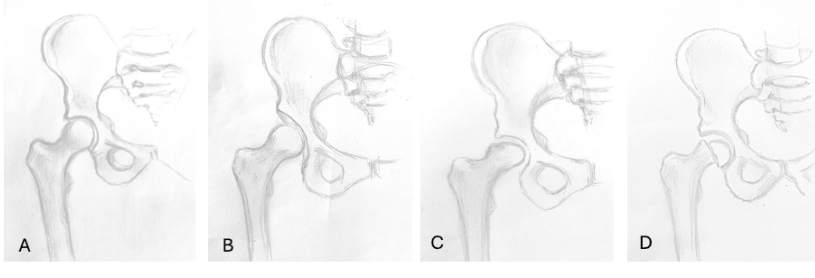

Figure 1: *The different hip deformities included in this thesis, with a normal hip joint as a reference. A: Normal hip joint. B: Developmental dysplasia of the hip. C: Legg-Calvé-Perthes disease. D: Slipped capital femoral epiphysis.*

Developmental dysplasia of the hip

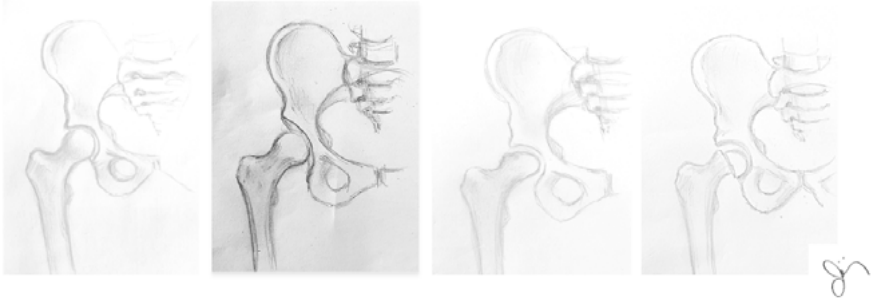

Figure 2: *Illustration of a hip joint with developmental dysplasia.*

Developmental dysplasia of the hip (Figure 2) is a condition that occurs when the hip joint does not develop properly in the fetus and during infancy. In many countries, it is screened for in newborns. Developmental dysplasia of the hip is a collective term for an innate incongruency between the femoral head and the acetabulum, which in turn can lead to various degrees of hip instability or, in the most severe case, dislocation, which leads to limping and eventually, to a painful motion of the hip joint [154, 156, 158].

Developmental dysplasia of the hip is more common in girls, and genetic, hormonal, and mechanical factors are linked to the etiology. In a review by Kuitunen et al. from 2022, the incidence of developmental dysplasia of the hip varied greatly geographically and was found to range from 20 (95% 10-40) to 12,030 (95% CI, 11,090 -13,050) infants per 100,000 newborns [68]. In the 1950s, a national screening program for hip instability and dislocations was initiated for all newborn babies at hospitals in Sweden, as late detection of hip dislocations leads to a much more complicated course of treatment and worse outcomes after treatment. Today, 12 per 100,000 live births are detected later than 2 weeks of age [149] compared with an estimated minimum level of 90 per 100,000 before the initiation of the screening program [129].

The importance of early detection and treatment of developmental dysplasia of the hip is well-established. However, the optimal screening strategy (universal ultrasound, selective ultrasound, or clinical examination alone) remains debatable [63, 67]. Selective ultrasound screening targets children with abnormal clinical examinations and developmental dysplasia of the hip risk factors, while the universal approach includes ultrasound examinations for all newborns within a specific age range [63]. While ultrasound can identify newborns with dysplastic hips needing early treatment, its ability to prevent acetabular dysplasia at skeletal maturity has not been demonstrated.

A Norwegian long-term follow-up study noted that all three screening programs studied (universal ultrasound, selective ultrasound, and clinical examination alone) resulted in similar rates of radiographic findings associated with acetabular dysplasia or early degenerative changes at skeletal maturity. Thus, concluding that offering universal hip ultrasound and treating those testing positive had no additional impact at the group level regarding these radiographic markers at skeletal maturity [69]. Still, other studies suggest that universal ultrasound screening programs for developmental dysplasia of the hip lead to earlier detection, lower treatment rates, fewer late surgeries, and reduced risk of avascular necrosis, indicating a potential shift towards universal screening over selective programs [11].

The diagnosis is typically set by clinical examination (Barlow and Ortolani tests) and ultrasound examinations. While some countries, such as Germany, Switzerland, and Austria, follow universal ultrasound screening programs, Sweden follows a selective ultrasound screening program [67]. Meaning, that in Sweden, all newborn babies are clinically examined by a physician. Newborns with suspicious findings are referred for an ultrasound examination and to a pediatric orthopedic surgeon, who then initiates treatment if necessary [25].

Treatment for developmental dysplasia of the hip in newborns typically involves harnesses or braces to hold the hip joint in abduction and flexion to enable proper development. “Late” detection of developmental dysplasia of the hip in Sweden is defined as detection later than 2 weeks after birth. Infants 6–12 months old can usually be treated with closed reduction and hip spica cast. In severe cases and with older children, open reduction and a capsuloplasty may be required. In children over 3 years of age, additional procedures such as pelvic osteotomy, with or without proximal femoral varus derotational osteotomy, may be necessary to achieve optimal hip alignment and stability [154]. Early detection and treatment of developmental dysplasia of the hip are of utmost importance to ensure the best possible outcome for affected individuals.

Residual acetabular dysplasia can persist even after treatment, necessitating follow-up radiographic monitoring [126]. Some patients treated for developmental dysplasia of the hip in childhood may experience residual dysplasia that progresses or becomes symptomatic during skeletal maturation and adolescent growth [126].

While developmental dysplasia of the hip is typically diagnosed and treated during infancy, it is increasingly recognized that hip dysplasia can also develop later in childhood or adolescence [112]. Previously, acetabular dysplasia diagnosed in adolescence was considered a late diagnosis of childhood

developmental dysplasia of the hip. Although some cases are indeed delayed diagnoses, the acetabulum continues to develop through early adolescence, and dysplasia may not become evident until late adolescence. Thus, adolescent-onset acetabular dysplasia is now seen as distinct from childhood developmental dysplasia of the hip [79, 138]. Hip dysplasia should be viewed as a spectrum, with some cases requiring additional interventions like periacetabular osteotomy later in life to address residual or newly developed deformities. This underscores the importance of long-term follow-up and recognizing hip dysplasia as a potential ongoing process beyond infancy.

Developmental dysplasia of the hip is a significant risk factor for early-onset secondary osteoarthritis and the need for total hip arthroplasty in young adulthood. The work by G. Wiberg from 1940, is considered one of the most influential studies in orthopedic literature linking acetabular dysplasia to the development of hip osteoarthritis [152]. Later studies have shown that 25-50% of patients with hip dysplasia develop radiographic osteoarthritis by age 50 [20]. The progression of osteoarthritis usually develops gradually, and progression to total hip arthroplasty might emerge in the third or fourth decade [98, 155]. Secondary osteoarthritis as sequelae after pediatric hip disease accounts for 1.5% of all primary total hip arthroplasties in Sweden. It is the most common cause of total hip arthroplasties in patients under 55, according to the Swedish Arthroplasty Register's annual report 2022 [148]. A recent British study found a 14% incidence of total hip arthroplasty by age 34 in this patient population [98]. Additionally, an Irish publication revealed that over 40% of patients under 50 undergoing total hip arthroplasty had underlying hip dysplasia [96]. In Denmark, developmental dysplasia of the hip accounts for 2.6-9.1% of all total hip arthroplasty cases and is the leading cause of total hip arthroplasty in young adults, representing 21-29% of these cases [30, 137].

Legg-Calvé Perthes disease

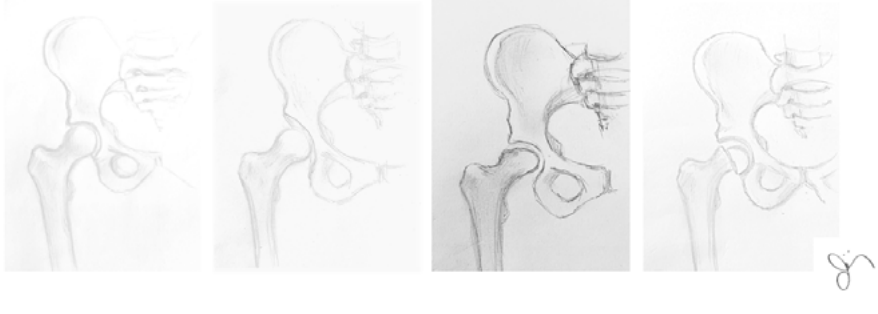

Figure 3*: Illustration of a hip joint with Legg-Calvé-Perthes disease.*

Legg-Calvé-Perthes disease (Figure 3), is an ischemic necrosis of the femoral head that mainly affects boys aged 2-12 years and leads to changes in the hip joint congruency, commonly with pain and stiffness as a result [64]. The exact cause of Legg-Calvé-Perthes disease is still unknown but associations with different factors have been addressed, such as coagulation disturbances, genetic-, prenatal-, and metabolic factors [108]. The etiology is suggested to be “a local manifestation of a systemic disease” [43]. Reduced blood supply to the femoral head leads to ischemia and apoptosis of bone cells, which in turn leads to loss of resistance to the forces applied to the hip joint. The mechanical stress results in the deformation of the femoral head. Remodeling after the necrosis is often unsatisfactory and contributes to an enlarged femoral head with lateral displacement, a short femoral neck, and relative overgrowth of the greater trochanter, resulting in leg-length discrepancies, limping and pain.

There are variations in the incidence worldwide, ranging from 0.4 to 29.0 per 100,000 yearly [85]. In Sweden, the incidence is estimated to range between 4-9/100,000 yearly [57, 91].

Clinical features are typically pain in the hip or groin, sometimes with accompanied knee pain, limited range of motion, and limping. Diagnosis is made by clinical examination and imaging (radiography and MRI) [70].

To define the course of Legg-Calvé-Perthes disease, Waldenström radiographical stages are used. This classification includes four stages; the initial stage (ischemia-induced sclerosis with a higher density of the femoral epiphysis and loss of height of the epiphysis), the fragmentation stage (resorption process of the necrotic cells, subchondral fractures, and lateral osteolysis with variable collapse), the reossification stage (blood vessels are regenerated in the epiphysis, the dense islets are resorbed conjunct with irregular bone formation), and the healed stage (regeneration of necrotic bone is complete and the femoral head presents its residual shape. These shape changes are not definitive until skeletal maturity) [66, 85]. The duration of the disease usually lasts 2-4 years [58]. A modified Elizabethtown classification was presented by Joseph et al. 2003, to assist in determining the evolution of the disease by dividing the first three Waldenström stages into early and late stages (Ia, Ib, IIa, IIb, IIIa, IIIb, and IV) [60].

The radiographic Lateral Pillar classification system suggested by Herring et al. is commonly used to measure femoral head involvement and the extent of necrosis in the active phase of the disease. It was introduced in 1992 [55] because of other commonly used classification systems' poor reproducibility and poor prognostic capacity (Salter-Thomson, and Catterall) [55]. The classification is based on a radiographic anteroposterior view and the femoral head

epiphysis is divided into three zones: the lateral, the central, and the medial pillar. There are three main groups (A–C), based on the extent of involvement of the lateral pillar (Figure 4). A modified lateral pillar classification system was presented in 2004, adding a B/C group [54], due to difficulties in classifying the hips in the borderline of B and C groups. It serves as a prognostic model during the fragmentation stage and has shown good value in predicting the final outcome of Legg-Calvé-Perthes disease [73]. The inter-observability ranges widely from fair to good, with weighted kappa values of 0.39-0.64 [71, 116] and, good with a modified weighted kappa of 0.71 [54].

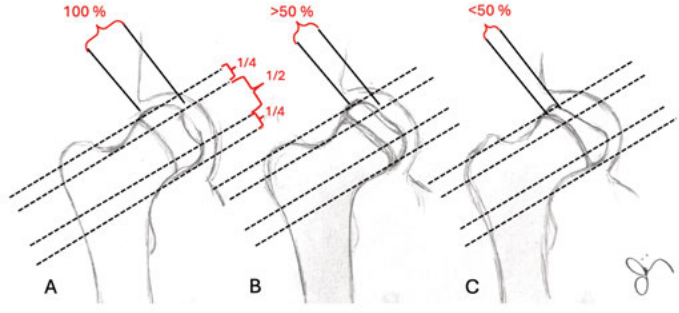

Figure 4: *Illustration of the lateral pillar classification. The Herring Lateral Pillar classification assesses the height of the lateral third of the femoral head epiphysis during the fragmentation stage in relation to the unaffected hip. In group **A**, the femoral head retains its full height, meaning there is no loss of height in the lateral third of the epiphysis. Essentially, the structural integrity of the femoral head is preserved. In group **B**, there is a partial loss of height in the lateral pillar, but more than 50% of the original height is maintained. This suggests some degree of collapse has occurred, but the remaining structure remains relatively intact. Group **B/C**, is an intermediate category representing cases falling between Group B and Group C. The classification into this borderline group indicates that the loss of height is precisely around 50%, making it difficult to categorize strictly into Group B or C. Group **C**, is the most severe category, with a significant collapse of the femoral head and where the lateral pillar has lost more than 50% of its height.*

The congruency of the hip joint and the shape of the femoral head are used to predict the prognostic long-term clinical and radiographical outcome by the Stulberg classification. The classification was developed by Stulberg et al. in 1981 and is based on radiographs categorizing the hip joint into several classes based on the final shape and congruency at skeletal maturity. Three types of hip congruency have been identified: (1) spherical congruency (Class I and II), where premature osteoarthritis does not develop; (2) aspherical congruency (Class III and IV), which leads to mild to moderate osteoarthritis arthritis in late adulthood; and (3) aspherical incongruency (Class V), where severe osteoarthritis develops before age fifty (Figure 5) [133].

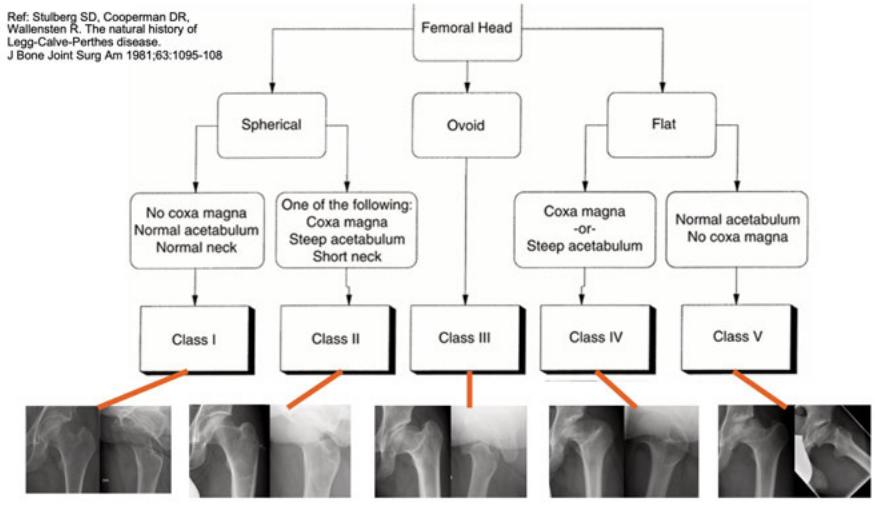

***Figure 5**: Schematic description of the Stulberg classification system. Reprinted with permission from SPOQ.*

Treatments for Legg-Calvé-Perthes disease typically involve a combination of non-surgical and surgical approaches. Non-surgical methods include physiotherapy, bracing, restricted weight bearing, and active surveillance. Still, there is no robust evidence indicating which method is the most effective, and there is a large international variation in the strategies for treatment [12, 33]. Restricted or non-weight-bearing strategies are widely discussed [24] especially because of the concerns that restricted weight-bearing might lead to increased weight gain in those children [101]. As the diagnosis is associated with a high prevalence of overweight and obesity, both in childhood and in adulthood, weight gain does not seem to be caused by weight restriction alone, but rather has a multifactorial explanation [101].

The choice of treatment largely depends on the patient's age and the severity of the disease. Surgical strategies aim to restore the hip joint's range of motion and ensure adequate coverage of the femoral head within the socket. Surgery is more frequently performed in severe cases where the femoral head damage is significant and is particularly beneficial for children older than six years. However, from which age patients benefit from surgery is still debated [14, 58]. Several methods have been described, such as proximal femoral varus osteotomy, Salter osteotomy, triple innominate osteotomy, or combined osteotomy [1, 12, 64, 120, 125]. Negative prognostic factors are considered to be older age at onset and a larger extent of femoral head osteonecrosis [118]. The hip joint’s long-term outcome in terms of the advancement of osteoarthritis is directly related to the femoral head’s shape and congruency of the hip joint at skeletal maturity.

Slipped capital femoral epiphysis

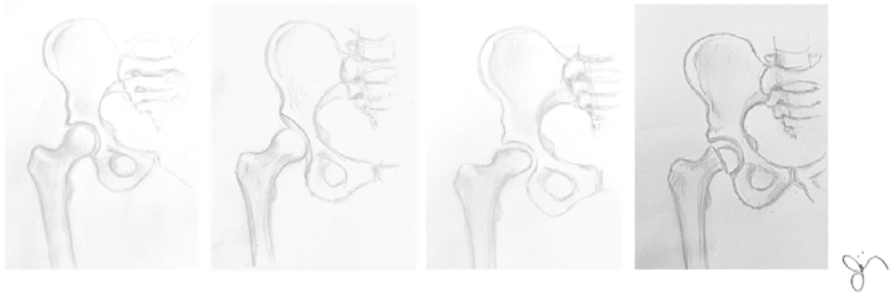

Figure 6: *Illustration of a hip joint with slipped capital femoral epiphysis.*

Slipped capital femoral epiphysis (Figure 6) is a disease of the older child, typically affecting children aged 9-16 years. It presents as slippage in the growth plate between the femoral head and femoral neck, where the femoral neck metaphysis migrates in an external rotation and proximal direction, and the proximal femoral epiphysis is still contained in the acetabulum [87]. 7% of patients with slipped capital femoral epiphysis in Sweden are reported to be bilaterally affected [52].

This slippage usually occurs during a period of rapid growth with a weakness in the epiphyseal plate. The etiology is not fully known and is considered multifactorial. Different causative factors are suggested, such as mechanical stress due to obesity [52, 97], sports activities [16, 82], and certain endocrine disorders [107].

The average annual incidence of slipped capital femoral epiphysis in Sweden is 0.4/100,000 for girls and 0.6/100,000 for boys, between the ages of 9-15 years. [52]. Globally, the incidence is 0.3/100,000 to 24.6/100,000 children 8 to 15 years of age with an ethnic variation [84].

Sudden or increasing pain in the hip thigh or knee in combination with a decreased range of internal rotation and the typical radiographic changes give the diagnosis. The clinical classification described by Loder et al. is based on the stability of the physis, as stable or unstable [81]. Slipped capital femoral epiphysis is regarded as stable if the child can walk with or without crutches and unstable if the child cannot ambulate even with double crutches. Approximately 1/5 of cases are unstable. Physeal instability is considered to be the major risk factor for avascular necrosis [51, 131]. In unstable cases and the event of a major slippage, the blood supply to the caput femoris is at risk of being disrupted, and avascular necrosis which in turn can lead to permanent deformation of the articular head can occur.

The severity of the slip can be graded radiographically in Lauenstein or lateral views according to Southwick or Billing, as mild (13° to 29°), moderate (30° to 49°), or severe (> 50°) [53]. The severity is related to the duration of symptoms as the diagnosis might be missed when the patient presents pain from the knee rather than the hip [80, 82]. In addition, the severity of the slip correlates to the risk of developing femoroacetabular impingement [123].

Treatment is typically minimally invasive internal fixation with pins or screws for stable slipped capital femoral epiphysis, to prevent further slippage. In severe forms of slipped capital femoral epiphysis, in situ pinning is not sufficient to restore the anatomy of the hip joint, and the value of reduction is debated. In specific cases, a Dunn osteotomy modified by Ganz method is recommended [7, 31, 38].

In a review by Loder et al. [81], avascular necrosis was found in 21% of the patients with unstable slipped capital femoral epiphysis. This severe complication was associated with unstable slipped capital femoral epiphysis occurring within the first 12 months, but the rate varies in the literature [81, 83]. In Sweden, about 6% develop avascular necrosis according to Swedish registry data [51]. In situ pinning of slipped capital femoral epiphysis deformity is strongly associated with femoroacetabular impingement and an increased risk of cartilage and labral lesions with subsequent secondary osteoarthritis development in young adults [2, 34].

Rationale

What are the demographics and risks for containment surgery of Legg-Calvé-Perthes Disease in Sweden?

Legg-Calvé-Perthes disease is rare, which makes larger studies difficult to conduct. Thus, we have only limited knowledge of demographics in Sweden, long-term results after different treatments, and prognostic predictors. The need to close these knowledge gaps has led to the start-up of the Swedish Pediatric Orthopaedic Quality Register. This national quality register started registering patients with Legg-Calvé-Perthes disease in 2015. Through this registry's structure, with regular follow-up of the patients from the time of diagnosis to the age of 18 years, population-based information on patients with Legg-Calvé-Perthes disease is gathered. Here, detailed information is collected linked to clinical and physiological parameters as well as treatment methods and outcomes. Data collection in the Swedish Pediatric Orthopedic Quality Register provides valuable information and the possibility to explore the incidence, patient characteristics, and factors influencing the choice of surgical intervention for patients with Legg-Calvé-Perthes disease nationwide. Such information may prove useful in the clinical evaluation of Legg-Calvé-Perthes disease patients, including assessment of prognosis and choice of treatment strategies.

What is the adult patient’s perspective on Legg-Calvé-Perthes Disease?

Legg-Calvé-Perthes and chronic or long-lasting conditions alike often entail a period of restrictions and pain, which is a strong contributing factor to lessened well-being [37]. Living with pain can become a limiting factor in a person's everyday life and may restrict participation in school, sports, and social activities. The study by Pinto et al. highlights the importance of understanding the long-term physical, emotional, and social impact of chronic childhood conditions from the perspectives of affected children and their families [110]. While that study focused on clubfoot, its findings can provide valuable insights into the experiences of individuals with other chronic pediatric conditions, such as Legg-Calvé-Perthes disease. As noted in the

study, children with clubfoot expressed concerns related to pain, stiffness, difficulty performing activities, social interactions, and physical appearance. Drawing parallels, it is reasonable to expect that children with Legg-Calvé-Perthes disease may face similar challenges.

Given that the duration of Legg-Calvé-Perthes disease typically spans over several years, often beginning in early school years, impacts throughout the patient's life can endure. However, there is a lack of comprehensive research on how children with Legg-Calvé-Perthes disease perceive pain and illness, and how such events shape their lives over the long term, particularly when articulated and interpreted through the individual's perspective. In a survey study by Kim et al., it was noted that adult patients with Legg-Calvé-Perthes disease had significantly worse pain and physical, social, and mental health than the general population [65]. Only limited research provides in-depth insight into the young adult Legg-Calvé-Perthes disease patient's own experiences, linked to the diagnosis and treatment in healthcare and how these experiences affected them throughout life. One previous study has described the disease's social, physical, and emotional impact, from the child's and the parent's perspective with a mixed-method approach [75].

The purpose of this qualitative study is, therefore, to provide insight into the young adults' experiences linked to Legg-Calvé-Perthes disease and the impact of these experiences. It aims to promote more positive approaches and contribute to better healthcare for patients with Legg-Calvé-Perthes disease. The information from this study can also be helpful for patients and parents with long-term illnesses other than Legg-Calvé-Perthes disease and can contribute to a better understanding of how to deal with stressful situations and life-changing events.

Are patients with pediatric hip disease at increased risk of long-term pain and depression?

Legg-Calvé-Perthes disease and slipped capital femoral epiphysis are both associated with pain during the active phase of the disease, but there are very limited studies examining the course of pain in these patients. Patients with previous childhood hip disease are at risk of secondary osteoarthritis development and subsequent total hip arthroplasty later in life. It can be feared that these patients also have an increased risk of a prolonged period of pain preceding a surgical intervention such as hip arthroplasty, as patients with primary osteoarthritis present a period of pain before such surgery [141].

Long-term pain and pain relief are costly and pain itself is often associated with social disabilities and reduced quality of life [88]. Long-term pain is also closely linked to depression [95, 111]. In the treatment of pain, opioids are often used in combination with paracetamol and non-steroidal anti-inflammatory drugs, and these three preparations are 1st line drugs in Sweden for the therapy of nociceptive pain. Over-prescribing and overconsumption of opioids have serious consequences for public health and have received great attention in recent years [134, 143]. An opioid epidemic has evolved, which includes an increase in addictions, related overdoses, and deaths. It has not been investigated whether exposure to Legg-Calvé-Perthes disease and slipped capital femoral epiphysis is associated with an increased risk for use of pain- or antidepressant drugs later in life.

Are patients with pediatric hip disease at risk of increased mortality after total hip arthroplasty?

Patients with Legg-Calvé-Perthes disease and slipped capital femoral epiphysis have an increased comorbidity burden compared with the population at large [42, 44], and it could be feared that a combination of increased comorbidity and increased risk of total hip arthroplasty early in life would entail increased risks for this patient group. However, there is only limited research in this area. It is not known whether patients who had total hip arthroplasty surgery because of secondary osteoarthritis as a sequelae to pediatric hip disease have an increased risk of mortality compared to the general population.

Aims

Given the complex nature of pediatric hip diseases, as well as their potential long-term impact on health outcomes, there is a clear need for research that can improve our understanding of the progression of these diseases across the entire lifespan. Through a comprehensive approach and with special attention to Legg-Calvé-Perthes disease, we aim to provide insight into the lifelong impact of these diseases. We hypothesize that individuals diagnosed with pediatric hip diseases will experience enduring psychosocial effects, lifelong restrictions in physical functioning, have increased rates of pain and depressive symptoms, and have a higher mortality risk following hip arthroplasty surgery compared to the general population. We aim to shed light on these hypotheses through four studies:

Study I - The demographics and risks for containment surgery of Legg-Calvé-Perthes Disease in Sweden: Aimed to describe the incidence, demographics, and risk for containment surgery in patients with unilateral Legg-Calvé-Perthes disease patients in Sweden.

Study II - The adult patient's perspective on Legg-Calvé-Perthes Disease: Intended to qualitatively assess the impact of a long-term illness in childhood into young adulthood and explore the potential for enhancing the quality of care provided to affected individuals.

Study III - Risk for chronic pain and depression after Legg-Calvé-Perthes disease or slipped capital femoral epiphysis: Aimed to investigate if young adults with a history of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis will more commonly be prescribed analgesic- or antidepressant drugs, compared to their peers without the disease.

Study IV- Mortality risk after total hip arthroplasty following previous pediatric hip disease: Examined if patients with pediatric hip disease had an increased risk of 90-day and overall mortality after total hip arthroplasty compared to the general population.

Ethics and data source

Ethics

Ethical approval for studies III and IV was approved by the Regional Ethical Review Board in Uppsala (active between 2004-2018). Studies I and II have been granted by the Swedish Ethical Review Authority (initiated in 2019) and all studies have been carried out following the guidelines of the Helsinki Declaration. Informed consent was waived for the quality registry studies (I and IV). Study I was approved on the 31st of May 2022 with register number 2022-02369-01 and on January 30, 2024; with approval number 2023-07307-01. All patients in study II signed an informed consent form before participating. The study received ethical approval on the 21st of July 2022 with the registration number 2022-01781-01. Study III was approved on the 21st of March 2012 (reg. nr 2012/065). Study IV was granted by the Regional Ethical Review Board in Gothenburg on the 20th of May 2013 (reg nr 2013:360/13).

Registries

Swedish National Population Register: All citizens in Sweden are registered in the Swedish National Population Register through a personal identification number as an identifier. This personal identification number is provided at birth or permanent immigration and is consistent throughout life. It enables data collection and merging of different data sources at an individual level from different national registries.

Swedish Pediatric Orthopedic Quality Register: The Swedish Pediatric Orthopedic Quality Register was established in 2015. Diagnoses included in this national population-based registry are Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, developmental dysplasia of the hip, pes equino varus adductus, and patellar dislocation. The Legg-Calvé-Perthes disease subregistry has structured registrations at the time of diagnosis, 2 years after diagnosis, at 10 years of age, at 13 years of age, and 18 years of age and all surgeries (Table 1). Data provided by the Swedish Pediatric Orthopedic Quality Register are clinical observations, physiological and radiographic parameters, whether they had surgery or not, and the development of the disease over time. Since 2022, it has a national coverage of 100%, and an estimated 70-80% completeness [50].

Table 1: *The structure of the SPOQ register with regular follow-up visits where clinical and physiological variables and radiologic controls are collected. In addition, all treatments are registered.*
** Patient reported outcome measures*

Type of data collected	Time of diagnosis	2 years after diagnosis	At 10 years of age	At 13 years of age	At 18 years of age
Clinical	X	X	X	X	X
Radiological	X	X	X	X	X
PROM*			X	X	X

Swedish Patient Register: The Swedish Social Welfare Board started this registry in 1964. It collects inpatient and outpatient data using the ICD code system and Nordic Medico-Statistical Committee codes. This registry can retrieve information about diagnoses and treatments related to healthcare visits. At the start of the registry, only inpatient data was collected, but since 2001, it additionally covers outpatient visits. Reporting to the Swedish Patient Register has been mandatory since 1987.

Swedish Prescribed Drug Register: This registry started in 2005 and is one of the registries by the Swedish Social Welfare Board. It contains information on all prescribed drugs in Sweden dispensed at pharmacies. It provides information for the national official statistics regarding drug administration in Sweden. The purpose of this registry is to improve the knowledge about the safety and effects of different drugs and by this, increase the safety and benefits for the patients. The quality of the scientific output from the Swedish Prescribed Drug Register is generally good [146]. The risk for input errors is low as the in-data process is automized and the risk for statistical loss is low (Swedish Social Welfare Board).

The Swedish Arthroplasty Register: Was established in 1979. It is a national quality registry that provides information about patients who have undergone hip replacement and any subsequent revision or reoperation of the index joint. It includes data on the patient's age, sex, diagnosis, type of implant, surgical technique, and more. This registry aims to contribute information accessibility for research and quality control, to improve patient care. The quality of the registry is generally good. The structure for the continuous quality of the registry is described in The Swedish Arthroplasty Register's annual report 2022 [148]. It has been validated by Söderman [132] showing 100% coverage and 95% completeness. Yet, it has not been validated for secondary osteoarthritis after pediatric hip disease.

Swedish Cause of Death Register: This registry provided by the Swedish Social Welfare Board, includes information about causes of death for all deceased individuals in Sweden and was implemented in 1991. The purpose of the registry is to provide national official statistics about causes of death and to follow the development of mortality in Sweden.

Methods

Study population and outcome variables

Study I

The demographics and risk for containment surgery of Legg-Calvé-Perthes Disease in Sweden

The study population was collected from the Swedish Pediatric Orthopedic Quality Register (SPOQ). The data used for the analysis was from the time of diagnosis, follow-up visits, and 2 years after diagnosis. To ensure the validity of our results and avoid potential confounding factors, the analysis was limited to patients with unilateral involvement of Legg-Calvé-Perthes disease. The decision was made to exclude patients with bilateral involvement because this condition is less common and may have different etiological factors, such as associations with systemic conditions or genetic factors [61, 62], compared with those with unilateral involvement. Including these cases could introduce complexities and obscure the study findings, as well as affect the external validity. Additionally, the varying etiologies and different times of onset in the two hips can significantly influence clinical management and prognosis. Thus, all patients with unilateral Legg-Calvé-Perthes disease between 2015 and January 24th, 2024, were included.

The yearly incidence was estimated using the Swedish population register in the age group 2–12 years. The primary outcome of this study was the treatment choice (non-surgical or containment surgery) and the progression of clinical and radiographic variables from diagnosis to the 2-year follow-up. This study does not analyse other surgical procedures, aimed at preventing limping (e.g., trochanteric apophyseodesis) or improving range of motion (e.g., adductor tenotomy, iliopsoas lengthening). Containment surgery aims to contain the femoral head in the acetabulum, maintain the range of motion, and mold a congruent joint during the remaining growth period and includes procedures such as femoral varus osteotomy and/or pelvic osteotomy [59]. Analyses were conducted to explore potential associations with containment surgery and sex, age, BMI (Body Mass Index), Trendelenburg limp, hip joint abduction, or the severity of the disease (Lateral pillar classification). The BMI is calculated by dividing weight in kg by height in m^2. For children, the BMI is related to the

child's age and gender, to obtain a value comparable to the BMI for adults (BMI >25–29,9: overweight, BMI >30: obese).

Study II

The adult patient's perspective on Legg-Calvé-Perthes Disease

The study included twelve patients aged 18-35 diagnosed and treated for Legg-Calvé-Perthes Disease (ICD 10: M91.1) during childhood. Participants were identified using the local patient database at Uppsala University Hospital. Selection criteria focused on those with moderate radiographic severity (Stulberg class 2–4), intentionally excluding both mild and severe cases. Eligible patients received contact through mail, which included a consent form. Interviews were then conducted either in person or digitally, depending on the participants' preference. All interviews were conducted with an interview guide with open-ended questions. The interviews aimed to highlight the adult patient's experience of being diagnosed with Legg-Calvé-Perthes disease as a child, and how this event may have impacted their paths in life.

Study III

Risk for chronic pain and depression after Legg-Calvé-Perthes disease or slipped capital femoral epiphysis

This register-based cohort study included 1,292 patients with a history of Legg-Calvé-Perthes disease and 1,613 patients with a history of slipped capital femoral epiphysis who were >17 years old between 2005 and 2011.

A cohort study design was considered appropriate for this study, as we aimed to investigate the potential association between exposure to Legg-Calvé-Perthes disease or slipped capital femoral epiphysis to the outcomes of long-term pain and depression. The Swedish Patient Register was used to identify all patients between 1964 (when the Swedish patient register started) to 2011, with the diagnosis of Legg-Calvé-Perthes disease (ICD-7: 732.04, ICD-8: 722.11, ICD-9: 732B, ICD-10: M91.1 and M91.2) and slipped capital femoral epiphysis (ICD-7: 732.03, ICD-8: 722.10, ICD-9: 732.2, ICD-10: M93.0). The Swedish national population register provided up to 10 individuals free of pediatric hip disease (unexposed) to every patient with previous pediatric hip disease (exposed), matched for age, sex, and residency. The cohort flow chart is illustrated in Figures 6a and 6b. Data on first prescriptions of pain and antidepressant drugs were derived from the Swedish Prescribed Drug Register.

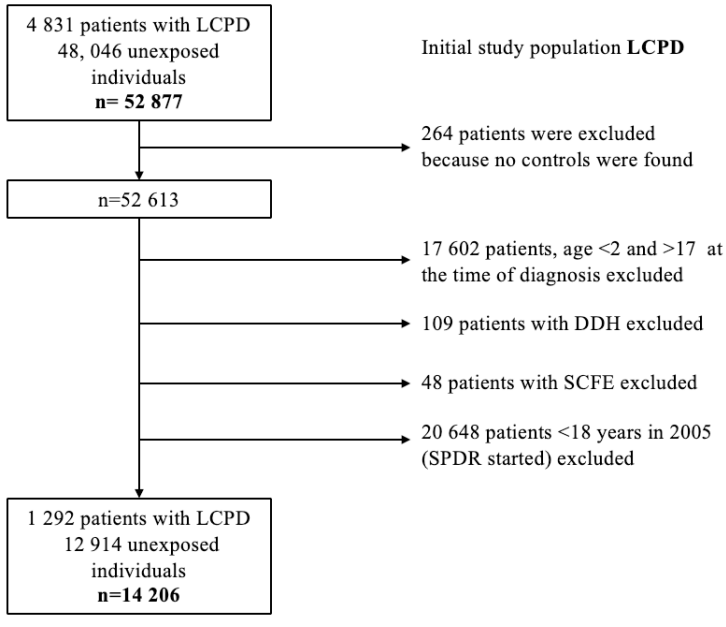

Figure 6a: *Flow chart illustrating the selection process of the study population of LCPD (Legg-Calvé-Perthes disease) patients in study III. (SPDR= Swedish Prescribed Drug Register).*

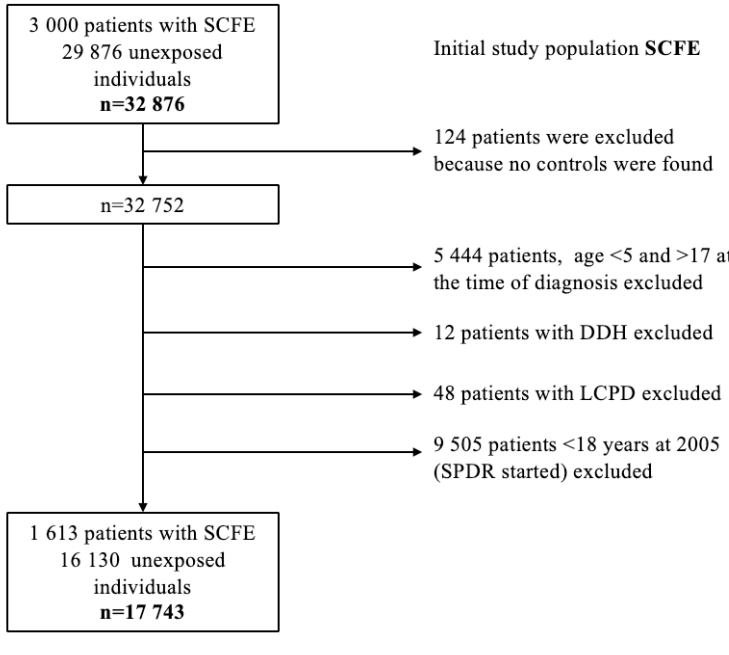

Figure 6b: *Flow chart illustrating the selection process of the study population of SCFE (slipped capital femoral epiphysis) patients in study III. (SPDR= Swedish Prescribed Drug Register).*

Study IV

Mortality risk after THA following previous pediatric hip disease

This national population-based cohort study aimed to investigate the association between pediatric hip disease, subsequent total hip arthroplasty, and mortality outcomes. We identified 4,043 patients from the Swedish Hip Arthroplasty Register who had a history of pediatric hip diseases such as developmental dysplasia of the hip, Legg-Calvé-Perthes disease, or slipped capital femoral epiphysis, and who underwent total hip arthroplasty between 1992 and 2012. Each patient was matched with five individuals without a history of pediatric hip disease or total hip arthroplasty, selected from the Swedish Population Register, and matched for age, sex, and place of residence. The inclusion date for both groups was the date of the exposed individual's total hip arthroplasty surgery. This study design allowed us to assess the potential association of pediatric hip disease and total hip arthroplasty with a 90-day and overall mortality during the study period.

Additional information on the study population's socioeconomic parameters (income level and education level), comorbidities, and causes of death was collected from the Swedish population register, the Swedish patient register, and the Swedish cause of death register. The comorbidity level is expressed as Charlson Comorbidity Index (CCI). It is a weighted scoring system used to predict the risk of death within one year of hospitalization for patients with certain comorbid conditions. The index includes nineteen different conditions, each assigned a weight ranging from 1 to 6, that sums up to 3 categories (CCI = 0, CCI = 1–2, CCI > 2). The comorbidity burden relates to increasing scores. It is often utilized as a proxy for comorbidity burden in regression models [17, 18, 128].

Statistics

Study I

The demographics and risk for containment surgery of Legg-Calvé-Perthes Disease in Sweden

Descriptive statistics using mean, median, range, and frequencies were used to analyse demographics and disease characteristics. The chi-squared test was used to evaluate differences in categorical variables and Student´s t-test was used to analyse the differences between means. Regression models were fitted to estimate the risk for containment surgery, expressed as odds ratios (OR) with 95% confidence intervals (CI), adjusted for age, sex, lateral pillar class, hip abduction, and BMI. R statistical software, version 4.3.2, and R studio,

version 2023.12.1+402 (R Foundation for Statistical Computing, Vienna, Austria), were used to perform statistical analyses.

Study II

The adult patient's perspective on Legg-Calvé-Perthes Disease

In qualitative research, the concept of saturation is crucial in determining the appropriate sample size. Saturation refers to the point at which no new themes or information emerge from additional data collection. For phenomenological studies, which aim to understand the lived experiences of individuals, a sample size of 10 to 15 participants is often considered appropriate to reach saturation [114]. Semi-structured interviews were conducted and analysed. Thematic saturation was reached after 12 interviews, and this was confirmed when no new concepts were identified from additional interviews. All interviews have been transcribed with a professional transcription service and a phenomenological approach was used to analyse and synthesize the data. A phenomenological approach is a qualitative method that seeks to understand and describe a phenomenon's universal essence by exploring individuals' lived experiences and perceptions while suspending the researchers' preconceived assumptions [22]. The data was coded independently and investigator triangulation by three researchers was applied. Triangulation is to have multiple researchers independently analyse the data and compare their interpretations to reduce individual biases. The data was categorized into clusters of meaning that represent the phenomenon of interest. Taken-for-granted assumptions from the researchers were analysed and special attention was given to descriptions of what was experienced and how it was experienced. The data was analysed through thematic data analysis using NVivo software version 12.

Study III

Risk for chronic pain and depression after Legg-Calvé-Perthes disease or slipped capital femoral epiphysis

In this study, conditional logistic regression models were used to estimate the risk (OR) with 95% confidence intervals (CI) of prescribing the selected drugs. By the design and regression method, the OR was adjusted for the matching variables (age and sex). The drugs analyzed included analgesics (non-steroidal anti-inflammatory drugs, paracetamol, and opioids) and antidepressants (selective serotonin receptor inhibitors, serotonin-norepinephrine receptor inhibitors, and tricyclic antidepressants). The risk of prescription of the selected drugs for patients with Legg-Calvé-Perthes disease or slipped capital femoral epiphysis was compared to that in unexposed individuals. By conducting a sub-group analysis of prescriptions lasting longer than 12 months,

we ensured that the results represented patients with long-term prescriptions. The follow-up time was set until December 31, 2011, emigration or death. All statistical analyses were performed using R statistical software, version 4.1.2, and R studio, version 1.4.1717, with packages dplyr, survival, ggplot2, (R Foundation for Statistical Computing, Vienna, Austria).

Study IV

Mortality risk after THA following previous pediatric hip disease

The study cohort included patients from the start of 1992 with the inclusion date of the exposure to the first surgery, and follow-up ended on December 31, 2012, of emigration or death, whatever occurred first. The mortality, as the endpoint, was noted after the first surgery in the exposed cohort. The Cox proportional hazards model was used to assess patients' risk of 90-day and overall mortality during the study period compared to the group of individuals free of pediatric hip disease and total hip arthroplasty. The Cox proportional hazards model is considered a more appropriate and powerful tool for analyzing the complex, time-to-event data in this study compared to Conditional logistic regression model. We estimated unadjusted and adjusted HRs. The adjustment was made for confounders of interest (Charlson Comorbidity Index (CCI), income levels, and education) and the matching variables (age group, sex, and place of residence). Means (with standard deviations) were used to describe continuous variables, and the student t-test was used to compare means of continuous variables. Associations of categorical data were explored using the chi-square test. For analyses, R statistical software, version 3.5.3, package “survival” 2.43-3, and R studio version 1.2.1335 were used (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study I

The demographics and risk for containment surgery of Legg-Calvé-Perthes Disease in Sweden

The study population comprised all patients reported in the registry as of January 24th, 2024, and included 334 patients and 359 hips. Among these, 309 patients had unilateral involvement. Of those with unilateral involvement, 253 had been in the registry for at least two years, and 201 (80%) had a recorded two-year follow-up visit. 160 patients were aged 6 years or younger, while 149 patients were older than 6 years (Figure 7).

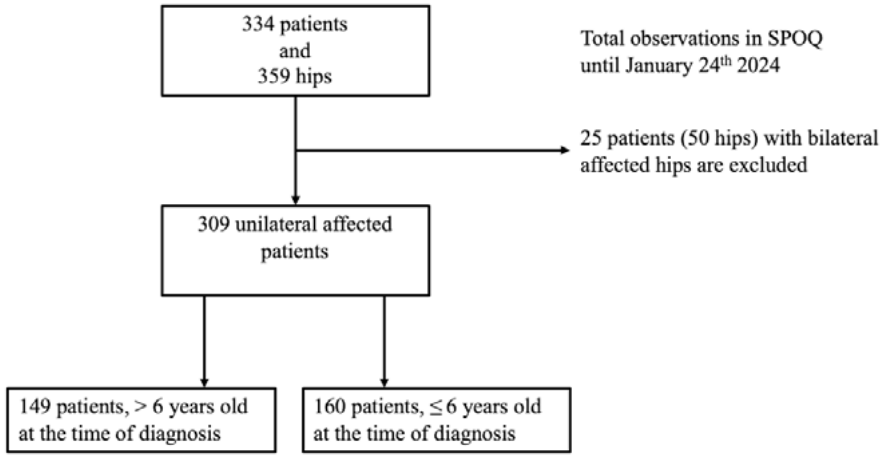

Figure 7: *Flowchart illustrating the study population in Study I.*

The incidence of Legg-Calvé-Perthes disease in Sweden among 2-12-year-olds in Sweden during 2019 was estimated to be 4.2/ 100,000 individuals. Of the 309 patients with unilateral Legg-Calvé-Perthes disease registered in SPOQ, 77% were boys. At the time of diagnosis, 29% had a Trendelenburg sign. The mean age of diagnosis was 6 (2-13) years; 35% were under 5 years of age at the time of diagnosis, and 19% were older than 8 years of age. 61% were treated non-surgically in the total cohort. In the female sub-cohort, only

52 % were treated non-surgically, whereas, in the male sub-cohort, 64% were treated non-surgically (Table 2).

Table 2: *Outline of the study population in Study I, retrieved from SPOQ, consisting of patients with unilateral Legg-Calvé-Perthes disease at the time of the diagnosis.*

	Total n = 309 patients	**Surgically treated** n = 120	**Non-surgically treated** n = 189
Sex n (%)			
Female	71 (23)	34 (28)	37 (20)
Male	238 (77)	86 (72)	152 (80)
Age mean (range)	6 (2–13)	7 (3–13)	5 (2–13)
Age group			
<5 years	108 (35)	20 (17)	88 (47)
5–8 years	141 (46)	65 (54)	76 (40)
> 8years	60 (19)	35 (30)	25 (13)

Patients older than 6–8 years old were more commonly treated surgically compared to the younger patients (Figure 8).

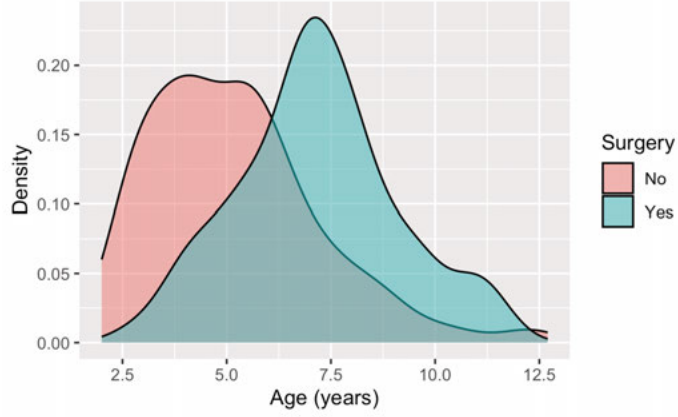

Figure 8: *Density plot of the age diagnosis of the patients reported to the treatment groups (surgical versus non-surgical treatment).*

30% of the patients presented with overweight or obesity at the time of diagnosis, at the 2-year follow-up visit, the proportion of overweight or obese children increased in both the group that were treated surgically (31% to 39%) and in the non-surgically treated group (28% to 40%) (Table 3).

Table 3: *The weight distribution of patients at the time of diagnosis and 2-year follow-up (2-year FU) for patients treated surgically and non-surgically.*

	All	Surgically treated		Non-surgically treated	
	Diagnosis	**Diagnosis**	**2-Year FU**	**Diagnosis**	**2-Year FU**
	n =309 (%)	n = 120 (%)	n= 84 (%)	n = 189 (%)	n= 117 (%)
BMI					
Under-to normal weight	132 (71)	50 (68)	27 (61)	82 (72)	25 (61)
Overweight	35 (19)	12 (16)	11 (25)	23 (20)	8 (20)
Obese	20 (11)	11 (15)	6 (14)	9 (8)	8 (20)
Missing data	122	66	40 (52)	75	41 (35)

When stratifying by sex, we could see that female patients had a greater proportion of overweight or obese than males, both at the time of diagnosis and the 2-year follow-up (Figure 9).

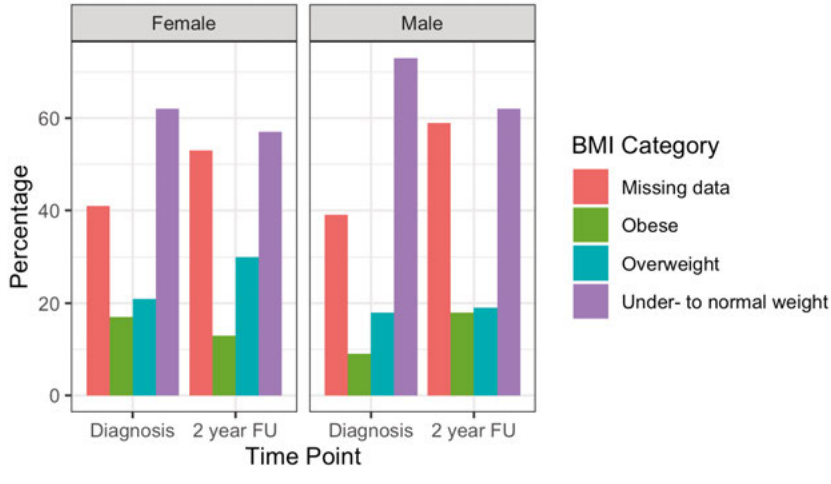

Figure 9: *Sub-group analysis of the weight distribution in female versus male patients at the time of diagnosis and the 2-year follow up (2 year FU).*

Comparing the change in hip abduction between the surgically treated and non-surgically treated groups, both exhibited a slight increase in mean abduction after 2 years. Additionally, the difference in abduction between the affected hip and the unaffected hip decreased in both groups (Table 4).

Table 4: *Hip joint abduction in patients with unilateral Legg-Calvé-Perthes disease at the time of diagnosis and the 2-year follow-up (2-Year FU).*
** -20 degrees represents one patient with abduction contracture*
*** Average difference, non-affected versus affected side*

	All	**Surgically treated**		**Non-surgically treated**	
	Diagnosis n =309 (%)	**Diagnosis** n = 120 (%)	**2-Year FU** n= 84 (%)	**Diagnosis** n = 189 (%)	**2-Year FU** n= 117 (%)
Abduction (mean, range)	39 (0–90)	33 (0–80)	34 (-20*–70)	42 (10–90)	47 (8–80)
Abduction (degrees difference)**	15	20	15	13	6

The likelihood of undergoing containment surgery was found to increase with age (adjusted OR 1.3, 95% CI: 1.1–1.6) and the presence of a Trendelenburg sign at diagnosis (adjusted OR 4.1, 95% CI: 1.8–9.9), while it decreased as hip abduction range increased (adjusted OR 0.95, 95% CI: 0.92–0.98) (Figure 10). In the univariable analysis, there was a slight, statistically insignificant increase in the risk of containment surgery among female patients, overweight or obese).

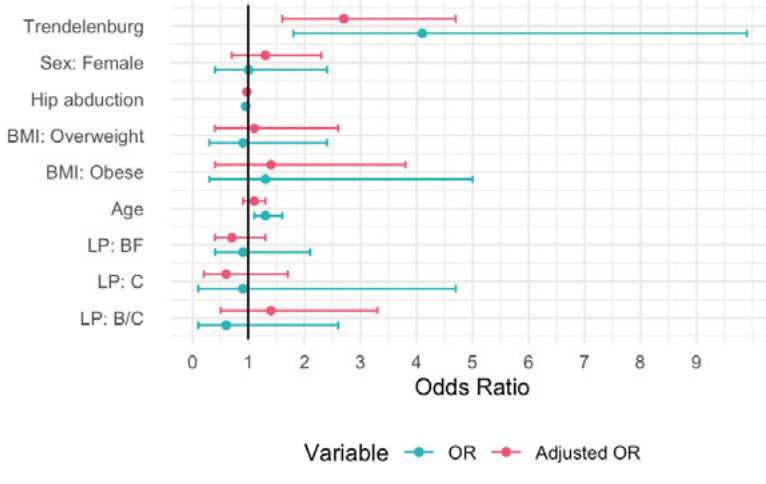

Figure 10: *Forest plot illustrating the adjusted OR (adjusted for age, sex, LP, BMI, abduction, and Trendelenburg) with a 95% confidence interval.*

Study II

The adult patient's perspective on Legg-Calvé-Perthes Disease

Three key themes surfaced in the transcribed interviews. Each key theme contains second-order themes. Some examples of the citations are presented in Figure 11:

1. Navigating Life's Weave: Self-reinvention
    a. Impact of social dynamics and self-perception
    b. Adaptive Resilience
    c. Gratitude
2. Temporal Worries and Regrets
    a. Anticipating the unknown
    b. Sense of remorse in the moment
    c. Echoes from the past
3. Lost in Translation: Transitioning Without Guidance
    a. A feeling of being alone in a room full of people
    b. Unheard and diminished
    c. Losing the safety

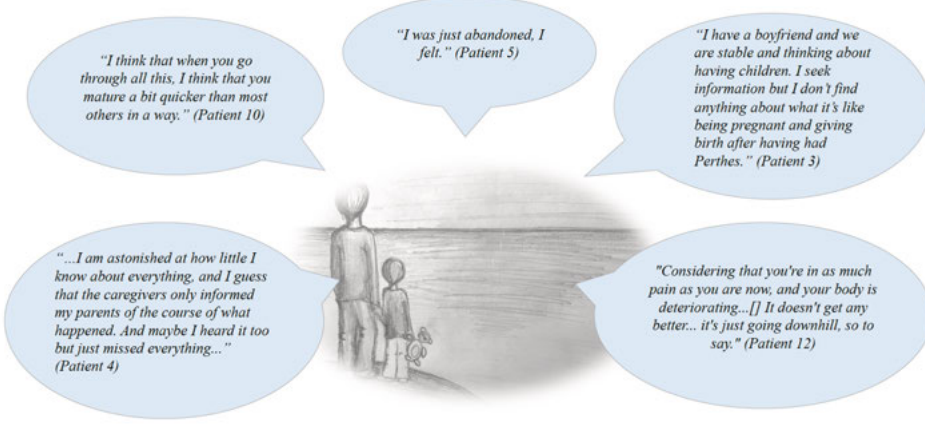

***Figure 11**: Example citations from the interviews that formed the themes*

1. Navigating Life's Weave: Self-reinvention

This theme illustrates how patients with Legg-Calvé-Perthes disease adapt to their condition and construct new identities. The patients described situations where they often found themselves unable to keep up with peers in physical activities, leading to social isolation or the development of less physically demanding interests. This adaptation can be seen as a form of resilience, where patients mature early and develop unique life experiences. Some patients recounted that they felt burdened by their condition, while others viewed it as a challenging life event that strengthened them. Despite challenges, many

patients found new social contexts and hobbies, transitioning from feeling like outsiders to finding acceptance within new social circles.

1a. Impact of social dynamics and self-perception: As some patients struggled to match their peers' physical activities and often felt discouraged from participating, they formed friendships based on shared interests that were less physically demanding and that accommodated their limitations. This shift led to feelings of being an outsider or "not normal" but was crucial in integrating into new social environments. Patients desired inclusion and resented being judged differently due to their condition.

1b. Adaptive Resilience: Patients reported early maturation due to their disease and a different life trajectory compared to their peers. The adaptation of less physically demanding interests in childhood persisted throughout life in some patients, potentially affecting career choices and hobbies in adulthood. They expressed acceptance of their condition, recognizing that they may require hip replacement surgery in the future. Despite daily reminders of their condition through pain and limitations, patients exhibited an accepting attitude, acknowledging and living with the consequences of Legg-Calvé-Perthes disease.

1c. Gratitude: Some patients felt fortunate to have a milder form of Legg-Calvé-Perthes disease or to have avoided surgical treatment. Those diagnosed before school age often experienced fewer disruptions to their school and social lives. Patients also expressed gratitude for the support from their families, who listened to their pain and trusted their experiences, providing strength and a sense of normalcy in their lives.

2. Temporal Worries and Regrets

This theme explores the temporal dimensions of the Legg-Calvé-Perthes disease experience. It reveals anxieties about the future, regrets about past actions, and reflections on family dynamics.

2a. Anticipating the unknown: Patients expressed concerns about future surgical interventions, such as total hip arthroplasty, and uncertainties surrounding potential pregnancy and parenthood. This led to anxiety and a sense of life's unfairness. Some patients also felt guilty for perceived failures in well-being habits and physiotherapy. This theme highlights the internal struggle patients face in navigating their current phase of life in the shadow of Legg-Calvé-Perthes disease.

2b. Sense of remorse in the moment: Some patients regretted not being more active as children and not utilizing available assistance, especially regarding physiotherapy. They also expressed regret for not advocating for themselves

more and not communicating clearly with teachers and peers about their condition.

2c. Echoes from the past: Patients felt guilty for causing worry, being perceived as a burden, or drawing attention from siblings. They reported that their parents were more worried than them during the onset of their Legg-Calvé-Perthes disease, attributing this to their parents not understanding why they were in pain. This sense of guilt from the past underscores the emotional toll on the entire family, shaping the patients' self-perception and potentially influencing future relationships.

3. Lost in Translation: Transitioning Without Guidance

This theme explores the sense of disconnection individuals with Legg-Calvé-Perthes disease can experience regarding their condition, both in childhood and adulthood. It reveals feelings of isolation and frustration, even in social settings, despite being surrounded by others. The lack of clear, age-appropriate information about their disease leads to confusion and uncertainty, highlighting the need for better communication and support as these individuals transition into adulthood.

3a. A feeling of being alone in a room full of people: Being diagnosed at a young age often left patients feeling isolated and disconnected, as they struggled to understand their condition and its implications. Many expressed a desire for more information and peer support during childhood, recognizing a need for better guidance and counseling. The sudden change in their abilities due to the disease triggered feelings of frustration and desolation, compounded by a sense of isolation and exclusion from the process. These emotional challenges can have lasting effects on their well-being as they transition into adulthood.

3b. Unheard and diminished: The patients described feeling unheard and diminished, especially in physical education class. They experienced that the teachers were skeptical and distrusting, viewing their disease as an excuse to skip activities. Without visible aids like crutches, explaining their condition was even harder. These feelings of disbelief extended to social contexts, where peers sometimes doubted their pain and limitations, creating a negative atmosphere. This misunderstanding led to anxiety and frustration, impacting their overall communication and engagement. Such experiences could influence their approach to communication and engagement in various life aspects.

3c. Losing safety: In Sweden, pediatric and adult healthcare are managed in separate departments, creating challenges during the transition between the two. Patients in this study noted the transition as problematic, particularly the experience of losing the safety of follow-up routines. They expressed a desire for more follow-ups and support in adulthood, wanting to know where to seek

support and when to contact physiotherapists. Additionally, patients mentioned a need for a summary of their entire course of care.

One patient stated that knowing how Legg-Calvé-Perthes disease typically evolves in adulthood would have been valuable information during their childhood. Another patient expressed uncertainty about future checkups, wondering if it was up to them to seek help if they felt unwell. A third patient simply felt abandoned. The abrupt end of support on their 18th birthday contrasted sharply with the close support they received during childhood, leading to feelings of abandonment and insecurity. This experience impacted their overall sense of safety and well-being as they navigated adulthood.

Study III

Risk for chronic pain and depression after Legg-Calvé-Perthes disease or slipped capital femoral epiphysis

The characteristics of the study population in Study III are outlined in Table 5. The mean follow-up time for patients with Legg-Calvé-Perthes disease was 36 years (9–62), and for patients with slipped capital femoral epiphysis, the mean follow-up time was 40 years (6–60).

Table 5: *Characteristics of the population in Study III.*
**FU =Follow Up*

	LCPD		**SCFE**	
	Unexposed n = 12,914 (%)	**Exposed** n = 1,292 (%)	**Unexposed** n = 16,130(%)	**Exposed** n = 1,613 (%)
Sex				
Female	2,530 (20)	253 (20)	6,030 (37)	603 (37)
Male	10,384 (80)	1,039 (80)	10,100 (63)	1,010 (63)
Age at FU* mean (range)		37.3 (25.0–62.3)		38.9 (25.0–63.7)

Prescription of analgesic drugs in patients with a history of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis

A 1.3-fold higher adjusted risk (OR) for any period of analgesic drug prescriptions (95% CI: 1.2-1.5) compared to age and sex-matched individuals without a history of Legg-Calvé-Perthes disease (unexposed), was found in patients with a history of Legg-Calvé-Perthes disease. After stratifying for sex, we found higher risks for pain drug prescriptions in females than in males compared to their unexposed cohorts. The differences were greatest for anilids and opioids (Figure 12). When estimating the long-term prescriptions, we found

that 37% of the individuals with a history of Legg-Calvé-Perthes disease had analgetic drug prescriptions that lasted for more than 12 months, compared to 28% of the matched unexposed individuals, with an adjusted OR of 1.5 (95% CI: 1.3–1.8).

In patients with a history of slipped capital femoral epiphysis, we found an adjusted 1.5-fold increased risk (OR) for any period of analgesic drug prescriptions (95% CI: 1.3-1.6) compared to age and sex-matched individuals without a history of slipped capital femoral epiphysis (unexposed). Stratification for sex showed a higher risk for analgesic drug prescriptions in females than in males, compared to their respectively matched unexposed individuals (Figure 12). For long-term prescriptions lasting longer than 12 months, 45% of patients with a history of slipped capital femoral epiphysis, and 31% of the matched unexposed individuals had analgetic drug prescriptions for more than 12 months. The adjusted risk for a long-term prescription (>12 months) of analgesics was 1.8 (95% CI: 1.6–2.1) for patients with a history of slipped capital femoral epiphysis.

Prescription of antidepressant drugs in patients with a history of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis

No increased risk for antidepressant drug prescriptions was noted in patients with a history of Legg-Calvé-Perthes disease, compared to their age and sex-matched unexposed individuals. We did not reveal any sex-specific risk changes after stratification for sex (Fig 12). For long-term prescriptions for antidepressant drugs, 12% of patients with previous Legg-Calvé-Perthes disease compared to 15% of the unexposed population prescriptions lasting more than 12 months. A slightly decreased OR 0.8 (95% CI: 0.6–1) at the long-term prescriptions was noted.

Compared to their age- and sex-matched unexposed individuals, patients with a history of slipped capital femoral epiphysis, had an adjusted overall risk for the prescription of antidepressant drugs of 1.2 (95% CI: 1.1-1.4). A slightly higher risk for antidepressant drug prescriptions was noted in females than in males compared to their matched unexposed individuals respectively (Fig 12). Prescriptions for antidepressant drugs lasting longer than 12 months, were found to be present in 17% of patients with previous slipped capital femoral epiphysis and 15% of the unexposed population, resulting in an adjusted OR of 1.1 (95% CI: 0.9–1.3).

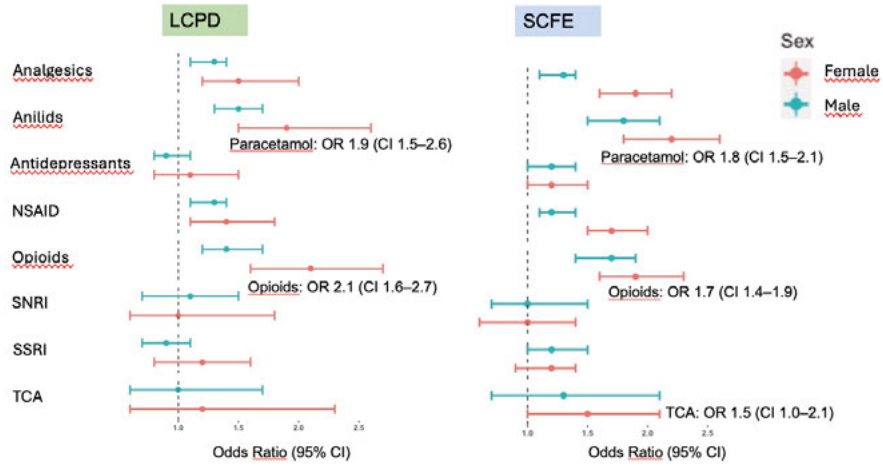

Figure 12: *Forest plot illustrating adjusted OR (adjusted for sex and age) with 95% CI for the prescription of analgesics and antidepressants, after stratifying for sex.*

Study IV

Mortality risk after THA following previous pediatric hip disease

6% of the exposed cohort had a history of Legg-Calvé-Perthes disease, and 38% were female. 2% had slipped capital femoral epiphysis, comprising 44% females, and 92% had developmental dysplasia of the hip, of which 67% were female. The socio-economic characteristics in the study cohort revealed that the exposed cohort had lower incomes, a lower educational level, and a higher degree of comorbidity than their matched unexposed cohort. However, the majority of the exposed cohort had a low comorbidity level in general and had at least a high school degree (Table 6).

Table 6: *Characteristics of the study population in study IV.*
CCI = Charlson Cormorbidity Index.

	Unexposed n = 19,388 (%)	**Exposed** n = 4,043 (%)
Dead	1,879 (10)	351 (9)
Age		
<50	7,519 (39)	1,570 (39)
50–59	5,835 (30)	1,220 (30)
60–74	4,758 (25)	989 (25)
≥ 75	1,276 (7)	264 (7)
Sex		
Female	12,488 (64)	2,600 (64)
CCI		
0	18,263 (94)	3,662 (91)
1–2	974 (5)	345 (9)
>2	151 (1)	36 (1)
Income		
1st quartile	4,945 (26)	1,062 (26)
2nd quartile	4,893 (25)	1,047 (26)
3rd quartile	4,869 (25)	987 (24)
4th quartile	4,667 (24)	943 (23)
Education		
None	284 (2)	75 (2)
9 years	5,302 (27)	1,111 (28)
High school	8,387 (43)	1,824 (45)
University	5,415 (28)	1,033 (26)

For patients with unilateral total hip arthroplasty, the mean age was 54 years (SD 13). For patients with bilateral total hip arthroplasty surgery, the mean age at the time of the first total hip arthroplasty surgery was 53 years (SD 11) and 56 years (SD 12) at the time of the second surgery.

In the exposed group, the endpoint mortality was determined after the first total hip arthroplasty. Within 90 days from the first surgery (inclusion date), 72 individuals also had surgery on the contralateral hip and 46 patients had one-stage bilateral total hip arthroplasty. None of the patients with bilateral total hip arthroplasty died within 90 days of surgery. During the entire

observation period, 974 individuals (24%) also had surgery on the contralateral hip with a 2.5-year mean delay between the 1st and 2nd total hip arthroplasty.

90-day mortality after total hip arthroplasty

Of the cohort exposed to pediatric hip disease and total hip arthroplasty, 0.20% (8 patients) died within 90 days after surgery. In the unexposed cohort, 0.24% (43 individuals) died within 90 days after the inclusion date. The adjusted HR for death was 0.9 (CI 0.4–2.0) within 90 days after total hip arthroplasty surgery. When analyzing the mortality risk based on the underlying pediatric hip diagnoses (Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and developmental dysplasia of the hip) it revealed a non-statistically significant risk reduction only in patients with developmental dysplasia of the hip.

Overall mortality risk after total hip arthroplasty during the observation period

Within the entire study period, 8.7% (351 individuals) of the cohort exposed to pediatric hip disease and total hip arthroplasty patients died. In comparison, 9.7% (1,879) of the unexposed individuals died during the entire study period. Of the 351 individuals that died in the exposed cohort, 8% (29 individuals) had a history of Legg-Calvé-Perthes disease, 3% (10 individuals) had slipped capital femoral epiphysis, and 89% (312 individuals) had developmental dysplasia of the hip.

The overall mortality risk during the observation period in patients with pediatric hip diseases and total hip arthroplasty was lower than in the cohort with unexposed individuals. Cox regression analyses implied a reduced adjusted HR among the exposed individuals (HR 0.8; CI 0.7–0.9). When stratifying the results based on the underlying pediatric hip diagnoses (Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and developmental dysplasia of the hip), we observed a decreased overall mortality risk during the study period, in patients with Legg-Calvé-Perthes disease and developmental dysplasia of the hip. This attenuated risk was only statistically significant in patients with developmental dysplasia of the hip (table 7).

Table 7: *Overall mortality during the study period, adjusted for confounders and matching variables (age group, sex, and place of residence).*

[a] *Adjustment for confounding factors, without matching variables*
[b] *Adjustment for confounding factors and matching variables (age group, sex, and place of residence (calculated as strata variable due to many variable levels >300)).*

	Crude HR (95% CI)	**Adj. HR** (95% CI)[a]	**Adj. HR** (95% CI)[b]
All cases	0.9 (0.8–1.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)
DDH	0.9 (0.8–1.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)
LCPD	0.8 (0.6–1.3)	0.8 (0.6–1.3)	0.7 (0.4–1.3)
SCFE	0.9 (0.4–1.7)	0.9 (0.4–1.8)	2.1 (0.8–5.7)

Causes of death

Cardiovascular disease (43%) and cancer (27%) were the most common causes of death among individuals exposed to total hip arthroplasty because of previous pediatric hip disease. In the unexposed cohort, 35% died of cardiovascular disease and 34% of cancer (Table 8).

Table 8*: Most common categories of cause of death in the exposed and unexposed cohort.*

	Exposed n (%)	**Unexposed** n (%)
Cardiovascular	150 (43)	657 (35)
Cancer	95 (27)	637 (34)
Pulmonary disease and infections	29 (8)	140 (8)
Neurologic, psychiatric or drug-related	19 (7)	147 (8)

Discussion

Possible consequences of long-term illness in childhood are important to highlight and further research with a holistic focus is therefore crucial. In this Phd-thesis, we have given attention to three classical pediatric diseases affecting the musculoskeletal system: developmental dysplasia of the hip, Legg-Calvé-Perthes disease, and slipped capital femoral epiphysis, with special focus on Legg-Calvé-Perthes Disease.

A brief discussion of the main results

Study I

The demographics and risk for containment surgery of Legg-Calvé-Perthes Disease in Sweden

This study aimed to describe the incidence, demographics, and risk for containment surgery in patients with unilateral Legg-Calvé-Perthes disease in Sweden. We found the incidence of Legg-Calvé-Perthes disease in Sweden to be 4.2 cases per 100,000 individuals in 2019, a decline compared to previous estimates [57, 91], potentially due to stricter inclusion criteria and comprehensive follow-up, unlike earlier broader studies [57, 91]. The male predominance persisted, with onset typically around age 6, consistent with previous studies [85]. Contrary to some literature, no significant differences in disease severity or treatment outcomes between sexes were observed, challenging previous hypotheses on hormonal influences on disease presentation [35, 41] and indicating the need for further exploration of sex-based differences in Legg-Calvé-Perthes disease. The Trendelenburg sign detected at diagnosis was likely due to pain rather than disrupted hip biomechanics. Our findings indicate that surgical decisions are influenced by age, Trendelenburg sign, and restricted abduction of the hip joint. This aligns with previous studies showing better outcomes with non-operative treatment in younger children and surgical benefits in older children with severe disease [76, 153]. The increased risk for containment surgery associated with a positive Trendelenburg sign and restricted abduction likely reflects a more severe disease and serves as a prognostic indicator, aligning with existing literature [46, 118]. However, no statistically significant risk increment for containment surgery was found for those with a more severe lateral pillar class in our results.

Study II

The adult patient's perspective on Legg-Calvé-Perthes Disease

This study intended to qualitatively assess the impact of a long-term illness in childhood into young adulthood and explore the potential for enhancing the quality of care provided to affected individuals. It highlights the lived experience of Legg-Calvé-Perthes disease and its lasting impact from childhood into adulthood, consistent with previous research on chronic childhood diseases' long-term effects and increased healthcare resource utilization [9, 144]. The study emphasizes the significant physical and social challenges patients face. Despite generally unaffected academic performance, patients often struggle with physical activities, leading to more sedentary lifestyles and hobbies. This finding aligns with Leo et al.'s research, which also noted similar academic impacts among children with Legg-Calvé-Perthes disease [75]. Patients frequently reported mistrust from physical education teachers and difficulties explaining their invisible illness, issues common among individuals with non-visible disabilities, as seen in studies on juvenile arthritis [40]. Patients expressed a need for better communication from healthcare providers, feeling often overlooked and uninformed. They also voiced concerns about future health, particularly regarding pregnancy and potential future hip replacement surgery. Effective communication and inclusion in their care are suggested in previous studies to improve the patient's understanding and coping mechanisms, as well as reduce fears and uncertainties [147]. Moreover, communication should be age appropriate as the child grows into adulthood. Overall, a holistic and inclusive approach to patient care is crucial for improving outcomes and addressing the long-term needs of individuals with Legg-Calvé-Perthes disease.

Study III

Pediatric hip disease and its association with chronic pain and depression

In this study, we aimed to investigate if young adults with a history of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis will more commonly be prescribed analgesic- or antidepressant drugs, compared to their peers without the disease. We found that patients with a history of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis are at an increased risk of being prescribed analgesic drugs and, to a lesser extent, antidepressant drugs. Prescription rate is used as an objective measure of pain and depression in this study and our results could be interpreted as though these patients would be at risk for developing long-term pain depression. Chronic pain and depression are closely associated [6]. However, a significant increase in antidepressant prescriptions was only observed in patients with slipped capital femoral epiphysis, not in those with Legg-Calvé-Perthes disease. This is opposed to a previous study by Hailer and Nilsson [45], which did show an association between Legg-Calvé-Perthes disease and depression. In the study by

Hailer and Nilsson, the depression rate was estimated by the International Classification of Diseases (ICD)-coding system from the Swedish patient register, contrary to our study that estimated the depression rate as a mirroring of the prescribed antidepressant drugs from the Swedish prescribed drug register. This discrepancy might also be because not all depressions are treated with antidepressant drugs but rather psychotherapies in the first line [21]. In Sweden, chronic pain affects approximately 18% of the population [47], and in our study, we found that 37% of the individuals with a history of Legg-Calvé-Perthes disease and 45% of patients with a history of slipped capital femoral epiphysis had analgetic drug prescriptions that lasted for more than 12 months. Further, these patients have a statistically significant increased risk for opioid prescription. Although opioids are one of the first-line drugs for treating acute pain, the use of opioids in treating chronic pain is not advisable because of the high risk of dangerous adverse effects linked to chronic opioid use [134]. Alternative treatment strategies for treating chronic pain are emerging, including non-opioid drugs such as non-steroidal anti-inflammatory drugs, anticonvulsants, and antidepressants [102], and these should be considered rather than opioids. Early identification and management of chronic pain and depression are crucial to initiating appropriate prevention programs and therapies for these patients at risk.

Study IV

Mortality risk after total hip arthroplasty

In this study, we examined if patients with pediatric hip disease possessed an increased mortality risk after total hip arthroplasty compared to the general population. We observed a statistically non-significant decrease in 90-day mortality and a significant attenuation in long-term mortality among individuals with a history of pediatric hip disease undergoing total hip arthroplasty, compared to those without such a history. This pattern aligns with findings in patients undergoing total hip arthroplasty for primary osteoarthritis [19, 77] but contrasts with studies suggesting increased mortality in arthroplasty patients under 59 years compared with the general population [77, 119]. Patients with prior pediatric hip disease constitute about 3.9% of total hip arthroplasties in Scandinavia [29]. Despite higher comorbidity and mortality risks associated with conditions like Legg-Calvé-Perthes disease and slipped capital femoral epiphysis [42, 44], our study did not find increased mortality post-arthroplasty, even after stratifying the analyses for the underlying pediatric hip diseases. Although total hip arthroplasty is generally a safe procedure regarding mortality risks, as shown in this study, it still entails a period of pain, restrictions, absenteeism from work, and other known surgical risks [49].

Discussion in a broader perspective

Pediatric hip disease and body weight

Many of our habits are formed early in life [27, 157]. A prolonged period of illness during childhood significantly impacts individuals, not only as children but also into adulthood, as highlighted in Study II. Long-term pain and prolonged restrictions in daily life activities in childhood can lead to more sedentary habits, increasing the risk of developing obesity and related diseases. These can leave lasting effects and increase healthcare resource utilization [9, 144]. Legg-Calvé-Perthes disease patients were traditionally described as "undersized". However, recent studies found an increasing incidence of overweight and obesity among patients with Legg-Calvé-Perthes disease and slipped capital femoral epiphysis [72, 94, 99, 130]. While the association of patients with slipped capital femoral epiphysis and obesity is well established [42, 78], this association is not evident in patients with developmental dysplasia of the hip. In the cohort of Study I, 30-40% of the children were overweight or obese, which is significantly higher than the general population in Sweden, where 13% of 4-year-olds and 23% of 6-9-year-olds are overweight or obese, according to the Public Health Agency of Sweden. It could be argued that weight gain is due to pain and activity restrictions but this has been reported as unlikely in previous studies [93, 101]. As in our study, the children were overweight or obese already at diagnosis, suggesting pre-existing conditions rather than weight gain due to disease-related activity restrictions. In addition, childhood and adolescent obesity pose a significant risk for premature morbidity and mortality [74] such as osteoarthritis development [92], cardiometabolic disease, and the prevalence of metabolic syndrome. But, even a small weight loss before puberty can decrease these risks considerably [86]. Given this higher prevalence of overweight and obesity among these children, as demonstrated in Study I, it is imperative for healthcare providers and society to develop strategies to counteract this.

Comorbidities and cause of death

It is reported that patients with a history of pediatric hip disease undergo hip replacement surgery at a younger age than those with primary osteoarthritis [29, 139]. However, it is unclear whether osteoarthritis leads to inactivity, obesity, and associated conditions, or vice versa. Nevertheless, studies indicate that patients with Legg-Calvé-Perthes disease and slipped capital femoral epiphysis have a higher comorbidity level and a generally increased mortality risk [42, 44] leading to the assumption that they might also have a higher risk for death after total hip arthroplasty surgery. However, this was not the case in our study. When we analysed the cause of death in our cohorts, we found the most common cause of death after total hip arthroplasty in patients with pediatric hip disease was cardiovascular death. Additionally, patients with pediatric hip disease were found to present in a lower proportion of cancer-

related deaths than in the matched control group. The leading cause of death in our study is in accordance with the World Health Organization [4]. The most common cause of death worldwide is ischemic heart disease, responsible for 16% of total deaths, followed by stroke and chronic obstructive pulmonary disease. However, cardiovascular-related deaths seem to present a greater proportion of deaths in individuals with a history of pediatric hip disease and subsequent total hip arthroplasty (43%), than in the general population (35%). A possible explanation for our findings could be the known association between patients with primary osteoarthritis of the hip or knee and the increased risk of cardiovascular disease, cardiovascular disease-related mortality, and diabetes mellitus. This association is closely linked to lower physical activity levels. Patients with primary hip or knee osteoarthritis often have a reduced activity level due to pain [48], which could explain our observations.

The decreased mortality risk presented in study IV, might have several explanations. For one, socioeconomic factors might influence the results. The importance of socioeconomic status in healthcare utilization and outcomes has been highlighted in several studies [13, 106, 115] showing that socioeconomic factors were powerful discriminators of mortality risk. Patients with previous pediatric hip disease who undergo total hip arthroplasty may have had long-term exposure to healthcare systems, potentially leading to better health literacy and access to care. This could contribute to improved outcomes and lower mortality rates. Another factor to consider is the potential selection bias in mortality studies highlighted by Whitehouse et al. [151]. Patients with previous pediatric hip disease may represent a select group that has survived childhood conditions and received ongoing medical care, potentially leading to better overall health status and lower mortality risks. However, the risk reduction persisted even after adjusting for confounding variables. Patients with previous pediatric hip disease often undergo total hip arthroplasty at a younger age compared to those with primary osteoarthritis. This younger age at surgery could be argued to contribute to the lower mortality risks as it is shown that increasing age and comorbidities were associated with higher mortality after total hip arthroplasty [10, 77]. But even after adjusting for age, the lower mortality risks remained. The fact that the majority of the study population in this study comprised patients with previous developmental dysplasia of the hip must be raised, as this form of pediatric hip disease is not known to be associated with the same risk factors as those with Legg-Calvé-Perthes disease and slipped capital femoral epiphysis [42, 45, 94, 130]. However, we could not detect any significant differences in the comorbidity level between the different pediatric hip disease groups. Further, no major differences in the mortality risk were revealed between the groups after stratifying for the different underlying pediatric hip diseases. Another reason for our results could be an effect of selection for surgery, where the patients with good overall health,

socioeconomic prerequisites, and potential for rehabilitation are identified as most likely to benefit from and survive the procedure.

Pain and depression

Another long-term consequence highlighted in this thesis is the increased risk for patients with a history of Legg-Calvé-Perthes disease or slipped capital femoral epiphysis to be prescribed analgesics in adulthood, including long-term opioids, as demonstrated in Study III. Increased pain levels in adult patients with Legg-Calvé-Perthes disease compared to the general population are also noted in a web-based survey study in 2022 [89]. Previous studies show these patients are more likely to develop osteoarthritis at a young adult age often leading to total hip arthroplasty [29], and the association between osteoarthritis and chronic pain is well-known [23, 145]. Thus, it could be reasoned that the increased risk for prescriptions of analgesic drugs we see, could be related to the development of osteoarthritis. However, it remains unclear whether these patients are generally at a heightened risk of developing depression, despite the known association between chronic pain and depression [6, 121]. Although we observed an increased risk for long-term analgesic prescriptions, there was no corresponding rise in the prescription of antidepressants. This discordance could be due to several factors not captured in our results. Pain management in these patients often focuses on addressing orthopedic issues and providing targeted pain relief rather than treating mood disorders. Additionally, regular medical attention and early interventions received by these patients may help mitigate the risk of developing depressive symptoms. However, our study may not have captured all instances of depression, particularly milder cases that might not result in formal diagnosis or treatment. Using antidepressant prescriptions as a proxy for depression has limitations and may not fully reflect the true prevalence of depressive symptoms in this population.

The findings in study III, that these patients seem to be at risk for developing long-term pain is problematic in many ways, especially given the ongoing opioid epidemic and its devastating consequences for both individuals and society [3]. Living with chronic pain can result in economic losses for the individual and can negatively impact social life as many with chronic pain have higher rates of absenteeism from work and are limited in many social activities [122]. This was also seen in Study II, where several patients reported changing their social structures and hobbies in childhood. Beyond the individual consequences, society also incurs increased costs related to sick leave and healthcare needs [100].

Communication

Another important factor that emerged during the work on this thesis is the need for improved, structured, continuous communication appropriate for the phase of life the patients are in. Patients expressed a need for better communication with healthcare providers, often feeling overlooked during consultations as shown in Study II. They felt that physicians focused primarily on the hip condition and directed information more frequently to their parents rather than to them as individuals. Concerns about future health, particularly regarding pregnancy, highlight the need for comprehensive information from healthcare providers [117]. As previously shown there is room for improvement in the transition of care [159]. Transitioning adolescents and young adults with chronic diseases and/or disabilities to adult care services is a complex process that necessitates coordination and continuity of health care. Even if structured transition programs have been developed for patients with cystic fibrosis diabetes mellitus [159], there are no structured transition processes developed for patients with pediatric hip disease.

Gender perspective

The results from this thesis suggest that women may be more susceptible to the long-term consequences of pediatric hip disease. This gender disparity is observed across multiple aspects. In Study I, girls demonstrated a marginally higher likelihood of requiring containment surgery and exhibited a greater prevalence of overweight or obesity compared to boys. Study II revealed that women expressed heightened anxiety about future implications, particularly concerning pregnancy and their capacity to fulfill maternal roles. Women with chronic diseases generally face increased risks of adverse pregnancy outcomes, though their risk perceptions are highly individualized as previously reported [117]. This supports our findings and underscores the importance of considering the gender-specific long-term impacts of pediatric hip disease. Addressing these potential concerns early on can reduce stress and uncertainty. It would prove to be beneficial for obstetricians, midwives, and gynecologists to be better informed about these issues, fostering improved collaboration with specialized orthopedic surgeons to provide comprehensive support and care. Furthermore, Study III indicated that women face an elevated risk of being prescribed pain-relieving medications. These findings collectively suggest a potential gender-specific vulnerability in the context of pediatric hip disorders, which may persist into adulthood. This observed pattern aligns with broader research on gender differences in musculoskeletal conditions and pain perception, showing that musculoskeletal issues such as neck pain, back pain, osteoarthritis, and rheumatoid arthritis are more common and severe in females than in males [105]. The concerns voiced by women regarding future pregnancies and motherhood highlight the need for comprehensive, long-term care plans that address both physical and psychosocial aspects of

the condition. The higher likelihood of women receiving pain medication prescriptions could be attributed to various factors, including differences in pain reporting, healthcare-seeking behaviors, or physiological pain responses [103, 136].

Reducing the long-term effects of pediatric hip diseases throughout life is not easy, but we can see in this thesis that these diseases should not be seen as only childhood diseases. Instead, the effects often follow individuals throughout their lives. By raising awareness of these effects, encouraging a return to physical activity, and communicating with patients and their families about what to expect in terms of the long-term impact of their pediatric hip disease, we can contribute to better quality of life and health outcomes by reducing stress and anxiety. It is important to listen to patients' needs, thoughts, and concerns, and to help them form appropriate expectations and constructively manage these.

Further Elaboration

The findings from this PhD thesis underscore the need for a multidisciplinary approach to managing the long-term consequences of pediatric hip diseases. Healthcare providers should focus on early intervention and continuous monitoring to mitigate the risk of chronic conditions such as obesity, cardiovascular diseases, and chronic pain.

Physical Activity and Lifestyle Interventions: Encouraging physical activity from a young age is vital. Tailored exercise programs that accommodate the limitations of those with musculoskeletal issues can help establish healthy habits. Schools and community programs should also be aware of the specific needs of these children to prevent them from becoming sedentary.

Psychosocial Support: As shown in the qualitative findings of Study II, patients often feel a sense of disconnection and lack of guidance during their transition from pediatric to adult care. Implementing structured transition programs that provide continuous, age-appropriate support can improve their overall well-being. Mental health services should also be integrated to address issues like depression, anxiety, and pain management.

Healthcare Policies and Economic Considerations: From an economic standpoint, understanding the rate of absenteeism from work and school and its impact on productivity is crucial. Investing in preventive care and early interventions can reduce long-term healthcare costs. Policies should support research into the long-term economic impact of pediatric hip diseases to help better allocate resources.

Gender-Specific Research: The differences observed between male and female patients suggest the need for gender-specific research and interventions. Understanding why women are more prone to certain complications can lead to better-targeted treatments and support systems.

In conclusion, the results presented in this thesis highlight the lifelong impact of pediatric hip diseases. A comprehensive approach that includes medical treatment, lifestyle interventions, psychosocial support, and economic considerations is essential for improving outcomes for these patients. By recognizing the broad and long-lasting effects of these diseases, we can develop more effective strategies to support individuals from childhood through adulthood.

Strengths and weaknesses

This thesis investigates the long-term progression of pediatric hip diseases by integrating detailed patient narratives with extensive national data sets. It offers new insights into disease progression and the lifelong impacts of these conditions.

The use of several different registers together with interview studies adds strength to the thesis, as the data analysed comes from various sources and builds on a broader information base. Additional strengths are the size of the study populations (study I, III, IV) and the national coverage.

Study I: The demographics and risk for containment surgery of Legg-Calvé-Perthes Disease in Sweden

In study I, certain limitations need to be raised. Quality registries like SPOQ, rely on healthcare professional input, which can lead to errors and missing data, and non-mandatory measures may affect validity. For example, hip abduction measurements are examiner-dependent, although SPOQ provides detailed instructions and previous studies show high agreement in these measurements [124]. Additionally, information bias is a type of systematic error that can significantly impact the internal validity of clinical research and may arise from inaccuracies in data recording or reporting, potentially impacting the study's findings [140]. Moreover, factors such as individual treatment preferences, surgeon experience, and socioeconomic factors influencing surgical treatment choice are not fully captured in the registry. Finally, the study is limited by some loss of follow-up, particularly in patients with 2-year follow-up. The SPOQ employs a rigorous approach to internally validate their registry data. This includes implementing logical data controls, conducting regular sub-register reviews, performing national and targeted coverage analyses, carrying out regional data checks, organizing quality improvement meetings, engaging expert radiographic reviewers, and

performing central data assessments. By employing these comprehensive validation strategies, the SPOQ ensures a high level of data accuracy and reliability.

Study II: The adult patient's perspective on Legg-Calvé-Perthes Disease

Quantitative studies generally have high reliability and generalizability but have difficulties with in-depth analysis. This is compensated for in this thesis by the qualitative design in study II. Combining qualitative and quantitative studies in this thesis provides a more comprehensive understanding of the research topic. Qualitative research, as described by Pyo et al. (2023), is necessary for exploring complex phenomena, generating hypotheses, and providing in-depth insights into the experiences and perspectives of individuals [113]. The issue of convenience sampling can be argued since the entire population in this study is recruited by the local medical registry at Uppsala University Hospital. However, the patients in these records are referred to this hospital from other regions and should represent a general population of Legg-Calvé-Perthes disease patients from the central regions of Sweden. In addition, both genders are represented in a balanced number, as Legg-Calvé-Perthes disease is primarily a disease among boys. Another issue to be raised is the changes and improvements in healthcare over time. The adult patients interviewed in this study were diagnosed 10–15 years ago, and their experiences may not accurately reflect the current experiences of patients diagnosed today.

Study III: Pediatric hip disease and its association with chronic pain and depression

In study III, we used the Swedish prescribed drug register, which was first established in 2005. The register provides comprehensive data on drug exposure and allows for the study of drug utilization patterns. The register's coverage accounts for approximately 84% of total drug utilization and 77% of total drug expenditures in Sweden, as highlighted by Wettermark et al [150]. This might underestimate the risks for drug prescription, but this applies to both patients and unexposed individuals. While the register provides information on dispensed prescriptions, it does not guarantee that patients actually consumed the medications as prescribed. This could lead to an overestimation of drug exposure in some cases [146]. However, this potential overestimation should be consistent across both the exposed and unexposed groups. Further, the Swedish prescribed drug register only includes drugs that were prescribed by a physician and dispensed at a pharmacy. This also is a factor that may lead to an underestimation of the use of paracetamol and non-steroidal anti-inflammatory drugs, as these drugs can be acquired "over the counter". However, most patients who need large amounts of these drugs seemingly get a prescription [5], therefore, we do not expect this to affect our results greatly.

From the data available for this cohort, we could not comment on any factors associated with chronic pain such as biological, psychological, socio-demographic, and lifestyle determinants [90]. In addition, we lack access to prescription indications in the register, which means that the medications prescribed might have been for conditions other than hip pain. We don't know how these issues impacted our results, and these are therefore limitations to consider in study III. Selection bias is another potential source of systematic error, that could occur because of errors in the selection of study participants. This could lead to a sample that doesn't accurately represent the target population [140]. But, by clearly defining and applying the inclusion and exclusion criteria as described in the methods section, we consider that the study sample is representative of the target population and thus, reduces the risk of selection bias

Study IV: Mortality risk after total hip arthroplasty

Several factors should be considered when interpreting the results of study IV. Firstly, most of the study population consisted of female individuals with developmental dysplasia of the hip. Neither of these factors is known to be independently associated with increased mortality, which may influence the generalizability of our findings.

A potential source of bias is the regular contact with the healthcare system that patients with a history of pediatric hip disease typically maintain from childhood. This consistent monitoring may result in better overall health management, potentially influencing mortality outcomes, and skewing our results towards better outcomes. However, a study based on the Norwegian arthroplasty register showed an unspecific increase in mortality in the young population after total hip arthroplasty [77]. Additionally, selection bias may be present due to the tendency to consider sicker patients unfit for surgery, suggesting that patients selected for total hip arthroplasty often have better health profiles than the general population, leading to longer life expectancy [8, 77]. However, with a longer follow-up time (28 years), the inverse was revealed. The initial reduction in overall mortality changed with time because the increase in mortality was restricted to younger patients and the longer the follow-up, the greater the proportion of patients operated on at a young age [119]. Despite these potential biases, our conclusions remain valid within the context of real-life patient selection for total hip arthroplasty, where orthopedic surgeons likely choose patients fit enough for the procedure.

Another factor that could affect our results is immortal time bias. This is a type of bias that can occur in observational studies when there is a period during which the outcome of interest cannot occur, often referred to as "immortal time" [142]. This bias can affect study results by artificially inflating the survival time of the exposed group, leading to misleading conclusions about the

effectiveness of an intervention or exposure. In our study design, immortal time bias could arise as the patients with bilateral total hip arthroplasty (conducted at different time points) are guaranteed to be alive between the two procedures. This can lead to an overestimation of the survival benefit of the surgery because patients who survive long enough to have the surgery are inherently a healthier subset.

The classification of osteoarthritis etiology in our study relied on orthopedic surgeons' diagnoses, primarily based on radiographic evidence rather than comprehensive medical histories. This approach likely results in a low rate of false-positive pediatric hip diagnoses. However, false negatives may be more common, with some patients potentially misclassified as having primary osteoarthritis instead of secondary osteoarthritis due to pediatric hip disease.

The selected control group warrants discussion. The choice of five matched controls per case in this study is based on balancing adequate statistical power and maintaining study feasibility. Studies show that increasing the number of controls up to a ratio of about 4:1 significantly improves the study's power. However, beyond this ratio, there is little gain in power. Increasing the control-to-case ratio primarily affects the confidence interval, enhancing the precision of the results, but does not address bias [39, 109, 135]. As we have access to the Swedish population registry, it is possible to select random controls that accurately reflect the exposed population. While we could have chosen to use primary osteoarthritis patients as an unexposed cohort, these individuals are generally older than those with secondary osteoarthritis resulting from pediatric hip disease [28, 29, 96]. Comparing two groups with very different age profiles could lead to misleading results, referred to as confounding by age particularly when examining mortality risk, which is strongly associated with age [26]. Even though this confounding can be handled by statistical models, we chose to select an age-matched unexposed cohort from the general population. By this, we aimed to more clearly delineate the effect of total hip arthroplasty on mortality risk in patients with a history of pediatric hip disease.

Lastly, the potential impact of unmeasured confounding factors cannot be overlooked. Factors such as lifestyle choices, and access to healthcare may influence both the likelihood of undergoing total hip arthroplasty and overall mortality risk but were not fully accounted for in our study.

Methodological considerations

Study design

When designing a study, the choice between quantitative and qualitative research methods is guided by the distinct values each approach contributes. Quantitative studies excel in precisely measuring outcomes and providing numerical data for statistical analysis. However, measurable outcomes do not necessarily capture the entirety of a patient's lived experience or the nuances that shape their perspectives. Qualitative methods offer a complementary depth, enabling researchers to gain a rich understanding of participants' subjective experiences, beliefs, and motivations. By employing qualitative techniques like in-depth interviews or focus groups, researchers can uncover insights that may be overlooked by quantitative measures alone. This thesis embraces a mixed-method approach, integrating both quantitative and qualitative components. This synergistic approach not only enhances the depth and breadth of the findings but also facilitates a more holistic understanding of the complex interplay between measurable outcomes and the lived realities of those affected by a pediatric hip disease. It is essential to recognize that quantitative and qualitative research methods are complementary, and their strengths and limitations often balance each other out. A mixed-method approach, combining quantitative and qualitative techniques, can provide a more comprehensive understanding of complex phenomena and address the limitations of either approach alone.

Quantitative research

Quantitative research methods involve the collection and analysis of numerical data to test hypotheses, identify patterns, and establish relationships between variables. These methods offer several advantages, including objectivity, precision, generalizability, replicability, and the ability to employ powerful statistical techniques. Quantitative data can be easily compared across studies and populations, facilitating meta-analyses and systematic reviews. However, quantitative approaches also have limitations. They may overlook rich contextual factors, nuances, and subjective experiences that shape human behavior and phenomena. By reducing complex phenomena to numerical values or categories, quantitative research can oversimplify or fail to capture the full complexity and depth of the subject under investigation. Additionally, while quantitative methods aim for objectivity, choices in study design, measurement instruments, and analytical techniques can still introduce biases or limitations. Furthermore, quantitative methods typically rely on predefined measures, limiting the ability to capture participants' unique perspectives, experiences, or unanticipated insights. Establishing causal relationships can also be challenging without experimental designs or additional qualitative insights [15, 36, 104].

Qualitative research

Ensuring trustworthiness is crucial in qualitative research, and there are different aspects to address. Credibility refers to the congruence between the findings and reality, which can be enhanced through techniques like triangulation and member checking. In addition, an interview guide with open-ended questions was also developed to correspond to the study aim and minimize interviewers' bias, by conscious or subconscious influence on the subject's responses. Dependability, analogous to reliability, involves documenting the research process to enable replication. This is achieved through recorded and transcribed interviews and documented analysis trails. Confirmability requires demonstrating that the findings emerge from the data rather than researcher bias, which can be facilitated through reflexivity, with the researcher's self-awareness and critical reflection on their own biases and assumptions being transparent. Transferability, akin to generalizability, involves providing thick descriptions to allow readers to assess the applicability of the findings to other contexts [36, 127]. These aspects are addressed in study II, through applying appropriate strategies, for establishing the trustworthiness and rigor of qualitative research.

Conclusions

This thesis offers a comprehensive analysis of pediatric hip diseases, with special attention to Legg-Calvé-Perthes disease, integrating qualitative patient experiences and quantitative national data with a mixed method approach.

We found a lower national yearly incidence of Legg-Calvé-Perthes disease (4.2 per 100,000) compared to previous Swedish studies, with patients being diagnosed at a younger age and showing a higher prevalence of overweight and obesity. Increased age, a positive Trendelenburg sign, and limited hip joint abduction at diagnosis were linked to a higher likelihood of surgical intervention, emphasizing the need for early detection and intervention.

The qualitative data highlighted the importance of patient-centered communication, direct engagement with patients, age-appropriate information, and family involvement to improve outcomes. A multidisciplinary approach involving various healthcare professionals is crucial, along with addressing future concerns, especially for female patients regarding pregnancies and long-term health. Ensuring a smooth transition from pediatric to adult healthcare services with detailed summaries and clear future care instructions is vital.

Pediatric hip diseases seem to profoundly impact patients' lives even in their adult years. They have a higher risk for prescription of analgesic drugs in adulthood, including opioids, and in patients with slipped capital femoral epiphysis, also of antidepressant drugs. However, adult patients with previous pediatric hip disease, exposed to total hip arthroplasty do not seem to have an increased risk of 90-day or overall long-term mortality compared with the general population.

Overall, this thesis underscores the necessity of a holistic, patient-centered approach to the care of pediatric hip diseases. By integrating patient experiences with large-scale data, the research offers valuable insights into the lifelong impacts of these conditions and provides information that could be used for practical improvements in the enhancement of the care of these patients.

Future Studies

The progress of Legg-Calvé-Perthes disease will be better described when more follow-up data in the Swedish Pediatric Orthopedic Quality Register is collected, this data will provide valuable information and will improve patient care. This information will enable more consistent and reliable prognostic factors and will assist in the decision-making of treatment methods.

Future research should include more qualitative studies to identify potential regional or geographical differences in patient experiences. This will help draw more generalizable conclusions and mitigate biases related to the local population included in our study. Moreover, as treatment programs and general awareness of Legg-Calvé-Perthes disease continuously improve, the experiences of healthcare described in this study may not be fully representative of current patient experiences. Conducting additional qualitative research with patients treated more recently will provide a current understanding of the evolving landscape of Legg-Calvé-Perthes disease management and its impact on patient well-being. Additionally, incorporating the perspectives of children in the active phase of the disease, their parents, and their treating orthopedic surgeons could offer valuable insights into the comprehensive care of these patients.

Given that patients with pediatric hip diseases appear to be prone to long-term pain, it would be valuable to conduct a study examining the rate of sick leave among these adult patients. This would provide important insights into the health and economic impact of these conditions. Additionally, further research is needed to investigate if different treatment approaches in association with the disease's severity or proactive treatment plans for the sequelae of pediatric hip disease can reduce the analgesic prescription risk and the burden of Legg-Calvé-Perthes disease and slipped capital femoral epiphysis patients.

The literature about comorbidities and mortality rates in adult patients with previous developmental dysplasia of the hip is very limited. Further studies are warranted to better understand why patients with a history of developmental dysplasia of the hip would be less affected in the long-term regarding the risk of mortality and comorbidities, than patients with previous Legg-Calvé-Perthes disease and slipped capital femoral epiphysis.

Why the causes of death in the exposed group in study IV are not in accordance with the general population is not conclusive from our material. The underlying mechanism for the higher representation of cardiovascular-related deaths and a relatively lower rate of cancer-related deaths is yet to be studied.

Summary in Swedish

Sjukdomar i barns höfter, såsom höftledsdysplasi, Legg-Calvé-Perthes sjukdom och höftfyseolys, kan leda till bestående formförändringar av höften och leda till tidig artrosutveckling. Genom att integrera patienternas egna upplevelser med nationella registerdata ämnar denna avhandling beskriva en helhetsbild av hur dessa patienter påverkas genom livet av sin sjukdom. Denna avhandling kan bidra med information som kan användas som underlag för att förbättra vården och säkerställa kontinuitet från barndom till vuxen ålder, med det slutliga målet att förbättra patienternas hälsa och livskvalitet.

I studie I undersökte vi förekomst och demografi av Legg-Calvé-Perthes sjukdom i Sverige. Vi undersökte också om det finns faktorer som ökar riken för att behöva kirurgisk behandling. Resultaten baserades på data från ett nationellt kvalitetsregister, Svenskt Pediatriskt Ortopediskt Qvalitetsregister. Studien omfattade 309 patienter som registrerats i registret mellan 2015 och 2024. Vi fann en årlig förekomst av Legg-Calvé-Perthes sjukdom på 4.2 per 100 000 barn i åldern 2–12 år, med en högre andel pojkar (77%) och en genomsnittlig diagnosålder på 6 år. Noterbart var att 30% av patienterna var överviktiga eller feta vid diagnos, vilket ökade till cirka 40% vid tvåårsuppföljningen. Begränsad höftabduktion kvarstod över tid och var sämre hos kirurgiskt behandlade patienter. Studien identifierade ålder, positivt Trendelenburgs tecken och begränsad höftabduktion som viktiga faktorer som ökade sannolikheten för kirurgisk behandling.

Studie II undersökte de långsiktiga effekterna av Legg-Calvé-Perthes sjukdom ur patientens eget perspektiv. Denna kvalitativa studie använde en fenomenologisk metod och genomförde semi-strukturerade intervjuer med patienter i åldern 18–35 år som hade en historia av Legg-Calvé-Perthes sjukdom, som behandlades på Akademiska Sjukhuset Uppsala. Nyckelteman inkluderade självutveckling, oro för framtida hälsa och kirurgiska ingrepp, och svårigheter med fysisk aktivitet vilket ledde till stillasittande livsstil. Patienterna upplevde en känsla av vara distanserade från vården som planerades för dem, att det mesta fokuset låg på deras höft och sjukdom, inte på dem som personer. De upplevde även brist på vägledning vid övergången från barn- till vuxenvård. Trots dessa utmaningar hade patienterna en stor förmåga att utveckla strategier för att hantera svårigheter och anpassa sig till

livets förändringar. Studien betonar vikten av kontinuerlig, åldersanpassad information och en strukturerad övergång i vården för att förbättra välbefinnandet hos individer med kroniska barndomssjukdomar.

I studie III undersökte vi om personer med Legg-Calvé-Perthes sjukdom eller höftfyseolys i barndomen har en ökad risk att förskrivas smärtstillande eller antidepressiva läkemedel i vuxen ålder jämfört med matchade personer utan höftsjukdom. Denna registerbaserade kohortstudie inkluderade 1 292 vuxna patienter med Legg-Calvé-Perthes sjukdom och 1 613 vuxna patienter med höftfyseolys. Resultaten visade att patienter med Legg-Calvé-Perthes sjukdom hade en 1.3 gånger högre risk och patienter med höftfyseolys en 1.4 gånger högre risk att få smärtstillande läkemedel förskrivna i vuxen ålder. För antidepressiva läkemedel fann vi ingen ökad risk för patienter med Legg-Calvé-Perthes sjukdom, medan patienter med höftfyseolys hade en 1.2 gånger högre risk för förskrivning av antidepressiva. Dessa resultat tyder på behov av långsiktig smärthantering hos dessa patienter. Fynden betonar vikten av att optimera långsiktiga smärtbehandlingsstrategier och att tillhandahålla psykologiskt stöd för dessa patienter eftersom de riskerar överanvändning och långtidsanvändning av smärtlindrande läkemedel.

I studie IV undersökte vi om det fanns en ökad risk för att dö efter att ha opererats med total höftledsartroplastik hos patienter som tidigare haft en barnhöftsjukdom, jämfört med normalbefolkningen. Studien omfattade 4 043 patienter från det svenska höftprotesregistret som opererats med total höftledsartroplastik och tidigare diagnosticerats med höftledsdysplasi, Legg-Calvé-Perthes sjukdom eller höftfyseolys. Dessa patienter matchades med individer från den allmänna befolkningen. Trots att patienter med tidigare barnhöftsjukdom hade lägre inkomster, lägre utbildningsnivåer och högre samsjuklighet visade resultaten ingen signifikant skillnad i 90-dagars dödlighet efter total höftledsartroplastik och uppvisade även totalt sett lägre risk för död jämfört med befolkningen i övrigt. Således är en total höftledsartroplastik hos patienter med tidigare barnhöftsjukdom en säker behandling vid artros avseende dödlighet.

Denna avhandling försöker ge en omfattande bild av de långsiktiga effekterna av barnhöftsjukdomar, med särskilt fokus på Legg-Calvé-Perthes sjukdom. Demografi, patientegenskaper, riskfaktorer för kirurgisk behandling och de psykosociala utmaningar som drabbade individer står inför belyses i studierna. Avhandlingen lyfter det ökade behovet av smärtbehandling och stöd i vuxen ålder och visar att höftledsartroplastik inte medför en ökad dödlighet hos dessa patienter. Resultaten betonar också behovet av kontinuerliga och åldersanpassade vårdstrategier för att förbättra livskvaliteten för patienter med långvarig höftsjukdom, som följer med från barndom till vuxen ålder.

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