Abstract

Introduction; It is well established that there is a strong association between Perthes' disease and worsening socioeconomic deprivation. It has been suggested that the primary determinant driving this association is exposure to tobacco smoke. This study aimed to examine this hypothesis.

Method: A hospital case-control study (n=149/146) examined the association between tobacco smoke and Perthes' disease, adjusting for area-level socioeconomic deprivation. Tobacco smoke exposure was assessed by parental questionnaire of smoking habits during pregnancy, and by quantitative assay of current exposure; urinary cotinine-creatinine ratio – a widely used and validated measure of tobacco smoke exposure.

Results: The odds of Perthes' disease significantly increased with reported in-utero exposure after adjustment for socioeconomic deprivation (maternal smoking odds ratio (OR) 2.06 (95% CI 1.17 – 3.63), paternal smoking - OR 2.09 (95% CI 1.26 – 3.46). The cotinine-creatinine ratio was significantly greater in cases (OR 1.63 (1.09 – 2.43)), suggesting a greater 'dose' of current tobacco exposure.

Conclusion: An association exists between tobacco smoke exposure and Perthes' disease, however we remain unable to disentangle the association with socioeconomic deprivation.

Take Home Message: Perthes' Disease is associated with tobacco smoke exposure, but we are unable to determine if this is causal; it may be the result of residual confounding.

Introduction

Perthes' disease is one of the most common diseases presenting to children's orthopaedic surgeons, with a nationwide study suggesting a lifetime incidence of approximately 1:850[1]. Internationally, children of white ancestry and residing at higher latitudes have an increased risk of disease[2]. There is strong evidence of a major association with socioeconomic deprivation[1,3-7] with disease incidence rates in the most deprived communities consistently greater than in the most affluent. There are few other diseases in children with such a strong association with deprivation, yet the underlying explanatory determinant remains elusive.

In much of the world, and particularly the UK, a strong association is known to exist between socioeconomic deprivation and tobacco smoke exposure[8-9]. This has led to the hypothesis that tobacco smoke may be one explanatory 'link' between socioeconomic deprivation and Perthes' disease. This hypothesis was first suggested because early studies of Perthes' disease identified a possible association between low birth weight and Perthes' disease[10], and children of smokers were known to have significantly reduced birth weights[11]. There is increasing evidence to suggest that no association exists between birth weight and Perthes' disease[12-13], however tobacco smoke exposure continues to be of significant aetiological interest as it may exert an effect in the early postnatal period. One currently proposed mechanism includes the development of tobacco smoke-related vessel wall damage leading to arterial infarction in the femoral epiphysis[12].

Studies of tobacco smoke exposure are difficult to perform. Parental smoking questionnaires are vulnerable to both recall and guilt/concealment bias. An

alternative, objective means of quantifying tobacco smoke exposure is the measurement of cotinine (a metabolite of nicotine) within body fluids (saliva/ serum/ urine). Cotinine is a widely used validated, quantitative measure of tobacco smoke exposure that offers a 'snapshot' of recent tobacco smoke exposure. It has demonstrated associations between passive smoking and middle ear infections[14], asthma[15-16] and respiratory syncytial virus[17]. Urinary cotinine is non-invasive and quantifies tobacco exposure over the previous 3 to 4 days[18-20].

This study is the first to begin to quantify the association between environmental tobacco smoke and Perthes disease using a parent-reported tobacco smoke exposure questionnaire to capture exposure during the life of the child, and urinary cotinine as a biological measure of current tobacco smoke exposure.

Methods

A case-control study was undertaken at a large tertiary referral centre and the sole provider of care for children with Perthes' disease within a wide geographic area. The study was part of a broader study, some of which has been described previously[21-22]. Cases were drawn from a regional Perthes' register. Cases were aged 5 – 16 years and were undergoing observation following a diagnosis of Perthes' disease, with exclusions made for multiple epiphyseal dysplasia (MED), cerebral palsy and developmental hip dysplasia (DDH) owing to a known independent association with avascular necrosis of the hip. No cases were actively being treated with immobilisation, and all were at least 4 months following the last surgical intervention, to try to ensure that measures of 'current exposure' to tobacco smoke were as representative as possible of normal exposure.

The protocol for managing Perthes' disease at the centre, and the justification for this approach, is documented elsewhere[23]. In brief, patients with a marked restriction of hip abduction (>20 degrees), undergo surgical containment of the hip, and patients without such restriction undergo active observation without the use of any immobilisation device.

Controls were an age and sex stratified sample of the orthopaedic outpatient population, frequency matched on a 1:1 basis. Frequency matching is a technique to match patient characteristics of the groups broadly, rather than trying to match patients on a 1:1 basis, this is simpler to perform and the analysis generally becomes less complex enabling different statistical techniques (i.e. unconditional regression vs. conditional regression). Age matching occurred within 2 groups: 5 – 10 years old, 11 – 16 years old. Controls were drawn from a number of children's orthopaedic outpatients clinics at the study centre, including knee clinic, general orthopaedic clinic, normal variants clinic and trauma clinic. Any controls with a restriction in hip movement, unless a clear alternative diagnosis was apparent, were excluded. On each sampling day all eligible controls were approached for inclusion. Controls with MED, cerebral palsy and DDH were excluded, as were patients actively immobilised (irrespective of site of pathology) and those within 4 months of surgery.

We assessed current and in-utero tobacco smoke exposure using two complimentary approaches. Firstly, a parental smoking questionnaire was administered which included questions from the 'Environmental Health Surveys in Merseyside'[24]. This is a previously developed questionnaire that details current and prenatal tobacco smoke

exposure in children. For children actively exposed to tobacco smoke at home, it sought an estimate of the quantity of cigarettes consumed per day by the mother and father. The questionnaire was completed by whichever parent attended the hospital visit with the child. In-utero exposure was determined based on a bivariable response (yes/no) to the question "Did the mother/father of the child smoke during this child's pregnancy?" – information for each parent was asked separately. Parents were also asked to recall their child's birthweight.

In addition to the questionnaire, each child was asked to provide a urine sample for urinary cotinine measurement. Urine samples were refrigerated immediately after donation and frozen within 6 hours at -20 °C. Cotinine was measured on all samples en masse using Tandem Mass Spectrometry (TMS). Cotinine values are typically expressed as a ratio of the urinary creatinine concentration to overcome any dilutional effect.

A measure of deprivation was included in the analysis because deprivation is the only consistently reported risk factor for Perthes' disease. This was assessed using the 2007 index of multiple deprivation (IMD-2007) score[25]. The IMD Score is a UK national tool for measuring deprivation, which is based upon routinely collected national data that is applied to a local geographic area. This is broadly based on seven domains of information, namely (1) household income, (2) employment status, (3) health deprivation and disability (4) education, skills & training, (5) barriers to housing and services (6) crime, and (7) the living environment[26]. Addresses are assigned a score based on their postal code (akin to zip code) which quantifies the degree of area deprivation. England and Wales is divided into 34,378 Lower Super

Output Area (LSOA) with approximately 400 households or 1,500 residents for each area. The IMD has undergone several iterations since 2007, but the IMD-2007 was the most temporally well-matched version of the score for the period of the study.

This study received research ethical approval (REC-09/H1001/71).

Statistical Analysis

Analysis was conducted using bivariable analyses, and then a multivariable model. Logistic regression analysis was conducted adjusting for age at the time of the study as a continuous variable and sex. Adjustment for socioeconomic deprivation was made within a separate logistic model based on the area deprivation score derived from the postcode. All data analysis was conducted using Stata 10 (Statacorp, College Station, TX, USA).

The distribution of urinary cotinine-creatinine ratio (CCR) was positively skewed, and a log transformation was used for analyses. P values less than 0.05 (two tailed) were considered statistically significant.

Results

Two hundred and ninety five individuals participated (149 cases and 146 controls). 63% percent (149 of 235 individuals) of cases approached agreed to participate. There was no difference in the age and sex distribution of non-participants, but they were typically from more deprived areas compared to participants based upon postcode deprivation score (Case IMD Score 31.62 (95% CI 28.3 – 34.9), Controls IMD Score 37.6 (95% CI 34.1 – 41.1), non-participants IMD Score 46.9 (95% CI 41.1 – 52.8)).

The demographic composition of cases and controls is illustrated in table 1. The composition of controls by region of pathology and the nature of the aetiology (trauma/ elective) is also detailed.

Table 1 - Characteristics of the study population.

Measure	Cases	Controls	P-value
Demographics			
Age, years. (95% CI)	10.7 (10.1 – 11.2)	11.2 (10.7 – 11.7)	0.2
Sex (M:F)	4.1: 1	4.8: 1	0.6
Side of Disease			
Right	67 (45%)	-	-
Left	57 (38%)	-	-
Bilateral	25 (17%)	-	-
Time Since Diagnosis (95% CI)	4.7 years (4.1 – 5.29)	-	-
Source of Control Population			
Trauma Patients	-	49 (33%)	-
Anterior Knee Pain	-	35 (24%)	-
Physiological Foot Deformities	-	35 (24%)	-
'General Orthopaedic'	-	27 (18%)	-

The smoking questionnaire was omitted or only partially completed in 7 individuals (4 cases and 3 controls). Cotinine was available in 139 cases and 135 controls. One

sample (case) leaked prior to analysis and was therefore unavailable. The remainder of children declined to donate a sample. One child (14-years-old) was a notable outlier with a cotinine level of 4845 μg/L (laboratory qualitative guides define an active heavy smoker >2500 μg/L[27]) and was therefore excluded. Urinary cotinine (>5μg/L) was detected in 54% of children whose parents reported home tobacco exposure, and 9% of children whose parents denied exposure. The cotinine-creatinine ratio correlated closely with self-reported cigarette smoke exposure in the mother ($p<0.001$), but not the father ($p=0.20$) - see Table 2.

Table 2 – Relationship between reported tobacco exposure and cotinine-creatinine ratio.

Self Reported Smoke Exposure (Cigarettes per day)	Mean Cotinine-Creatinine Ratio (g/mmol)					
	Cases		Controls		Overall	
	Mother	Father	Mother	Father	Mother	Father
0	0.8	0.8	1.1	1.1	1.0	1.0
0 – 10	6.7	12.7	0.8	6.1	3.4	9.7
10 – 20	9.12	7.0	1.1	0.9	6.0	4.7
> 20	11.8	1.7	8.1	1.2	10.4	1.5

Bivariable analysis (Table 3) revealed an association between Perthes' disease and self-reported paternal tobacco smoking in pregnancy. Maternal smoking showed a similar association, though this failed to reach statistical significance. There was no difference in current self-reported tobacco smoke exposure between cases and controls. The number of children with detectable cotinine within the urine was not significantly different between cases and controls, although the cotinine-creatinine ratio was significantly higher amongst cases (Table 3, Figure 1).

Table 3 – Bivariable analysis of tobacco smoke exposure.

Characteristic	Number of Individuals (% of total)		P-value
	Cases (n=149)	Controls (n=146)	
Self Reported Questionnaire *			
Current Smoke Exposure			
Any Smoking at Home	61 (42%)	51 (36%)	0.27
Mother (cigarettes per day)			0.22
0	99 (66%)	110 (75%)	
0 – 10	7 (5%)	9 (6%)	
10 – 20	21 (14%)	13 (9%)	
> 20	22 (15%)	14 (10%)	
Father (cigarettes per day)			0.28
0	85 (57%)	98 (67 %)	
0 – 10	22 (15%)	19 (13%)	
10 – 20	26 (17%)	16 (11%)	
> 20	16 (11%)	13 (9%)	
In-Utero Exposure			
Paternal Smoking in Pregnancy	67 (46%)	47 (32%)	0.02
Maternal Smoking in Pregnancy	47 (32%)	22 (23%)	0.07
Cotinine Assay			
Detected, >5µg/L	38 (27.3%)	37 (27.4%)	0.93
Log (Cotinine-Creatinine Ratio, g/mmol (95% CI)	1.36 (0.87 – 1.85)	0.51 (0.61 – 0.97)	0.01

**as a percentage of individuals completing question. Part completed in 4 cases and 3 controls.*

Figure 1 - Cotinine-creatinine ratio amongst cases and controls

Adjustment for area deprivation strengthened the association with reported current tobacco smoke exposure. The risk of Perthes' disease was greater in those reporting higher levels of tobacco smoke exposure (dose-response) (Table 4). Tobacco use by either the mother or father in pregnancy was associated with an increased risk of Perthes' disease, the magnitude and significance of which strengthened after adjustment for deprivation.

The proportion of individuals with detectable urinary cotinine did not differ between cases or controls, even after adjustment for deprivation. However, the magnitude of cotinine (cotinine-creatinine ratio) detected was significantly greater in cases, suggesting greater current exposure to tobacco smoke.

Table 4 – Multivariable model of cigarette smoke exposure.

Exposure	**Odds Ratio with adjustment for deprivation (95% Confidence Interval)**	
	Unadjusted	**Adjusted for area deprivation**
Self Reported Questionnaire		
Current Smoke Exposure		
Any Smoking at Home	1.35 (0.84 – 2.18)	1.71* (1.02 – 2.86)
Mother (cigarettes per day)		
0	1 (Ref)	1 (Ref)
1 – 10	0.86 (0.31 – 2.41)	0.80 (0.28 – 2.30)
10 – 20	1.86 (0.88 – 3.93)	2.73* (1.23 – 6.06)
> 20	1.84 (0.89 – 3.83)	2.79* (1.26 – 6.16)
Father (cigarettes per day)		
0	1 (Ref)	1 (Ref)
1 – 10	1.41 (0.71 – 2.80)	1.75 (0.86 – 3.57)
10 – 20	1.95 (0.98 – 3.90)	2.62* (1.26 – 5.46)
> 20	1.36 (0.62 – 3.01)	1.73 (0.76 – 3.95)
Maternal Smoking in Pregnancy	1.62 (0.96 – 2.74)	2.06* (1.17 – 3.63)
Paternal Smoking in Pregnancy	1.76* (1.09 - 2.85)	2.09* (1.26 – 3.46)

Cotinine Measures		
Cotinine (>5μg/L) Detected (Yes/ No)	0.98 (0.58 – 1.68)	1.19 (0.68 – 2.08)
Log [Cotinine-Creatinine Ratio (g/mmol)]	1.56 (1.07 – 2.27)*	1.63 (1.09 – 2.43)*

 All are adjusted for current age and sex.
** indicates statistical significance (p<0.05)*
Area - adjustment for IMD-2007

Birth History

There was no evidence that those affected with Perthes' disease (cases) or controls differed in terms of birth weight or prematurity (Table 5). However, as expected there was a significant negative association between birth weight and maternal smoking during pregnancy (p=0.002) and paternal smoking during pregnancy (p=0.04).

Table 5 - Birth weight and prematurity

Measure	Mean (95% CI)		
	Cases	Controls	P
Mean Birth Weight, Kg	3.4 (3.3 – 3.4)	3.4 (3.3 – 3.5)	0.98
Percentage of Premature Individuals (<37 weeks)	8.7 (5.2 - 14.3)	10.2 (6.4 – 16.3)	0.65

Discussion

This study adds support to an increasing body of literature identifying an association between tobacco smoke and Perthes' disease [12,28-29]. For the first time, this study used a biologically validated questionnaire to demonstrate an association with tobacco smoke. No association was identified between Perthes' disease and either birth weight or prematurity.

The ideal means by which to investigate the effects of tobacco exposure would be a prospectively collected and biologically validated exposure assay. This would include sampling from the prenatal period through birth and until disease onset. However,

such data is unavailable. Parental recall of smoking habits, and biological assays of current tobacco exposure are the best-available methods by which to quantify exposure in this population.

The most robust evidence for an association between Perthes' and tobacco smoke comes from a large case control study within the Swedish inpatient register, with linkage to prospectively acquired maternal smoking data[12]. This study eliminated recall bias by collecting data prior to disease onset, and adjusted for socioeconomic deprivation (by occupational category), demonstrating a dose-response relationship with a greater risk of Perthes' disease corresponding to a greater degree of maternal tobacco smoke exposure (1-9 cigarettes, OR 1.36 (95% CI 1.10 – 1.68). >10 cigarettes, OR 2.02 (95% CI 1.59 – 2.58). These results are very supportive of the association, with a similar magnitude and direction of association to that demonstrated within this study.

The proportion of children with detectable urinary cotinine was no different between the two groups, though the 'tobacco dose' (as measured using both the questionnaire and cotinine-creatinine ratio) was significantly greater amongst cases. The increased risk of Perthes' disease with 'high dose' exposure gives credibility to the observed association being influential in the disease aetiology – in terms of Hill's criteria for causation[30]. However, a key difficulty in establishing a causal association is the absence of an accepted and plausible biological mechanism by which tobacco smoke exposure might initiate Perthes' disease. The most commonly proposed mechanism, with biological and clinical plausibility, is that Perthes' disease develops as the result of an arterial infarction. Bahmanyar et al. hypothesised that smoking may precipitate

Perthes' disease through vessel wall damage, similar to other forms of vascular disease[12]. Bahmanyar et al. demonstrated that young adults who had Perthes' disease in infancy also had an increased risk of cardiovascular disease in adulthood[31].

Given the association between tobacco use and low birth weight, it appears contradictory that smoking during the antenatal period may predispose to Perthes' disease, yet children with Perthes' disease do not appear to have a reduced birth weight. This may therefore suggest that tobacco smoke exerts an effect in the post-natal period.

Understanding the relationship between disease and tobacco smoke exposure can be difficult owing to confounding, bias (recall bias and guilt/ concealment bias) and recall error. Confounding is one of the most difficult factors to overcome, owing to the shared strong associations of both Perthes' disease and tobacco smoke with deprivation [6,9,32]. The effects of smoking were strengthened after adjusting for socioeconomic deprivation. Studies often poorly adjust for deprivation, and it is unclear if the observed association is merely a proxy marker of unmeasured deprivation. Criticism may be made of the use of an area measure of deprivation rather than an individual deprivation measure, with the potential for ecological errors introduced by area assumption. However measures of individual deprivation introduce other difficulties that are overcome by area IMD, such as categorical data with few categories, and coding difficulties perpetuated by subjective occupation titles [33-34].

Recall bias and guilt bias are both important considerations when examining the

association with tobacco smoke. The use of a hospital control group may partially control for such biases as both groups have children who have, or are perceived to have, a 'disease', and therefore recall bias is likely to be a non-differential misclassification bias. The extent to which this was controlled is unquantifiable. Recall error is a further important consideration, particularly when asking individuals to recall details of a period (i.e. pregnancy), which may have occurred many years ago. Previous studies have demonstrated that maternal smoking recall is still high many years after pregnancy. Studies from the Netherlands and Cardiff demonstrated very good agreement (kappa of 0.77 and 0.80 respectively) between a dichotomised response (yes/no) to a question regarding tobacco exposure in pregnancy, at up to 10 years after birth when compared to data prospectively collected during pregnancy [35-36]. Similarly, parental recall of birth weight up to 16 years after birth has been demonstrated to be a good measure in epidemiology, with studies suggesting 75%-90% accuracy within 8oz (227g) [35-38]. There may be a modest reduction in accuracy in those of lower social educational attainment, however even in manual workers the overall accuracy remains >75%. This therefore suggests that parental recall is sufficient to identify large differences in birth weight or tobacco smoke exposure in pregnancy between cases and controls.

This study, like previous studies, has demonstrated that the urinary cotinine-creatinine ratio is more closely correlated with maternal, rather than paternal tobacco use[39]. Within this study 54% of children whose parents reported home tobacco use tested positive for cotinine, and only 9% of those who did not report home tobacco use tested positive. Detectable cotinine in children without a history of home exposure may reflect exposure from another caregiver, a peer or active cigarette smoking in the

child. Likewise, undetectable cotinine levels in children whose parents reported smoking may reflect, for instance, an environment in which smoking at home only occurred outdoors. Only one child had a disproportionately elevated cotinine-creatinine ratio consistent with active smoking.

Conclusion

This study has demonstrated an association between Perthes disease and tobacco smoke using a biologically validated smoking questionnaire. The greatest risk of Perthes' disease appeared in those with the greatest exposure to tobacco smoke. Exposure in the early life of the child appeared to have a stronger association than with current tobacco smoke exposure, which supports suggestions that the key disease determinant acts early in the development of the child. We remain unable to ensure that the association is not the result of residual confounding, and the biological plausibility of the association remains unclear.

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