Legg-Calvé-Perthes Disease – Is it just the hip?

Epidemiological, Clinical and Psychosocial Studies with special focus on Etiology

YASMIN D. HAILER
The overall aim of the thesis was to add some pieces to the etiological puzzle of LCPD with special focus on vascular origin and hyperactivity. Furthermore we wanted to evaluate some consequences of LCPD in adulthood.

Swedish registry data were used to identify a cohort of patients with the diagnosis of LCPD. This cohort was compared with a general population– based cohort without LCPD to assess the relative risk of cardiovascular diseases, blood or coagulation defects, injury, ADHD, depression and mortality.

In a clinical study we assessed health-related quality of life (EQ-5D-3L), physical activity level (IPAQ) and screened for ADHD (ASRSv1.1) in 116 patients with a history of LCPD who were diagnosed or treated in Uppsala University Hospital between 1978 and 1995.

The results confirmed our hypothesis: Patients with a history of LCPD had a 1.7-fold higher risk of cardiovascular diseases, and a 1.4-fold higher risk for blood or coagulation defects compared with gender- and age-matched individuals without LCPD. We found a 1.2-fold higher risk for injuries requiring hospital admission than in gender- and age-matched individuals without LCPD. The risk was more pronounced among females. Furthermore, we found a 1.5-fold higher risk for ADHD. Stratified analysis revealed a 2.1-fold higher risk for ADHD among females with LCPD than among females without LCPD. The risk for depression was 1.3-fold higher, and more pronounced among females with LCPD. Patients with LCPD had a slightly higher mortality risk with higher risk for death from suicide and cardiovascular causes.

Patients with a history of LCPD reported a lower health-related quality of life and were more physically active than the Swedish population norm. 28% of 116 patients were likely to have ADHD or had already been diagnosed with ADHD.

Both vascular and blood diseases could be present even in childhood and could, in combination with hyperactive behavior pattern and a high physical activity level, contribute to the etiology of LCPD. The lower health-related quality of life and higher risk for depression might reflect the mental burden of LCPD. Patients with LCPD have a higher mortality risk with higher risk for death from suicide and cardiovascular causes.

Keywords: Legg-Calvé-Perthes disease, hypertension, ischemic heart disease, coagulation, risk factors, etiology, injury, quality of life, EQ-5D, IPAQ, physical activity, ADHD, ASRS, depression, mortality

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“Learn from yesterday, live for today, hope for tomorrow. The most important thing is not to stop questioning”

Albert Einstein

To my beloved husband Nils and my wonderful three children
Tim, Nick and Linus
List of Papers

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


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Cover picture by Nils P. Hailer, back-side picture by Tim V. Hailer and Nick B. Hailer. Illustrations in the thesis by the author (Yasmin D. Hailer)
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“Errare humanum est, perseverare autem diabolicum”................................................... 45
## Abbreviations

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<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
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<td>ASRS</td>
<td>ADHD Self-Reporting Symptom checklist</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>DDH</td>
<td>Developmental Dysplasia of the Hip</td>
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<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>IPAQ</td>
<td>International Physical Activity Questionnaire</td>
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<td>LCPD</td>
<td>Legg-Calvé-Perthes disease</td>
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<tr>
<td>MET</td>
<td>Metabolic Equivalent Task</td>
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<td>MRI</td>
<td>Magnet Resonance Imaging</td>
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<td>PIN</td>
<td>Swedish Identity Number</td>
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<td>SHAR</td>
<td>Swedish Hip Arthroplasty Register</td>
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<td>SNHDR</td>
<td>Swedish National Hospital Discharge Register</td>
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<td>SNPR</td>
<td>Swedish National Patient Register</td>
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<td>VAS</td>
<td>Visual Analogue Scale</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Legg-Calvé-Perthes disease
Almost simultaneously, in 1910, Arthur Legg, Jacques Calvé and Georg Perthes described a disease of the femoral head in children, today called Legg-Calvé-Perthes disease (LCPD) (Calvé 1910, Legg 1910, Perthes 1910), although each proposed a different etiological theory. Legg described trauma as a possible etiological factor, Calvé thought it was due to an abnormal osteogenesis and Perthes felt it was due to an inflammatory condition giving the femoral head its abnormal appearance on X-rays.

Although the etiology of LCPD remains unknown, clinical and experimental evidence support the notion that the disruption of the blood supply to the femoral head is a key pathogenic event associated with the disease’s process (Kim 2011).

Epidemiology
The annual incidence of LCPD ranges between 0.45/100 000 reported among black children in South Africa (Purry 1982), and 21/100 000 for children in Liverpool (Hall et al. 1983). In Sweden (Uppsala) the annual incidence is estimated to be about 8.6 per 100 000 (Moberg and Rehnberg 1992). Boys are affected four times as often as girls, and in 8-24% of patients the disease is bilateral (Salter 1984, Guille et al. 1998). LCPD is usually diagnosed among children younger than 15 years of age, with a peak for onset between 5 and 8 years of age (Wiig et al. 2006).

Symptoms, clinical and radiological examination
The clinical symptoms of LCPD are variable, especially in its early stages: Limping, thigh or knee pain, weakness and a reduced range of motion in the hip joint are some of the typical signs which lead to suspicion of the diagnosis of LCPD. The clinical examination often shows a reduced abduction and external rotation, with an inability to achieve the “position of 4” (Figure 1) in the affected hip. Ultrasound examination can detect joint effusion.
Radiologically, LCPD progresses through 4 stages: condensation, fragmentation, repairing and healing (Waldenström 1938).

Radiographic findings are often normal in the early stage. It is not until 2-3 months after the onset of symptoms that the characteristic findings appear on X-ray: increased epiphyseal density, wide inferio-medial joint space, small epiphyseal nucleus and, in about 25%, a subchondral fracture line.

There are several radiological classifications of the disease (Catterall, Salter-Thompson, Lateral Pillar)(Figure 2 and 4), all of which are used to indicate the severity of the disease (Farsetti et al. 1995, Gigante et al. 2002, Akgun et al. 2004, Sugimoto et al. 2004). While describing “the natural history of Perthes’ disease”, Catterall classified the femoral head’s appearance on X-rays into 4 groups in order to predict the radiological outcome, and “the chances of a good result steadily decrease from Group I to IV” (Catterall 1971). By adding the so-called “head-at-risk signs”, Catterall tried to improve the classification, especially in cases that were classified to have a good prognosis but turned out worse (Figure 3). The head-at-risk signs consist of I: calcification lateral to the epiphysis, II: radiolucency in the lateral portion of the epiphysis, III: horizontal proximal femoral physis, IV: metaphyseal engagement (added later by Murphy et al. (1978) and V: lateral subluxation of the femoral head.

Herring et al. suggested a classification based on the height of the lateral aspect of the femoral head’s epiphysis in a frontal X-ray of the hip at the stage of fragmentation, called Lateral Pillar Classification (Herring et al. 1992) (Figure 4). Good inter- and intraobserver reliability was found in the Lateral Pillar Classification, especially in less experienced observers.
(Podeszwa et al. 2000). However, the reliability of the Lateral Pillar Classification was poor in borderline cases (Akgun et al. 2004).

Salter and Thompson proposed a two-group classification system with focus on the extension of the subchondral fracture line (Salter and Thompson 1984) but this has been almost abandoned due to its absence in some cases and because of inferior inter-observer and intra-observer reliability (Park et al. 2012). Nevertheless, this was also true for the Catterall classification (Wiig et al. 2002). According to Gigante et al. (Gigante et al. 2002), the Catterall classification does not give a significant prognostic correlation with the final outcome. This was also true for the Lateral Pillar Classification alone, but it becomes prognostic when it is related to the age at onset (Gigante et al. 2002).

The Stulberg classification (Stulberg et al. 1981) appraises the congruency of the femoral head in relation to the acetabulum and estimates the risk for osteoarthritis in these hips before the age of 50 years (Table). Wiig et al. found a good correlation between the Lateral Pillar Classification and the Stulberg outcome (Wiig et al. 2008).

<table>
<thead>
<tr>
<th>Catterall Classification</th>
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<tr>
<td>I</td>
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<td>II</td>
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<td>III</td>
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<td>IV</td>
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</tbody>
</table>

*Figure 2. Catterall Classification in frontal and axial view*
Figure 3. Head-at-risk signs: I: calcification lateral to the epiphysis, II: radiolucency in the lateral portion of the epiphysis, III: horizontal proximal femoral physis, IV: metaphyseal engagement, V: lateral subluxation of the femoral head.

Figure 4. Lateral Pillar Classification
Table: Stulberg classification (1981)

<table>
<thead>
<tr>
<th>Class</th>
<th>Appearance of the femoral head</th>
<th>Features</th>
<th>Prognosis</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Spherical</td>
<td>Normal hip joint</td>
<td>Good</td>
</tr>
<tr>
<td>II</td>
<td>Spherical</td>
<td>Coxa magna or short femoral head or steep acetabulum</td>
<td>Good</td>
</tr>
<tr>
<td>III</td>
<td>Ovoid/mushroom-shaped</td>
<td>Coxa magna, short femoral neck, steep acetabulum, aspherical congruent</td>
<td>Moderate</td>
</tr>
<tr>
<td>IV</td>
<td>Flat</td>
<td>Short femoral neck, steep acetabulum with some coverage</td>
<td>Moderate</td>
</tr>
<tr>
<td>V</td>
<td>Flat and incongruent</td>
<td>Normal femoral neck, normal acetabulum</td>
<td>Poor</td>
</tr>
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</table>

**Treatment**

Because of the loss of congruency of the hip joint, LCPD is considered to be a promoter for premature osteoarthritis of the hip. Not only the classification and stage grading, but also age-at-onset are important indicators of the disease’s severity and final outcome. According to Herring et al. and Wiig et al., these indicators are considered of importance for treatment decisions (Herring et al. 2004, Wiig et al. 2008). Both authors agree that no surgery is required in patients less than 6 years at onset and Lateral Pillar A or B or Catterall I and II. Herring et al. broadens this age limit to less than 8 years at onset.

Non-surgical treatment is not evidence-based and consists of physiotherapy to maintain the remaining range of motion with a special focus on abduction. Maintaining abduction is important in the event that intertrochanteric varus-osteotomy of the proximal femur is needed to improve hip containment (Figure 5). Anti-inflammatory and analgesic therapy is used to manage pain and inflammation. The role of restricted weight bearing is still under discussion, as the importance of restriction from sports activities (Kamegaya 2011). The use of an abduction splint is now widely abandoned because of the psychological strain for the children and parents over several months or years, with an unverified effect (Hardesty et al. 2011). Regular clinical and radiological controls should be done to follow the disease’s progress. There is some evidence that containment surgery improves the final radiological outcome (Wiig et al. 2008) in cases of radiological lateralization of the femoral head, where the age at onset is over 6 years and the case is classified as Lateral Pillar B or B/C (Catterall III or IV). Today, the most common surgical procedure is an intertrochanteric derotation and varisation os-
teotomy of the femur (Terjesen et al. 2011) followed by Salter or innominate osteotomy of the pelvis (Figure 6), or both in combination to achieve more coverage of the femoral head. To minimize a greater trochanteric overgrowth, especially when doing a femoral osteotomy, Weiner et al. (Weiner et al. 1991) recommends a simultaneous proximal femoral greater trochanteric epiphysiodesis. In severe cases and in older patients, triple osteotomy (Figure 7) might be an additional option (Vukasinovic et al. 2009, Wenger and Pandya 2011). The treatment of patients classified with Lateral Pillar C or Catterall IV remains a future challenge, as the prognosis is poor both with and without surgery and regardless of age (Herring et al. 2004).
Etiology

The etiology and underlying pathophysiology of LCPD are still not completely understood. However, it has been reported that there is an association between this disease and maternal smoking during pregnancy (Gordon et al. 2004), small stature, skeletal retardation (Burwell 1988, Rao et al. 1995,
Eckerwall et al. 1996) and low birth weight (Lappin et al. 2003). It is hypothesized that LCPD may be the result of a vascular malfunction or vascular mal-development in the femoral head. This may be caused by venous stasis due to increased intra-articular and intraosseous pressure, (Green and Griffin 1982, Liu and Ho 1991) or because of thrombo-embolic events as a result of coagulation abnormalities. Factor V Leiden mutations (Eldridge et al. 2001, Balasa et al. 2004) and decreased levels of protein C and S (Glueck et al. 1994, Levin et al. 2000) have been reported for patients with LCPD (illustrated in Figure 8), but the findings are inconsistent (Lopez-Franco et al. 2005). It is also suggested that anatomical changes in the blood supply, such as a diminished number or capacity of blood vessels, may cause LCPD (Catterall 1971, Axer and Schiller 1972, de Camargo et al. 1984, Alpaslan et al. 2007). Repetitive trauma can affect the blood supply of the femoral head, leading to LCPD (Ebong 1977, Douglas and Rang 1981, Purry 1982, Sharma et al. 2005). This phenomenon has been simulated and proven in an animal model in which mechanical stress was applied to the hip joints of ordinary growing Wistar Kyoto rats by forcing them to stand upright on the hindlimbs at feeding time (Mihara and Hirano 1998, Suehiro et al. 2000, Suehiro et al. 2005). According to anecdotal reports of parents and orthopedic surgeons, children with LCPD have hyperactive behaviors. At the same time, these children seem to have a higher pain threshold, which could increase the risk for repetitive trauma (Sharma et al. 2005). However, these observations are very difficult to quantify objectively.

Loder et al. (1993) found in 24 LCPD patients a three-fold higher incidence of ADHD compared to the overall incidence in the general population. As children with hyperactive behavior are known to experience more injuries and fractures (Loder et al. 1995, Uslu and Uslu 2008), it has been suggested that hyperactivity disorder or ADHD might be more common among patients with LCPD.
Figure 8. Clotting cascade and its associations with LCPD
Hypothesis

Most studies focus on investigating possible vascular or coagulation abnormalities in childhood with newly diagnosed or ongoing LCPD, resulting in inconsistent findings. We hypothesize that if a vascular abnormality exists in childhood, it should have consequences not only locally on the femoral head, resulting in LCPD, but also systemically. However, the systemic effect could be compensated for in childhood but might appear in adulthood in the form of hypertension, cardio- or cerebrovascular insults or blood diseases such as anemia.

Hyperactivity is another possible etiological aspect of LCPD. While hyperactive children were considered to be bothersome but “normal” in former times, both the personal environment and medical and psychological professionals are today more aware of these behavior patterns and keener to search for possible causes such as testing for ADHD and other behavioral syndromes. Hyperactive behavioral pattern might trigger the outbreak of LCPD.

The two main hypotheses of this thesis are that patients with LCPD

- have a higher risk for vascular and blood diseases compared to a control group
- have a higher risk for hyperactive behavior pattern
Aims

The overall aim of the study was to identify persons at risk and to find pathways to other diseases possibly leading us to a better understanding of LCPD’s etiology. We focused especially on diseases of vascular origin and hyperactivity. Because it is difficult to evaluate hyperactivity itself, we investigated for diseases and factors which are associated with hyperactive behavior pattern, such as injury risk, ADHD, depression and overall physical activity.

Furthermore, we wanted to evaluate the quality of life in patients with a history of LCPD and possible correlations to age at onset of LCPD, severity of LCPD, treatment or radiological and clinical outcome.

The specific aims were to evaluate:

- If patients with a history of LCPD, registered in the Swedish National Hospital Discharge Register (SNHDR), demonstrate an altered risk for co-morbidities of vascular or hematological origin compared to their controls (Study I)

- If patients with a history of LCPD, registered in the Swedish National Hospital Discharge Register (SNHDR), demonstrate an altered risk for injuries (soft-tissue injuries and fractures) compared to their controls as a possible consequence of hyperactivity or other co-morbidities which alter injury resistance (Study II)

- If patients with a history of LCPD, diagnosed at or referred to and treated in Uppsala University Hospital, have increased scores in the Adult-ADHD self reporting checklist (ASRS-v1.1) indicating a higher risk for ADHD prevalence, poorer health-related quality of life or altered physical activity compared to the population norm (Study III)

- If patients with a history of LCPD, registered in the Swedish Patient Register (SNPR), have higher risks for ADHD, depression and mortality compared to their controls (Study IV)
Materials and methods

For the epidemiological assessment, Swedish register data were used to identify a cohort of patients with a diagnosis of LCPD. This cohort was compared with a general population-based cohort without LCPD to assess the risk of cardiovascular and blood diseases and risks for injuries, ADHD, depression and mortality risk (Study I, II and IV). For the clinical study (III), we identified patients with LCPD referred to or diagnosed with LCPD at Uppsala University Hospital.

Swedish Identity Number (PIN)

Beginning in 1947, each individual residing in Sweden on a permanent basis for at least one year has been given a personal number and has been entered into the Total Population Register (Ludvigsson et al. 2009). Today the personal number consists of a person’s date of birth and additional 4 numbers (YYYYMMDD-XXXX) of which the next-to-last number gives information on the individual’s gender (odd number for males and even number for females). Each PIN is unique for one resident in Sweden.

International Classification of Diseases (ICD) - number

ICD is a “standard diagnostic tool for epidemiology, health management and clinical purposes” (WHO 2009). It translates diseases and health problems into a number-code and is used to report patients’ diseases and health problems in the registers. In Sweden the 10th version of the ICD-coding system has been used since 1997 (Figure 9).
Swedish registers

The Register of Population and Population Changes

This register is held by Statistics Sweden and contains sociodemographic information on all residents in Sweden. It allows for population-based random samples from the Swedish population and for censoring when study subjects emigrate.

Swedish National Hospital Discharge Register (SNHDR) from 1964 to 2000 and Swedish National Patient Register (SNPR) (since 2001)

In 1964 the National Board of Health and Welfare founded the SNHDR to collect all information on patients receiving medical care at a hospital. In the beginning, 84% of registered data were from psychiatric care. The coverage of individual hospitalizations has been about 99% since 1987 (Socialstyrelsen 2009). In 2001, outpatient visits including day-surgery and psychiatric consultations from both private and public caregivers were included and the name of the register was changed to SNPR. Primary care is not yet covered. Each record contains information on sex, age, place of residence, hospital, dates of admission and discharge or visits and medical data, including diagnoses at discharge and surgical procedures coded according to different versions of the ICD-coding system.
The Swedish Multi-Generation Register

The Swedish Multi-Generation Register was used to identify first-degree relatives and siblings. In this register, information on parents, siblings, and offspring of individuals born 1932 or later and alive in 1961 or later is collected and individuals can be identified using their unique PIN. This register can provide information on the socioeconomic status of a given patient’s family at birth and during childhood. Using this register, we created measures of socioeconomic index for mothers and fathers of patients in our studies, based on their occupation.

The Swedish Cause of Death Register

The Swedish Cause of Death Register provides information concerning all deaths that have occurred in Sweden since 1961 and is updated annually. This register includes data on all deceased persons who were registered in Sweden in the year they died, and the diagnoses are coded according to ICD-coding system. The cause of death is determined by the treating physician or a pathologist.

Questionnaires

Health-related quality of life

The burden of a disease is difficult to assess on radiographic images or clinical examination. Normal X-rays do often not perfectly correlate with a patient’s satisfaction. In the last decennium, health-related life quality has been increasingly taken into consideration by decision makers in medicine and politics. Several tools exist to measure health-related quality of life, e.g. the EQ-5D-3L (EuroQol), the SF-6D (derived from RAND-36/SF-36), the HUI (Health Utilities Index Mark II/Mark III), and the AQoL (Assessment of Quality of Life) (Kopec and Willison 2003). Since 2002 the EQ-5D-3L has been part of the Swedish Hip Arthroplasty Registry (SHAR). To allow for the possibility of linking our cohort to SHAR, we chose the EQ-5D-3L to assess health-related quality of life.

The EQ-5D-3L is a standardized health-related quality of life questionnaire developed by the EuroQol Group to provide a simple, generic measure of health (Szende 2004). It provides a straightforward descriptive profile and a single index value for health status. The EQ-5D-3L consists of a descriptive system and a visual analogue scale, the EQ VAS. The EQ-5D-3L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Answers of level 2 or 3 result in a reduction of the health status score; this score is then transformed into an EQ-5D-3L index score using the scoring algorithm based on the preferences of
the UK population (range -0.594 to 1, where negative values are valued as “worse than dead”). The EQ VAS records the respondent’s self-rated health, where the endpoints are labeled “best imaginable health state” (=100) and “worst imaginable health state” (=0). There were 9 individuals under the age of 18 in our study. An EQ-5D-3L reference population for ages 15-17 is not available, so for this age group we used the reference population from the EQ-5D-Y – a child-friendly version of the EQ-5D-3L (Ravens-Sieberer et al. 2010). In this age group, however, the VAS scale had limited reliability and is not applicable for comparison.

Physical activity
The International Physical Activity Questionnaire (IPAQ) was developed on behalf of the World Health Organization (WHO) as a surveillance instrument to measure physical activity and thus estimate the attributable risk of physical inactivity on the global burden of non-communicable diseases (Ezzati et al. 2002). We used the short version of the IPAQ instrument (Craig et al. 2003) to quantify physical activity in our study group and then compared the scores to the Swedish general population as assessed by Bauman et al. (Bauman et al. 2009). The IPAQ measures the time respondents have spent walking and performing other moderate- to vigorous-intensity activities during the last 7 days, and counts only those activities lasting 10 minutes or longer. The data are handled according to the scoring protocol of the IPAQ group, which is available at www.ipaq.ki.se. We applied both the categorical score divided into 3 categories (low, moderate and high) and the continuous IPAQ score (expressed in MET-minutes per week multiplied by the appropriate metabolic equivalent task (MET), where 1 MET equals the energy expenditure of sitting down quietly, 3.5 ml O$_2$·kg$^{-1}$·min$^{-1}$) (Ainsworth et al. 1993, Ainsworth et al. 2000).

Hyperactive/inattentive behavior pattern
The Adult ADHD self-reporting symptom checklist was developed by the WHO and exists in two versions, a short one with six questions (ASRS screener v1.1) and the long checklist (ASRS symptoms checklist v1.1); we used the latter in our study. The symptoms checklist consists of eighteen questions according to criterion in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Kessler et al. 2005). Questions 1-9 (part A) are focused on inattentiveness, and questions 10-18 (part B) on hyperactivity/impulsivity. The total score ranges between 0-72 points.

If the patient receives $\geq 17$ points on either part, it is likely that the patient has symptoms consistent with ADHD. Scores $\geq 24$ points indicate high probability for ADHD.
The sensitivity of the ASRS symptoms checklist v1.1 is 56.3% and the specificity is 98.3%. As Sweden is a low prevalence country, the prevalence of ADHD is estimated to be between 2 and 5 %, which gives a positive predictive value of 40 to 64% and a negative predictive value of 97-99%.

Study population

Study I and II

The SNHDR was used to identify 2579 patients with ICD-codes for LCPD (ICD, Seventh Revision, code 732.04; ICD, Eighth Revision, code 722.11; ICD, Ninth Revision, code 732B; and ICD, 10th Revision, codes M91.1 and M91.2) (Socialstyrelsen 1996, WHO 2009), diagnosed between 1964/65 and 2005.

Subjects with LCPD were matched individually with up to 5 members of the Swedish general population who did not have the disease. The matching criteria were date of birth, region of residence (county), and gender. The matched individuals had to be alive at the time the patient received the diagnosis of LCPD. In total, we included 2579 patients with LCPD and 13748 individuals without the disease in the study.

Administrative registries were used to identify information on dates of birth, death, immigration and emigration, and to calculate the follow-up period available for each individual. Census data were used to create a 6-category socioeconomic index based on the occupation of the patient’s father (manual workers, non-manual workers, professionals, self-employed workers, farmers, and others).

For study I we also used same-sex siblings as an additional comparison group. The Swedish Multi-Generation Register identifies first-degree relatives and was used to identify siblings of the study subjects. We used only same-sex siblings of the patients with LCPD; when there were more than 2 siblings, we used the sibling closest in age to the patient.

Study III

Patients with a history of LCPD who were diagnosed at or referred to and treated in Uppsala University Hospital between 1978 and 1995 and who had an age at follow up in November 2011 of 15 years or older were sent an invitation to participate in the study. The EQ-5D-3L health-related quality of life questionnaire including VAS-scale, as well as the international physical activity questionnaire (IPAQ), Adult-ADHD self reporting checklist (ASRS-v1.1) and a short general information questionnaire including height, weight, occupation and prior health problems were sent to each patient. All patients
were invited to a hospital visit for general orthopedic examination, assessment of the Harris-hip-score and for conventional X-ray of the hip.

Those patients unable to answer the questionnaires by mail or telephone, were asked to answer the questionnaires at the hospital visit.

**Inclusion criteria**
- All patients diagnosed at, referred to and treated in Uppsala University Hospital between 1978 and 1995
- Age at onset between 2 and 15 years
- Age at follow-up 15 or older

**Exclusion criteria**
- Alcohol or drug addiction or psychiatric disorders that endanger the patient’s credibility
- Diseases or previous hip conditions which could be associated with secondary LCPD (e.g. previous hip trauma, developmental dysplasia of the hip, slipped capital femoral epiphysis, etc.)
- Misclassification

In total we identified 167 patients. 22 patients had to be excluded either because of misclassification (3 patients) or due to the exclusion criteria (19 patients). Of the remaining 145 with LCPD diagnoses, 19 declined to participate, 4 were deceased and we were unable to reach 6 patients. Ultimately, 116 patients answered the questionnaires (Figure 10). This resulted in an answering rate of 80%. Only one patient refused to answer the ASRS checklist but completed the other questionnaires. 72 of the 116 patients (78 hips) accepted X-rays of the hip and an orthopedic examination. Their radiological outcome by Stulberg is shown in Figure 11. 4 patients had already received a total hip arthroplasty, but previous X-rays of the hip were available.
Figure 10. Patients included and excluded in study III
Study IV

The Swedish National Patients Register was used to identify a cohort of patients with the diagnosis of LCPD by ICD-code from 1964 to 2011. Since 2001, ambulatory consultations have also been included. 4194 patients with the diagnosis of LCPD were identified. 137 patients also had records of hip diseases other than LCPD (developmental dysplasia of the hip, slipped capital femoral epiphysis) and were excluded, leaving 4057 patients with LCPD for the study. Using the Total Population Register, we identified each individual’s date of birth, sex, region of residence at diagnosis and date of death or emigration. Patients with LCPD were individually matched with 10 individuals of a population-based cohort without LCPD. The matching criteria were date of birth, sex, region of residence and being alive at the time when the patient was diagnosed with LCPD. These two groups were compared in order to assess the risk of ADHD (ICD-9: 314.0; ICD-10: F90.0), depression (ICD-7: 790.29; ICD-8: 790.20; ICD-9: 308, 311; ICD-10: F32-38, F92.0) and mortality.
Statistical analysis
Study I, II and IV

In these studies, Cox proportional hazard regression was used to estimate the relative risk of co-morbidities of interest in the cohort of patients with LCPD compared to the cohort without LCPD. Follow-up was from 1964/65, when the Inpatient Register was established, or from birth or immigration if this occurred subsequently. Follow-up continued until diagnosis of co-morbidity disease of interest, death, emigration, or 31st December 2005 (Study I and II) or 31st December 2011 (Study IV). A person could have more than one study endpoint (different disease outcomes). The underlying time scale for all models was attained age. The analyses were performed both unadjusted and adjusted for socioeconomic index (study I and II) and for the matching variables (study IV).

Study III

Descriptive statistics were used to summarize the characteristics of the patients and the data collected. Some variables (age at onset, IPAQ, ASRS v1.1) were analyzed both as continuous measures and as categorical or dichotomous measures after translation in order to simplify the presentation of the results. Age at onset of LCPD has a prognostic value at the outcome which deteriorates with increasing age (Farsetti et al. 1995). We used <6 years or ≥6 years of age as the cut-off in this study, as described by Wiig et al. (Wiig et al. 2008).

For continuous variables with no apparent deviation from normality (determined by inspection of histograms), comparisons between groups were performed using the Student’s t-test or One-Way ANOVA. For skewed continuous variables, comparisons between groups were done using the non-parametric Mann-Whitney U-test or Kruskal Wallis test. For categorical measures we used either a Chi-square or Fisher’s exact test. Correlations between variables were calculated using the Pearson product-moment correlation coefficient (r) for parametric data and Spearman’s rho (ρ) correlation coefficient for non-parametric data. Linear regression analysis for continuous variables and logistic regression analysis for categorical variables were performed to compare the questionnaires. We set the α-level at p ≤ 0.05; all results significant to this level have been marked with (*), and those significant to the p ≤ 0.01 level with (**).
Ethical considerations

The ethics research committee at the Karolinska Institute, Stockholm, Sweden, has approved study I and II (Nr.: 2005/1004-31/2).

The study protocol for study III has been subjected to the Ethics Research Committee of the Medical Faculty, University of Uppsala, Sweden and has been accepted (Nr:2008/192).

Patients were enrolled in the study only after written and oral information, and written consent. Study IV was approved by the Ethics Research Committee of the Medical Faculty, University of Uppsala, Sweden, reg. number 2012/065, date of issue 21st March 2012.

All studies comply with the Declaration of Helsinki.
Results and discussion

Study I
Vascular and blood diseases
Patients with LCPD had a 1.7-fold higher risk for cardio- and cerebrovascular diseases, compared with gender- and age-matched individuals without LCPD. In particular, the risk for hypertension was 2.2-fold, for diseases of the vessels 1.9-fold and for cerebrovascular diseases 1.8-fold higher than for individuals without LCPD. Patients with LCPD also had an almost 2-fold higher risk of diseases of the blood and blood-forming organs – including nutritional, hemolytic and aplastic anemia, coagulation defects, purpura and other hemorrhagic conditions – compared with the individuals without LCPD. Patients with LCPD had also higher risks for cardiovascular diseases and blood diseases when compared with their same-sex siblings.

These findings seem to support our hypothesis (1) that the pathophysiology of LCPD might not only exist locally in the epiphysis of the femoral head but that there might also be a systemic predisposition toward vascular diseases. LCPD can be induced experimentally both through hypertension in spontaneous hypertensive rats (Suehiro et al. 2005) and also by anemia (Fadda et al. 1992). We know of no study investigating blood pressure in children and its association with LCPD, but hypertension is a highly under-diagnosed disease in children (Hansen et al. 2007). In Sweden, blood pressure controls are not included in the age-specific examinations (Socialstyrelsen 2007) and therefore, possible asymptomatic hypertension in children could remain undetected. The higher risks for cardiovascular and blood diseases were also present when comparing the patients with their siblings, making environmental or genetic factors as a possible explanation unlikely.
Study II
Injuries
Patients with a history of LCPD have a 1.2-fold higher risk of injury (soft-tissue injuries and fractures) requiring hospital admission than in gender- and age-matched individuals without LCPD. The risk was more pronounced among females. Stratification for the location of the injury revealed that the higher risk was present in the trunk/skull and in the lower extremities. In the upper extremities, the association of LCPD and injuries could only be seen in female patients with LCPD compared to those without LCPD.

This population-based study revealed that LCPD was associated with a higher risk of injuries. It is possible that trauma may be causally implicated in LCPD etiology. The susceptibility for injuries requiring hospitalization could be due to a higher activity level itself or a more risk-taking behavior pattern. Burwell et al. (1978) and Kristmundsdottir et al. (1987) found a delay in skeletal maturation and disproportional growth in children with LCPD. If other children of the same age are physically superior in playground games or in sport activities, children with LCPD may be more susceptible to injuries, which could affect the femoral head’s blood supply. Even balance or coordination problems due to pain or altered biomechanics in the hip joint could contribute to the higher injury risk in patients with LCPD. However, we observed a higher risk of injuries both before and after LCPD diagnosis, even after excluding events that happened during the period of 1 year before and 5 years after the date of LCPD diagnosis. Decreased muscle strength, derangement of joint mobility, coordination problems, or bone mineral loss due to immobility associated with acute LCPD and its treatment might not be the sole reason for the elevated injury risk.

Study III
Health-related quality of life, physical activity and ADHD
Adult patients with a history of LCPD treated at Uppsala University Hospital had poorer health-related quality of life than the Swedish general population. This was expressed in lower EQ-5D-3L_{index} and EQ VAS scores in all age categories. Neither age at onset of LCPD (<6 years or ≥6 years), age at follow-up, nor treatment (non-surgical or surgical) influenced the EQ-5D-3L_{index} and EQ VAS scores. A sub-analysis of the 72 patients with recent radiographs of the affected hip at follow-up revealed no significant differences of EQ-5D-3L or EQ-VAS be-
between the different Stulberg classes, and showed no correlation between these factors.

Adult patients with a history of LCPD are physically active to a high extent. Male patients are more active than female patients.

33 (28%) of 116 patients are likely or highly likely to have ADHD or have already been diagnosed with ADHD and are under medication. The sensitivity of ASRS is 56.3% and the specificity is 98.3%. Sweden is considered to be a low-prevalence country for ADHD and the prevalence of ADHD in adults is estimated to be 2-5%. This gives a positive predictive value of ASRS of 40-64%, which means that 13-21 patients out of 116 may actually have ADHD.

Health-related quality of life measured with EQ-5D-3L and EQ VAS seems to be associated with ASRS-score. The higher the ASRS score, the more likely the patient is to have ADHD, and to report having a lower health-related quality of life. Higher ASRS-scores were also associated with a higher incidence of self-reported injuries.

These findings support our hypothesis that patients with a history of LCPD had a lower health-related quality of life and a higher physical activity level compared to the Swedish population norm. In agreement with Loder et al. (1993) and Perry et al. (2013), these patients seemed to have a tendency for hyperactive/inattentive behavior pattern, based on the results of the ASRS checklist. In general, physical activity has a positive impact on health-related quality of life, both in healthy individuals and in patients with chronic diseases (Arne et al. 2009, Anokye et al. 2012). Only 9 of 116 patients were physically active at a low level, which makes it impossible to draw conclusions concerning the association of physical activity level and health-related quality of life in this study group.

Study IV
ADHD, depression and mortality

Patients with a history of LCPD had a 1.5-fold higher risk for ADHD compared to sex- and age-matched individuals without LCPD. A stratified analysis including only patients before 2001 (only inpatient data) revealed a HR of 1.5 (95% CI: 1.2-2.0) and after 2001 (in- and outpatient data) a HR of 1.5 (95% CI: 1.1-2.2). The hazard ratio for ADHD among females with LCPD was 2.1-fold higher than for females without LCPD. The same pattern was seen for the risk for depression, which was 1.3-fold higher among individuals with a history of LCPD compared to those without LCPD and was higher for females (HR= 1.5).
In the LCPD-cohort, the mortality risk was increased by 1.2 compared to the controls. Excluding individuals with the diagnosis of depression and/or ADHD did not change the slightly higher mortality risk in patients with LCPD compared to individuals without LCPD (HR: 1.2; 95% CI: 1.0-1.4). Patients with LCPD had a 2.9-fold higher risk of committing suicide and a slightly higher risk (HR= 1.2) of dying of vascular diseases. Other causes of death such as hemato-oncological diseases, cancer, injuries or neurological diseases did not differ between the cohorts.

These findings support our hypothesis of an association of LCPD and hyperactive behavior pattern expressed in a higher risk for ADHD and depression in the cohort with a history of LCPD. Furthermore, the study provides epidemiological confirmation of the findings of study III with a clinical assessment of the hypothesis. This contributes to a better understanding of LCPD and its associations to other diseases, which could lead us closer to the etiology. Patients who are showing hyperactive behavior pattern at orthopedic consultation could have severe difficulties coping with LCPD. It remains to be seen whether these patients would benefit from a psychological consultation for ADHD screening in order to offer adequate medication, or whether the hyperactive behavior pattern may be a result of the physical and psychological burden of LCPD.
Strengths and limitations

Register studies (I, II and IV)

Strengths of our study include the large sample size, cohort design and relatively long follow-up. The data in the Swedish Patient Register are collected prospectively and undergo no further selection, so they provide a nationwide perspective and a sample that is representative of the population. However, the coverage of the Swedish Patient Register was not complete until 1987. Another caveat is that we were not able to verify the diagnostic accuracy of LCPD among the patients, or the diagnoses of the co-morbidities investigated. However, the positive predictive value of coded diagnoses in the Swedish Patient Register is estimated to be accurate for 85–95% of cases, and generally higher for somatic diseases (Ludvigsson et al. 2011). Furthermore, the ICD-coding errors in the Swedish Patient Register are less common in the records for younger patients compared with those of older patients (Socialstyrelsen 2009). Another possible confounder could be that patients with LCPD might be more easily diagnosed with other diseases because of these patients receiving more healthcare attention (surveillance bias). To minimize this confounder, we analyzed the data by excluding timeframes from one to five years before and after the diagnosis of LCPD, and this did not change the estimates notably.

As in most register-based studies, we lack some potentially important information. For example, both incident and prevalent cases of LCPD were included in the exposed cohort. Therefore, we did not have the exact age of diagnosis and it is possible that timing for some diseases or injuries which happened after the first diagnosis of LCPD may have been misclassified as occurring before the disease’s onset.

In addition, information on BMI, smoking habits, physical activity, ethnicity, the site (right/left) of LCPD and the site of the injuries is not available from the register, which makes it impossible to adjust the analysis for these factors. Furthermore, we had no information about the severity of any diseases reported (LCPD, hypertension, anemia, injuries, etc.). The lack of outpatient data in study I and II could lead to an underestimation of the investigated co-morbidities and even of the LCPD diagnoses themselves. Consequently, we investigated only the more severe cases and severe co-morbidities requiring hospital admission, since most diseases, such as vascular and psychiatric diseases or injuries of the upper extremity, are generally
diagnosed and treated in outpatient settings. However, study IV provided us with both in- and outpatient data and stratified analysis revealed no significant change of the estimates concerning ADHD or depression.

Clinical study (III)

To the authors’ best knowledge, this is the first study investigating health-related quality of life, physical activity and behavioral aspects in adult patients with a history of LCPD. The relatively large number of patients with a long follow-up and a high participation adds additional strength to our results. The large database of the Swedish general population which exists for the EQ-5D-3L and IPAQ provides a basis for comparison of our sample to the Swedish general population. A limitation of the study is the lack of a control group, which is why we compared our results with the existing databases on EQ-5D-3L and IPAQ, both of which have a large sample size. However, the data in the databases and for our study were not collected simultaneously, and trend changes over time could have occurred. Furthermore, we do not know if the results of health-related quality of life are attributable to LCPD or other circumstances in the patients’ health status or environment as we lack pre-disease data for health-related quality of life.

Another weakness of the study (III) is the assessment of physical activity. Although IPAQ is a widely used, well-established and documented questionnaire with good reliability, it is dependent on the patient’s honesty and self-evaluation. The major advantage is that IPAQ provides a validated sample of the Swedish population, is easy to use in both telephone and face-to-face interviews and does not overburden the participant’s patience when performed in addition to the other questionnaires. However, a combination of the IPAQ with an activity diary or a more objective method (accelerometry, heart rate monitoring) would have improved the validity.

The ASRS v1.1 checklist is a screening tool. But no patient underwent a psychiatric consultation in order to verify a possible ADHD diagnosis. However, the checklist is used as a standard tool in clinical practice.
Discussion in a broader perspective

LCPD is an osteonecrosis of the femoral head in children – why not focus on the hip?

Orthopedic surgeons are often very target-oriented. The target is disproportional or mal-aligned growth, broken bones, osteoarthritis of a joint or torn ligaments or tendons. This focus has led to excellent developments in orthopedic surgery e.g. osteosynthetic devices (Miclau and Martin 1997), arthroplasties (Knight et al. 2011) and other techniques to provide improved healing to restore the human anatomy and biomechanics. However, we have to realize that despite a nearly perfect surgical and radiological result, some patients haven’t been as enthusiastic about the outcome as the surgeon or radiologist. Therefore, there must be other factors compromising the orthopedic surgeon’s work: etiological factors, co-morbidities, psychological factors or physiological factors like age and gender. These are probably the same factors which could facilitate our work by identifying those persons at risk and preventing them from getting worse.

Etiological factors in particular are often unknown in pediatric orthopedic diseases such as developmental dysplasia of the hip (DDH), slipped capital femoral epiphysis, adolescent idiopathic scoliosis, LCPD and numerous more. This means that we sometimes have to deal with treating the consequences of the disease. And in many cases ‘timing’ is an important factor. Identifying an individual at risk early or diagnosing them early, facilitates the treatment and improves the outcome. This is very illustrative in the treatment of DDH, for example: if diagnosed within the first weeks of life bracing-treatment is required for only 6-12 weeks; if diagnosed later, treatment is more complicated and significantly longer in duration.

Co-morbidities may work as a catalyst for diseases and may expose individuals to greater risks for inferior or delayed recovery.

Lately, research on health-related quality of life has become more popular and accepted both for patient management and policy decision making in health care. Most Quality Registries in Sweden include a measurement of health-related quality of life (Kvalitetsregister, Sveriges kommuner och lansting 2014). Psychological aspects are taken into account, making it easier to estimate how the patient copes with the disease and its consequences like pain, limited range of motion, upcoming surgery, etc. (Turner and Kelly 2000).
In this process we have to ask ourselves if a given treatment makes sense, not only locally but also in terms of holistic health. One example is the use of hip braces in the non-surgical treatment of LCPD. Some studies assured the beneficial effect on the femoral head (Petrie and Bitenc 1971, Thompson and Salter 1987), but due to the significant psychical burden of this treatment relative to the effect and compared with treatment alternatives (Price et al. 1988), this option has almost been abandoned. In cases in which containment has to be improved, surgical methods, especially varisation osteotomy of the proximal femur, replace abduction braces (Wiig et al. 2008). Even though there is more and more evidence on predicting which patients might have good outcomes (under 6 years of age and Lateral Pillar A or B), we still are confronted with a lack of consensus on how to treat patients not meeting these criterion, as shown in a European survey of pediatric orthopedic surgeons on the management of LCPD (Hefti and Clarke 2007). The next challenge will be how to treat the sequelae of LCPD in the very young patient: with arthrodesis or arthroplasty of the hip?

Clinical implications of the results

Cardiovascular diseases

Patients with LCPD had a higher risk for cardiovascular diseases and in particular, a higher risk for hypertension (study I). Cardiovascular diseases ranked second in the occurrence of causes of death with in patients with a history of LCPD compared to those without LCPD (study IV). These findings raise two questions: (1) is hypertension prevalent when LCPD occurs and a causal or catalyzing factor as shown in an animal study (Hirano et al. 1988) or (2) does hypertension occur later in life and patients with a history of LCPD have for some reason a higher risk for hypertension?

If (1) is true, it would be possible to identify persons at risk for LCPD and thus develop prevention strategies against LCPD. In Sweden, blood pressure controls are not included in the regular health checks for children and adolescents (Socialstyrelsen 2007). However, hypertension in children is a growing problem (Ostchega et al. 2009) and often under-diagnosed (Hansen et al. 2007). But, if question (2) is true, a cost-benefit analysis could evaluate whether we should inform patients with a history of LCPD about the raised risk for hypertension in order to prevent the consequences of hypertension. There seems to be little evidence that general health checks in adults reduces morbidity and mortality from disease (Krogsboll et al. 2012). However, this applies to the general population and not from an individual perspective or after having identified individuals at risk. These two questions broaden the horizon for further research by investigating if patients with newly diagnosed LCPD also suffer from hypertension, and by investigating with an
epidemiological approach whether patients with hypertension have a higher risk for having suffered from LCPD in childhood.

Injuries, Hyperactivity and Depression

Our study revealed a higher risk for injuries in patients with a history of LCPD compared to the controls (study II). Furthermore, we found a raised risk for ADHD in the epidemiological study of associations between LCPD and ADHD (study IV). When we screened for ADHD in a clinical setting, 28% of 116 patients with a history of LCPD were considered likely or highly likely to have ADHD and had a significantly higher incidence of self-reported injuries (study III). Study III only included patients with an age at follow-up older than 14 years. Hence, we were not able to know whether or not ADHD-symptoms were present at the time of diagnosis for LCPD to ascertain if it really could be considered as an etiological factor of LCPD. However, ADHD often persists over an individual’s lifetime but the symptoms change (Ebejer et al. 2012, Barbaresi et al. 2013). Even the epidemiological study (IV) could only reveal an association between the two diagnoses but did not permit any conclusions about temporal sequences. Time at diagnosis for ADHD cannot be considered as a reliable variable because of a diagnostic delay (Dulcan 1997, McIntosh et al. 2009). Even though mostly diagnosed in schoolchildren, the symptoms often exist already in pre-school aged children (Lavigne et al. 2009). This makes it more probable that hyperactive and risk-taking behavior pattern (Groen et al. 2013) might predate LCPD and appear as an etiologic factor.

Arguments that hyperactivity may result from LCPD and its consequences (cessation of sports, partial weight bearing, pain) might be true if hyperactivity would be the only symptom. However, it might not be true in the case of ADHD, because hyperactivity is only a part of the whole symptom spectrum. An orthopedic surgeon might be overextended in distinguishing between these subtleties, but for the patient it could be of high importance and could help them to better cope with LCPD by getting adequate medication in the case of ADHD prevalence. The high IPAQ scores of patients with LCPD compared to the Swedish general population (study III) might be a further indicator of physical and even psychical restlessness. Furthermore, neurobehavioral aspects of ADHD can later change to inattentiveness and depression (McIntosh et al. 2009, Yang et al. 2013) which could potentiate the psychical burden of a chronic disease like LCPD (Cassileth et al. 1984, Moussavi et al. 2007). We could confirm an association of LCPD and depression in our study together with a raised risk for suicide in patients with LCPD compared to controls (study IV). These findings are in concordance with those of Barbaresi (2013) who found a higher suicidal rate and comorbid psychiatric disorder in a birth cohort with ADHD compared to individuals without ADHD of the same birth cohort.
Taking into consideration associations with injuries (as a possible expression of risk-taking behavior), high physical activity, ADHD, depression and suicide as cause of death, collaboration with a psychiatrist could be beneficial for patients with LCPD.

Gender aspects

LCPD is more common in males than in females, but females have a less favorable prognosis (Catterall 1971, Guille et al. 1998). Gender differences are also described for the incidence of injuries/fractures (Landin 1997, UNICEF 2001, Hedstrom et al. 2010) and ADHD (Biederman et al. 2002, Skogli et al. 2013) being higher in males. Surprisingly, both the risk of injuries and of ADHD was more pronounced in female patients with LCPD. An interesting finding, because the impulsive aspect of ADHD is less distinctive in female than in male patients, making it more difficult to diagnose (Hasson and Fine 2012). The worse prognosis of LCPD in females could be explained by the earlier puberty and skeletal maturity in females, giving the femoral head less time for re-modeling. But the higher risks for injuries and ADHD in females with LCPD remain unexplained. Speculatively, the differences in incidence could be due to hormonal or other neurobiological mechanisms having an impact on behavior patterns and secondarily on LCPD. Another speculation is that the differences could be due to surveillance bias: When girls have contact to healthcare because of LCPD, other diseases may also be diagnosed. While such a bias may exist for ADHD diagnosis, it does not seem plausible for the diagnosis of injuries, as these are more or less independent events.

Health-related quality of life

Patients with a history of LCPD had significantly lower EQ VAS scores than the Swedish general population in the same age group. The EQ-5D-3L index score was also significantly lower in patients with LCPD compared to the Swedish general population. Concerning the dimension mobility, anxiety/depression and pain/discomfort categories, more patients reported some or moderate problems compared to the Swedish general population in the same age group (study III).

The EQ-5D-3L questionnaire is a simple, generic instrument for measuring of health and is used in many Swedish Quality Registers, e.g. the Swedish Hip Arthroplasty Register. With regards to this register we decided to use this questionnaire in order to provide the possibility of following our patient group and comparing the results over the years and after potential hip arthroplasty. However, the EQ-5D-3L has limitations in being a very generic instrument and we expected that no differences in health related quality of
life would be observed because of the young age of the patients. Surprisingly, we detected differences compared to the Swedish general population, which confirms the impact of LCPD and its consequences on health-related quality of life. Even so, the EQ-5D-3L questionnaire is not specific enough to identify disease-specific factors influencing quality of life and is not able to detect small variations in the study population. Furthermore, it would be interesting to see the impact of LCPD on quality of life in the acute phase, healing phase and at skeletal maturity and in relation to different treatment strategies. This could even support decision making when considering the treatment options of the sequelae of LCPD in young patients regarding the question of hip arthrodesis or arthroplasty. However, it still remains unclear if potential changes in health-related quality of life represent a clinically important difference because it is problematic to interpret differences in these scores (Paulsen et al. 2013).

“Causa latet, vis est notissima”- The cause is hidden, the effect is well known

(Publius Ovidius Naso, 43 BC to 17/18 AD; Metamorphoseon libri IV, 287)

The effect of LCPD is well known. Particularly well known is the effect of LCPD when the age at onset is beyond 6 years and the case falls into Lateral Pillar group B, B/C and C (Catterall group III or IV) (Stulberg et al. 1981, Herring et al. 2004, Wiig et al. 2008): the result is a deformity of the femoral head with decreased range of motion and a higher risk for premature osteoarthritis (Larson et al. 2012).

Finding and understanding the cause or causes (etiology) of LCPD could provide us with new possibilities to impair the disease itself or its progress. Even though efforts can be made to prevent the collapse of the femoral head by inhibiting the osteoclastogenesis with bisphosphonates or OPG-Fc (RANK ligand inhibitor) experimentally, the anabolic effect in the femoral head still cannot be achieved (Little and Kim 2011, Young et al. 2012).

In 1984, Catterall stated the concept of the ”Susceptible Child” for LCPD, which “would be primarily boys between ages five and nine years who are smaller than their friends and first-degree relatives and have delayed bone age. In all other aspects healthy, and very active children; many of them are hyperactive.” (Catterall 1984). In 2005, Sharma stated, “… many children with Perthes’ disease seem to be hyperactive. We have not been able to quantify this but it is a constant theme reiterated by parents and observed in our clinics that many of these children are more active than average.” (Sharma et al. 2005). In addition to our research, some other authors have also documented hyperactive behavior pattern in children with LCPD (Loder
et al. 1993, Perry et al. 2013). However, an altered blood supply of the femoral head’s epiphysis seems to be the key pathogenetic cause of LCPD. Recently, Perry et al. (2012) showed that children with LCPD had abnormal small artery caliber and reduced vascular function. More evidence for the possible role of vascular abnormalities in the pathogenesis of LCPD comes from identification of common risks for LCPD and cardiovascular diseases, including low birth weight (Lappin et al. 2003, Lenfant 2008, Strufaldi et al. 2008). Maternal and passive smoking during pregnancy has been implicated in the pathogenesis of atherosclerosis (Kosecik et al. 2005, Aycicek and Ipek 2008), hypertension among children (Lawlor et al. 2004) and LCPD (Garcia Mata et al. 2000). The nicotine could provoke oxidative stress in the offspring which could affect not only vascular formation but also growth and could also have neurotoxic effects by disrupting neurodevelopment. It seems that on the basis of a possible systemic vascular fragility, hyperactivity might trigger or catalyze LCPD in the femoral head’s epiphysis.

An interesting issue is the pathway of insulin-like growth factor (Neidel et al. 1992, 1992, Matsumoto et al. 1998) in the discussion of LCPD. Lower levels were found in patients at the onset of LCPD. IGF-1 plays an important role in the growth of many tissues during childhood and could explain the delayed skeletal maturation, hyperactive behavior (Kim 2011) and possibly also vascular abnormalities. That said, other pathways could also have a similar impact on both angiogenesis and neurodevelopment in patients with LCPD.

Because of the fact that we still cannot treat LCPD in a way to achieve a normal hip at maturity, it is important to develop new treatment strategies and search for the causes of LCPD. “We cannot yet cure Legg-Calvé-Perthes disease. But we are working on it.” (Karol 2010).

Presumably, it is not just the hip!
Patients with a history of Legg-Calvé-Perthes disease had a higher risk of cardiovascular and blood diseases including anemias and coagulation defects compared to the control group (study I).

Patients with a history of LCPD had a higher risk for severe injuries requiring hospital care than individuals without LCPD. The risk was more pronounced in female patients with LCPD than in female patients without the disease (study II).

Adult patients with a history of LCPD had a lower health-related quality of life compared to the Swedish general population in the same age group (study III).

Over 90% of our patient group was physically active on a moderate or high level even though 52% reported moderate or severe problems with pain in the EQ-5D-3L questionnaire (study III).

28% of the patients had ASRS-scores corresponding with a likelihood for ADHD and these scores correlated negatively with health-related quality of life (study III).

Patients with a history of LCPD had a higher risk for ADHD and depression and a slightly higher mortality risk than individuals without LCPD. The risks for ADHD and depression were more pronounced in females with LCPD (study IV).
To my deepest disappointment, study I gave us cause for serious concern. The ICD codes that we used to identify a diagnosis of LCPD included some non-specific codes that may have included diagnoses other than LCPD. Unfortunately, we detected the error first after publication in Pediatrics (Pediatrics 2010;125:e1308-e1315; originally published online May 3, 2010; DOI: 10.1542/peds.2009-2935). We therefore reanalyzed the data using only ICD codes specific to LCPD (ICD-7 code 732.04; ICD-8 code 722.11; ICD-9 code 732B; and ICD-10 codes M91.1, M91.2). As expected, the overall results did not change notably. As a matter of cause we wrote an ERRATUM to be published in Pediatrics (Pediatrics 2013 Jul;132(1):186-7). However, the journal denied publishing the full revised version of the manuscript and only published the new abstract and new tables. In order to avoid publishing the wrong version once again, we decided to attach the corrected manuscript in this thesis and the published ERRATUM. We deeply apologize for this error.

Målet med den aktuella avhandlingen var att kartlägga om patienter med LCPS också drabbas av andra sjukdomar som är kopplat till blodcirkulationen till exempel hjärt- och kärlsjukdomar och andra blodsjukdomar så som blodbrist (anemi) eller koagulationsrubningar. Barn med LCPS upplevs oftast som mycket aktiva och i tidigare studier har beskrivits en möjlig koppling till upprepande trauma som en möjlig orsak till sjukdomen, vilket också undersöckes i avhandlingen.


I delarbete II undersökte vi ett samband mellan LCPS och skadebenägenheten som ett indirekt tecken till hyperaktivitet. Patientgruppen med LCPS hade en 20 % högre risk att skada sig (mjukdelsskador och benbrott som kräver behandlingen på sjukhuset) jämfört med de som inte hade LCPS.

I delarbete IV undersökt risken för ADHD och depression och mortalitetsrisken hos 4057 patienter med LCPS jämförd med 40570 individer utan LCPS med hjälp av svenska patient- och befolkningsregistret. Det framkom att patienter med LCPS har en 50 % högre risk för ADHD, en 30% högre risk för depression och en antytt högre mortalitetsrisk. Som dödsorsak var risken för självmord nästan 3 gånger högre hos patienter med LCPS, följd av hjärt- och kärlsjukdomar.

Sammanfattningsvis bekräftar avhandling misstanken om att LCPS har en koppling till blodcirkulationsrubningar som yttra sig inte bara lokalt i höftled men även i hela kroppen. Samtidigt verkar det finnas en tendens till hyperaktivitet som möjligen bidrar till utvecklingen av LCPS i barndomen och kan påverka patientens förmåga att hantera sjukdomens psykiska påfrestelse.

Ziel der vorliegenden Doktorarbeit war es, herauszufinden, ob Patienten mit MP auch ein erhöhtes Risiko für andere Zirkulationskrankheiten, wie Herz- und Gefäßerkrankungen, Blutarmut, Thrombose- oder Blutungsneigung, haben. Kinder mit MP werden häufig als hyperaktiv bezeichnet und frühere Studien weisen auf einen Zusammenhang von wiederholten Trauma und MP hin, was in dieser Arbeit ebenfalls untersucht werden sollte.

In Studie I verglichen wir das Risiko für Zirkulations- und Blutkrankheiten von 2579 Patienten mit der Diagnose MP und 13748 Patienten ohne MP. Die Daten wurden mit Hilfe des schwedischen Patientenregisters (Patienten und erkrankungsspezifische Daten) und Bevölkerungsregisters (Kontrollgruppe) erhoben. Es zeigte sich ein Zusammenhang zwischen Zirkulationskrankheiten und MP: Patienten mit MP hatten ein doppelt so hohes Risiko an Bluthochdruck zu erkranken, ein um 50% erhöhtes Risiko für Erkrankungen der Herzkrankengefäße inklusive Herzinfarkt und ein doppelt so hohes Risiko für Blutarmut im Vergleich zur Kontrollgruppe ohne MP.

In Studie II untersuchten wir einen eventuellen Zusammenhang zwischen MP und Verletzungsneigung als indirektes Zeichen für Hyperaktivität. Es zeigte sich, dass Patienten mit MP im Vergleich zu der gesunden Kontrollgruppe ein um 20% erhöhtes Verletzungsrisiko (stationär behandelte Weichteilverletzungen und Knochenbrüche) hatten.

vorliegen, verglichen. Es zeigte sich, dass Patienten mit MP, im Vergleich zur schwedischen Allgemeinbevölkerung, eine schlechtere gesundheitsbezogenen Lebensqualität hatten sowie in hohem Grad körperlich aktiv waren. Außerdem beantworteten 28% der Patienten das ADHS Frageformular in der Form, dass die Diagnose ADHS in Erwägung gezogen werden kann.


Acknowledgements

You cannot travel alone, you always need somebody to guide you, to help you back on the right road, to help you understand, to warn you of danger, to show you secrets, to push you when you are tired, to calm you down when you want to see the whole world in one day. I am really privileged to have so many people around me who cared about my journey and about me! I would like to especially thank the following:

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Pia – thank you for understanding my weird humor and for having other things in common. Bless your former knee pain!

Aili – for being my friend and for being just as enthusiastic about new recipes. I miss our cooking session … and training session!

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   Auch wenn Euch die medizinische Welt fremd ist, Ihr habt von Anfang an mich geglaubt. Danke, dass Ihr immer stolz auf mich ward und es mich habt spüren lassen!

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I would like to thank the Skofonden for financial support during the thesis work.
Appendix

ASRS v1.1

### Adult Self-Report Scale (ASRS) Symptom Checklist

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Today’s Date</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very Often</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

1. How often do you make careless mistakes when you have to work on a boring or difficult project? 0 1 2 3 4
2. How often do you have difficulty keeping your attention when you are doing boring or repetitive work? 0 1 2 3 4
3. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly? 0 1 2 3 4
4. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done? 0 1 2 3 4
5. How often do you have difficulty getting things in order when you have to do a task that requires organization? 0 1 2 3 4
6. When you have a task that requires a lot of thought, how often do you avoid or delay getting started? 0 1 2 3 4
7. How often do you misplace or have difficulty finding things at home or at work? 0 1 2 3 4
8. How often are you distracted by activity or noise around you? 0 1 2 3 4
9. How often do you have problems remembering appointments or obligations? 0 1 2 3 4

#### Part A – Total

| 10. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time? | 0 1 2 3 4 |
| 11. How often do you have your seat in meetings or other situations in which you are expected to remain seated? | 0 1 2 3 4 |
| 12. How often do you feel restless or fidgety? | 0 1 2 3 4 |
| 13. How often do you have difficulty unwinding and relaxing when you have time to yourself? | 0 1 2 3 4 |
| 14. How often do you feel overly active and compelled to do things, like you were driven by a motor? | 0 1 2 3 4 |
| 15. How often do you find yourself talking too much when you are in social situations? | 0 1 2 3 4 |
| 16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves? | 0 1 2 3 4 |
| 17. How often do you have difficulty waiting your turn in situations when turn taking is required? | 0 1 2 3 4 |
| 18. How often do you interrupt others when they are busy? | 0 1 2 3 4 |

#### Part B – Total

| 0 1 2 3 4 |

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AT 24/7® PRINTED IN USA 3008020936 0303150  ASRS SYMPTOM CHECKLIST COPYRIGHT © 2003 World Health Organization. Reprinted with permission of WHO. All rights reserved.
<table>
<thead>
<tr>
<th>Your own health state today</th>
<th>Your own health state today</th>
</tr>
</thead>
<tbody>
<tr>
<td>By placing a tick in one box in each group below, please indicate which statement best describes your own health state today. Do not tick more than one box in each group.</td>
<td></td>
</tr>
<tr>
<td><strong>Mobility</strong></td>
<td></td>
</tr>
<tr>
<td>I have no problems in walking about</td>
<td></td>
</tr>
<tr>
<td>I have some problems in walking about</td>
<td></td>
</tr>
<tr>
<td>I am confined to bed</td>
<td></td>
</tr>
<tr>
<td><strong>Self-care</strong></td>
<td></td>
</tr>
<tr>
<td>I have no problems with self care</td>
<td></td>
</tr>
<tr>
<td>I have some problems washing and dressing myself</td>
<td></td>
</tr>
<tr>
<td>I am unable to wash and dress myself</td>
<td></td>
</tr>
<tr>
<td><strong>Usual activities (eg. work, study, housework, family or leisure activities)</strong></td>
<td></td>
</tr>
<tr>
<td>I have no problems with performing my usual activities</td>
<td></td>
</tr>
<tr>
<td>I have some problems with performing my usual activities</td>
<td></td>
</tr>
<tr>
<td>I am unable to perform my usual activities</td>
<td></td>
</tr>
<tr>
<td><strong>Pain/discomfort</strong></td>
<td></td>
</tr>
<tr>
<td>I have no pain or discomfort</td>
<td></td>
</tr>
<tr>
<td>I have moderate pain or discomfort</td>
<td></td>
</tr>
<tr>
<td>I have extreme pain or discomfort</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety/depression</strong></td>
<td></td>
</tr>
<tr>
<td>I am not anxious or depressed</td>
<td></td>
</tr>
<tr>
<td>I am moderately anxious or depressed</td>
<td></td>
</tr>
<tr>
<td>I am extremely anxious or depressed</td>
<td></td>
</tr>
</tbody>
</table>

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.
INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. This is part of a large study being conducted in many countries around the world. Your answers will help us to understand how active we are compared with people in other countries.

The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Your answers are important.

Please answer each question even if you do not consider yourself to be an active person.

THANK YOU FOR PARTICIPATING.

In answering the following questions,

♦ **vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.

♦ **moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.
1a. During the last 7 days, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

Think about only those physical activities that you did for at least 10 minutes at a time.

________ days per week ⇐ 1b. How much time in total did you usually spend on one of those days doing vigorous physical activities?

or

none

2a. Again, think only about those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

________ days per week ⇐ 2b. How much time in total did you usually spend on one of those days doing moderate physical activities?

or

none

3a. During the last 7 days, on how many days did you **walk** for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking that you did solely for recreation, sport, exercise or leisure.

________ days per week ⇐ 3b. How much time in total did you usually spend walking on one of those days?

or

none

The last question is about the time you spent **sitting** on weekdays while at work, at home, while doing course work and during leisure time. This includes time spent sitting at a desk, visiting friends, reading traveling on a bus or sitting or lying down to watch television.

4. During the last 7 days, how much time in total did you usually spend sitting on a week day?

____ hours ______ minutes

This is the end of questionnaire, thank you for participating.
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