Systematic Reviews and Meta- and Pooled Analyses

Racial and Geographic Factors in the Incidence of Legg-Calvé-Perthes’ Disease: A Systematic Review

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Legg-Calvé-Perthes’ disease (Perthes’ disease) is a childhood osteonecrosis of the hip for which the disease determinants are poorly understood. In this review, the authors identify studies of Perthes’ disease incidence published up to December 2010 and make denominator populations comparable in order to allow meaningful between-study evaluation. Incidence rates and confidence intervals were determined, and, where appropriate, denominator populations were obtained from national statistical offices. Poisson regression was used to determine the influence of race and geography. The review included 21 studies that described 27 populations in 16 countries, with 124 million person-years of observation. The annual incidence among children under age 15 years ranged from 0.2 per 100,000 to 19.1 per 100,000. Race was a key determinant, with East Asians being least affected and whites most affected, though data were insufficient to consider incidence among blacks (for South Asians vs. East Asians, incidence rate ratio = 2.9, 95% confidence interval (CI): 2.4, 3.5; for whites vs. East Asians, incidence rate ratio = 8.8, 95% CI: 8.2, 9.6). Latitude was a strong predictor of disease, even after adjustment for race. Each 1° increase in latitude was associated with an incidence increase of 1.44 (95% CI: 1.30, 1.58) times. While much of the international variation appears to be a function of race, latitude demonstrates a strong association. This observation may offer new epidemiologic insights into the determinants of Perthes’ disease.

continental population groups; geography; incidence; Legg-Perthes disease; osteoarthritis; race

Abbreviations: CI, confidence interval; MOOSE, Meta-analysis of Observational Studies in Epidemiology.

Legg-Calvé-Perthes’ disease (Perthes’ disease) is an idiopathic osteonecrosis of the developing femoral head. The underlying mechanism of disease and the disease determinants are unknown. It occurs 5 times more commonly in boys than in girls. Within the United Kingdom, it typically arises between the ages of 4 and 8 years, although presentation occurs later in India (1).

A number of studies have examined the incidence of Perthes’ disease over the last 60 years. Drawing comparisons between descriptive studies and deriving meaningful conclusions is often difficult because of the heterogeneity of study methods. Therefore, differences in disease incidence may be real or may be an artifact resulting from differences in study design or the denominator populations used. Incorrect incidence rates are widely cited throughout the literature, based upon propagated confusion as to the most appropriate population denominator to use. Accurate awareness of the incidence of a disease according to time, place, and person is important in forming causal hypotheses.

Here we present findings from a systematic review of epidemiologic incidence studies of Perthes’ disease. We aimed to present the data in a manner that would allow for international comparisons to be made and allow for identification of characteristics that may account for observed differences.

MATERIALS AND METHODS

Our results are presented in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology)
guidelines (2). (The MOOSE checklist is available as a Web Appendix (http://aje.oxfordjournals.org/).)

Search strategy

To identify all relevant studies, we searched 3 medical databases (Medline, Scopus, and ISI Web of Knowledge) up to December 1, 2010. The keyword “Perthe*” was used together with “epidemiolog*,” “incidence,” or “population.” Both English- and non-English-language studies were included and were translated when required.

All titles and abstracts were screened by two of the authors (D. P. and D. M.) to identify studies that might have elicited data on the incidence of Perthes’ disease. If either author included the article or if the abstract was absent, the full paper was obtained. The reference lists of all full papers and all reviews of Perthes’ disease epidemiology identified through the above search strategy were additionally screened. Additional articles or published theses were obtained as required. Disagreements were resolved through discussion.

Figure 1 illustrates the results obtained at each stage of the search.
Racial and Geographic Factors in Perthes’ Disease

Study selection

Case definition. Perthes’ disease was defined as a radiographic diagnosis characterized by sclerosis, flattening, or fragmentation of the capital femoral epiphysis in the absence of local or systemic initiating pathology. There are no universally accepted or validated criteria for the diagnosis of Perthes’ disease; therefore, we accepted all cases as defined by the authors of the original manuscripts.

Inclusion criteria. For inclusion, a paper had to be a full-text article (including published theses) describing results from an original study of Perthes’ disease incidence that met the following criteria.

1. The study had a population-based design with a clearly defined source population.
2. The results included, or allowed calculation of, the overall incidence of Perthes’ disease.
3. The study population was representative of the population in general.
4. The upper age limit for case inclusion was less than 15 years.
5. Case-finding included the involvement of all hospitals in the region or a single provider of children’s orthopedic care that served the region.

Exclusion criteria. Articles were excluded under the following conditions.

1. The study was published only as an abstract.
2. There was evidence of incomplete case ascertainment.
3. The source population was unclear (e.g., the geographic boundary of the study area was poorly defined), preventing clear definition of the population denominator.

Data collection

From each individual study, we gathered the following information using a data extraction form: author, year of publication, period of case ascertainment, number of incident cases, population definition, population size, middle year of the study period, and location of study. The search strategy, study selection, and data extraction were performed independently by D. P. and D. M. If a single population was studied in 2 or more periods, the incidence rates identified for each study period were considered separately. If, in a single study, investigators had calculated incidence rates for different regions and each region had been considered entirely separately, then we similarly considered the incidence of Perthes’ disease separately within each region in this analysis. If the investigators had broken participants down into smaller subsets (i.e., defined by gender, region, or race), we considered the larger “all-encompassing” incidence rates primarily.

Additional population information

The widely used population denominator in studies of Perthes’ disease incidence is the population of children under 15 years of age. If incidence was expressed in a different form, if the investigators did not report incidence, or if the investigators failed to express the population denominator for a defined population frame, we sought data from the statistical office of the relevant country. We ensured that population denominators were appropriate to the study time period and geographic location. If the study period was unclear, we contacted the authors of the article for clarification.

Data analysis

For each of the selected studies, the overall incidence was verified or calculated as necessary. Ninety-five percent confidence intervals were calculated on the basis of the Poisson distribution using Stata 10.0 (StataCorp LP, College Station, Texas), and Poisson regression was used to examine trends. Incidence with respect to race and geography was analyzed. Geographic variation was assessed using the midpoint of the study region, and latitude was established with Google Maps (Google, Inc., Mountain View, California) using a JavaScript command. The forest plot was drawn using StatsDirect (StatsDirect Ltd., Altrincham, United Kingdom).

RESULTS

From a total of 675 electronic “hits,” we read 47 papers in full and selected 21 studies for inclusion. (Web Table 1 contains details on the studies excluded.) Of these 21 studies, 10 lacked sufficient detail within the published article to calculate incidence rates (per 100,000 children aged <15 years) and/or corresponding Poisson confidence intervals. For each of these 10 studies, we contacted the appropriate national statistical office to obtain relevant population denominators, carefully considering study population boundaries and the period of investigation. We were unable to determine the study period for 1 study.

The review encompassed 124 million child-years at risk, and the time period ranged from 1964 to 2009. Studies arose from Asia, Africa, Europe, and North America, with the majority (12/21 studies) coming from Northern Europe (Nordic countries and the United Kingdom). Only 1 study originated within the Southern Hemisphere (3).

Incidence rates

Incidence rates varied considerably between studies, ranging from 0.2 per 100,000 children aged <15 years to 19.1 per 100,000. Table 1 outlines the studies’ findings in order of year of publication. These data are illustrated graphically in Figure 2. Incidence rates appeared to be higher at greater latitudes, as demonstrated in Figure 3.

Overall there was a strong association between latitude and incidence; however, racial group may clearly have confounded this relation. To adjust for race, we considered American and European studies in isolation and also accounted for race within the regression model. Race was defined according to the principal ethnic group within each geographic region and divided into the broad categories of white, South Asian, and East Asian. There were no studies that identified Perthes’ disease among children from a predominantly black population. The South African study was not considered within this analysis, owing to the large racial mix within that study population (3).
Overall, for every 10° increase in latitude, the incidence of Perthes’ disease increased by a factor of 2.35 (95% confidence interval (CI): 2.27, 2.43) (Table 2). This remained significant when European and American studies were considered in isolation, although the effect size was smaller at 1.36 (95% CI: 1.22, 1.52).

The unadjusted incidence rate ratio from predominantly white regions was 8.8 times greater than that in East Asian regions (referent), whereas the incidence in South Asian regions was 2.9 times greater. Despite adjustment for race, latitude remained a significant factor within the model.

DISCUSSION

To our knowledge, this was the first systematic review to examine incidence studies of Perthes’ disease. The results

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demonstrated marked differences in disease frequency throughout the world, varying by almost 100 times between studies. Much of the research had a strong Northern European focus, which is perhaps unsurprising given the high occurrence of the disease in this region. The case numbers and denominator population sizes varied considerably, and it is therefore important to consider the size of the confidence intervals in order to make meaningful comparisons between studies.

Factors to consider when reviewing studies of Perthes’ disease

When reviewing studies of Perthes’ disease incidence, the following factors need to be considered.

Case ascertainment. All of the studies published to date, with the exception of one (4), drew cases from a hospital setting. The general assumption is that persons with Perthes’ disease will go to a hospital or be referred to a hospital for care. It may be the case that some persons within the sampling frame were unknowingly managed at a different institution than the recruiting hospital and hence were not recorded within the numerator population. Variations in health-care systems, health-care-seeking behaviors, and population dynamics will all influence individual visits to health-care providers and consequently affect the amount of disease detected. Therefore, all studies of incidence should be considered studies of “minimal incidence,” with improvements in case ascertainment being possible through community case ascertainment.
Case definition. A basic premise of epidemiologic research is that the case definition of a disease is clear, consistent, and reproducible. Perthes’ disease is a radiologic diagnosis which progresses through stages of sclerosis, fragmentation, and remodeling. While the radiologic features of the disease are clear, there may be some confusion with other causes of avascular necrosis of the developing femoral head (i.e., following treatment for developmental dysplasia of the hip or following chemotherapy) or the appearance of other skeletal dysplasias. In the majority of studies, investigators go to great lengths to exclude such persons, thereby minimizing misclassification of disease. Despite this, there is some degree of inconsistency between studies concerning exclusion criteria, which may have some influence on incidence rates.

Clarity of study population. A prerequisite of a study of incidence is that the denominator population is clearly defined. This review considered only studies where clear geographic boundaries existed, with collaboration from all providers of orthopedic care within each region, or studies of databases, which are able to effectively provide the same clear population denominator for the number of cases identified. A greater propensity to travel in the modern world is increasingly encroaching on investigators’ ability to ensure a defined study population. In time, database studies of primary care and national data collection from all health-care providers may be the only valid ways to quantify disease incidence.

Principal study outcomes

The results of this analysis confirm some of the notions previously suggested regarding Perthes’ disease and highlight new trends in Perthes’ disease that have not previously been discussed.

Race. Race was the most important factor influencing international disease occurrence identified by this study. It is unclear whether the additional risk associated with race is a function of a genetic predisposition or a dietary or lifestyle influence.

To date, 2 studies have directly analyzed people of different races living in the same place (3, 5). The most significant of these investigated Perthes’ disease incidence in South Africa. That study demonstrated that black persons were least affected by Perthes’ disease (0.5 cases (95% CI: 0.2, 1.0) per 100,000 children aged <15 years), mixed-race persons were moderately affected (1.7 cases (95% CI: 0.9, 3.1) per 100,000 children aged <15 years), and white persons had the highest disease frequency (8.8 cases (95% CI: 7.6, 14.8) per 100,000 children aged <15 years) (3). While the investigator went to great lengths to appropriately identify

Figure 3. Relation between Perthes’ disease incidence and latitude in a systematic review, 1964–2009.

Table 2. Incidence Rate Ratio for Perthes’ Disease According to Latitude and Race, 1964–2009

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<td>East Asian</td>
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<td>South Asian</td>
<td>2.88 2.37, 3.50</td>
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<td>White</td>
<td>8.85 8.16, 9.59</td>
<td>4.33 3.52, 5.32</td>
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Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

* Adjusted for latitude and race.

b IRR for an increase of 10° North in latitude from the equator.
Perthes’ disease cases, the population dynamics in the study region must be considered. The study was conducted in South Africa during the period of apartheid; hence, access to health-care services may have differed between racial groups, with the potential for disease detection to be affected by race. The second study was carried out in Bradford, United Kingdom, and suggested higher rates of Perthes’ disease among white persons than among South Asians (5). However, case ascertainment in that study was almost certainly incomplete, given that all patients, irrespective of race, were unusually old (all were over 5 years of age).

In other studies of incidence, investigators have commented on a paucity of blacks and Asians among the study groups. Studies of Perthes’ disease in areas with significant black populations have identified few cases of disease; in New York City, there were 14 black children among 358 cases (6), and in Connecticut, there were 2 black children among 203 cases (7). However, such studies are without clear population boundaries and denominators, such that incidence rates cannot be quantified. To our knowledge, there have been no other studies of Perthes’ disease incidence among black people sufficient to make comparisons with international data; this is perhaps a reflection of the rarity of the disease. In order to address issues of genetic predisposition, diet, and lifestyle, future investigators should attempt to identify disease rates among first- and second-generation black and Asian persons living in Europe and North America, or among migrants from low-incidence regions living in high-incidence regions.

**Latitude.** Even after adjustment for race, the latitude of the study region has a significant influence on the rate of disease occurrence. An association with latitude has not previously been demonstrated for Perthes’ disease, though a number of other diseases are thought to be associated with latitude. Multiple sclerosis is perhaps the most widely recognized disease to be associated with latitude; a large cohort study suggested that women born north of 41°–42° North latitude have a risk of multiple sclerosis 3.5 times greater than those born south of 37° North latitude (8), though more recent studies have suggested a less pronounced association (9). Other diseases, such as ischemic heart disease and osteoporosis, have similarly been associated with latitude (10). Commonly suggested mechanisms include exposure to infectious agents and vitamin D deficiency owing to inadequate sunlight exposure.

While our results demonstrate a strong association with latitude, the influence of race appears to have attenuated this effect. While this may offer clues as to etiologic determinants, caution must prevail in interpreting such ecologic analyses, since 1) a proposed mechanism in Perthes’ disease is unclear, 2) there is notable variation in the time periods in which studies were performed, and 3) findings may simply be the result of unmeasured confounding or chance. The relevant components of latitude contributing to this finding are unclear; yet variations in climate (i.e., hours of sunlight exposure) may be one etiologic possibility. Studies of Perthes’ disease incidence in the Southern Hemisphere would be helpful in order to assess whether the same trend exists as in the Northern Hemisphere.

Potential confounding factors include socioeconomic deprivation. This review demonstrated high disease incidence in wealthy Northern European countries and the United States, as compared with poorer equatorial regions. Thus, the socioeconomic gradient is opposite that in the published literature, which shows a positive relation between increasing deprivation and Perthes’ disease incidence at both the area (11, 12) and the individual (13) levels. It might therefore be argued that access to health care may explain the observed effect, since health-care access is greater in Northern Europe and the United States and all studies except one (4) used hospital populations to define “cases.” However, the study from India (1) was validated by an accompanying community prevalence study of 16,838 schoolchildren that yielded an incidence estimate similar to that of the hospital incidence study, and recent evidence from Japan, a wealthy country with a universal health-care system, demonstrated a low incidence of Perthes’ disease (14). This suggests that the incidence gradient observed is independent of bias caused by access to health care.

Studies of disease incidence are the keystone of epidemiology and provide a springboard for further research. A century after its description, Perthes’ disease remains a poorly understood disease in need of some epidemiologic attention.

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