A Century of Perthes' Disease:

Unraveling the Enigma

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Abstract

2010 marked a century since three independent observers (A. Legg, J. Calve and G. Perthes) described a syndrome of hip pain and restriction in children, with a corresponding radiographic collapse of the femoral head[1-3]. The aetiological determinants were uncertain and the disease mechanism was unclear. Little progress was made in understanding this disease until over half a century later (1965), when Holdsworth delivered an insightful 'Robert Jones Lecture' that shed new light on the disease mechanism[4]. Holdsworth's experiments, on the proximal femurs of immature rabbits, demonstrated Perthes' disease-like changes to the femoral head in response to occlusion of the arteries around the femoral neck which offered new mechanistic insights into the disease. From this point on, little has advanced in understanding the origins of this disease. The consensus of opinion continues to support a vascular disease mechanism, though the precipitants of a vascular infarct in a well child remain as mysterious as ever.

In recent years advances in medicine and technology have reinvented the way in which diseases are investigated, and has led to the development of new concepts relating to genes, the environment and their interactions. One of the cornerstones in understanding any disease process is an appreciation of the epidemiology, which may reveal characteristic population-level clues to causation. Like all basic sciences, epidemiology has been modernised in recent years with the use of computerised disease registries, national patient databases and more readily accessible international population data. Are these new sources of data able to offer fresh understanding into the aetiology of Perthes' disease?

This essay is structured to firstly provide an overarching background of Perthes' disease, in order to outline the historic context, disease burden and pathological theories. It then reviews a series of recent descriptive epidemiological studies, and uses these to synthesise ideas in the quest to solve this puzzling disease.

Section A: History, Biology and Theories

1. History

Hugh Owen Thomas, a Liverpool surgeon and the pioneer of orthopaedic surgery, wrote in 1876 of an obscure condition affecting children's hips that spontaneously occurred and spontaneously recovered; albeit sometimes with deformity[5]. Wilhelm Röntgen's discovery of x-rays in 1895 offered new opportunities to investigate this phenomenon. In 1909 Waldenstrom published a description of seven children with hip pain, all with similar radiographic features characterised by flattening of the femoral head[6]. He believed that this was caused by a benign form of tuberculosis that interfered with the blood supply to the proximal femur.

A year later, three independent observers Arthur T Legg (Boston, USA), Jacques Calvé (Berck, France) and Georg C Perthes (Tübigen, Germany)[1-3] recognised that this disease was not tuberculosis. In 1913 Georg Perthes wrote the classic monograph describing the disease as a *"a self limiting, non inflammatory condition, affecting the capital femoral epiphysis with stages of degeneration and regeneration, leading to a restoration of the bone nucleus"*[7].

The disease has subsequently had many names. Some are based upon radiological descriptions such as coxa plana, osteochondritis of the femoral head or arthritis deformans juvenilis. Others are based on the pathological description, such as idiopathic osteonecrosis of the femoral epiphysis. However, more commonly it is known by the individuals who described it, such as Legg-Calvé-Perthes' disease, Legg-Perthes' disease or Legg-Calvé disease. However, it is most commonly known simply as 'Perthes' disease'.

2. Clinical Aspects of the Perthes' Disease

2.1 Clinical Presentation, Differential Diagnosis & Investigation

Perthes' disease typically presents in the same manner as any 'irritable hip in the child', with a limp, or pain in the groin, thigh or knee. The symptoms usually occur insidiously; however sometimes there is a history of trivial injury. Careful clinical assessment must therefore be undertaken to correctly identify the source of the pathology, and initiate appropriate investigation.

Differential Diagnosis of Irritable Hip:

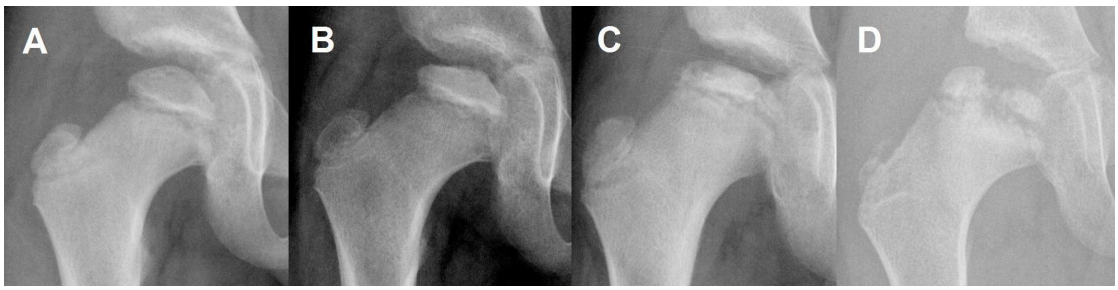
- Transient Synovitis (Most common)
- Septic Arthritis
- Perthes' Disease
- Slipped Capital Femoral Epiphysis
- Juvenile Idiopathic Arthritis

2.2 Radiological Appearance

The diagnosis of Perthes' disease is usually made from plain radiographs, though very early disease may only be detected by additional imaging, such as magnetic resonance imaging or technetium labeled radionucleotide bone scans. Once established the disease radiologically progresses through four stages over a 2 to 3 year period (Figure 1)[8].

These radiographic appearances are similar for a number of hip diseases, and careful clinical and radiological consideration must be given to alternative diagnoses. Such diagnoses include bony dysplasias, hypothyroidism, sickle cell disease, other haemoglobinopathies and lysosomal storage diseases.

Figure 1 – Waldenstrom's radiological Stages of Perthes' Disease



A - Early Stage

The early stage of disease is subtle. The only abnormality is that the joint space is widened compared to the contralateral side (Waldenstrom's Sign).

B- Sclerotic Stage

The architecture of the femoral head is disrupted and the shape begins to alter. Radiologically this is seen as increased density (sclerosis), flattening and a loss of height of the epiphysis.

C - Fragmentation Stage

The epiphysis begins to break up (fragment).

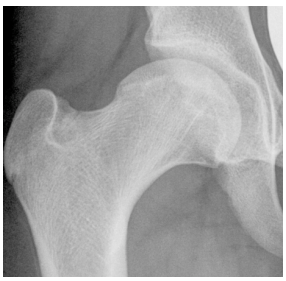
D - Healing (Late) Stage

New bone begins becomes evident after the sclerotic bone has been removed. The central portion of the epiphysis is the last to re-ossify, which is seen as a central lucency on the anteroposterior radiograph.

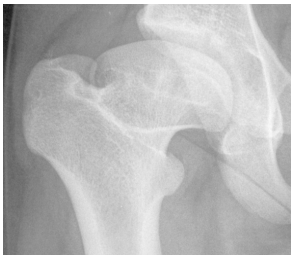
2.3 Clinical Importance of Perthes' Disease

Once established, Perthes' disease weakens the structural integrity of the bone and results in damage to the architecture of the hip. When radiographs demonstrate fragmentation of the epiphysis, the pathological appearance is that of unossified cartilage. This cartilage is malleable and the shape is heavily influenced by external forces across the joint. This can result in the hip becoming flattened (coxa plana) or misshapen. At the point of re-ossification (late stage) the shape of the epiphysis again becomes fixed, such that external forces may not influence it[9].

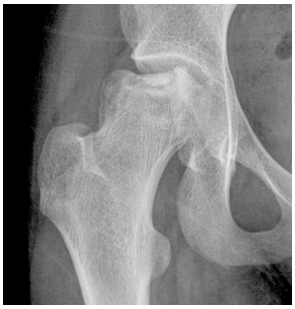
There are broadly three radiographic outcomes following Perthes' disease (Figure 2). These give an indication of long-term prognosis, based upon the shape of the hip after re-ossification[10].



SPHERICAL & CONGRUENT - A head that is spherical within a reciprocal acetabulum. These show no propensity to premature degeneration.



ASPERICAL AND CONGRUENT - A head that is aspherical, often ovoid in shape, within an acetabulum that has grown to match the shape of the femoral head. Such hips do degenerate prematurely, but usually after middle adult life.



ASPHERICAL AND INCONGRUENT - A head that is aspherical and flattened, but the acetabulum remains round and is incongruent with a shape mismatch. Such hips degenerate prematurely, often before middle adult life.

Figure 2 - Radiographic outcomes following Perthes' disease.

2.4 Treatment

An in-depth discussion of the nature and intricacies of the treatment options are beyond the scope of this essay. A broad overview of treatment is illustrated for completeness, in order to emphasise the burden of disease on the individual, their family, and the costs to society.

The treatment concept in Perthes' disease is to minimise or control the external forces across the joint. How best to control the forces is the source of much controversy, though a number of techniques are recognised.

Non-Weight Bearing

This was the earliest form of treatment for Perthes' disease. The belief was that by restricting load bearing, the forces across the hip were lessened, therefore minimising any resulting deformity. Crutches and callipers were therefore used, however biomechanical studies demonstrated that such treatments had very little influence on the muscular forces across the hip, and any benefit was probably achieved by slowing the walking pace[11]. Adequate treatment by non-weight bearing therefore necessitated prolonged recumbence. This was practiced for many years, often with hospital admission and bed rest for in excess of 2 years. This traditionally took place in former 'tuberculosis hospitals', built in the countryside allowing access to "fresh air" (Figure 3). This approach has now largely been abandoned due to the impracticalities of treatment, and the significant burden and costs to the individual, the family and society.

Figure 3 – Children with Perthes' disease circa 1944.

(From the Marguerite Hepton Orthopaedic Hospital, Thorp Arch, near Leeds, UK. Photograph printed with the kind permission of Mr. T Swift of Townville, West Yorkshire. Mr. Swift is seen in the seventh bed along in this photograph. His treatment consisted of 3 years of bed-rest, and "plenty of fresh air".)

The Theory of 'Containment'

'Containment' embraces the vulnerability of the malleable epiphysis by directing it into the fixed hemispherical shape of the acetabulum - like jelly poured into a mould.

The following forms of containment are currently used:

- Abduction Bracing.

Good early results were reported using bilateral cylinder plaster casts linked by broomstick – a 'Petrie cast'[12]. The aim was to abduct the hips, directing the femoral head into the dished acetabulum. These casts prevented mobility, and were required for 2 to 3 years making prolonged treatment similarly unacceptable in modern society. Newer braces were therefore developed which would allow mobility whilst maintaining abduction. Such braces appear less efficacious than newer surgical methods[13] and therefore there is an increasing tendency towards operative containment.

- Femoral Osteotomy.

Probably the most common form of operative treatment for Perthes' disease is a femoral varus osteotomy. This redirects the head of the femur to face directly into the acetabulum (Figure 4). This is normally achieved with an intertrochanteric osteotomy fixed with varus angulation. Children are kept immobilised in plaster for around 6 weeks, and then allowed to mobilise freely.

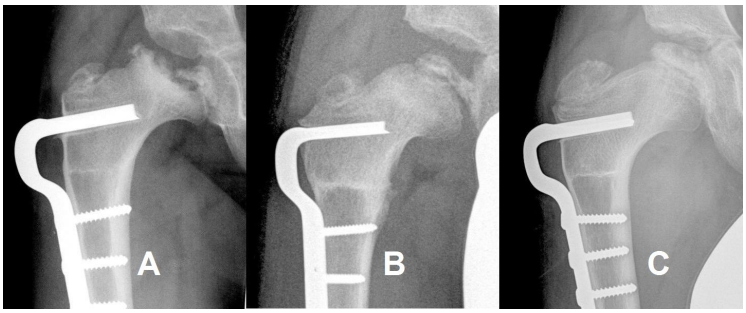


Figure 4 – Radiographs of a femoral varus osteotomy.

(The images demonstrate progressive healing of Perthes' disease following a varus osteotomy with 10 to 15 degrees of varus angulation. The stages of healing demonstrated are fragmentation (A), re-ossification (B) and remodeling (C). The resulting hip appears spherical and congruent.

- Pelvic Osteotomy.

The Shelf osteotomy is a form of acetabular augmentation that extends the acetabular roof to cover the uncovered anterolateral femoral epiphysis (Figure 5). The augmented roof therefore 'moulds' the femoral epiphysis. Shelf osteotomies are less frequently used, but have gained popularity in recent years with some promising results[14-16]. Children are permitted to mobilise on crutches within days of the operation.

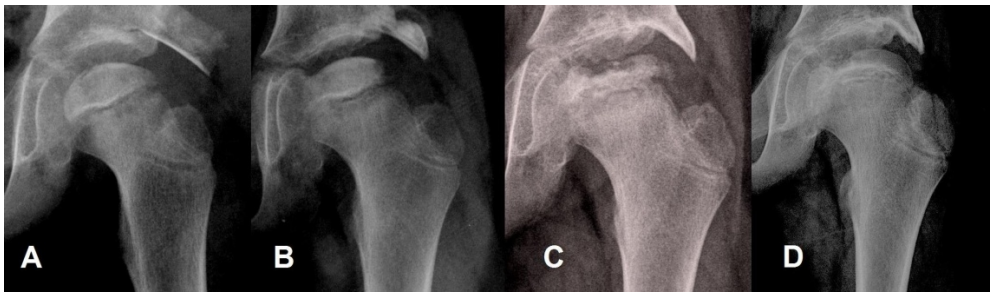


Figure 5 – Radiographs of a shelf augmentation.

(The shelf augmentation can be seen abutting the side of the acetabulum, and its integration can be seen in images A-D. The healing process is again evident with initial stage (A), sclerosis (B) fragmentation (C) and late stage (d). The resulting hip appears spherical and congruent)

3. The Biology of Disease

3.1 Pathology

A biopsy from one of the original patients described by Georg Perthes demonstrated abnormal cartilage extending into normal bone[7]. Perthes' believed the disease to be a "peculiar atrophy" of the boney epiphysis, related to destruction of the subchondral region. Legg believed that such changes were a consequence of a disruption at the epiphyseal plate[2]. Both thought that this was the due to diminished blood flow, with the favoured mechanism being trauma.

A traumatic theory of disease has caused controversy since it was first proposed. In 1916 Kidner suggested that it was difficult to conceive that a trauma could be so small to be of little concern to the patient or family, but so great to disturb the "*deeply buried and thoroughly protected*" circulation of the femoral head[17]. Kidner proposed that a low-grade infection was the cause; to which trauma may be a predisposing factor. However, organisms were rarely isolated from diseased specimens and the infective origin lost support – so much so that in 1926 Kidner published a report doubting his earlier suggestions, and agreeing with Legg and Perthes' regarding a circulatory disturbance. The infective theory of disease had been completely disregarded by 1966[4].

It is now widely believed that a vascular phenomenon underpins the mechanism of disease, though the cause of this insult is uncertain. More modern pathological techniques similarly support a vascular mechanism as autopsy examination of five children with Perthes' disease, who died from unrelated causes, demonstrate changes consistent with vascular ischaemia[18-20].

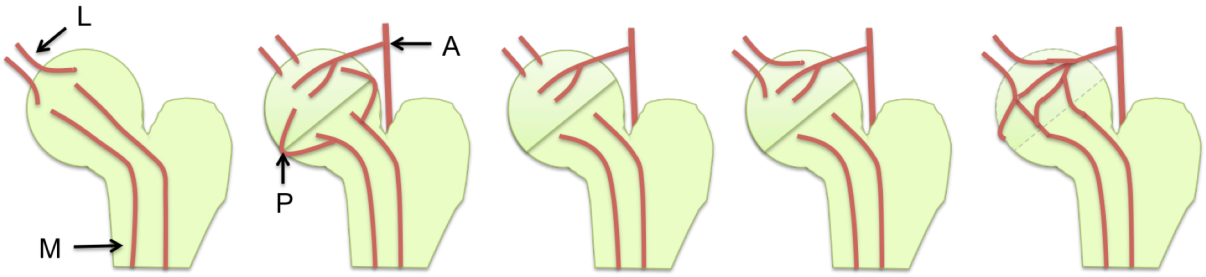
3.2 Anatomy

Central to the theory of a vascular insult is the anatomy of the vasculature of the femoral head in infancy and childhood. Throughout development, the epiphysis has a very tenuous blood supply, and it is the precariousness of this blood supply that is thought to underpin the process of Perthes' disease. An awareness of the vasculature of the hip is therefore important in understanding this theory (illustrated in Figure 6 (adapted from Trueta et. al[21]) and Figure 7 (reproduced with permission from Chung et. al[22])).

The vascular supply to the epiphysis between 3 and 10 years old is especially tenuous (Figure 6) which corresponds to the peak ages of Perthes' disease onset. The vascularity has been observed to be better in females, and in black children who have a more abundant vascular network[22].

During the anatomically vulnerable period the principle artery to the epiphysis, the ascending cervical artery, arises from the posterolateral aspect of the femoral head. The area of the epiphysis furthest from the vascular origin is therefore the anterior portion. Perthes' disease clinically always affects the anterior portion of the femoral epiphysis[23]. This clinical observation therefore appears to reflect the vascular anatomy, and adds clinical support to a vascular mechanism of disease.

Figure 6 – The changing blood supply to the femoral head in childhood.



Fetal & Neonatal **18 months old** **4 years old** **> 7 years old** **Adolescence**

(Metaphyseal Arteries (M), Physis (P), Ascending Cervical Artery (A), Artery from Ligamentum Teres)

Late fetal and early neonatal life: Long straight metaphyseal arteries (M) commence in the shaft of the femur and pass into the femoral head across the metaphysis, and through the cartilage cells that will later form the physis. There is an additional vascular supply through the vessels of the ligamentum teres (L). Over time there is decreasing reliance on the blood supply of the ligamentum teres.

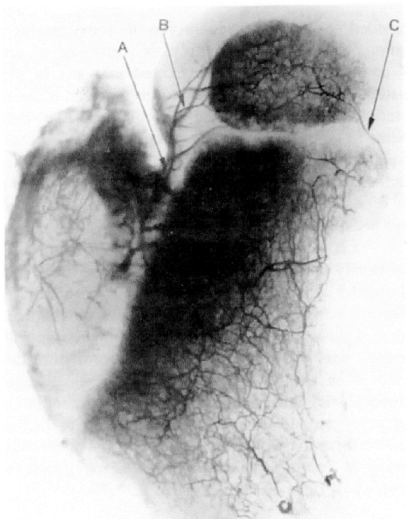
By 18 months old: The physis (P) has developed, forming an impermeable barrier for blood vessels. Metaphyseal vessels no longer cross the physis and instead leave the metaphysis and skirt the outer perimeter of the physis to enter the epiphysis. The ligamentum teres offers no significant blood supply. A prominent vessel called the lateral ascending cervical artery (A), a branch of the medial circumflex artery, becomes the primary blood supply to the epiphysis.

By four years old: The metaphyseal vessels and the ligamentum teres offer little supply to the epiphysis. The epiphysis is now entirely dependent on the lateral epiphyseal artery, although racial variation may exist.

After seven years old: The artery of the ligamentum teres increases in importance and begins to penetrate the epiphysis. Epiphyseal blood supply at this time is from both the ligamentum teres and the lateral epiphyseal arteries.

Adolescence: The vascularity of the metaphysis increases, and the physis fuses. Blood supply to the epiphysis and metaphysis forms a well-anastomosed network across the metaphysis and epiphysis.

Figure 7 - An arteriogram of the hip in a child aged 5 years old.



The principle supply to the epiphysis, the lateral ascending cervical artery (A) is clearly visualised with branches (B) passing through the perichondral ring. No vessels are seen crossing the physis. The small medial ascending cervical artery is also seen skirting the physis on the medial aspect (C).

Reproduced with permission from the American Journal of Bone and Joint Surgery.

Chung SM. J Bone Joint Surg [Am] 1976; 58(7): 961-70.

3.3 Experimental support for a vascular disease

Animal experiments similarly support a vascular mechanism of disease. The first animal studies designed to replicate Perthes' disease were conducted by Holdsworth in 1966[4]. He demonstrated that if the blood supply to the metaphysis in rabbits was interrupted then epiphyseal ossification was delayed but cartilage proliferation continued, giving the radiographic appearance of a widened joint space. If however the epiphyseal arteries were interrupted the cartilage proliferation ceased resulting in a flattened distorted epiphysis. Radiographic sclerosis became apparent once revascularisation had begun, and investigators have subsequently demonstrated that this radiographic change is due to calcification of necrotic bone marrow[24].

Holdsworth also demonstrated that re-ossification occurred by invasion of peripheral metaphyseal vessels into the epiphysis, resulting in the central portion of the femoral head being the last to re-ossify.

These findings therefore explain the radiographic appearances seen in Perthes' disease. Initial joint space widening (Waldenstom's sign) is caused by epiphyseal cartilage proliferation, but delayed ossification. Sclerosis occurs as revascularisation ensues and the marrow calcifies. Fragmentation occurs due to resorption of necrotic bone. Finally re-ossification of the cartilage occurs with the central portion being the last to re-ossify.

Holdsworth's work therefore replicated many of the changes seen in human disease, however the animal experiments resulted in rapid revascularisation of the epiphysis. In humans this repair process lasts 2 to 3 years. Other authors therefore proposed that the delay in healing in humans may be the result of multiple infarctions[20], which autopsy findings similarly suggested[18,20].

Subsequent animal experiments replicating multiple infarctions, resulted in changes similar to Perthes' disease, with a similar delay in regeneration[25]. This finding has been reproduced by other investigators who have also identified that only multiple episodes of infarction behave like Perthes' disease[20,26-28].

Angiographic studies of individuals with Perthes' disease have sought to confirm an arterial infarct, with some demonstrating occlusion at the origin of the lateral epiphyseal artery[8,29,30]. However this finding is not universal, with other authors noting venous occlusion[31] or venous hypertension through increased intraosseous pressure[32]. Angiographic investigations in individuals with Perthes' disease may however be unreliable, owing to the delay between disease onset and radiographic diagnosis, which is at least several weeks and in many cases notably longer.

Multiple arterial insults therefore appear the most likely disease mechanism. Whilst other mechanisms, such as venous occlusion, may replicate disease in laboratory animals, they lack plausibility compared to the considerable anatomical, clinical, radiological and experimental evidence of an arterial mechanism.

4. The Aetiology

Many observers have sought a pathological process amongst those with Perthes' disease that may initiate vascular occlusion. Broadly these may be divided into intraluminal obstruction (e.g. coagulopathies), and extraluminal compression (e.g. tense intra-articular effusion).

Intraluminal Obstruction

The primary focus in the aetiological search over the last two decades has been the search for a coagulopathy, which would cause infarction of the hip and precipitate necrosis.

The possibility of thrombophilic tendencies were popularised by Glueck et al[33], though other observers had made similar suggestions prior to this[34]. Glueck et al. identified a thrombophilic tendency in 33 of 44 individuals with Perthes' disease, with over half having a deficiency in Protein C or S. This trend was supported by a later study, though results lacked statistical significance[35]. However, Glueck et al. used a relatively small control group of 30 children to define the 'normal range' for the laboratory values in a child population. In a similar experiment using a laboratory defined 'childhood normal range' only 5 of 64 cases demonstrated an abnormality in Protein S and Protein C levels [36]. More investigators have since investigated Protein S and Protein C deficiency, along with other coagulopathies such as Antithrombin III and Factor V Leiden deficiency and genetic markers of hypercoagulability[37-40]. These studies all fail to reach a consistent conclusion regarding a thrombophilic tendency.

A systematic review of literature concerning thrombophilias in Perthes' disease, which included 475 cases of Perthes' disease, concluded that there was no significant

difference in Antithrombin activity, protein S or C or antiphospholipid antibodies[41]. The review was equivocal for a possible relationship between Perthes' disease and the Factor V Leiden mutation, yet certainly no strong relationship was found.

The only study to investigate coagulopathies since the systematic review was undertaken was a case control study investigating 169 cases of Perthes' disease and 512 controls[42]. This study demonstrated a number of associations including a propensity toward factor V Leiden mutations (OR 3.3 95% CI 1.6 – 6.7) and high (>150iu/dl) factor VIII levels (OR 7.5 95% CI 2.2 – 25.2). This study however used a control group made up of two very different groups, one encompassing 38 asthma children who were frequency matched for sex (mean age 11.9 years) another a control group of 474 adults (mean age 46.6 years). The case group (mean age 12.5 years) was therefore very different to the bulk of the control group. This study therefore appears so flawed in its design it adds little to the existing literature.

Extraluminal Obstruction

External pressure on the artery has similarly been suggested as a possible mechanism. Investigators have sought to identify if pressure from an accumulation of fluid within the hip capsule may occlude the vasculature[43,44]. This theory has arisen because the most common differential diagnosis of Perthes' disease is transient synovitis, a self limiting hip effusion thought to be associated with a viral illness[45]. Transient synovitis is, like Perthes' disease, more common in boys and typically affects those between four and eight years old[46].

Kemp (a past winner of the Robert Jones Prize) demonstrated that an intra-articular effusion, caused by trauma or a sterile synovitis, may increase the pressure within the capsule and potentiate a vascular insult[47]. Animal studies have similarly demonstrated that raised intra-articular pressure may result in tissue hypoxia and changes similar to Perthes' disease[43,44].

The majority of Perthes' patients however do not report bouts of preceding hip pain, and it is believed that such bouts of ischaemia and necrosis are unlikely to occur silently[48]. It is also suggested that there is a seasonal variation in the frequency of transient synovitis, with higher incidence during winter months corresponding to peaks in viral illness[49]. Perthes' disease shows no seasonal peaks in incidence[50]. Similarly follow-up studies of children with transient synovitis rarely reveal Perthes' disease. In those cases of Perthes' disease that do follow episodes of transient synovitis retrospective review of initial radiographs often show early evidence of Perthes' disease that was overlooked[46,51,52].

Other extraluminal sources of compression have also been proposed. Chung noted that the entry of the lateral epiphyseal artery into the joint capsule was through an extremely narrow space between the trochanter and capsule[53]. He observed that this was especially so in children less than eight years old, and as the child gets older children the neck lengthens and this space widens, proposing it as a potential site of arterial compression in the young. No other investigators have elaborated upon this theory.

Summary

The cause of Perthes' disease, despite a century of research, remains poorly understood. The likely disease mechanism appears to be an interruption of the lateral ascending cervical artery with resulting ischaemia of the femoral epiphysis. It is unclear how occlusion of this artery may occur; however it appears unlikely to be due to a currently known coagulopathy.

Section B: Temporal Trends and Geographic Patterns in Incidence

There has been a paucity of large, robust epidemiological studies that have investigated the descriptive epidemiology of Perthes' disease – i.e. the distribution of disease relating to geography and time. This, along with a similar inadequacy of analytical epidemiology, has prorogated the formulation of a number of poorly substantiated hypotheses pertaining to the disease aetiology. The discussion that follows is an up-to-date review of the descriptive epidemiology of Perthes' disease, based on studies undertaken by the author.

1. Geographic Patterns

International Disease Distribution

The international distribution of Perthes' disease has been poorly understood, due to problems of heterogeneity in study methodology, and widespread confusion owing to differing population denominators. A systematic review of incidence studies of Perthes' disease has recently overcome these problems[54]. This review identified robust studies of incidence, and obtained relevant population data from reliable international sources in order to homogenise the denominator population. This has consequently enabled reliable comparisons to be drawn between studies of incidence.

The systematic review included 21 studies, almost all of which arose within the Northern Hemisphere, and the majority within Northern Europe (Figure 8). The propensity of studies to be conducted within Northern Europe appears to be a reflection of a greater disease affinity to disease within these regions. After considering the effects of race and latitude, it was identified that race appeared to have the greatest effect on incidence with East Asian individuals least affected, White individuals most affected and South Asian individuals in-between. There were no robust studies of incidence amongst individuals of predominantly Black ancestry, which is likely to be a reflection of the scarcity of disease in this group – this is supported by the infrequency of Perthes' disease amongst black individuals from

large series of disease - New York, 14 black children amongst 358 cases[55], Connecticut, 2 black children amongst 203 cases[56], Liverpool, no black children amongst 1082 cases[57].

Figure 8 - Worldwide geographic distribution of incidence studies included.

Even after adjustment for race the latitude of the study region also appeared to influence Perthes' disease incidence (Figure 9). After adjustment for race (and exclusion of the South African study owing to the very mixed ethnicity of participants), every 10 degrees more Northerly from the equator resulted in an increase in the incidence of Perthes' disease of almost 50%. This was the first time that an association with latitude was demonstrated in Perthes' disease, though a number of other diseases share a similar association. Multiple sclerosis (MS) is the disease most widely known to be associated with Northerly latitudes[58,59], however other diseases similarly share this pattern; such as ischaemic heart disease and osteoporosis[60]. Aetiological determinants that have been suggested to explain the latitude phenomena include vitamin D deficiency, through inadequate sunlight exposure, or exposure to infectious agents.

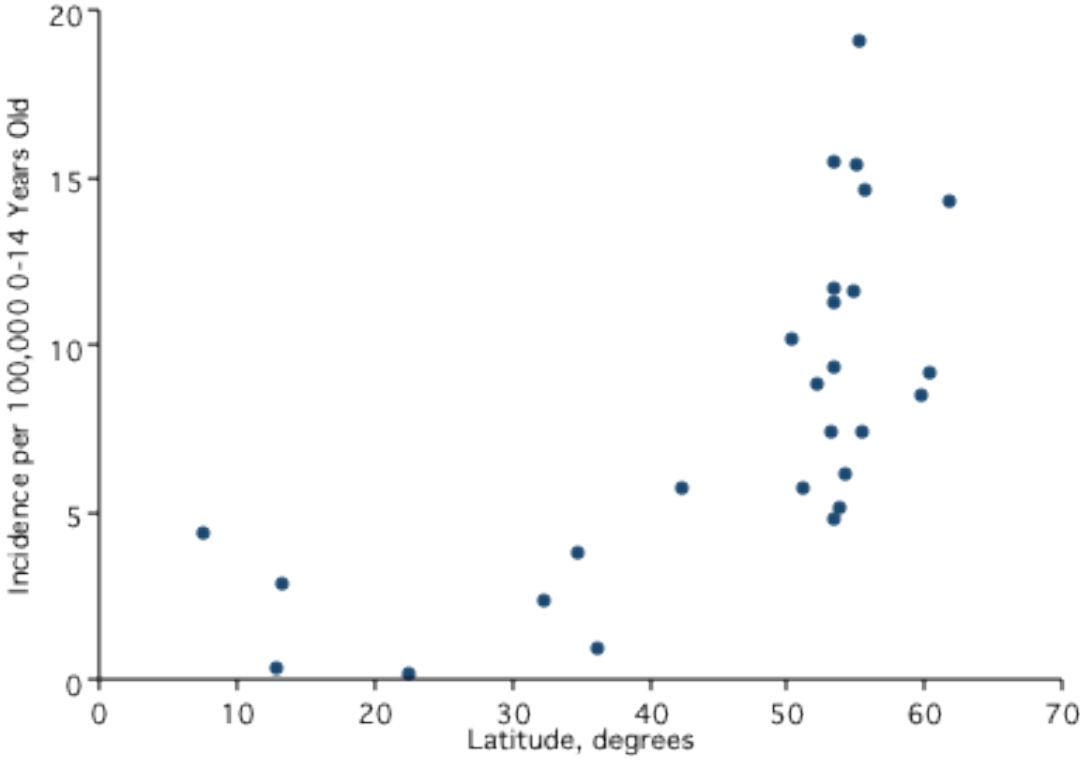


Figure 9 - Realtionship between Perthes' disease incidence and latitude.

(Reproduced with permission Am J Epi)

National Disease Distribution (UK)

In 1978 Barker identified marked variation in incidence between three different health board regions of the UK[61]. Barker demonstrated that Wessex in the south of England had half the incidence of Merseyside in the north, with Trent in the Midlands having an intermediate value (11.1 vs. 7.6 vs. 5.5 cases per 100,000 children 0 – 14 years old per annum). However, the true disease distribution across the whole UK was unknown. Other observers have consequently undertaken studies of incidence within various regions of the UK, the results of which have continued to vary widely[50,62-65]. It is therefore unclear if this variation is real, fluctuation secondary to small sample sizes or due to differences in study design, case definition or the time period of the study. Previous studies are also based upon hospital case ascertainment, which introduces the assumptions that Perthes' disease cases reach secondary care, and that no case attends a hospital that is not outside the anticipated catchment hospital (an assumption necessary in order to formulate an appropriate population denominator).

A recent investigation has overcome many of the previous problems, and mapped Perthes' disease across the UK, at a health board level[66]. This investigation used, for the first time, a community database - the General Practice Research Database (GPRD). The GPRD is the world's largest primary database, extensively validated and collected as part of 'routine patient care'. It encompasses over 68 million person years of data, and enumerates approximately 8% of the UK population. The denominator population is clear, owing to the general practitioner having a known number of patients, and the numerator tightly defined owing to the practitioner being the 'gate-keeper' to secondary care services.

The GPRD study identified a striking pattern of Perthes' disease incidence across the UK (Figure 10). The Southeastern UK and London were least affected by Perthes' disease, with a gradual increase in incidence at more Northerly latitudes, such that the incidence of Perthes' disease in Scotland was double that in London. This geographic pattern seen is similar to that in a number of other diseases such as ischaemic heart disease[67], hypertension[67] and all-cause mortality[68]. Could the aetiological determinant precipitating this national geographic distribution, be the same as that precipitating the international latitude effect? If duration of sunlight exposure may be considered a determinant for an international latitude effect it appears interesting that the UK map of Perthes' disease incidence and the UK map of sunshine exposure are strikingly similar, illustrated in Figure 11.

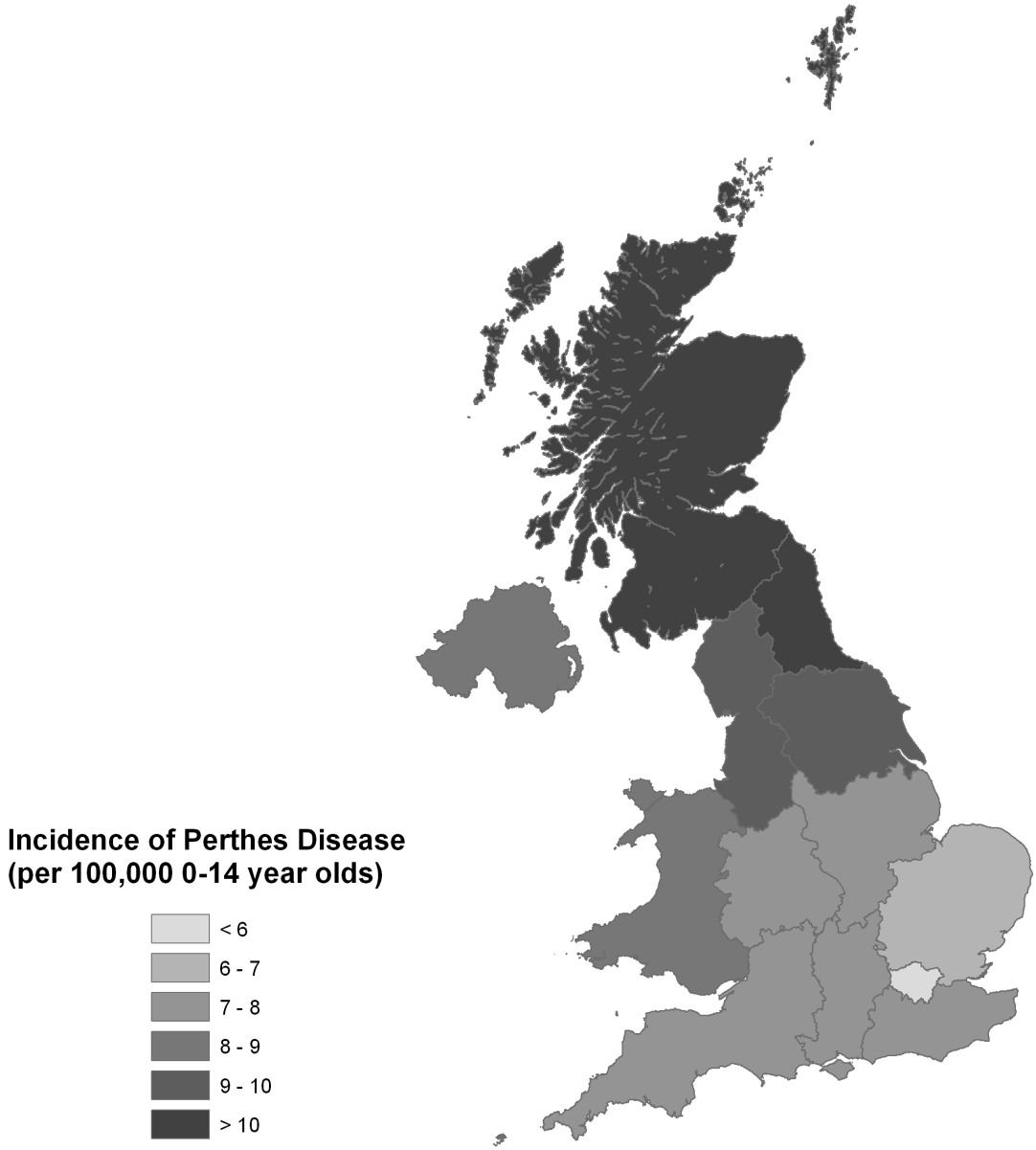


Figure 10 - Geographic illustration of the incidence of Perthes' disease

(by English Strategic Health Authority, Wales, Scotland and Northern Ireland).

(Reproduced with permission Arthritis & Rheumatism)

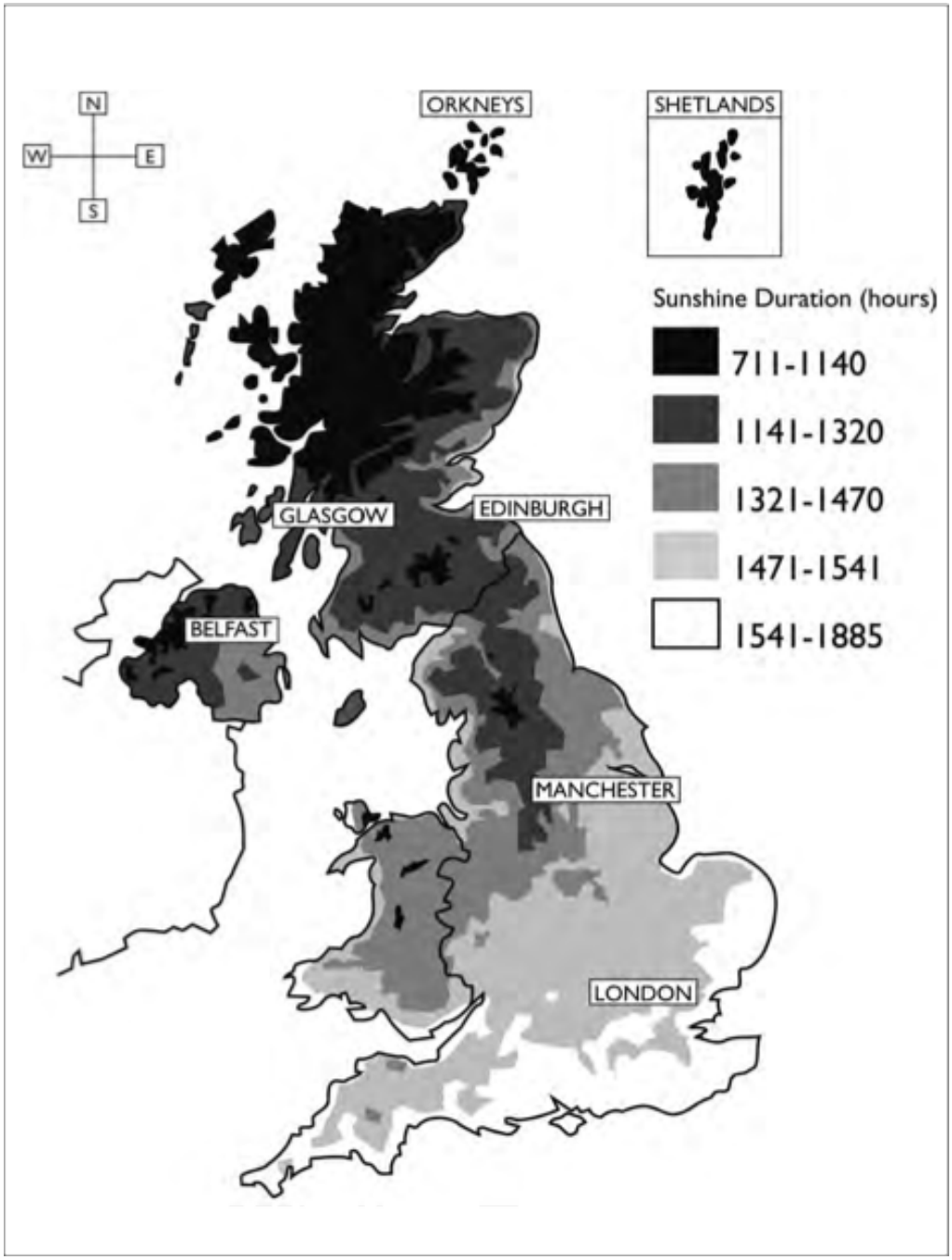


Figure 11 - Sunshine Map of the UK

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Local (Merseyside) Disease Distribution

Even at the local level the incidence of Perthes' disease is believed to vary considerable by region. Hall investigated the incidence of Perthes' disease within Merseyside and Yorkshire, demonstrating marked variation within these counties. In Merseyside, a very high incidence was observed in inner city Liverpool prompting investigators to examine the relationship between deprivation and disease[50,64]. This indicated a steep social class gradient associated with Perthes' disease, with rates rising from 4 per 100,000 per annum in Social Class 1 (highest social standing) to 31.7 per 100,000 per annum in Social Class 5 (lowest social standing)[50]. Similar social class and deprivation trends have been reported in other studies[65,69], though these observations remain the source of some controversy[70].

Established through the work of Barker & Hall (1970s and 1980s) the Merseyside Perthes' register is currently the longest maintained and largest database of Perthes' disease cases in the world. The most recent analysis of this database examined patterns of Perthes' disease incidence over the 14 years period from 1996 to 2009. This study used computerised allocation of postcodes to ward region, and validated deprivation scores, to ensure accurate assessment of region and deprivation. This study identified marked variation in the incidence of Perthes' disease within Liverpool at a Ward level (Figure 12).

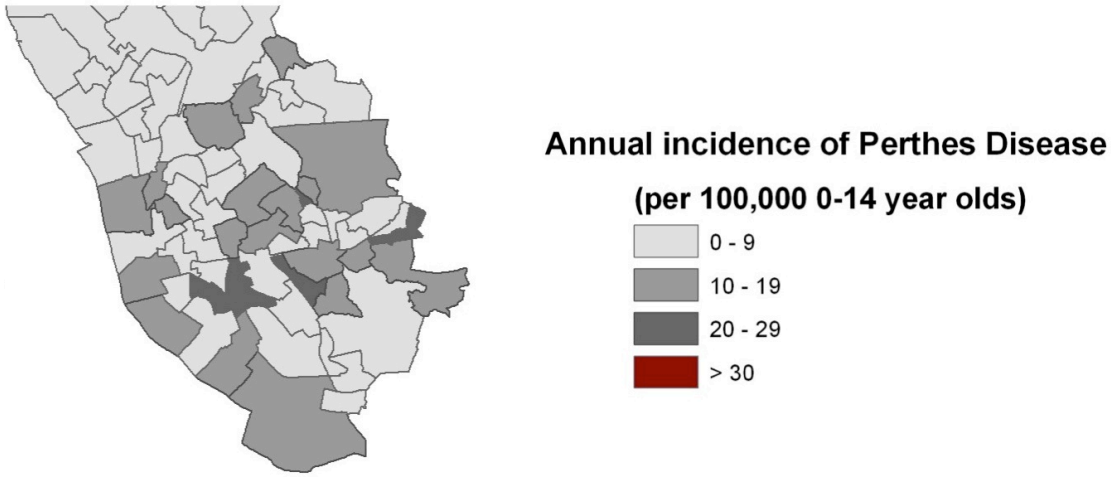

Figure 12 - Incidence of Perthes' Disease within Merseyside 1996 – 2009.

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This variation, like in previous studies, correlated strongly with deprivation – using area deprivation scores at a ward level (Figure 13), and using Lower Layer Super Output Areas (LLSOAs) which are the smallest UK administrative subunit of geography thereby minimising ecological error introduced through area based assumptions. The strongest association with deprivation was seen at the LLSOA level, using a child-specific measure of deprivation[71] (which is derived from the extensively validated English indices of multiple deprivation[72]) - Figure 14.

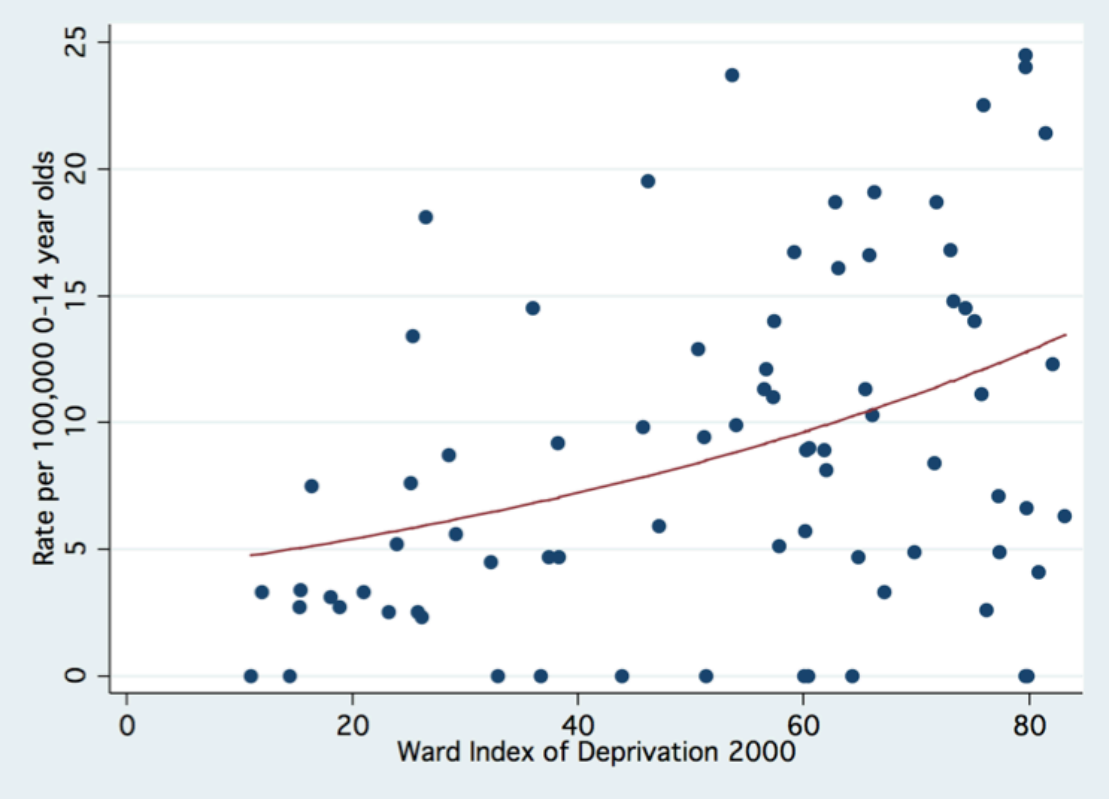

Figure 13 – Relationship between Ward Level Deprivation and Incidence.

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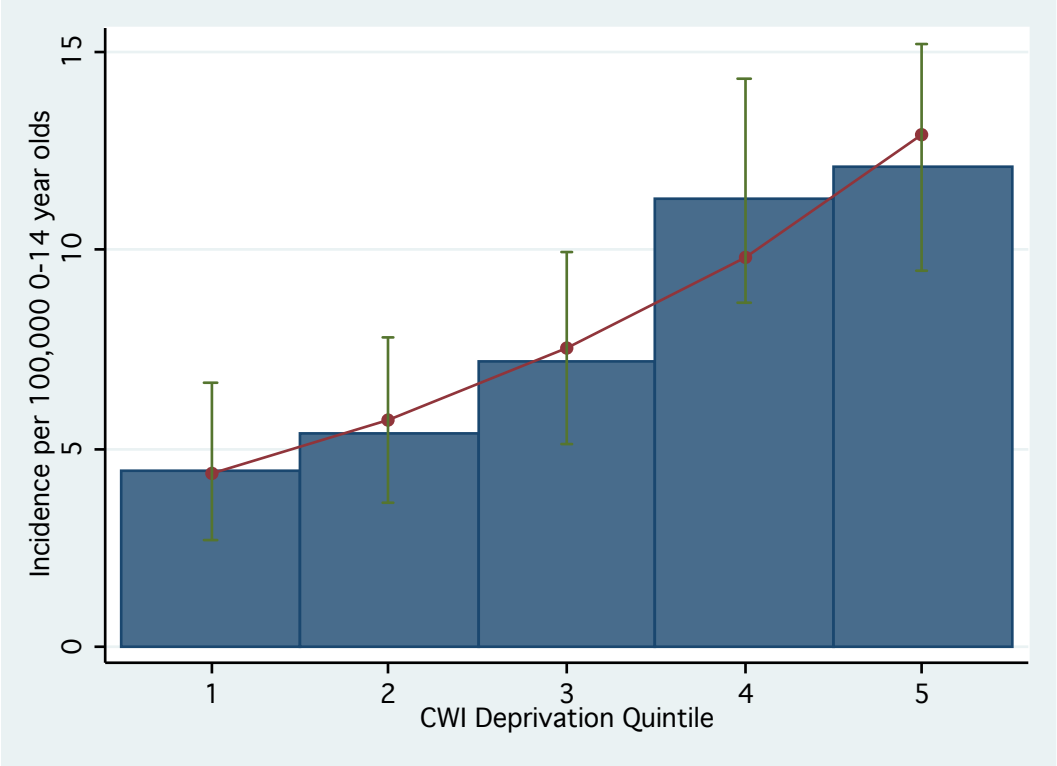

Figure 14 – Relationship between worsening quintiles of childhood area deprivation, and Perthes' disease incidence.

(Adapted from data published within Arch Dis Child)

Discussion

There is widespread variation in Perthes' disease incidence, at all geographic levels (i.e. varying at a local-level to an international-level). At the local level this variation appears to closely mirror measures of deprivation inequality in childhood. Could socioeconomic inequalities explain the national and international distribution of disease?

At the National Level deprivation inequalities may be assessed using the percentage of children, by region, in the most deprived quintile of UK deprivation (Figure 16). Using deprivation markers adapted for strategic health authorities, it was shown that after excluding London, Perthes' disease incidence appears intimately related to regional deprivation. London may differ due to its multi-ethnicity, as it is already demonstrated that those of African and south Asian origin are at low risk of Perthes'

disease. London acts similarly as an outlier in numerous diseases related to deprivation, such as cardiovascular disease[73] and hypertension[74], and therefore exclusion appears plausible.

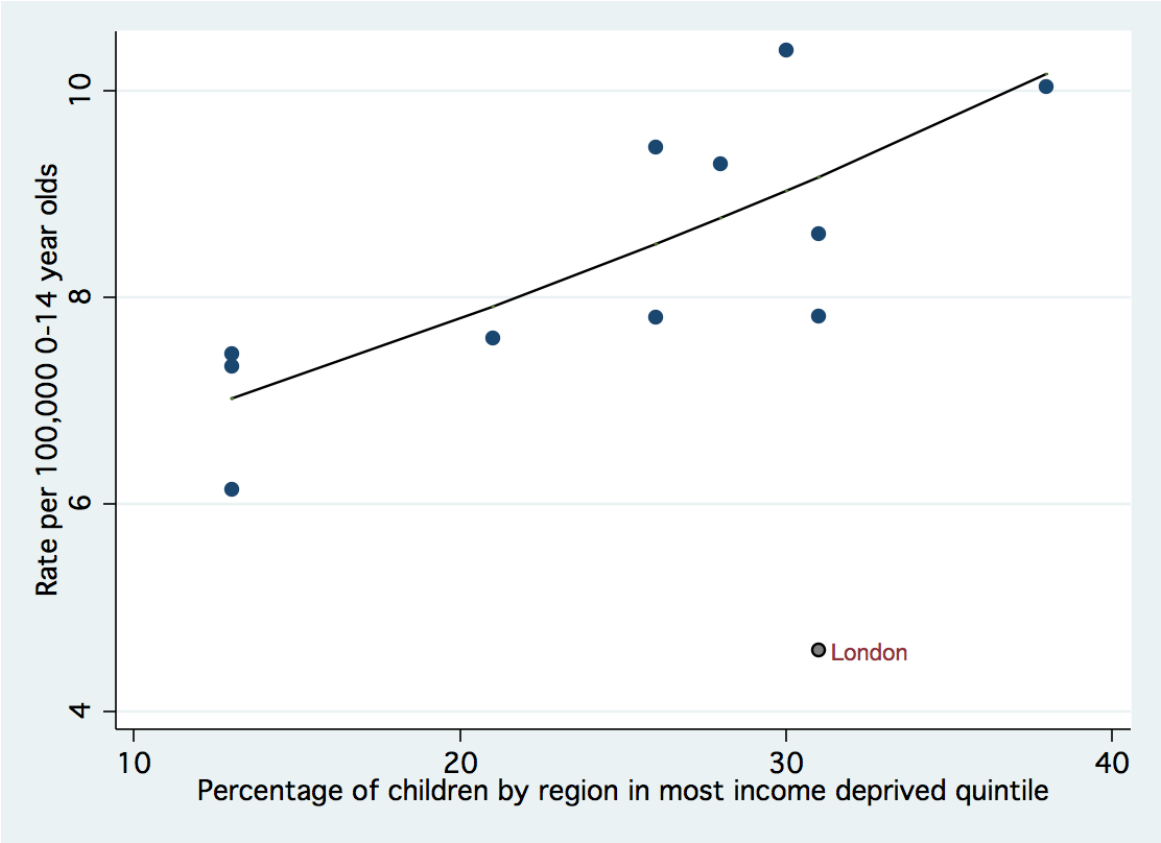

Figure 15 - Perthes' disease incidence by child income deprivation.

(Smooth line is the Poisson regression line, after excluding London. London is illustrated as an outlier)

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At an international level the incidence was associated with latitude, but could this be a consequence of deprivation differences? The systematic review demonstrated high disease incidence in wealthy Northern Europe and USA, compared to poorer equatorial regions. The socioeconomic gradient is therefore opposite to that in the published literature, which shows a positive relationship between increasing deprivation and Perthes' disease incidence. It may therefore be argued that 'access to health care' may explain the observed effect, as healthcare access is greater in Northern Europe and USA, and studies generally used hospital populations from

which to define 'cases'. However, the study from India was supported by a prevalence study of 16,838 school children that yielded similar incidence estimates to the hospital incidence study[75], and recent evidence from wealthy Japan demonstrates a low incidence of Perthes' disease, in a region with a universal health care system[76]. This therefore suggests that the incidence gradient observed is independent of bias caused by healthcare access.

At a local and national level the incidence appears to closely mirror childhood deprivation inequalities, though this does not hold true at an international level. Other influences (i.e. sunlight) may therefore be influential, and may interact with the deprivation-related exposure to heighten the risk of disease in more deprived communities at more Northerly latitudes.

2. Temporal Trends

Up to 2011 only one study offered any insight to the temporal trends in Perthes' disease incidence. Margetts et al used the Merseyside Perthes' Disease Register to compare incidence rates between 1982 – 95 with the earlier studies of Barker and Hall[64]. This study identified a significant fall in the incidence of Perthes' disease over this period, with rates almost halving over this time-frame. There was no evidence that this was the result of differences in diagnosis, case ascertainment or population dynamics and therefore believed to be a genuine decline. No other study has confirmed these findings, or tested the generalisability of these findings outside Merseyside.

The recent analysis of the Merseyside database has allowed temporal trends to be reexamined – now over a 34-year period. This looked at the three local council areas within Merseyside (Sefton, Knowsley and Liverpool). There was a significant decline in disease incidence within Liverpool over the 34-year study period (Figure 16), with rates falling from 14.2 to 7.7 cases per 100,000 0 to 14 year olds. The Poisson model demonstrated an annual decline in incidence within Liverpool of 1.8% (95% CI 0.7% – 3.0%). 28 years of data was available from Sefton and Knowsley, which suggested a

more rapid decline in incidence within Knowsley with an annual fall of 3.1% (95% CI 0.6% - 4.4%), and no significant decline in Sefton (0.4% (95% CI -1.9% - 2.7%). For the three areas combined the annual decline was 1.4% (95% CI 0.3% - 2.75%). The most marked decline in incidence therefore appeared within the socioeconomically deprived regions of Liverpool and Knowsley, yet no significant fall within the more affluent neighboring region of Sefton.

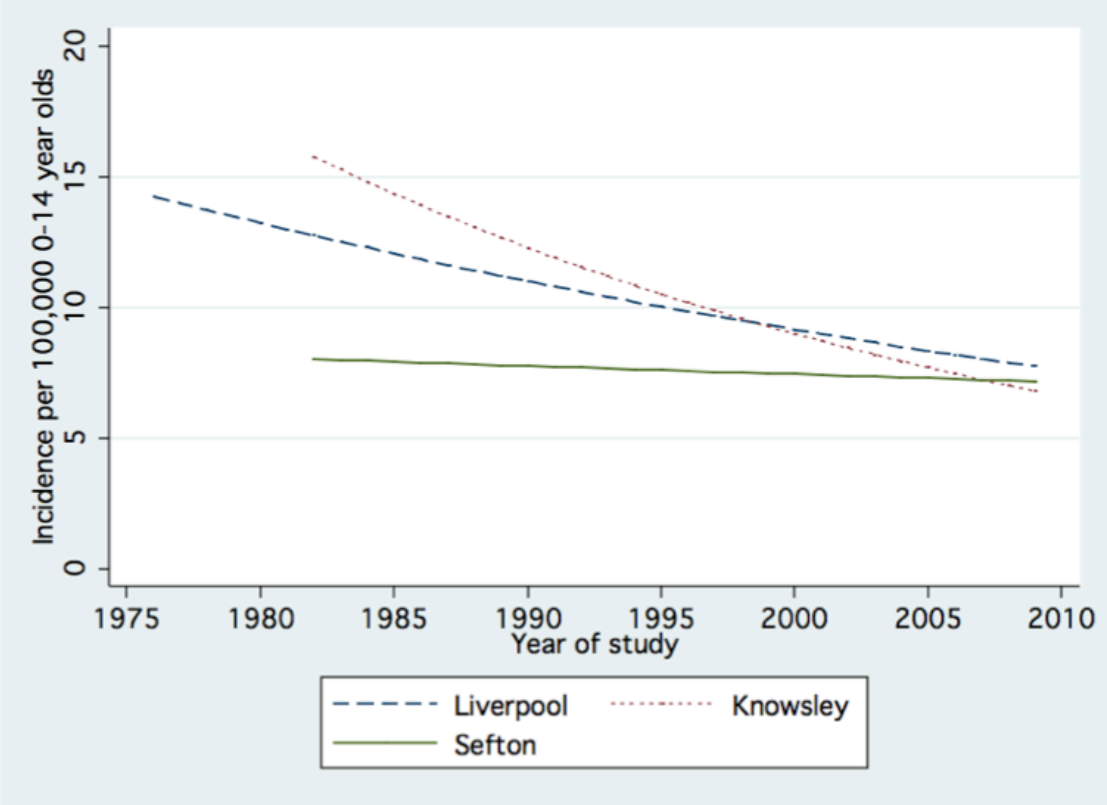

Figure 16 – Incidence of Perthes' disease within Merseyside.

(fitted line represents the Poisson model of incidence rates, by year, within each of the three regions)

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At a national level similar trends have been identified within the GPRD. Over the 19-year study period there was a decline in Perthes' disease incidence, with a year-on-year decline in incidence of 4.2% (2.7% - 5.5%). Using the Poisson regression model rates fell from 12.2 cases per 100,000 0 to 14 year olds in 1990, to 5.7 cases per 100,000 0 to 14 year olds by 2008. This is illustrated in Figure 17.

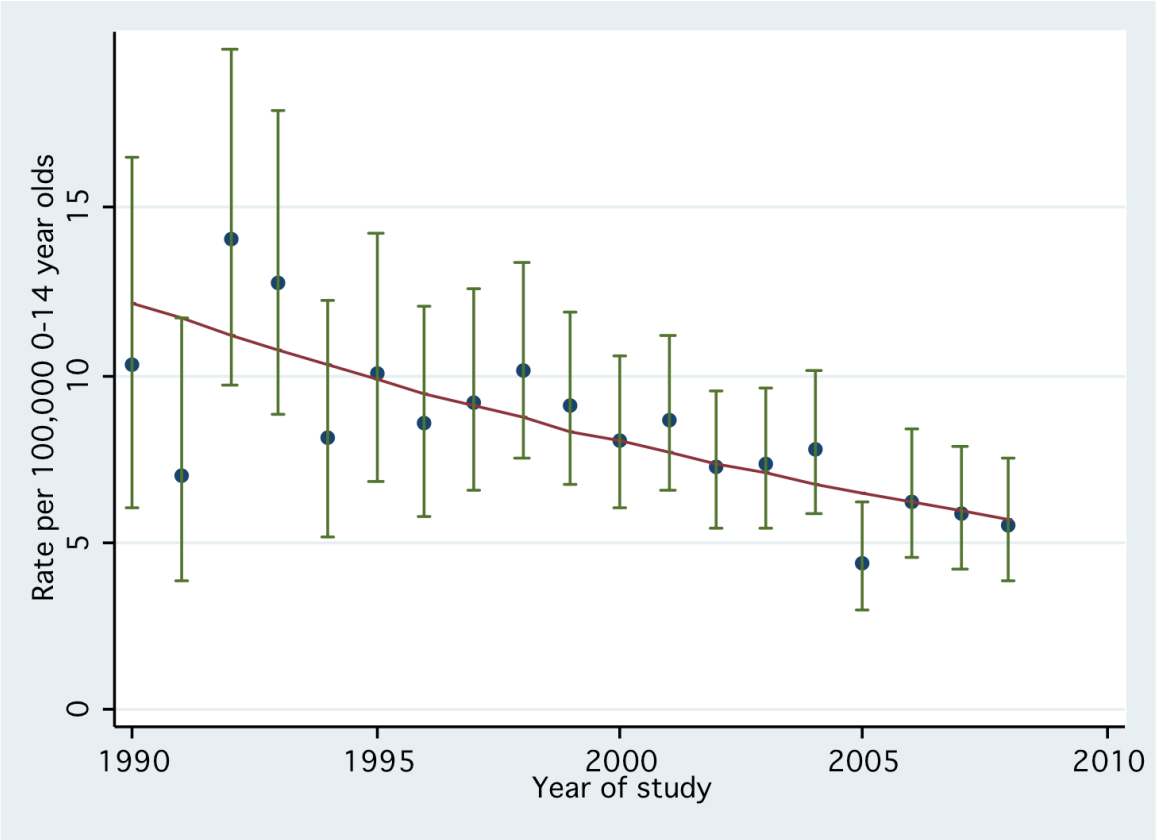

Figure 17 - Scatter plot of disease incidence of Perthes' disease by year.

(Each point represents the annual incidence rate with 95% exact Poisson confidence interval error bars. The smooth line represents the Poisson model of disease incidence.)

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Temporal trends were then further examined within 3 geographical strata <*previously unpublished data*>. (Figure 18) - North (Scotland, Northern Ireland, North West, North East, Yorkshire and Humber), Central (Wales, East Midlands, West Midlands, South West) and South (South Central, South East, East of England, London).

Figure 18 - Geographic distribution of subgroup analysis.

(Black – High Incidence (North - Scotland, Northern Ireland, North West, North East, Yorkshire and Humber), Grey – Medium Incidence (Central- Wales, East Midlands, West Midlands, South West), White – Low Incidence (South - South Central, South East, East of England, London).

A decline in incidence was statistically significant within each stratum. The rate of decline was greatest in the high incidence region in the North - Annual decline North (5.1% (95% CI 2.9% - 7.3%), Central 4.4% (95% CI 1.8 – 6.9%), South 2.5% (95% CI 0.0% - 5.0%). This is illustrated in Figure 19. The most marked decline was apparent in most deprived part of the UK and the most affluent South had decline of borderline significance.

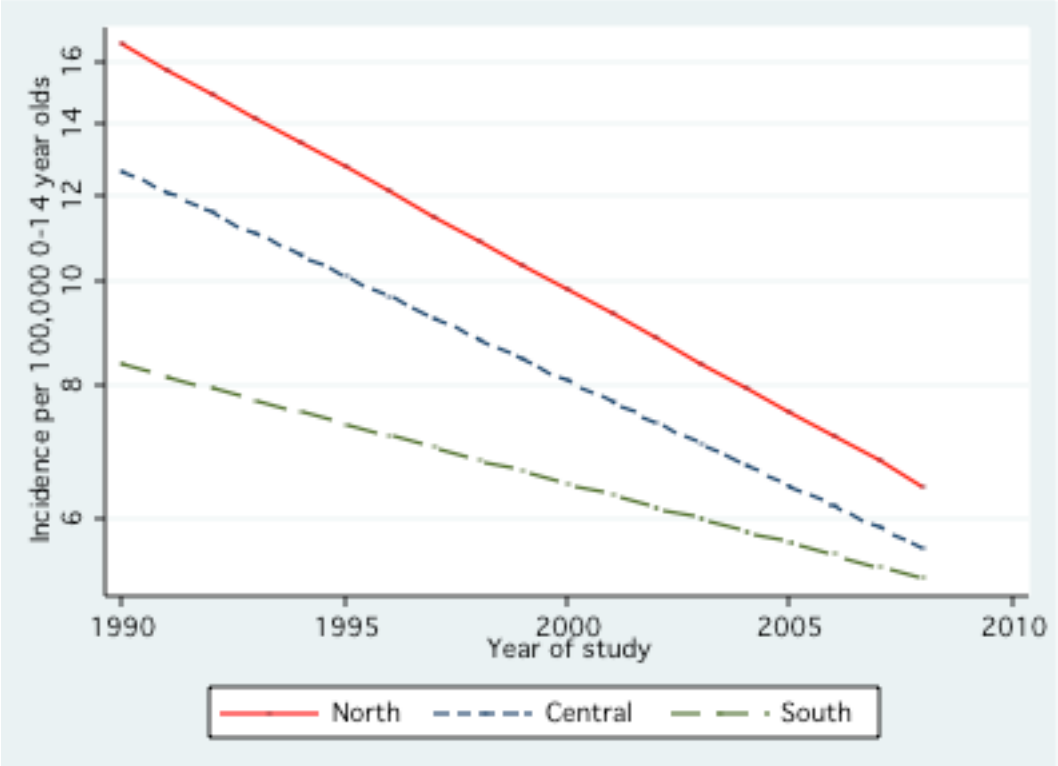

Figure 19 – Annual decline by regional division (y-axis is logarithmic)

Other (currently unpublished) studies using independent datasets (Hospital Morbidity Database, Scotland & National Disease Register, Northern Ireland) similarly confirm a decline in Perthes' disease incidence further adding support in the generalisability of these findings.

Discussion

Each of the descriptive studies to look at temporal trends independently demonstrated a falling incidence of Perthes' disease. They demonstrate that the incidence is declining most rapidly in regions that initially had the highest incidence of disease, i.e. the regions with greatest deprivation. By assuming that the fall in incidence will continue at the observed rates, the incidence of Perthes' disease is predicted to converge in 2010-2011 both within the three Merseyside regions studied, and within the three UK divisions studied. This therefore implies that the UK North-South divide in Perthes' disease incidence is narrowing. This is in stark contrast to many other

national indicators of health, which demonstrate that the North-South divide is widening, such as the national all-cause mortality[68].

3. Aetiological Implications

Each of the descriptive studies has confirmed a close relationship between Perthes' disease and deprivation. This relationship appears consistent, strong and plausible, thus fulfilling many of Hill's criteria of causality[77]. However, the responsible component of 'deprivation' remains unknown such that experimental models cannot be generated, temporality cannot be confirmed, or specificity cannot be established.

The incidence of Perthes' disease declined over the study periods, which is likely to reflect a reduction of an important deprivation-associated risk factor. It is however difficult to determine the component(s) of deprivation that may have mediated this change – e.g. diet, smoking, exercise, injury, alcohol, drugs or infection. An extra complexity in establishing risk factors for disease is that it is unclear if the key determinants act upon the child, the mother, or are part of a more complex gene-environment interaction.

Within the UK study London acted as an outlier to the deprivation trend. Such outliers may give added clues to the disease determinants. London acts similarly as an outlier in other diseases related to deprivation, such as ischaemic heart disease[73] and hypertension[74]. It has been suggested that London may have a lower than expected rate of cardiovascular disease for the high proportion of socioeconomic deprivation, owing to epigenetic influences resulting from the 19th century migration of well-nourished young healthy women to the city to work as domestic servants[78]. These healthy young women are believed to have propagated an intergenerational biological advantage in cardiovascular disease, which may similarly be influential in Perthes' disease. Likewise, epigenetic influences related to deprivation may similarly explain why Norway, a country of modern-day affluence, (evidenced by being the highest ranked nation in the United Nations Human Development Index[79]), has high rates of Perthes' disease. Up to the late 1960's Norway was a socioeconomically deprived

nation, which changed following the discovery of North Sea Oil at Ekofisk in 1969. Generations of socioeconomic deprivation may therefore have exerted epigenetic influences resulting in the high frequency of Perthes' disease seen in Norway. Deprivation related epigenetic influences might consequently influence the frequency of Perthes' disease many generations after the time of exposure.

Other comparisons may be made between Perthes' disease and Ischaemic Heart Disease. Both diseases primarily affect males with a similar sex ratio[80], and both are positively associated with higher latitudes[81]. The geographic distribution of both diseases within England, at a health authority level, is almost identical – Figure 33. This geographic similarity also exists at the level of Scottish Health Boards[80]. Both diseases are around three times more common in the most deprived groups of society compared to the most affluent[80,82]. There is similarly a decline in the incidence of both diseases, with a notable difference being that there is no convergence of ischaemic heart disease rates by quintiles of area deprivation over time. Perthes' disease and Ischaemic Heart Disease therefore share many descriptive epidemiological characteristics. Such observations may be an ecological fallacy, or may be evidence that the two diseases share specific aetiological determinants. It may even be that Perthes' disease is an early barometer for what is to come in cardiovascular disease. Such shared descriptive patterns undoubtedly warrant further consideration and investigation.

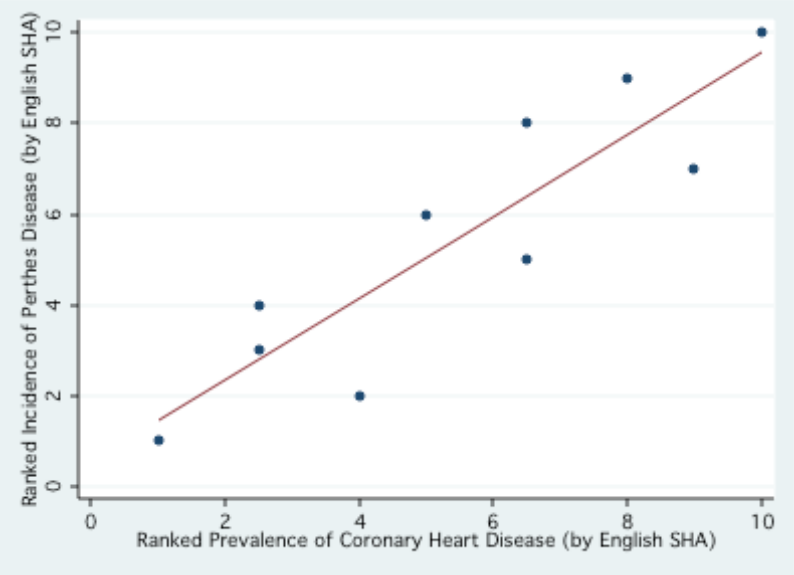

Figure 20 - Ranked incidence of cardiovascular disease by English SHA, correlated with ranked incidence of Perthes' disease

English Strategic Health Authorities (Data from South East Public Health Observatory - http://www.sepho.nhs.uk/).

Conclusions

A century has now passed since Perthes' disease was first described, but the aetiological determinant remains elusive. Within the UK, the occurrence of Perthes' disease is in decline. This reduction is in line with other markers of population health and wellbeing, such as infant mortality rates[83] and age-standardised cardiovascular deaths[80]. The decline in incidence, and the associated reduction in burden of Perthes' disease is encouraging; nevertheless the disease remains a debilitating condition that newly affects around 650 children each year in the UK (based on ONS 2010 population projections and GPRD predicted incidence rates). The unknown aetiology, the potential long-term morbidity and resultant costs to the individual and society, mean that Perthes' disease remains a notable public health concern. It remains unclear how deprivation may exert an effect to precipitate osteonecrosis in the juvenile hip, and perhaps more importantly when the exposure may act (i.e. acting on the child, acting on the mother, or acting through an intergenerational epigenetic effect). The current period of recession and financial austerity appears a scientifically important, and socially significant period in which to further investigate Perthes' disease, and demystify this enigma.

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