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Childhood allergies, birth order and family size

Childhood allergies, birth order and family size

P Cullinan

Further debate on the explanation for the association between sibship size/birth order and childhood allergic disease

Of the 10 plagues visited on the biblical Egyptians, the last was the most terrible; after the rain of frogs, the plague of boils, and the hailstorms came the indiscriminate slaughter of all firstborn animals including children. Infanticide of this degree is thankfully rare—but is it possible that the author(s) of *Exodus* were expressing a subtler truth?

ASSOCIATIONS BETWEEN BIRTH ORDER/SIBSHIP AND DISEASE

Studies of birth order—or sibship size—as a risk factor have a long history and have examined a wide variety of diseases. Thus, for example, the rates of Hodgkin's lymphoma in young adults,[1 2] HBsAg+ hepatocellular cancer,[3] acute lymphoblastic leukaemia,[4] and type I diabetes mellitus[5 6] all appear to fall with increasing birth order. In each case the pattern has been assumed to reflect the relatively late age at which children of low birth order (or their mothers during pregnancy) acquire common infections. A similar (but opposite) reasoning has been applied to the observations that children of low birth order are at reduced risks of non-Hodgkin's lymphoma,[7] schizophrenia,[8] gastric carcinoma and ulcer,[9] acute myeloblastic leukaemia,[10] and some congenital heart defects.[11] Children of low birth order are also more likely to have infantile pyloric stenosis, to be taller,[12] to be right handed[13] and, if they are male, to be heterosexual;[14] these are less easily attributed to patterns of early infection.

Nowhere, however, are the patterns of birth order/sibship clearer than with the childhood respiratory allergies. First observed by Butler and Golding in 1986,[15] reductions in the risks of hay fever, eczema, atopy and, less consistently, asthma with increasing birth order or sibling numbers have been reported in at least 30 studies and usefully reviewed by Karmaus and Botezan.[16] As with most of the diseases above, these observations have generally been attributed to different rates and timings of early (unspecified) childhood infection. Indeed, they form the cornerstone of the ''hygiene hypothesis'' whereby it is proposed that the risks of atopic disease are reduced by early contact with infection,[17] a proposal bolstered by the more recent suggestion that children born to Alpine farmers are protected in a similar manner.

ASSOCIATION BETWEEN SIBSHIP SIZE/BIRTH ORDER AND ALLERGIC DISEASE

In this issue of *Thorax*, Kinra *et al*[18] provide an historical perspective on the associations between allergic disease and sibship size/birth order. Their population comprised 14 000 students, predominantly male and about 50% of those eligible, who were screened at Glasgow University between 1948 and 1968. The students had a mean age of 19 years and were born between 1918 and 1952; for the purposes of this analysis, they were divided into three equally spaced birth cohorts. Intriguingly, there was no increase in the prevalence of self-reported allergic disease across the time frame of the three cohorts, although it is difficult to judge how representative this finding might be. The authors found clearly decreasing trends in reported allergic

diseases (especially hay fever) with both increasing family size and birth order. Although the differences were small and are readily explained by chance, the effects were strongest in the earliest cohort. If this is explained by greater interfamily differences in infection in that era, then the findings overall are compatible with a ''hygiene explanation''. Further support is provided by the finding that allergic diseases were less common among students from less affluent backgrounds, and by a (weak) interaction between birth order (but not family size) and childhood socioeconomic status. The report is valuable because it suggests that the sibship/birth order phenomenon is temporally robust and thus indicative of a relatively era independent mechanism.

HYGIENE HYPOTHESIS

As an explanation of family size effects (especially where these have been related to older siblings) and of other aspects of the epidemiology of childhood allergies (notably its geographical distribution), the hygiene hypothesis is both plausible and parsimonious.[19] There are, however, increasing doubts that it is a complete explanation. First is the very tenacity of the birth order/sibship observation. This, of course, is not in itself a counterargument, but consistency is unusual in the shifting sands of asthma epidemiology. If early contact with infection alone is crucial in the development of childhood allergy, then one might expect the effects of the surrogate of family size to have changed more clearly with shifts in the patterns of early infection. This does not appear to be the case. It is not even clear whether the rates and timings of childhood infections are indeed closely related to family structure in the heavily immunised small family societies where allergic diseases are so prevalent. Even in rural Poland where the prevalence of atopy is extremely low—presumably as a result of extensive microbial contact in early childhood—we have recently observed a clearly increased risk among firstborn children. Attempts to explain sibship effects by direct measurement of early infection have not been successful,[20 21] although this may reflect the poverty of our methods of measuring the subtleties of ''infective load''.

Equally as striking as its consistency is the strength of the effect. With the exception of family history and, in certain communities, a farming childhood, no other risk factors have been identified as being so powerful. There is, furthermore, a paucity of supporting analogous evidence. Studies of child care, for example—a surrogate for a large family—have produced inconsistent results,[22] and those that have examined the early use of antibiotics have found no consistent evidence that these are harmful.[23] Interestingly, even in classical infectious disease epidemiology the logic that birth order determines age of first infection and thus outcome is not always clear.[24]

Birth order and family size are inevitably correlated, especially when average family sizes are small. Distinguishing the effects of the two has proved to be very difficult and probably requires the use of large populations. Nonetheless, they may be indicative of different mechanisms. Children at the head of a sibship differ from others in ways that do not necessarily reflect their infectious experience. On the whole they are more often male, are born to younger parents, are of lower birth weight, and are more frequently from ''abbreviated'' families. Traditionally, children from small families have been from higher socioeconomic groups. Patterns of breast feeding may be related to birth order or family size as, intriguingly, may early exposures to domestic allergens.[25] Parents' reporting of their children's illnesses is likely to be heavily influenced by their level of previous experience. Studies of sibship effects need to consider each of these potentially confounding variables and to be aware that, on cross sectional analysis (the most common design used in asthma epidemiology), the probability of a child being in any particular birth position is dependent on time related changes in family size.[26]

OTHER POSSIBLE EXPLANATIONS

If variations in the pattern of early infection are not the whole explanation of the sibship effects in childhood allergies, what other explanations are there? Levels of IgE in cord blood are lower in multiparous women, as is the specific reactivity of cord blood mononuclear cells.[27 28] These findings may reflect higher rates of in utero infection of women who already have other children or, at least in the latter instance, higher maternal age. Alternatively, they may reflect the maternal experience of pregnancy itself. Pregnancy is an immunological challenge to the mother and child and it may be that the complex mechanisms associated with fetal survival vary systematically with increasing parity. These may, in turn, be reflected by shifts in maternal immunity. Women (but not men) who have had several children are less likely to be atopic, an observation that is not explained by age,[29] and they are less likely than nulliparous women to report symptoms consistent with allergic rhinitis[30] or conjunctivitis.[31] When studied prospectively, women who have had more pregnancies are more likely to ''lose'' their atopic state and their hay fever than are women who have had no (further) pregnancies.[32] Some have suggested that these apparent shifts in maternal immunity are hormone related.[33] It remains unclear how and whether they are transmitted to successive children, although there is some evidence that firstborn children respond differently to respiratory allergens encountered in the first weeks of life.[34]

Further attention to non-infectious explanations for the sibship effects in childhood allergy seems warranted. A useful starting point might be the experience of other diseases: for many years it has been known that the risks of pre-eclampsia fall sharply with parity but return to baseline when a woman is pregnant through a new partner. Paternity has not, as far as I am aware, been examined in the development of respiratory allergies. If nothing more, it might shed some light on the muddled area of parental inheritance.

The public health implications of a sibship effect that is not attributable solely to ''hygiene'' are not easily envisaged. After all, firstborn children cannot be avoided, but it may be that a better understanding of the nature of their risk will allow the more effective targeting of preventive strategies; and it may be time to revisit the discredited argument that changes in family structure have been an important part of the late 20th century epidemic of childhood allergies.

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Low dose spiral CT screening for lung cancer

Is screening for lung cancer using low dose spiral CT scanning worthwhile?

F V Gleeson

The benefits of low dose spiral CT scanning in screening for lung cancer are still under debate

Intuitively, lung cancer screening using low dose spiral chest computed tomographic (LDCCT) scanning would seem a good bet as it appears to fulfil the necessary criteria for a successful screening programme.[1] Lung cancer is very prevalent; it may be readily detected when asymptomatic using LDDCT; it may be cured at an early stage by surgical intervention; and, taking into consideration the lack of success and the possible costs of investigation and treatment in symptom detected patients, screening with LDDCT might prove to be cost effective. For LDDCT scanning to be an effective screening tool it must neither lead to an overdiagnosis bias nor to significant morbidity in patients with a false positive screen.

OVERDIAGNOSIS BIAS

The detection of clinically unimportant disease for a particular patient—or overdiagnosis bias—has been postulated as the possible cause for the failure of one of the most analysed chest radiography screening studies performed in the 1970s, the Mayo Lung Project.[2 3] This screening study, which used the conventional chest radiograph and randomised patients into screened and control arms, was initially reported as showing no mortality benefit between the two groups. A more recent analysis has shown that, despite a median follow up of 20.5 years, there was no significant reduction in lung cancer mortality in the screened group (337 lung cancers diagnosed, mortality rate 4.4 lung cancer deaths per 1000 patient years) compared with the control group (303 lung cancers diagnosed, 3.9 lung cancer deaths per 1000 patient years).[4] In keeping with this potential overdiagnosis bias are published data on ''clinically undiagnosed'' lung cancers discovered at post mortem examination.[5]

In view of the known limitations of chest radiography for pulmonary nodule detection compared with spiral CT scanning, it would seem sensible to be concerned about an increase in overdiagnosis using the more sensitive technology.

LUNG CANCER AND NODULE DETECTION

The initial reports on the use of LDDCT scanning in screening for lung cancer have confirmed its ability to detect early stage lung cancer and its superiority in detection compared with chest radiography.[6–10] The study most discussed is the Early Lung Cancer Action Project (ELCAP), a non-randomised prospective analysis of LDDCT scanning in which 27 lung cancers were detected in 1000 participants using LDDCT compared with seven using chest radiography.[6] ELCAP also reported increased detection of non-calcified nodules (NCNs) using LDDCT, the majority of which were not malignant. But, perhaps the most impressive results reported by ELCAP involved the work-up of the pulmonary nodules detected, with only 28 patients having a lung biopsy, 27 of whom were confirmed to have malignancy.[6]

COMPARISON OF STUDIES

The difficulties in extrapolating data from one population and medical system to another are highlighted by MacRedmond *et al* in this issue of *Thorax*,[11] and two studies from the USA and two from Europe are used here for