

Investigating the Correlation between Solar Irradiance and Legg-Calvé-Perthes Disease Incidence

Abstract

Introduction: Legg-Calvé-Perthes disease (LCPD) is a prevalent pediatric orthopedic disorder characterized by avascular necrosis of the juvenile femoral head due to disrupted blood flow. Revascularization of the necrosed fragment can lead to femoral head deformation and reduced hip joint longevity. The incidence of LCPD varies geographically, with higher prevalence in northern Europe. This study investigates the correlation between solar irradiance and LCPD incidence.

Materials & Methods: Incidence data for LCPD from 31 regions, reported per 100,000 children under 15 years, were retrieved from PubMed. Corresponding regional solar irradiance data were obtained from a geo-localization website and two open data sources. Pearson correlation coefficients were calculated to assess the relationship between latitude, solar irradiance, and LCPD incidence.

Results & Discussion: A significant negative correlation was found between regional solar irradiance and LCPD incidence, while a significant positive correlation was observed between latitude and LCPD incidence.

Conclusion: Evidence indicates: 1) a sharp increase in LCPD incidence at higher latitudes, 2) increased prevalence of vitamin D deficiency at higher latitudes due to reduced sun exposure, and 3) vitamin D deficiency can induce a hypercoagulable state. We propose the hypothesis that "Decreased vitamin D levels during the antenatal and/or early childhood periods are correlated with increased incidence of LCPD," warranting further clinical research for verification.

Keywords: Legg, calve, Perthes disease, Sunlight, Solar energy, Vitamin D, Geographic factor.

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Mohammadreza Azarpira, MD, MSc¹

1. Service of Orthopaedic and Traumatologic Surgery, Intercommunal Hospital Center of Meulan-les-Mureaux, Yvelines, France.

Introduction

Legg-Calvé-Perthes disease (LCPD), first described in 1910, is one of the most prevalent pediatric orthopedic disorders⁽¹⁾. Despite its frequency, the etiology of LCPD remains poorly understood. The disease is characterized by osteonecrosis of the femoral head, typically manifesting between the ages of four and eight years. LCPD is 3-4 times more common in boys and has a higher prevalence in northern European countries. Incidence rates vary significantly across different countries and regions, with estimates ranging from 0.2 to 19.1 per 100,000 children under 15 years of age⁽²⁾.

The initial event in LCPD is confirmed to be localized vascular occlusion of the lateral epiphyseal arteries. Between the ages of 4-7 years, the lateral epiphyseal branch of the medial femoral circumflex artery serves as the primary blood supply to the femoral head epiphysis⁽³⁾. A study conducted in Sweden identified several factors associated with an increased incidence of LCPD in families, including low socioeconomic status, Nordic lineage, and passive smoking⁽⁴⁾. Other studies have also noted an increased incidence of LCPD with socioeconomic deprivation^(5,6). Geographic variation in the disease may be attributed to racial differences and genetic susceptibility, as Black African children are less affected than Caucasians. Genetic susceptibility, an unidentified environmental factor, and a hypercoagulable state are the most likely etiologic explanations⁽⁷⁾.

Increased latitude and decreased sun exposure have been previously proposed as potential environmental risk factors⁽²⁾.

Corresponding Author:
Mohammadreza Azarpira, MD, MSc
Email address:
rezaazarpira@gmail.com

However, no studies have specifically investigated the relationship between solar irradiance and the incidence of LCPD. It is well established that solar irradiance decreases with increasing latitude⁽⁸⁾. In this study, we aim to explore the evidence related to the effects of increasing latitude and decreasing solar irradiance (solar energy) on the body, in search of a possible explanation for the observed variation in LCPD incidence at higher latitudes. Our objective is to propose a plausible hypothesis for further research.

Materials & Methods

We used incidence data from a meta-analysis published in 2011⁽²⁾. This article gathered published incidences from 27 different studies up to December 2010 and normalized them to represent the "incidence of LCPD in 100,000 children below the age of 15 years." We searched for new inclusion data on PubMed using the query 'Perthes' and 'incidence,' filtered by publication date after 2011. We found three additional articles reporting new geographic incidences^(1,6,9). One article reported incidence per 100,000 of the overall population⁽⁹⁾, which was excluded. The incidence in four new locations was obtained from the two remaining articles, bringing the total to 31 locations. The mean incidences were considered for analysis. The geographic coordinates of each location were obtained from a geo-localization website (www.latlong.net). Data on global solar irradiance were obtained from open data sources (<https://pvgis.com/pvmaps>⁽¹⁰⁾, <https://surlargis.com>), and the amount of solar irradiance relative to each location was retrieved (Figure 1).

Data analysis was performed using Pearson correlation test, p-value, and regression curves. We used the Math, Scikit-learn, and Seaborn libraries of Python (www.python.org) to process the data.

Results

We identified 31 regions with known LCPD incidences. The geographic coordinates of these 31 regions were retrieved (Table 1). We then calculated Pearson's correlation coefficients and corresponding p-values between each pair of parameters (Table 2). There is a significant positive correlation between latitude and the incidence of LCPD, and a significant negative correlation between regional solar irradiance and the incidence of LCPD.

We used the Seaborn library in Python to draw scatterplots with regression curves for each pair of data variables (Figure 2). The regression curves were drawn using the "local weighted scatterplot smoothing" (LOWESS) method to show the local patterns of regression⁽¹¹⁾.

Figure 2A shows a sharp decrease in LCPD incidence with increasing solar irradiance, reaching a plateau at a solar irradiance of about 150 Wh/m². Figure 2B is a scatterplot of LCPD incidence relative to latitude, showing a steady LCPD incidence up to about 40 degrees of latitude, followed by a sharp increase thereafter. Figure 2C illustrates the change in solar irradiance with increasing latitude; solar irradiance remains steady up to about 20 degrees of latitude and then sharply decreases at higher latitudes. The red lines indicate the latitude (and corresponding solar irradiance) above which a sharp increase in LCPD incidence is observed.

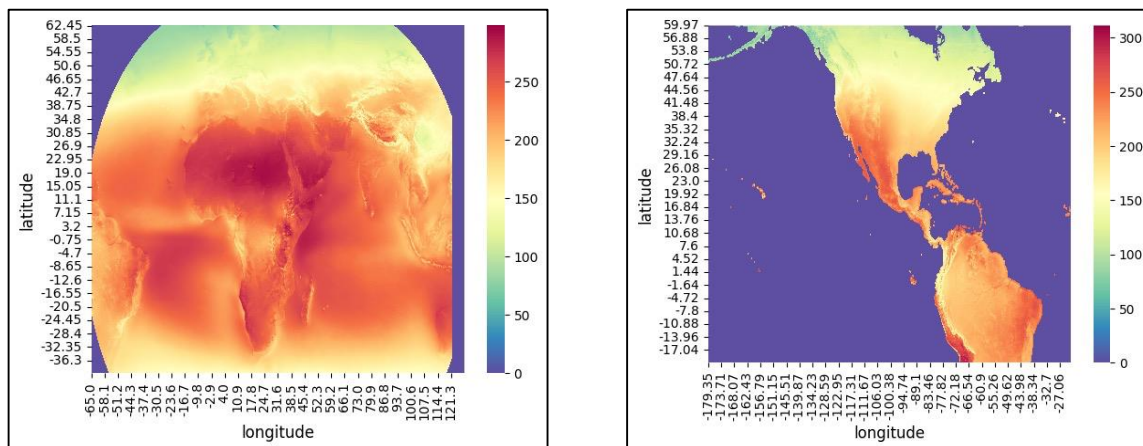


Figure 1: Yearly average global solar irradiance (solar irradiance) on a horizontal surface (wh/m²), period 2005-2020. (from PVGIS.com)

Table 1: List of our data for analysis

	Location	Latitude	Longitude	Incidence	Solar irradiance
1	Uppsala	59.9	17.65	8.5	106.4
2	Knowsley	53.45	-2.85	11.7	110.7
3	Liverpool1	53.45	-2.95	15.5	112.0
4	Hong Kong	22.3	114.2	0.2	171.9
5	Vellore	12.95	79.15	0.3	238.5
6	Kurunegala	7.5	80.4	4.4	228.9
7	Faroe Islands	61.9	-6.9	14.3	81.0
8	Malmo	55.65	13.05	14.6	120.1
9	Norway	60.5	8.5	9.2	95.4
10	Zealand	55.45	11.6	7.4	117.0
11	South Jutland	55.65	9.7	19.1	113.0
12	Dumfries and Galloway	55.1	-3.5	15.4	104.5
13	Northern Ireland	54.8	-6.45	11.6	103.5
14	Yorkshire and Humberside	53.6	-0.1	6.1	114.5
15	British Columbia	54.15	-126.55	5.1	123.8
16	Sefton	53.55	-2.95	4.8	112.8
17	Merseyside	53.4	-3.0	11.3	111.8
18	Trent	53.05	-2.15	7.4	107.6
19	Netherlands	52.15	5.3	8.8	116.8
20	Wessex	51.3	-0.75	5.7	119.5
21	Czech Republic	49.85	15.5	10.2	127.0
22	Massachusetts	42.45	-71.35	5.7	163.2
23	Japan	36.25	138.3	0.9	150.6
24	South Honam	37.6	127.0	3.8	142.9
25	Eastern Cape	-32.1	26.5	2.4	217.8
26	Manipal	13.4	74.8	2.9	233.2
27	Liverpool2	53.45	-2.95	9.3	112.0
28	California	36.8	-119.4	2.84	221.6
29	London	51.55	-0.1	4.6	119.8
30	Wales	52.15	-3.75	8.6	104.1
31	Scotland	56.5	-4.2	10.39	91.7

Table 2: Pearson Correlation and p-values between Latitude, Solar irradiance, and LCPD Incidence parameters

	Solar irradiance	LCPD incidence
Latitude	-0.86 (p<0.05)	0.61 (p<0.05)
Solar irradiance	-	-0.67 (p<0.05)

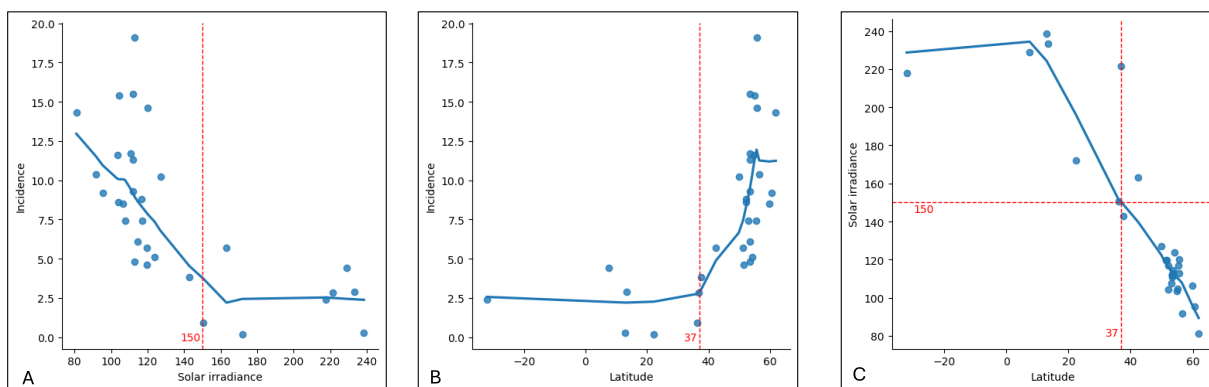


Figure 2: Scatterplot Between Pairs of Parameters with p-value < 0.05. The regression lines are drawn using the "LOWESS method" to show local patterns of regression.

Discussion

LCPD, or idiopathic osteonecrosis of the femoral head, initiates with a vascular insult to the femoral head⁽¹²⁾. The etiology of this disease remains unresolved. Previous studies have indicated that a local vascular occlusion at the lateral epiphyseal arterial supply of the juvenile femoral head is the initiating event⁽³⁾. However, vascular occlusion due to a hypercoagulable state caused by genetic deficiencies in protein C or S, factor V Leiden mutation, overactivity of FVIII, or prothrombin has not shown consistent relationships⁽¹³⁾. There is a strong association between social deprivation and increased incidence of LCPD^(5,6).

Synovitis of the hip joint and trauma to the hip joint have been proposed as contributing etiologic factors⁽⁷⁾. Genetic susceptibility of Northern Europeans (Caucasians) has been suggested as a factor⁽²⁾; however, there is no hereditary pattern of transmission⁽⁷⁾. In a robust Danish study using an identical twins registry, no co-occurrence was found in the co-twin of identical twins⁽¹⁴⁾. The Age of disease onset is similar across different geographic locations and some authors have suggested the presence of an unknown antenatal triggering phenomenon^(15,16). LCPD is associated with low birth weight, low APGAR scores, breech delivery, being preterm or post-term⁽¹⁷⁾, low birth height⁽¹⁶⁾, rostral-sparing dwarfism⁽¹⁸⁾, and congenital anomalies including Down's syndrome, inguinal hernia, and genitourinary malformations^(16,19). LCPD is associated with asthma, behavioral disorders⁽¹⁹⁾, and metabolic disorders including obesity and hypothyroidism⁽²⁰⁾. Socioeconomic deprivation can be a confounding factor for several LCPD associations, including asthma, passive smoking, low birth weight and height, and abnormal growth⁽⁷⁾ and behavior. Nutritional deficiency has also been proposed as an etiologic factor, investigation into the role of manganese deficiency in the initiation of LCPD have yielded inconsistent findings⁽²¹⁾.

Overall, besides a genetic susceptibility, it seems that the key triggering event is an environmental factor related to social deprivation during the antenatal or early childhood period, leading to (or making the femoral head ready for) a localized vascular occlusion of lateral femoral epiphyseal arteries⁽⁷⁾.

Vascular insufficiency of the femoral head results in osteonecrosis of a variable-sized part of the head, and the gradual revascularization of this necrosed

part progresses through three main stages: fragmentation, re-ossification, and remodeling⁽¹²⁾. The prognosis of LCPD depends on the final shape of the femoral head. A better prognosis is associated with younger age at disease onset (before six years of age), volume of necrosis (less than 50%), and shorter duration of the fragmentation stage⁽¹²⁾. During the fragmentation stage, absorption of the necrosed part of the head makes the head less rigid and more vulnerable to deformation by forces of weight-bearing or surrounding hip muscles⁽²²⁾.

In this study, we investigated whether decreased sun exposure at higher latitudes correlates with increased incidence of LCPD. Our results show a significant positive correlation between latitude and incidence of LCPD and a significant negative correlation between solar irradiance and incidence of LCPD. Analysis of regression curves indicates that at low latitudes, the incidence is minimal and steady, while it increases sharply at about 40 degrees of latitude (Figure 2B). This latitude corresponds with solar irradiance of approximately 150 Wh/m² (Figures 2A, 2C). The effect of sun exposure on the body is mediated through the production of vitamin D⁽²³⁾. Solar ultraviolet B photons (UVB) are absorbed by 7-dehydrocholesterol in the skin to produce provitamin D₃, which rapidly converts to vitamin D₃. Vitamin D₃ is then metabolized in the liver and kidney to produce 1,25-dihydroxyvitamin D₃, a biologically active molecule⁽²⁴⁾. Vitamin D plays a central role in maintaining normal physiological blood calcium levels by increasing gut absorption of calcium. In vitamin D deficiency, calcium is released from bones to maintain serum calcium levels, diminishing the structural rigidity of bones. Severe vitamin D deficiency causes rickets in children and osteoporosis and osteomalacia in adults. Deficiency of vitamin D₃ has also been associated with risks of cancers, type I diabetes mellitus, cardiovascular diseases, multiple sclerosis, mental health issues, allergies, and autoimmune disorders⁽²³⁻²⁵⁾.

We could not find any reports of vitamin D level measurements in the initial phase of LCPD patients. Therefore, we searched the literature to determine if there is a relation between decreased sun exposure at higher latitudes and decreased vitamin D levels in general population. The degree of solar irradiance depends on the zenith angle of the sun, which is the angle between sun rays and the vertical⁽²³⁾. Time of day, latitude, and season affect the zenith angle of the sun⁽²³⁾. UVB photons are efficiently absorbed by

the atmospheric ozone layer. During winter days and at high latitudes, due to the greater zenith angle, the sun rays pass through an oblique and longer distance through the ozone layer, significantly decreasing the amount of UVB reaching the surface. It is estimated that during winter at latitudes above 37 degrees, the production of vitamin D₃ decreases by about 80-100%^(23,24). Our data shows that above 37 degrees of latitude, there is a sharp increase in the incidence of LCPD (Figure 2B).

Besides the solar zenith angle, other factors can influence the amount of UVB absorbed by the skin, including skin color, time spent outdoors, use of sunscreens, and covered clothing. Some other factors can cause vitamin D deficiency despite sufficient solar exposure, including obesity (sequestration of vitamin D in adipose tissue) and malabsorption of dietary vitamin D (celiac disease or inflammatory bowel disease). There is also a genetic contribution to variation in 25(OH)D levels due to polymorphism of genes involved in vitamin D production, which is as significant as reduced solar exposure⁽²⁴⁾.

Vitamin D deficiency is more prevalent at extreme latitudes in Europe, the United States, and Canada in the Northern Hemisphere, as well as in New Zealand and southern Australia in the Southern Hemisphere. In these regions, there is insufficient UVB exposure during cooler months for adequate vitamin D production. It is estimated that 50% of the population is vitamin D insufficient (25(OH)D level < 30 ng/mL [50 nmol/L]) and 10% is vitamin D deficient (25(OH)D level < 10 ng/mL [< 50 nmol/L])⁽⁸⁾.

We found evidence in the literature indicating higher latitudes have more cases of vitamin D deficiency. Subsequently, we searched the literature to determine if any evidence exists to explain a hypercoagulable state in cases of vitamin D deficiency.

Several studies confirm the anti-thrombotic and anti-inflammatory roles of vitamin D. These effects are mediated by modulating the expression of thrombogenic and anti-thrombogenic molecules and the function of endothelial cells and platelets at the cellular level. Vitamin D directly or indirectly controls the expression of more than 200 genes responsible for regulating cellular proliferation, differentiation, apoptosis, and angiogenesis. Vitamin D deficiency increases the risk of deep vein thrombosis in stroke patients⁽²⁶⁾. Vitamin D deficiency is a known risk factor for cardiovascular disease. Vitamin D induces smooth muscle proliferation, increases vascular

endothelial growth factor, and decreases peripheral vascular resistance by inhibiting the renin-angiotensin-aldosterone system. Vitamin D is a strong inducer of miR-145, the most abundant miRNA in vascular smooth muscle cells, and a principal regulator of their contractile capacity. The association between vitamin D deficiency and acute myocardial infarction persists even after adjusting for major cardiovascular risk factors⁽²⁵⁾. The limitations of our study include chronological discordance between LCPD incidences and solar irradiance measurements due to limitations of available data sources. Ideally, these two observations should be made during the same period, as both the incidence of LCPD and solar irradiance fluctuate over time^(27,28). Another limitation is the disparity in available LCPD incidences. Data from European countries are more available than from other parts of the world (Table 1). The observed higher incidence in Northern Europe may be due to the major genetic susceptibility of the Caucasian race. Epidemiologic studies to find LCPD incidence in Caucasian populations in North Africa and among African immigrants to Northern Europe can be helpful in investigating the role of racial susceptibility in LCPD.

Conclusion

In summary, our findings suggest a potential link between vitamin D deficiency and the increased incidence of LCPD. The evidence supporting this includes:

1. Vitamin D deficiency induces a hypercoagulable state.
2. Vitamin D deficiency is more prevalent at higher latitudes due to reduced sun exposure.
3. There is a higher incidence of LCPD at higher latitudes.

Based on these observations, we propose the hypothesis that decreased vitamin D levels during the antenatal and/or early childhood periods are correlated with an increased incidence of LCPD. This hypothesis is scientifically plausible and merits further investigation through clinical research.

Declaration of Artificial Intelligence usage and conflict of interest

We used "Microsoft Copilot" to enhance the quality of the text, the author has no conflict of interest.

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