Research to elucidate the causes of diseases is a fundamental task of epidemiological enquiry and critical to the development of a scientific basis for preventive strategies. Inferences about causal relationships are, however, prone to bias, particularly when based on studies using ecological analyses where inferences are made about individuals based on aggregate data for a group.

Many factors have been implicated as causes of Perthes’ disease, which was first described almost a century ago. These include low socioeconomic status, as well as environmental factors associated with social deprivation such as small stature, dietary deficiencies, and passive smoking. Although originally considered not to have a genetic basis, more recent studies have suggested possible associations with an inherited predisposition to clotting disorders. The predominance of boys and those of Caucasian origin among those affected is well recognised.

Two studies in this issue of The Journal of Bone and Joint Surgery report contradictory findings regarding the association between low socioeconomic status and Perthes’ disease. No association was found by Sharma et al in their study of 240 children diagnosed in the urban area of Greater Glasgow. In contrast, Pillai et al reported a positive association with deprivation among 40 patients diagnosed during a 10-year period in Dumfries and Galloway, a rural area in Southwest Scotland. These findings appear to suggest that, within Scotland, the association of Perthes’ disease with socioeconomic status varies by geographic location. However before reaching such a conclusion, methodological issues related to study design, specifically those pertinent to case definition, case ascertainment, measurement of socioeconomic status, and sample size need to be considered.

Both studies used hospital data to ascertain cases. The study of Sharma et al included 240 patients with Perthes’ disease referred to and treated in a single hospital in the Greater Glasgow area: these cases were ‘collected’ over a 16-year period from 1988 to 2004. The diagnosis was made by a single consultant based on history, clinical examination and radiography although exact criteria are not specified. In the study reported by Pillai et al, 40 children with Perthes’ disease attending a single hospital between 1992 and 2002, were identified retrospectively from review of case notes. It is unclear whether these were only newly diagnosed during this period or whether existing cases were included. The diagnosis was made by one of several consultants, although, again the diagnostic criteria are not explicitly stated. In both studies it was assumed that all cases arising in the population at risk were identified, as each hospital served a defined population. Cases arising in the population but treated elsewhere were not sought.

Only one of the studies reported the frequency of the condition; in Dumfries and Galloway, the denominator comprised children aged 0 to 14 years and resident in this area and recorded in the 2001 General Register for Scotland Census. The authors calculated a mean annual incidence of Perthes’ disease of 15 per 100 000, which is consistent with earlier reports.

Both studies used area-based measurements of socioeconomic status, and the Glasgow study also used an individual measure based on parental occupation. Thus, Pillai et al used the Scottish Indices for Multiple Deprivation to rank the 47 individual electoral wards represented in their study into deciles. This index measures area level deprivation under five separate domains, namely income, employment, health deprivation and disability, education, skills and training, and geographic access to health services. Cases and the population-at-risk were assigned to electoral wards; in 22 of these there were no cases of Perthes’ disease during the period under study. The authors related the deprivation indices and population density to the incidence of Perthes’ disease in the remaining wards: they found that the inci-
dence was higher in wards of higher deprivation and lower population density.\textsuperscript{14} Sharma et al\textsuperscript{13} used a different area-based measurement of socioeconomic status: the Carstairs score of deprivation, which assigns socioeconomic status to one of seven categories on the basis of postcode sectors in Scotland. This score takes into account four measurements: overcrowding, male unemployment, low social class, and household car ownership. Scores of patients were compared to the scores of the population resident within the Greater Glasgow Health Board. No statistical analyses were performed, but the authors considered that there was no evidence for an excess of Perthes’ disease among those living in the most deprived areas. In addition, the authors reported that the proportion of parents in lower socioeconomic occupational groups was lower than expected for the local population.\textsuperscript{13}

Other factors were reported in the respective studies, but in the absence of a control group, their frequency could only be interpreted with respect to other local or national data. Thus, the findings of the Glasgow study supported previously published observations with respect to gender (male excess), age (peak age at diagnosis five to eight years), maternal age (older mothers), birth order (second or subsequent birth), height (shorter stature), and bone age (delayed). More than half the mothers of the cases smoked during or after pregnancy, which is comparable with the overall proportion for Glasgow, although much higher than for the United Kingdom. The findings of the smaller study from Southwest Scotland were similar with respect to sex and age but other factors were not reported.

Both studies were established to examine the hypothesis that the risk of Perthes’ disease is related to socioeconomic status. The choice of area-based measurements of the latter therefore merits discussion. As alluded to previously, assigning socioeconomic status to individuals according to an aggregate measurement may produce misleading results. This is in part due to misclassification of individuals; thus, not all individuals living in areas of low socioeconomic status are of low socioeconomic status. There is evidence that the Carstairs index is not a robust measurement\textsuperscript{15} when used as in the study of Sharma et al.\textsuperscript{13} A further bias may arise where inferences are drawn, as in these studies, that correlations between diseases and exposure measurements at the area level imply a causal relationship, the so-called ‘ecological fallacy’.

In summary, interpretation of these two studies and their apparently conflicting findings is limited as a consequence of a number of factors, including case definition, case ascertainment, methods used to assess socioeconomic status, sample size and lack of a control group. They neither confirm nor refute the hypothesis that the risk of Perthes’ disease is increased among children living in deprived circumstances. What is the take-home message for the orthopaedic surgeon managing children with Perthes’ disease? Despite a large number of published studies, the causes of Perthes’ disease remain elusive. Unfortunately, the limitations identified in these two studies are replicated in the literature, with relatively few adequately powered prospective case control studies, and none to our knowledge that have involved more than one centre. Although confounding may explain the associations observed with maternal smoking, this does emerge as a consistent finding in the larger case control studies, thus adding to the already substantial body of evidence linking parental smoking to adverse health consequences for children.

How can the puzzle of Perthes’ disease be unravelled? There is an urgent need now to establish a prospective, multicentre, collaborative, epidemiological study of children newly diagnosed with Perthes’ disease, and a comparable control group. This study should have sufficient statistical power to examine a number of promising hypotheses. While associations with socioeconomic status are intriguing, such studies should focus on more proximal causes and include biomarkers, for example of smoking and nutrition, as well as genetic samples to test promising candidate genes and to serve as a future research resource. Paediatric surgeons in the United Kingdom have a track record of proven collaboration in relation to multicentre studies of developmental hip dysplasia\textsuperscript{16} and are ideally placed to develop and carry out this much needed research.

References


THE JOURNAL OF BONE AND JOINT SURGERY