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The epidemiology and aetiology of Perthes' disease in Norway

A NATIONWIDE STUDY OF 425 PATIENTS

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A nationwide study of Perthes' disease in Norway was undertaken over a five-year period from January 1996. There were 425 patients registered, which represents a mean annual incidence of 9.2 per 100 000 in subjects under 15 years of age, and an occurrence rate of 1:714 for the country as a whole. There were marked regional variations. The lowest incidence was found in the northern region (5.4 per 100 000 per year) and the highest in the central and western regions (10.8 and 11.3 per 100 000 per year, respectively). There was a trend towards a higher incidence in urban (9.5 per 100 000 per year) compared with rural areas (8.9 per 100 000 per year). The mean age at onset was 5.8 years (1.3 to 15.2) and the male:female ratio was 3.3:1.

We compared 402 patients with a matched control group of non-affected children (n = 1 025 952) from the Norwegian Medical Birth Registry and analysed maternal data (age at delivery, parity, duration of pregnancy), birth length and weight, birth presentation, head circumference, ponderal index and the presence of congenital anomalies. Children with Perthes' disease were significantly shorter at birth and had an increased frequency of congenital anomalies.

Applying Sartwell's log-normal model of incubation periods to the distribution of age at onset of Perthes' disease showed a good fit to the log-normal curve. Our findings point toward a single cause, either genetic or environmental, acting prenatally in the aetiology of Perthes' disease.

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Great variability has been reported regarding the incidence of Perthes' disease in different populations. Several authors have reported a low incidence in Asian countries[1-4] and others an intermediate incidence varying from 5.1 to 11.6 per 100 000 per year.[5-10] The highest incidence has been reported in inner-city Liverpool,[11] and the Faroe Islands[12] of 21.1 and 29.4 per 100 000 per year, respectively.

The aetiology of Perthes' disease is unclear. Several authors have suggested contributory factors such as delayed skeletal maturity,[13] impaired and disproportionate growth,[14] short stature,[14,15] low birth-weight,[16,17] social and economic deprivation,[7,8,10,11,18] trauma and an association with congenital anomalies.[19-22] The aim of this study was to investigate the epidemiological and aetiological features of Perthes' disease in Norway.

Patients and Methods

In January 1996 the Norwegian Paediatric Orthopaedic Society started a nationwide study on Perthes' disease. All 28 hospitals with a paediatric orthopaedic department (six university clinics, 16 county hospitals and six local hospitals) in all 19 counties were asked to report all new cases of Perthes' disease over a period of five years. The diagnosis was established by a local orthopaedic surgeon on the basis of clinical and radiological examination. The cases comprised both in-patients and out-patients. Information concerning family history and clinical symptoms was recorded by the treating orthopaedic surgeon. The age at diagnosis for boys and girls and for both genders combined was analysed. The radiographs were classified according to the radiological classifications of Catterall,[23] Salter and Thompson[24] and Herring et al.[25]

A total of 399 patients were identified and registered. The radiographs were collected and reviewed by two independent paediatric orthopaedic surgeons (SS and TT).

In order to find new unreported cases of Perthes' disease we carried out an audit in 2003. The registries of all the participating hospitals were checked by the local orthopaedic surgeons to ensure that the reported incidence was as close to the true incidence as possible. All

Table I. Number of cases, mean annual incidence (per 100 000 up to 15 years of age) for Perthes' disease in Norway between 1996 and 2000

		Number of patients		Incidence		95% CI*		p values	
Region	**County**	**Region**	**County**	**Region**	**County**	**Region**	**County**	**Region**	**County**
East	Oslo	121	28	7.9	6.4	6.1 to 9.8	3.3 to 9.5	Reference value	0.323
	Akershus		41		8.1		4.9 to 11.4		reference value
	Hedmark		18		10.2		4.0 to 16.4		0.120
	Oppland		13		7.5		2.1 to 12.9		0.630
	Østfold		21		8.9		3.9 to 13.9		0.256
South	Vestfold	88	20	9.9	9.3	7.2 to 12.6	4.0 to 14.8	0.116	0.913
	Buskerud		24		10.3		4.9 to 15.8		0.084
	Telemark		12		7.4		1.9 to 12.8		0.683
	Aust-Agder		12		11.0		2.8 to 19.2		0.115
	Vest-Agder		20		11.5		4.9 to 18.2		0.044
West	Rogaland	113	45	10.9	10.3	8.3 to 13.6	6.3 to 14.2	0.014	0.049
	Hordaland		48		10.1		6.3 to 13.8		0.055
	Sogn og Fjordane		20		16.7		7.1 to 26.3		0.001
Central	Møre og Romsdal	76	35	11.3	13.4	8.0 to 14.6	7.6 to 19.3		0.003
	Sør-Trøndelag		33		12.1		6.7 to 14.6	0.015	0.013
	Nord-Trøndelag		8		5.8		0.5 to 11.1		0.804
North	Nordland	27	16	5.4	6.3	2.7 to 8.1	2.2 to 10.3	0.070	0.948
	Troms		8		4.9		0.4 to 9.4		0.514
	Finnmark		3		3.6		0.0 to 9.0		0.345
Total	Norway	425		9.2					

* 95% CI, 95% confidence interval. Eastern region and Akershus county were used for reference purposes for the statistical analysis

cases referred to the participating hospitals were identified either through the radiographic archives or through the computerised diagnostic coding systems. In this way 26 previously unreported children were detected. Thus, a total of 425 patients were included in the study. There were 325 boys and 100 girls, giving a ratio of 3.3:1.

The average annual incidence and occurrence rate were calculated for the country as a whole and for each county based on population data from Statistics, Norway.[26] The occurrence rate measures cases appearing in a group of children followed throughout the period of risk.[5] The total occurrence rate for Perthes' disease was computed by adding annual incidence rates up to the age of 15 years. Urban and rural incidence rates were calculated separately. The four largest cities (Oslo, Bergen, Trondheim and Stavanger) were considered as urban areas and the rest of the country as rural.

Confidence intervals for the incidences were calculated based on a Poisson assumption for the standard error. Differences between incidences were analysed in a Poisson regression model, with the most populus county (Akershus) and the east region of Norway as reference categories, against which the other counties or regions were compared.

There were 402 patients in the study who were linked to data from the Medical Birth Registry of Norway and compared to a matched control group (n = 1 025 952) of non-affected children born in Norway during the 17-year period between 1981 and 1998. The data were matched using the Norwegian 11-digit unique personal identification number, and thereafter anonymised. Owing to insufficient or incorrect birth numbers, we were unable to link 23 children. We analysed maternal data (age at delivery, parity, duration of pregnancy), birth length and weight, presentation (breech, transverse lie or other malposition), head circumference, ponderal index (kg/m^3) and the presence of congenital anomalies, including meningoencephalocoele, spina bifida, amelia or dysmelia of extremities, congenital dislocation of the hip, club foot, cleft lip and/or palate, atresia of the oesophagus and rectum, renal agenesia, omphalocoele, gastrochisis, hypospadias, hiatus hernia, transposition of the great vessels, hypoplastic left ventricle syndrome and Down's syndrome.

Children with a birth-weight under the tenth percentile for all categories of gestational week and for both genders were classified as small for gestational age. The data on congenital anomalies were reported by the attending physician or midwife after the mandatory examination at the time of birth, and coded at the Medical Birth Registry using the international statistical classification of diseases, injuries and causes of death (ICD)-8 (prior to 1998) and ICD-10 systems.

Sartwell[27] studied the incubation periods of infectious diseases and found that they were approximately normally distributed. Armenian and Lillenfeld[28] applied Sartwell's method to a number of neoplasms and found that the incubation periods approximated to a log-normal distribution. In 1981, Armenian and Khoury[29] found that different genetic diseases with onset after birth fitted the Sartwell

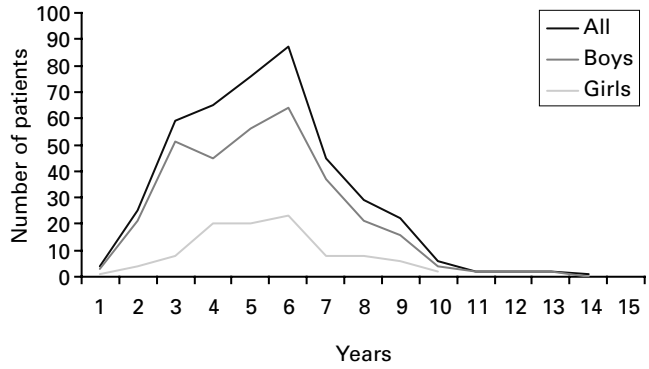

Fig. 1

Age distribution at time of diagnosis for Perthes' disease in Norway between 1996 and 2000.

model, whereas diseases with a multifactorial aetiology did not. We examined our series by Sartwell's log-normal model of incubation periods.

For the statistical analyses we used logistic regression with Perthes' disease as the dichotomous outcome. The numeric variables were categorised according to standards given by the Medical Birth Registry in Norway. All explanatory variables were run in simple models, only estimating the effect for the single variable one at a time. Thereafter, a multiple logistic regression was carried out for the explanatory variables that were statistically significant in the simple analyses. The categorical data were analysed by the chi-squared test. The Kolmogorov-Smirnov test was used to assess the fit to Sartwell's log-normal model. All analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois). A p value ≤ 0.05 was considered to be significant.

Results

The mean annual incidence of the 425 patients registered during the five-year period was 9.2 per 100 000 in subjects under 15 years of age, with a total occurrence rate of 1:714. The incidences are presented in Table I. They varied from 3.6 per 100 000 in Finnmark county to 16.7 per 100 000 in Sogn og Fjordane county. When using the highest populated county (Akershus) as reference category, Sogn og Fjordane, Møre og Romsdal and Sør-Trøndelag county had a significantly higher incidence (p = 0.001, 0.003 and 0.013, respectively). Occurrence rates varied from 1:1818 in Troms to 1:384 in Sogn og Fjordane.

We found a significantly higher incidence in the central (p = 0.015) and western (p = 0.014) regions (11.3 and 10.9 per 100 000) in subjects under 15 years of age), compared with the eastern region. The northern region had the lowest incidence rate (5.4 per 100 000). The mean annual incidence in the urban areas was 9.5 per 100 000 in subjects under 15 years of age. The rural areas had a slightly lower incidence (8.9 per 100 000). There was no variation in age distribution between urban and rural areas.

The age distribution is shown in Figure 1. Mean age at diagnosis for both genders combined was 5.8 years (1.3 to 15.2), for boys 5.8 years (1.3 to 15.2), and for girls 5.9 years (1.3 to 15.2). The difference was not statistically significant. No cases were reported under the age of 1.3 years or over the age of 15.2 years. Of the children, 95% (404) were between 3.0 and 10.0 years of age. There were two sets of twins and two pairs of siblings.

Bilateral disease occurred in 13% (55) of the patients. In unilateral cases there was no significant difference between presentation in the left hip (47.6% (202)) or the right hip (39.3% (167)) (p = 0.07). A total of 16 (4%) children had transient synovitis of the hip prior to developing Perthes' disease, and 20% (85) had a history of hip disease in the family. The mean duration of symptoms before diagnosis was 4.6 months (0 to 29) for boys and 4.2 months (0.5 to 16) for girls, and for both genders combined was 4.5 months (0 to 29).

At the time of diagnosis 91% (387) of the patients had pain or discomfort. Of those who complained of pain, approximately two-thirds had mild, and the remainder considerable pain. A total of 50% (213) of the children had pain in the hip and thigh, 18% (76) in the thigh and knee, 14% (60) in the knee only, 8% (34) had symptoms from hip, thigh and knee and 1% (4) had pain in other areas; 9% (38) of the patients had no pain. The majority of children (391; 92%) had a limp at the initial examination.

The results comparing our material and controls from the Medical Birth Registry in Norway are presented in Table II. We found that children with Perthes' disease were significantly shorter at birth (p = 0.007, odds ratio (OR) = 1.31). Omitting children with congenital anomalies from the analysis did not change this finding. In addition, there was a statistically significantly higher rate of congenital abnormalities (p = 0.001, OR = 2.00) in children with Perthes' disease. The multiple regression analyses adjusting for possible confounding factors showed similar results (Table III). There were nine cases of congenital dislocation of the hip among children with Perthes' disease (Table IV), which is significantly higher than among unaffected children (p < 0.001, 95% confidence interval 2.14 to 8.02). When dividing the congenital anomalies according to location, we found that anomalies in the lower body (pelvis and lower extremities) were more prevalent in children with Perthes' disease compared with the controls. This was also the case in the upper body, but there were few observations of rare anomalies and the 95% confidence intervals were wider. Hence these observations lack sufficient strength to be conclusive. We found no significant differences between children with Perthes' disease and the control group with regard to the other parameters analysed (Table II).

When applying Sartwell's[27] log-normal model of incubation periods to our series (Fig. 2), we found that age at onset approximated a log-normal model (p = 0.069).

Table II. Simple logistic regression analysis comparing Perthes' cases (n = 402) and controls (n = 1 025 952) from the Medical Birth Registry of Norway

Parameter		Controls*	Perthes'	Odds ratio	95% CI†	p value
Mother's age (yrs)	< 25	298 456	108	0.90	0.72 to 1.13	0.37
	25 to 35	628 288	252	1	-	-
	> 35	99 710	42	1.05	0.76 to 1.46	0.77
Plurality	1 child	999 716	389	1	-	-
	2 or more children	26 638	13	1.25	0.72 to 2.18	0.42
Parity	First born	430 433	154	0.86	0.70 to 1.05	0.14
	Later born	589 265	245	1	-	-
Malposition	No	971 796	378	1	-	-
	Yes	54 558	24	1.31	0.75 to 1.71	0.56
Breech birth	No	989 320	385	1		
	Yes	37 034	17	1.18	0.73 to 1.92	0.51
Child's birth-weight (g)	< 2500	53 222	25	1.26	0.84 to 1.90	0.27
	2500 to 4000	774 925	289	1	-	-
	> 4000	195 835	88	1.21	0.95 to 1.53	0.13
Child's birth length (cm)	< 50	389 276	179	1.31	1.08 to 1.60	0.007
	> 50	637 078	223	1	-	-
Gestational age (wks)	< 38	102 350	47	1.11	0.81 to 1.52	0.514
	38 to 40	512 871	212	1	-	-
	> 40	324 572	107	0.80	0.63 to 1.01	0.056
Head circumference (cm)	< 35	325 945	119	0.90	0.73 to 1.12	0.35
	> 35	700 409	283	1	-	-
Gender	Boys	527 865	308	1	-	-
	Girls	498 821	94	0.32	0.26 to 0.41	< 0.001
Congenital anomaly	No	993 410	377	1	-	-
	Yes	32 944	25	2.00	1.33 to 3.00	0.001
Major congenital anomaly	No	1 003 543	382	1	-	-
	Yes	22 811	20	2.30	1.47 to 3.61	< 0.001
Small for gestational age	No	945 269	366	1	-	-
	Yes	81 085	36	1.15	0.81 to 1.62	0.43
Ponderal index (kg/m^3)	< 28	515 391	185	1	-	-
	> 28	471 704	205	0.83	0.68 to 1.01	0.059

* owing to insufficient information only 402 children could be matched to the Medical Birth Registry of Norway control group

† 95% CI, 95% confidence interval

Table III. Multiple regression analysis comparing Perthes' cases (n = 402) and controls (n = 1 025 952) from the Medical Birth Registry of Norway

		Controls*	Perthes'	Odds ratio	95% CI†	p
Birth length (cm)	< 50	389 276	179	1.51	1.24 to 1.84	< 0.001
	> 50	637 078	223	1	-	-
Gender	Boys	527 865	308	1	-	-
	Girls	498 821	94	0.31	0.24 to 0.39	< 0.001
Congenital anomaly	No	993 410	377	1	-	-
	Yes	32 944	25	1.88	1.25 to 2.82	0.002

* owing to the insufficient information only 402 children could be matched to the Medical Birth Registry of Norway control group

† 95% CI, 95% confidence interval

Table IV. Comparison between children with Perthes' disease (n = 402) and controls (n = 1 025 952) regarding presence of congenital abnormalities and their localisation, divided into lower body (pelvic region and lower extremities), upper body (abdomen, thorax, viscera, upper extremities and head) and general (whole body)

Congenital anomalies†	Number of patients*		p value	95% CI‡	Localisation of abnormality in cases (n)	p value	95% CI
	Cases	Controls					
Congenital dislocation of hip	9	5470	< 0.001	2.14 to 8.02			
Undescended testicle	3	1570	0.005	1.62 to 15.72	Lower body	< 0.001	2.22 to 6.24
Clubfoot	2	1859	0.47	0.29 to 14.8	(15)		
Hypospadias	1	1463	0.56	0.25 to 12.83			
Reduction anomaly of upper lLimb	1	278	0.025	1.33 to 67.9	Upper body	0.001	2.12 to 15.23
Anomaly of skull and facial bones	1	231	0.015	1.60 to 81.9	(4)		
ASD	1	162	0.005	2.29 to 117.2			
VSD	1	1188	0.43	0.31 to 15.31			
Down's syndrome	5	858	< 0.001	6.37 to 47.31	General	< 0.001	7.84 to 39.53
Flexion contracture of limbs	1	46	< 0.001	8.05 to 425.7	(6)		
Total	25	13 125	0.001	1.33 to 3.00			

* owing to the insufficient information only 402 children could be matched to the Medical Birth Registry of Norway control group

† ASD, atrial septal defect; VSD, ventricular septal defect

‡ 95% CI, 95% confidence interval

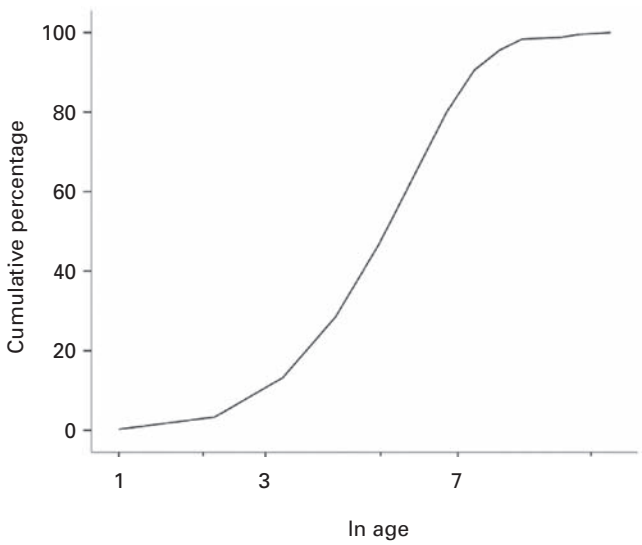

Fig. 2

Sartwell's log-normal model of incubation periods applied to age at diagnosis in Perthes' disease (n = 425) (ln is the logarithm of age at onset of Perthes' disease).

Discussion

The average annual incidence rate for the country as a whole was 9.2 per 100 000 in subjects under 15 years of age, and the occurrence rate was 1:714, which is higher than that reported in Massachusetts[5] (5.7 per 100 000) and Yorkshire[8] (6.1 per 100 000). Our incidence was similar to those reported for the Trent region in England[7] (7.6 per 100 000), Uppsala, Sweden[9] (8.5 per 100 000) and in the white population of South Africa[30] (10.8 per 100 000). The incidence in Norway was considerably lower than in the Faroe Islands[12] (29.4 per 100 000), Liverpool[11] (21.1 per 100 000) and Northern Ireland[10] (11.6 per 100 000). The lowest incidences have been reported in Asian countries[1-4] (1 in 0.45 million in South China; from 0.4 to 14.4 per 100 000 in South India) and British Columbia[6] (5.1 per 100 000). As reported in some English studies,[7,8,12] we found a somewhat higher incidence in urban regions.

We found the lowest incidence in the northern region of the country and the highest in the central and western regions. As the northern part of Norway is the most sparsely populated, one could argue that patients living at some distance from hospitals are less likely to be referred to an orthopaedic surgeon for treatment. However, it is unlikely that general practitioners would treat a child with a painful limp (92% of the patients in this study) without consulting a specialist. We therefore assume that the variation in the occurrence of Perthes' disease reflects variations in the true incidence. The male:female ratio of 3.3:1 was lower than that found in Massachusetts[5] (5:1) and British Columbia[6] (5.2:1). The mean age of onset was 5.8 years, which is in accordance with the findings of Kealey et al[10] and comparable with those of Barker et al.[7] The age distribution was similar to that of other studies.[5,7-9]

Several authors have reported short stature, above-average weight, impaired and disproportionate growth as well as decreased skeletal maturation at the time of diagnosis in children with Perthes' disease.[13-17] Our results showed that children with Perthes' disease were significantly shorter at birth than controls. This has not been reported previously.

Molloy and MacMahon[16] found significantly lower birth-weight among 74 white children with Perthes' disease compared to a matched control group, and Lappin et al[17] observed an association between low birth-weight and Per-

thes' disease in five sets of twins. However, like Fisher[31] we found no association between low birth-weight and Perthes' disease.

Catterall et al[19] reported an increased incidence of congenital anomalies of the genitourinary tract, both in children with Perthes' disease and in their near relatives. Several congenital anomalies associated with Perthes' disease were found by Wynne-Davies and Gormley.[20] Hall et al[21] found a high incidence of minor congenital anomalies in children with Perthes' disease. Katz[22] reported a high incidence of spina bifida occulta, although he did not find sufficient evidence to prove a relationship between the two conditions. Harper, Brotherton and Cochlin[32] were unable to confirm an association between Perthes' disease and congenital malformations of the genitourinary tract, and Fisher[31] found no association with regard to infections, trauma or congenital anomalies in children with Perthes' disease.

As opposed to Fisher,[31] and Harper et al,[32] and in accordance with Catterall et al,[19] Wynne-Davies and Gormley[20] and Hall et al,[21] we found a significantly increased rate of congenital anomalies among children with Perthes' disease. There was an unexpectedly high incidence of congenital dislocation of the hip (n = 9) in our cohort, and we were able to trace and interview seven of these children and their parents. The parents of three children recalled the location of the dislocation, and all of these developed Perthes' disease on the opposite side. All the parents reported that their children had been treated with a Frejka's pillow (Loren Bedriftservice A/S, Oslo, Norway) for at least four months, and that they recovered before developing Perthes' disease several years later. Hence it is improbable that these children developed avascular necrosis as a complication of splintage for their congenital dislocation of the hip initiating Perthes' disease later in childhood. Our findings agree with the assumption of Catterall et al[19] that there is a higher incidence of anomalies in the pelvic region in children who develop Perthes' disease later in life (Table IV).

Burwell et al[14] suggested that children with Perthes' disease have an abnormal allometric growth producing impaired and disproportionate growth at the time of diagnosis, which is more likely to be determined in prenatal life due to rostral sparing. Barker[33] referred to the fetal origin hypothesis, a contemporary theory that links low birth-weight and short-body length to disease later in life. Low birth-weight and short body-length at birth were associated with increased rates of cardiovascular disease and non-insulin-dependent diabetes in adult life. The hypothesis proposes that these conditions originate through adaptations that the fetus makes when it is undernourished. These early defects in the development, structure and function of organs lead to a programmed susceptibility that interacts with later diet and environmental factors, and causes disease later in life.[34]

In our study, children with Perthes' disease had normal birth-weight, normal head circumference, and were not small for their gestational age, but they were significantly shorter at birth ($p = 0.007$) than the control group. To the best of our knowledge, this has not previously been reported. This may indicate that short stature and a certain degree of disproportionate growth is already present at birth. In light of the theories put forward by Burwell et al[14] and Barker[33] combined with the results of our study, one could speculate whether a similar mechanism causing impaired skeletal growth *in utero* is partly responsible for the development of Perthes' disease in childhood.

Wynne-Davies and Gormley[20] found that Perthes' disease occurred particularly in children who were born third or later in the family. In addition, they found that one in ten affected children had had a breech or another abnormal presentation at birth, and they reported a significantly higher parental age than parents of non-affected children and a difference in birth-weight distribution compared to normal children. We were not able to confirm the findings of Wynne-Davies and Gormley[20] regarding the association between parity, plurality, parental age, breech birth and Perthes' disease.

Sartwell's[27] log-normal model was originally used to study incubation periods for infectious diseases in order to decide whether a particular epidemic was due to a simultaneous infection of all members of a group or whether successive infections took place over a period of time. He found that the incubation periods of diseases with a known single infectious agent fitted a log-normal curve, whereas diseases with a multifactorial aetiology did not. Armenian and Khoury[29] postulated that age at onset of genetic diseases corresponded with the incubation periods of these diseases, and considered conception as the 'exposure', and the duration of pregnancy plus age at onset as the incubation period for that particular disease. They reviewed the literature for well-defined genetic diseases and diseases with ill-defined genetic aetiology or strong environmental influences, and applied Sartwell's model to the age at onset of these diseases. They found that age at diagnosis for diseases with well-defined genetic aetiology fitted the log-normal curve, whereas diseases with an ill-fitted genetic aetiology or strong environmental influences did not. Hall and Barker[35] applied the Sartwell model to eight published series of Perthes' disease and found that all but two series fitted the log-normal curve. Their findings were consistent with a single cause acting before two years of age. We applied the Sartwell model to our series (Fig. 2) and found that the age at onset approximated a log-normal curve. As Figure 2 shows, the curve is flattened at the lower and upper ends where the case numbers are very few, and thus the presence or absence of a log-normal distribution will be uncertain.

Barker and Hall[18] stated that the balance of epidemiological evidence points to the major environmental determinants of Perthes' disease operating at a critical stage in early life before the age of two years. They are more likely to be post- than pre-natal and are associated with low social class and deprived areas of cities.

Our study shows a marked regional variation of incidence of the disease throughout the country, but only a slight difference between urban and rural areas. The log-normal distribution of age at onset, combined with short stature, disproportional growth at birth and an increased frequency of congenital anomalies, point toward a single agent, either genetic or environmental, acting pre-natally to cause a susceptibility to Perthes' disease later in childhood.

No benefits in any form have been received or will be received from a commercial party related directly or indrirectly to the subject of this article.

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