Clinical Research

Is Legg-Calvé-Perthes Disease a Local Manifestation of a Systemic Condition?

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Abstract

Background Osteochondrosis includes numerous diseases that occur during rapid growth, characterized by disturbances of endochondral ossification. One example, Legg-Calvé-Perthes disease, is characterized by disruption of the blood supply to the femoral head epiphysis, and a systemic etiology often has been suggested. If this were the case, secondary osteochondroses at locations other than the hip might be expected to be more common among patients with Legg-Calvé-Perthes disease, but to our knowledge, this has not been evaluated in a nationwide sample.

Questions/purposes (1) Do patients with Legg-Calvé-Perthes disease have an increased prevalence of secondary osteochondroses at locations other than the hip? (2) Is the concept of Legg-Calvé-Perthes disease a systemic etiology supported by a higher prevalence of the metabolic diseases obesity and hypothyroidism?

Methods We designed a retrospective population-based cohort study with data derived from the Swedish Patient Registry (SPR). The SPR was established in 1964 and collects information on dates of hospital admission and discharge, registered diagnoses (categorized along the International Classification of Diseases [ICD]), and applied treatments during the entire lifetime of all Swedish citizens with high validity. Analyzing the time span from 1964 to 2011, we identified 3183 patients with an ICD code indicative of Legg-Calvé-Perthes disease and additionally sampled 10 control individuals per patient with Legg-Calvé-Perthes disease, matching for sex, age, and residence, resulting in 31,817 control individuals. The prevalence of secondary osteochondroses, obesity, and hypothyroidism was calculated separately for patients with Legg-Calvé-Perthes disease and control individuals based on the presence of ICD codes indicative of these conditions. Using logistic regression analysis, we compared the adjusted relative risk of having either of these conditions develop between patients with Legg-Calvé-Perthes disease and their matched control subjects. The mean followup was 26.1 years (range, 2.8-65 years).

Results The prevalence of secondary osteochondroses was greater among patients with Legg-Calvé-Perthes disease (3.11%) than among control subjects (0.31%), resulting in an increased adjusted risk of an association with such lesions in the patients (relative risk [RR], 10.3; 95% confidence interval [CI], 7.7-13.6; p < 0.001). When stratified by sex, we attained a similarly increased risk ratio for females (RR, 12.5; 95% CI, 6.1-25.8; p < 0.001) as for males (RR, 9.9; 95% CI, 7.3-13.5; p < 0.001). Patients with Legg-Calvé-Perthes disease had an increased adjusted risk of an association with obesity (RR, 2.8; 95% CI, 1.9-4.0; p < 0.001) or hypothyroidism (RR, 2.6; 95% CI, 1.7-3.8; p < 0.001) when compared with control subjects.

Conclusions To our knowledge, this is the first population-based description of a robust association of Legg-Calvé-Perthes disease with osteochondroses at locations other than the hip, and we also found increased

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risk estimates for an association with obesity and hypothyroidism in patients with Legg-Calvé-Perthes disease. Our findings strengthen the hypothesis that Legg-Calvé-Perthes disease is the local manifestation of a systemic disease, indicative of an underlying common disease pathway that requires further investigation. Physicians should be aware that patients with Legg-Calvé-Perthes disease may present with secondary osteochondroses and metabolic comorbidities.

Level of Evidence   Level III, prognostic study.

Introduction

The etiology of Legg-Calvé-Perthes disease remains enigmatic despite decades of research, but a key pathogenic event is disruption of the blood supply to the femoral head epiphysis [21] that—possibly combined with mechanical overload—causes aseptic osteonecrosis [2, 12, 32]. The incidence of Legg-Calvé-Perthes disease varies geographically and ranges from 0.5 per 100,000 in South Africa [45] to 21 per 100,000 in the Liverpool area [13], although a more recent survey indicates a declining incidence in Great Britain [40]. In Sweden and Norway, the incidence of Legg-Calvé-Perthes disease has been estimated at approximately nine per 100,000 [33, 54].

Numerous risk factors for the development of Legg-Calvé-Perthes disease have been described, among them exposure to smoking [5, 6], social deprivation [19, 29, 42], low birth weight [22], and shorter length at birth [54]. The log normal distribution of the age at onset of Legg-Calvé-Perthes disease is interpreted as indicative of an intrauterine exposure to one or more etiologic triggers [44]. Once manifest, Legg-Calvé-Perthes disease seems associated with altered skeletal growth and maturation [46] and with congenital anomalies of the genitourinary system [41, 54]. Furthermore, patients with Legg-Calvé-Perthes disease have an increased risk of cardiovascular disorders [11], injuries [10], and attention deficit/hyperactivity disorder [12].

The association of cardiovascular or coagulation abnormalities [3, 43, 53], low plasma levels of insulin-like growth factor I [38], and familiar clustering [39, 51] in patients with Legg-Calvé-Perthes disease indicates that this condition may be the local manifestation of a systemic disease. In contrast, other studies do not support the concept of a systemic involvement in patients with Legg-Calvé-Perthes disease [4, 14, 26]. However, some of these studies are of an observational nature or are based on small cohorts with questionable external validity. Moreover, we know of no population-based study describing the development of osteochondroses other than the hip or

metabolic disorders in patients with Legg-Calvé-Perthes disease. Thus, it currently remains unclear whether Legg-Calvé-Perthes disease is a manifestation of a systemic disease. We theorized that some of the most frequent osteochondroses of childhood and adolescence and certain metabolic disorders would be more frequent in individuals affected by Legg-Calvé-Perthes disease.

In the setting of a nationwide, population-based, cohort study, we asked: (1) Do patients with Legg-Calvé-Perthes disease have an increased prevalence of osteochondroses at locations other than the hip? (2) Is the concept of Legg-Calvé-Perthes disease a systemic etiology supported by a higher prevalence of the metabolic diseases obesity and hypothyroidism?

Materials and Methods

This retrospective study is based on the Swedish Patient Register and the Swedish Total Population Register. At birth or immigration, every Swedish citizen receives a unique personal identification number, which is kept until death or permanent emigration. Through this number, every Swedish citizen is registered in the Total Population Register that collects information on dates and places of birth, sex, and residency, and thus all Swedish citizens can be followed until death or emigration. Additionally, whenever a citizen requires hospital care (in- or outpatient), it is mandatory for all public and private hospitals to deliver information on dates of admission and discharge, registered diagnoses (categorized by the International Classification of Diseases [ICD]), and applied treatments to the Swedish Patient Register. This register was established in 1964 for inpatient care and modified in 2001 to include outpatient consultations. In 1984 the Ministry of Health and Welfare made participation for all hospitals to report to the register mandatory, and the coverage of individual hospitalizations has been approximately 99% since 1987 [28, 34]. The registry has high validity, a positive predictive value for diagnoses of 85% to 95% (= the proportion of patients actually with a given condition relative to the number of patients who were registered with that specific condition), and a sensitivity > 90% [28]. In other words, 85 to 95 of 100 patients with a diagnosis code of Legg-Calvé-Perthes disease in the Swedish Patient Registry have actually had the disease. ICD coding errors in the Swedish Patient Register are less common in records of younger patients compared with those of older patients, indicating even higher validity in the cohort investigated in this study [34].

We investigated a nationwide population-based cohort of patients with Legg-Calvé-Perthes disease by identifying all individuals in the Swedish Patient Register with

a diagnosis code indicative of Legg-Calvé-Perthes disease, but without other pediatric hip diseases such as developmental dysplasia of the hip or slipped capital femoral epiphysis. We included individuals registered from 1964 to 2011 by the use of the ICD codes 732.04 (ICD-7), 722.11 (ICD-8), 732B (ICD-9), and M91.1 and M91.2 (ICD-10). For each individual with a diagnosis of Legg-Calvé-Perthes disease, 10 control subjects from the Swedish Total Population Register without Legg-Calvé-Perthes disease who were alive at the time of diagnosis of Legg-Calvé-Perthes disease of their respective study patient were matched for date of birth, sex, and region of residence at diagnosis. The study population was followed from 1964 until the diagnosis of interest, death, emigration, or December 31, 2011, whichever occurred first. For the analysis of the endpoint of osteochondroses, each individual with Legg-Calvé-Perthes disease and their respective control subjects were followed from birth until the registration of an osteochondrosis. However, for the analysis of the endpoints of obesity or hypothyroidism, the same individual was also followed further until the registration of either obesity or hypothyroidism. This means that each individual could experience multiple endpoints.

The initial database contained 51,151 individuals: 4654 patients with a diagnosis of Legg-Calvé-Perthes disease and 46,497 age-, sex-, and residence-matched control subjects. For 12 patients with Legg-Calvé-Perthes disease, we were unable to find 10 control subjects who met all matching criteria, but included the available number of control subjects (ranging from one to nine control subjects per patient with Legg-Calvé-Perthes disease). From 1964 until 2000, only patients with diagnosis codes registered during inpatient hospital episodes were included in the Swedish Patient Register, but since 2001, outpatient consultations were also registered. We excluded patients diagnosed with Legg-Calvé-Perthes disease who were younger than 2 years and those older than 15 years to avoid atypical presentations suggestive of other diagnoses than Legg-Calvé-Perthes disease. This resulted in a final study population of 35,000 individuals consisting of 3183 patients with Legg-Calvé-Perthes disease and 31,817 control subjects (Fig. 1). The median year of birth in the final study population was 1990 (range, 1949-2009). After the age restriction described, the mean age of patients at diagnosis of Legg-Calvé-Perthes was 7.4 years (Table 1). In the final study population, there were 6963 (19.9%) females and 28,037 (80.1%) males. The mean followup was 26.1 years (range, 2.8-65.0 years).

The independent variables for the analysis were age, sex, and occurrence of Legg-Calvé-Perthes disease, as defined by the presence of the specific diagnosis codes noted. The outcome measures were occurrence of Panner's, Scheuermann's, Blount's, Osgood-Schlatter's, and Köhler-Freiberg's diseases; Sinding-Larsson-Johansson's

syndrome; osteochondritis dissecans (in any joint); or Sever's disease (all identified by the specific ICD codes used at the time of registration); and occurrence of obesity, defined by the relevant ICD codes based on the World Health Organization (WHO) criterion of a body mass index (BMI) $\geq 30 \ kg/m^2$; or hypothyroidism, defined by relevant ICD codes based on the international diagnostics standards [47].

Statistical Analysis

Continuous data were described using means, medians, and ranges. Categorical data were crosstabulated and proportions were investigated using the chi-square test. Kaplan-Meier survival analysis was used to calculate cumulative unadjusted survival functions with the diagnosis of osteochondroses other than Legg-Calvé-Perthes disease as the primary endpoint, and differences between groups were investigated using the log-rank test according to Mantel-Haenszel. Binomial logistic regression analyses with or without adjustment for birth year and sex were used to estimate the relative risk (RR) of having osteochondroses other than Legg-Calvé-Perthes disease develop, and specifically for Scheuermann's, Osgood-Schlatter's, and Köhler-Freiberg's diseases; osteochondritis dissecans; obesity; or hypothyroidism. Because the endpoints investigated here were rare, odds ratio was used as an approximation of the RR, and estimation uncertainty was assessed by calculating 95% confidence intervals (CIs). Regression analyses could not be performed for the endpoints of Panner's and Blount's diseases, Sinding-Larsson-Johansson's syndrome, and calcaneal osteochondrosis, because of very rare events that only occurred in patients with Legg-Calvé-Perthes disease but not in the control subjects. Additional analyses were stratified by sex or by the different ICD coding periods described. We also performed sensitivity analysis excluding the diagnosis of Scheuermann's disease as an endpoint. All statistical analyses were performed using R statistic software (Version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria), including the "rms", "magrittr", and "Gmisc" packages. This study was approved by the Ethics Research Committee in Uppsala, Sweden (registration number 2012/065, date of issue March 21, 2012).

Results

Risk of Secondary Osteochondroses Among Patients With Legg-Calvé-Perthes Disease

The prevalence of secondary osteochondroses at locations other than the hip was greater among patients with Legg-
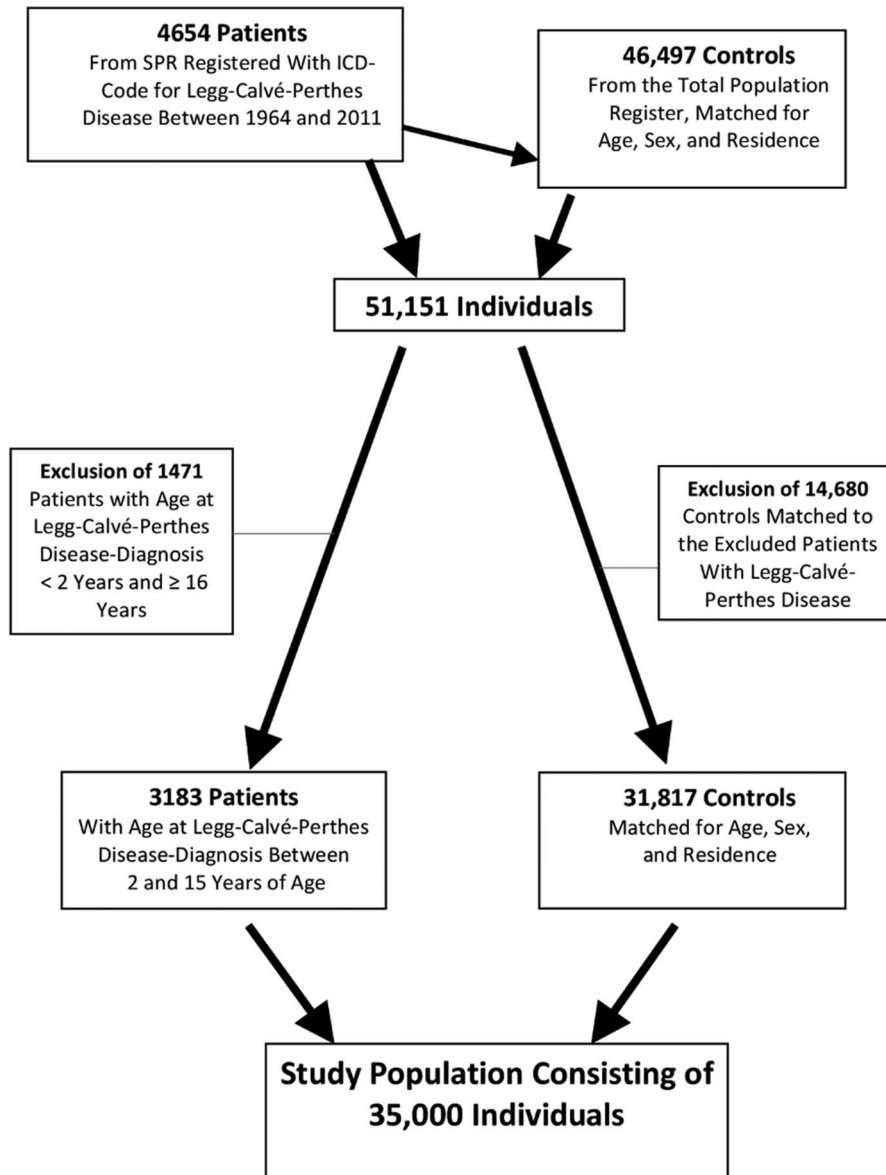
Fig. 1 This flowchart depicts the selection of the study population.

Calvé-Perthes disease than in control subjects (3.11% [99 of 3183] versus 0.31% [100 of 31,817]; adjusted RR, 10.3; 95% CI, 7.7-13.6; p < 0.001) (Table 2). When models estimating the risk of other osteochondroses than Legg-Calvé-Perthes disease developing were stratified by sex, we attained similar adjusted risk ratios for females (RR, 12.5; 95% CI, 6.1-25.8; p < 0.001) as for males (RR, 9.9; 95% CI, 7.3-13.5; p < 0.001) (Table 3). The mean age of patients with Legg-Calvé-Perthes disease affected by secondary osteochondroses was 7.5 years, and 83% were males. Osteochondrosis-free survival was inferior for patients with Legg-Calvé-Perthes disease compared with control subjects (96.8%; 95% CI, 96.1-97.4 at 20 years

versus 99.7%; 95% CI, 99.6-99.8; p < 0.001) (Fig. 2). The risk of having Scheuermann's disease develop was markedly increased for patients with Legg-Calvé-Perthes disease (RR, 222.8; 95% CI, 84.0-736.6; p < 0.001). In sensitivity analysis, patients diagnosed with Scheuermann's disease were excluded from the analysis, but the adjusted risk of being affected by osteochondroses other than the hip but excluding Scheuermann's disease was still higher for patients with Legg-Calvé-Perthes disease compared with control subjects (RR, 4.5; 95% CI, 3.1-6.4; p < 0.001). In all but five patients with Legg-Calvé-Perthes disease, the additional osteochondrosis was diagnosed subsequent to the Legg-Calvé-Perthes disease (Fig. 3A-B).

Table 1. Age of diagnosis of Legg-Calvé-Perthes disease and associated disorders

Disease	Number of patients	Mean age at diagnosis (years; range)
Legg-Calvé-Perthes disease	3183	7.4 (2.0-16.0)
Panner's disease	2	13.8 (13.7-14.0)
Scheuermann's kyphosis	49	8 (2.8-21.1)
Blount's disease	1	8.5 (8.5-8.5)
Sinding-Larsen-Johansson syndrome	2	12.8 (12.1-13.4)
Osgood-Schlatter's disease	51	14.2 (5.8-39.2)
Sever's disease	7	10.8 (8.5-12.4)
Köhler's disease	18	14.1 (5.2-42.3)
Osteochondritis dissecans	71	18.1 (4.9-44.2)
Obesity	184	21.1 (0.4-54.8)
Hypothyroidism	152	21.1 (0-49.4)

The mean delay between Legg-Calvé-Perthes disease and any other osteochondrosis was 3.2 years.

Risk of Obesity and Hypothyroidism Among Patients With Legg-Calvé-Perthes Disease

Patients with Legg-Calvé-Perthes disease were more likely to be obese according to the WHO criteria with a BMI ≥ 30 kg/m^2 than were control subjects (1.3% [40 of 3183] versus 0.5% [144 of 31,817], adjusted RR, 2.8 [95% CI, 1.9-4.0]; $p < 0.001$). Likewise, hypothyroidism was more common among patients with Legg-Calvé-Perthes disease than among control subjects (1% [31 of 3183] versus 0.4% [121 of 31,817], adjusted RR, 2.6 [95% CI, 1.7-3.8]; $p < 0.001$). The mean delay between the diagnosis of Legg-Calvé-Perthes disease and a diagnosis of obesity was 10.4 years, and a mean of 8.5 years elapsed between the diagnosis of Legg-Calvé-Perthes disease and a diagnosis of hypothyroidism.

Discussion

With approximately one per 10,000 children [17], Legg-Calvé-Perthes disease is relatively common, and the condition is associated with severe morbidity; it often requires surgery either to minimize the deformation of the femoral head [20] in childhood or to manage the sequelae of the disease in adulthood [52]. In addition, Legg-Calvé-Perthes disease leads to long-term impairment of physical function and quality of life [9]. There is no causal therapy. In pathophysiological terms, Legg-Calvé-Perthes disease is osteochondrosis of the femoral head, and a systemic etiology has been both suggested [11, 43] and contested [4, 26]. The interpretation of Legg-Calvé-Perthes disease as the local manifestation of a systemic disorder might change our way of diagnosing and treating this condition, but there is currently little evidence to strengthen this view. We therefore hypothesized that if systemic factors were causative for the development of Legg-Calvé-Perthes disease, additional osteochondroses in other locations than the hip and the increased occurrence of metabolic comorbidities should be expected in patients with Legg-Calvé-Perthes disease when compared with individuals not affected by this condition. Thus, we took advantage of the nationwide, population-based Swedish Patient Registry and analyzed the prevalence of osteochondroses and metabolic comorbidities in patients with Legg-Calvé-Perthes disease and matched control individuals from the general population. Briefly, we found that patients with Legg-Calvé-Perthes disease were more

Table 2. Prevalence and adjusted relative risk of osteochondroses and metabolic disorders developing

Disorder	Control (N = 31,817) Number	Percent	LCPD (N = 3183) Number	Percent	RR	95% CI	p value
Any osteochondrosis	100	0.31	99	3.11	10.3	7.7-13.6	< 0.001
Scheuermann's kyphosis	5	0.02	44	1.38	222.8	84-736.6	< 0.001
Osgood-Schlatter's disease	37	0.12	14	0.44	3.8	2-6.9	< 0.001
Köhler's disease	15	0.05	3	0.09	2	0.5-6.1	0.27
Osteochondritis dissecans	43	0.14	28	0.88	3.5	1.9-6.2	< 0.001
Obesity	144	0.45	40	1.26	2.8	1.9-4	< 0.001
Hypothyroidism	121	0.38	31	0.97	2.6	1.7-3.8	< 0.001

*Adjustment for sex and year of birth; RR = relative risk of patients compared with control subjects; LCPD = Legg-Calvé-Perthes disease; CI = confidence interval.

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Table 3. Sex-stratified adjusted relative risk of osteochondrosis and associated disorders developing in patients relative to control subjects

Sex-stratified adjusted* risk	RR	95% CI	p value
Females			
Osteochondrosis	12.5	6.1-26	< 0.001
Obesity	2.6	1.3-4.6	0.003
Hypothyroidism	1.3	0.6-2.7	0.44
Males			
Osteochondrosis	9.9	7.3-14	< 0.001
Obesity	3	1.9-4.5	< 0.001
Hypothyroidism	3.8	2.3-6	< 0.001

*Adjustment for sex and year of birth; RR = relative risk; CI = confidence interval.

likely to have other osteochondroses and to develop obesity and hypothyroidism, indicating that Legg-Calvé-Perthes disease is indeed a more complex, systemic disorder than previously recognized.

This study has some limitations. We must be aware that changes in diagnosing and coding practice from 1964 until 2011 have undoubtedly occurred. Although the Swedish Patient Register only reached 100% completeness of reporting diagnoses in 1987, the underreporting for in-patient data has currently been estimated to be < 1% [34, 35]. It seems unlikely that this would have introduced a serious selection bias, because patients with Legg-Calvé-Perthes disease and control subjects would probably be affected by failure to register any of the outcomes relevant to this study to a similar extent.

Furthermore, incomplete registration of conservatively treated Legg-Calvé-Perthes disease and other osteochondroses has a considerable influence on the number of registered patients with the investigated diagnoses. Legg-Calvé-Perthes disease and—even more so—many other osteochondroses may be managed on an outpatient basis, but until 2001, only diagnoses based on inpatient hospital episodes were registered in the Swedish Patient Register. As a result, an unknown number of patients with Legg-Calvé-Perthes disease or other osteochondroses who were
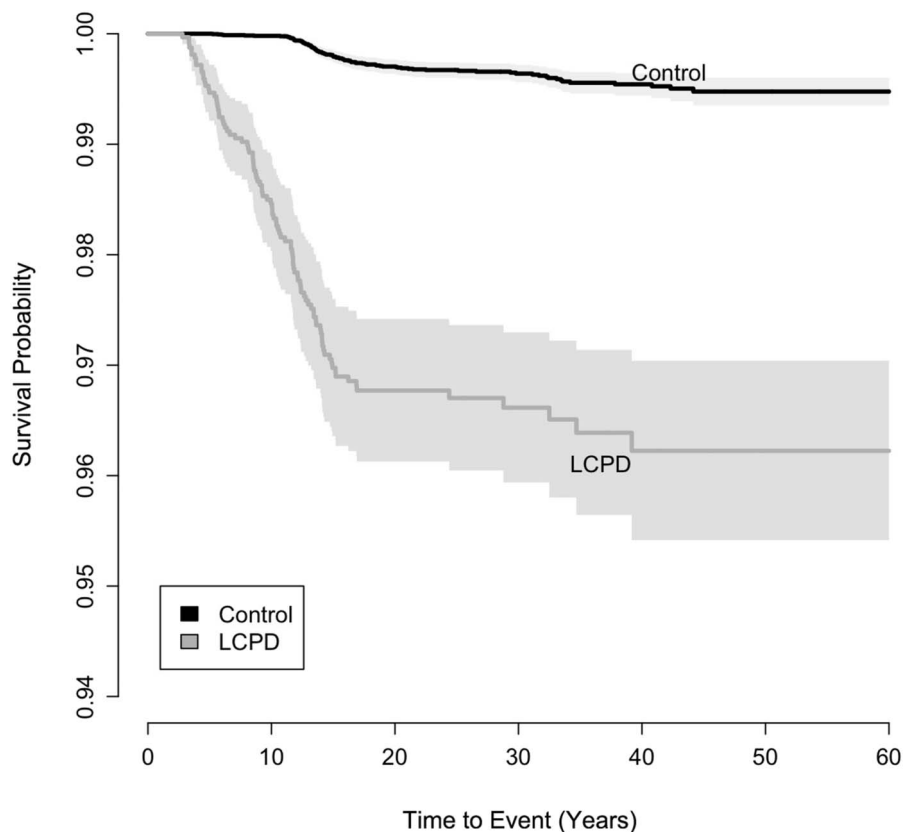

Fig. 2 This graph shows osteochondrosis-free survival (based on Kaplan-Meier estimates) for patients with Legg-Calvé-Perthes disease (LCPD) and control subjects. Error bars denote 95% CIs around estimated survival functions. The survival estimates were statistically significantly different (p < 0.001).
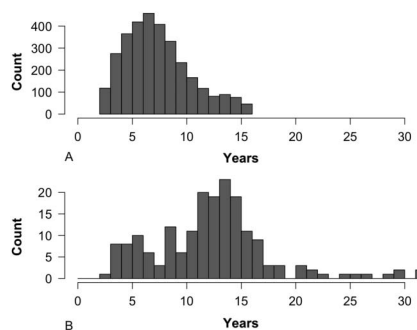
Fig. 3A-B These histograms show the distribution of the age at diagnosis of (**A**) Legg-Calvé-Perthes disease or (**B**) other osteochondroses.

treated on an outpatient basis before 2001 may have been missed. Stratified analyses performed on the time periods before and after 2001 and additional analyses stratified by the different ICD coding periods did not however result in notably different risk estimates (data not shown).

A drawback to this study is the lack of socioeconomic background variables, a confounder that generally is considered to be important in studies regarding Legg-Calvé-Perthes disease. Social deprivation has repeatedly been found to be associated with Legg-Calvé-Perthes disease [18, 40, 42, 49], but, conversely, the adjustment for education levels and family income in analyses on Swedish populations with Legg-Calvé-Perthes disease did not result in considerably changed risk estimates when compared with unadjusted analyses [11]. Thus, there is reason to believe that adjustment for socioeconomic background would not have substantially altered our conclusions.

Another concern is detection bias, because patients with Legg-Calvé-Perthes disease have established repeated contacts with healthcare providers and might be more prone to be diagnosed with other diseases than Legg-Calvé-Perthes disease. This might especially apply to the osteochondroses that are primarily diagnosed by orthopaedic surgeons and that might have been more easily diagnosed in patients with Legg-Calvé-Perthes disease who were under the surveillance of an orthopaedic surgeon. In contrast, metabolic diseases are normally diagnosed by other specialists than orthopaedic surgeons, and metabolic conditions should thus have been detected similarly in patients with Legg-Calvé-Perthes disease and control subjects. Selection bias is also a source of error, because some patients with atypical manifestations may not have been coded as having Legg-Calvé-Perthes disease, but having related hip disorders, thereby selecting patients with more severe Legg-Calvé-Perthes disease to our study population. The same applies to our outcome measures, in which patients with more severe conditions may have been coded as having the specific disease,

whereas less typical or subclinical manifestations may not have resulted in the diagnosis code of interest.

Risk of Osteochondroses Among Patients With Legg-Calvé-Perthes Disease

Our findings indicate that patients with Legg-Calvé-Perthes disease have a substantially increased prevalence of the secondary osteochondroses Blount's, Osgood-Schlatter's, Köhler-Freiberg's, Panner's, and Scheuermann's disease; Sinding-Larsson-Johansson's syndrome; and osteochondritis dissecans. Although the common occurrence of Legg-Calvé-Perthes disease and osteochondroses in locations other than the hip is rare, the association of Legg-Calvé-Perthes disease with subsequent osteochondroses indicates that a common pathophysiologic pathway may underlie the multilocular manifestation of osteochondroses. The scarcity of reports on this topic in the literature may be the result of the fact that the RR of having subsequent osteochondroses develop after Legg-Calvé-Perthes disease may be high, but the absolute number of individuals affected by both conditions is low, like in our cohort. Possibly, patients with multilocular osteochondroses such as those reported here have been categorized as having multiple epiphyseal dysplasia or spondyloepiphyseal dysplasia, but the clinical and radiographic findings in those dysplasias are usually characteristic and distinct from osteochondroses.

One could argue that Scheuermann's disease of the spine does not belong to the group of classic osteochondroses, but rather should be classified as a degenerative disease with herniations of the nucleus pulposus in the vertebral bodies attributable to mechanical stress as the main pathologic landmark [15, 16, 27, 48]. We thus conducted a sensitivity analysis and excluded Scheuermann's disease as an endpoint, only considering the other osteochondroses as relevant endpoints. The risk of having secondary osteochondroses develop was still elevated for patients with Legg-Calvé-Perthes disease when compared with control subjects, but the risk increase was considerably smaller than the estimates we attained in the main analyses including Scheuermann's disease.

The mean age of patients at diagnosis of Legg-Calvé-Perthes disease was 7.4 years in our cohort, which is consistent with a previous report [44]. In all but five patients, the age at diagnosis of other osteochondroses was consistently higher, indicating that Legg-Calvé-Perthes disease was the primary manifestation and that other osteochondroses were subsequent, secondary events. We cannot rule out that intrauterine exposure is involved in the pathogenesis of Legg-Calvé-Perthes disease, and it seems likely that genetically determined molecular and cellular disturbances cause osteochondroses. Perry et al. [43] found

the caliber of arterial vessels was smaller in 149 children with Legg-Calvé-Perthes disease when compared with 146 children without the disease. Furthermore, derangement in the coagulation cascade such as Factor V Leiden mutations and decreased levels of proteins C and S have long been suspected of playing a major role in the pathophysiology of Legg-Calvé-Perthes disease [1, 3, 7, 24], and altered blood flow also could explain the association we observed. The association of specific genes with the occurrence of Legg-Calvé-Perthes disease has shown evidence for mutations in genes encoding for proteins that are part of the coagulation cascade such as the previously mentioned Factor V Leiden mutation in patients with Legg-Calvé-Perthes disease [55]. Increased expression levels of proapoptotic factors such as Bax also have been described in a cohort of patients with Legg-Calvé-Perthes disease [50], and endothelial nitric oxide synthase polymorphisms are more frequent in patients with this disease than in control subjects [56]. Although specific genes are implicated in the pathogenesis of Legg-Calvé-Perthes disease, heritability of the disease has been questioned. A recent Danish study of mono- and dizygotic twins provided strong evidence against a genetic etiology [31], although that study was relatively small and the findings need to be replicated. Taken together, although the proportion of additive genetic effects may not be very high in Legg-Calvé-Perthes disease, the available molecular evidence indicates that numerous genes involved in the coagulation cascade or in regulation of apoptosis and inflammation are associated with the development of Legg-Calvé-Perthes disease [2, 8, 9, 12, 25].

Risk of Obesity and Hypothyroidism Among Patients With Legg-Calvé-Perthes Disease

A potential systemic involvement seems plausible given the increased risk for having obesity and hypothyroidism develop in patients with Legg-Calvé-Perthes disease compared with control subjects. Perhaps because children with Legg-Calvé-Perthes disease are often underweight at the time of disease onset, the prevalence of obesity in patients with Legg-Calvé-Perthes disease has not been extensively investigated. A possible explanation for the association of obesity with Legg-Calvé-Perthes disease found in our study is that obesity in patients with this disease may have been related to physical inactivity that in turn was a consequence of hip pain. However, a retrospective report on 150 patients with Legg-Calvé-Perthes disease indicates that 48% of these patients are either overweight or obese [36], and free leptin levels are higher in patients than in matched control subjects [23], indicating that there actually is an association between both diseases on a molecular level. Findings on thyroid dysfunction in patients with Legg-Calvé-Perthes disease are conflicting.

Although we found an association of Legg-Calvé-Perthes disease with hypothyroidism, a previous study describes elevated levels of free thyroxin in patients with Legg-Calvé-Perthes disease compared with control subjects [37]. In contrast, another study found no differences in concentrations of thyroid-stimulating hormone and free thyroxin between patients with Legg-Calvé-Perthes disease and control subjects [18]. The protein insulin growth factor-1 is reduced in patients with Legg-Calvé-Perthes disease, and this coincides with retarded skeletal maturation [30]. Thus, general metabolic dysfunction in patients with Legg-Calvé-Perthes disease seems plausible, but causal relationships remain to be elucidated.

The co-occurrence of Legg-Calvé-Perthes disease and osteochondroses at other locations than the hip is rare, but our analysis strengthens the notion that Legg-Calvé-Perthes disease and osteochondroses of the juvenile and adolescent skeleton may be multiple manifestations of a systemic disease. For the orthopaedic surgeon and the pediatrician alike, it is important to be aware that patients with Legg-Calvé-Perthes disease can have additional osteochondroses, obesity, or hypothyroidism develop later. If patients report pain at other locations than the hip, radiographs should be considered to detect such secondary osteochondroses. Perhaps body weight and thyroid function should also be more closely monitored in these patients to detect and possibly prevent secondary metabolic disorders. However, before such general recommendations can be given, a stringent cost-benefit analysis would have to be performed, investigating numbers of patients needed to screen to detect secondary osteochondroses, obesity, or hypothyroidism. In conclusion, Legg-Calvé-Perthes disease seems not to be an isolated joint disease but a systemic condition, and further research on Legg-Calvé-Perthes disease may benefit from this novel approach.

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