Invited Commentary: Sibship Effects and a Call for a Comparative Disease Approach

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Abbreviations: HLA, human leukocyte antigen; IDDM, insulin-dependent diabetes mellitus; MHC, major histocompatibility complex; Th, T helper.

Golding and Peters (1) broke new ground in 1986 when reporting the protective effect of a larger sibship (children of the same parents) against the risk of allergic disorders. Subsequent studies have repeatedly shown strong negative associations between sibship size and asthma, atopic eczema, hay fever, and allergy markers (2, 3). These effects are stronger than most other risks of allergic manifestations and are based on epidemiologic associations without an a priori biologic foundation.

Based on various immunologic explanations, a number of hypotheses related to the etiology of allergic disorders have emerged over the last 20 years. To begin with, T helper (Th) cell immune responses were polarized into either Th1 or Th2 (4). The nonallergic Th1 phenotype leads to secretion of immunoglobulin G antibodies and removal of the allergen (5, 6). The allergic Th2 response is characterized by the secretion of cytokines that promote immunoglobulin E production, the forerunner of atopic manifestation (7, 8). A further refinement of this explanation is based on the idea that T regulatory cells may act as “police” (9), suggesting that both Th1 and Th2 responses are under their control (10, 11). More recently, roles for alloimmune responses have entered the field of explanations (12, 13). Alloantigens are proteins that distinguish individuals belonging to the same species. Major alloantigens are termed major histocompatibility complex (MHC) antigens, class I and class II (in humans, also referred to as human leukocyte antigen (HLA)). In the case of conventional allergen presentation, the antigen-presenting cell and the responder T cell share the same MHC whereas, in an alloantigen response, the antigen-presenting cell from another individual, such as the fetus, presents the alloantigen. For example, Prescott et al. (12) reported that maternal lymphocytes collected at birth responded more strongly to alloantigens presented by fetal cells of offspring that developed allergy 6 years later. This is in comparison with maternal responses to fetal cells from offspring that remained nonallergic.

These immunologic explanations are being integrated into two, not necessarily mutually exclusive, hypotheses: prenatal and postnatal programming based on different factors acting either before or after birth. The idea of postnatal programming was developed around the hygiene hypothesis (14). It is assumed that, during pregnancy, the fetomaternal immune system is shifted in a Th2 direction (15, 16). Following birth, upon the child’s exposure to infectious agents via siblings (17), an immune maturation takes place, leading to a switch to a Th1 (nonallergic) response. Prenatal programming supposes that the immune system of the neonate is primed and that T cells are largely immunocompetent at birth (18). The idea of prenatal programming is supported by findings that humoral (e.g., immunoglobulin E) and cellular reactivities, detectable as early as at birth, are associated with birth order (19–21). Prenatal priming may vary with maternal history of allergy, immune response, and environmental exposures during pregnancy. The concept of prenatal programming challenges the hygiene hypothesis, since the role of infectious agents is conceptualized differently. Prenatal programming suggests that some children, by virtue of their genetic makeup and prenatal environment, may respond to infectious agents with a Th2 response, resulting in asthma or allergy. Others may develop a Th1 response and infections. These different responses could then result in a negative association between...
infection and allergy, which has been interpreted under the hygiene hypothesis as a causal relation. Furthermore, studies of the association between infectious exposures and asthma (22), as well as atopic eczema (23, 24), have left a trail of inconsistent findings.

The intriguing results of the Danish study by Tine Westergaard et al. (25) in this issue of the American Journal of Epidemiology make a new empirical contribution to the relation between sibship size and allergy. At the same time, the dilemma of the dispute remains, since these results can be used to support both the prenatal and postnatal hypotheses.

**WHAT DOES SIBSHIP EXPLAIN?**

Sibship is a marker of an unknown exposure. A number of different characterizations are used: number of siblings, number of brothers or sisters, number of younger or older siblings, being firstborn, birth order, or parity. Associations with younger siblings are more likely to be explained by postnatal mechanisms, whereas firstborn status and lower birth order (also expressed as parity or the number of older siblings) can be interpreted as either prenatal or postnatal programming. In several previous studies, different aspects of sibship have been used interchangeably. When analyzing sibship in the present study, Tine Westergaard et al. (25) considered the number of both older and younger siblings. It is recommended that future studies follow this practice.

In addition, associations with the number of younger siblings are often confounded by the number of older siblings and vice versa. The Danish study on sibship characteristics, allergic rhinitis, and asthma has the advantage of a large data set, which facilitates disentangling the effect of younger and older siblings. Tables 1 and 2 in the paper by Westergaard et al. (25) show for allergic rhinitis and table 5 for asthma with rhinitis (but not without) that the protective effect of older siblings is more consistent and stronger than the effect of younger ones. In fact, when there are no older siblings, there is no effect of younger siblings (table 3). For a summary, see table 1 in this commentary. However, despite the description of their results, the authors claim in the conclusion that allergic rhinitis was associated with the number of younger siblings and that the findings support the hypothesis of postnatal mechanisms.

**THE SIBLING EFFECT AND THE INCREASING INCIDENCE OF ASTHMA AND ALLERGIES**

A characteristic of Western societies is decreasing parity. In the United States, the total fertility rate decreased from approximately three births per woman in 1965 to 2.1 in 1995 (26) and, in Europe, from 2.4 births per woman in 1970 to 1.48 in 2000 (27). Given that the risk of asthma and allergies is approximately 20–40 percent lower in children of higher birth order, as reported by Westergaard et al. (25), a reduction in the number of second- and thirdborn children in Western societies has been presumed to contribute to the increased prevalence of allergic disease in Western countries (28). However, Wickens et al. (29) refuted this view, reporting that, in New Zealand and England/Wales, the decrease in family size combined with the sibship effect explains only a small proportion of the increase in asthma and hay fever.

We repeated this projection using US data based on the number of children of women aged 40–44 years (representing complete family size) in 1976 and 2000 (30) (table 2 in this commentary). The proportion of women with four or more children was lower in 2000, and so was the percentage of children with one or more siblings. However, when estimating the expected number of asthma cases in children with a different birth order (10, 8.1, 7.1, 5.6 percent for birth order from 1 to ≥4), based on the protective gradient used by Wickens et al. (29), we found that only a small increase in pediatric asthma is explained (from 8.2 to 8.6 percent; table 2, herein). The same projection using the total number of siblings (instead of birth order) also did not result in a substantial increase in childhood asthma from 1976 to 2000 (results not shown). Similar to results from Wickens et al., these data do not support the assumption that the reduction in family size in Western countries plays a major role in the increase in allergic diseases.

Interestingly, Rona et al. (31) demonstrated that the gradient in the prevalence of asthma between firstborn and higher birth order has increased over the last 20 years. Using a steeper sibship gradient for the year 2000 resulted in a raised prevalence of asthma (table 2, herein). Nevertheless, more data are needed to corroborate an increase in the gradient over the last decades. Women who participated in the study by Westergaard et al. (25) over the period from 1997 to 2000 were aged 15–43 years, born between 1954 and 1985. Hence, the Danish data could provide some information on whether the gradient varies among different birth cohorts during this period.

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**TABLE 1. Summary of findings reported in tables 1, 3, and 5 of the paper by Westergaard et al. (Am J Epidemiol 2005;162:125–32) (25)**

<table>
<thead>
<tr>
<th>Allergic rhinitis</th>
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<th>Younger siblings</th>
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*↓*, significant prevalence reduction; ¬, no significant effect; ↑, significant increase in prevalence.
INTERPREGNANCY INTERVALS

Wegienka et al. (32) were the first to report that a short interpregnancy interval (≤2 years) reduced the risk of childhood atopy (adjusted relative risk = 0.46, 95 percent confidence interval: 0.24, 0.92) compared with children of mothers without a prior pregnancy. A limitation of this study was its small sample size (n = 415). The paper by Westergaard et al. (25) in this issue provides results using a much larger sample. Similar to the analysis of Wegienka et al., the referent group for comparison of interpregnancy intervals in the study by Westergaard et al. was children with no siblings (table 4), which produced inconsistent results. However, to test the effect of longer interpregnancy intervals, a natural referent is a child with at least one sibling and with a short interval between two deliveries. Results applying this natural referent are presented by Westergaard et al. in their table 3. Compared with a short interpregnancy interval (≤2 years), longer intervals posed a significant increased risk of having asthma without allergic rhinitis, but not for asthma with rhinitis nor for allergic rhinitis.

It is likely that the maternal immune system changes over the course of several pregnancies, as indicated by a reduction in maternal immunoglobulin E with increasing birth order (33). In addition, Somerset et al. (34) reported that the median proportion of T regulatory cells doubled during pregnancy, declined 6 weeks following delivery, but remained significantly higher than prepregnancy levels. This regulatory process may disappear if there is a longer period between pregnancies, thus resetting the risk of the second offspring to that of the first. Moreover, there is evidence that longer pregnancy intervals are associated with a change of partners (35), which may potentially result in a renewed maternal immune challenge. This may then stimulate a maternal response to the new fetus comparable to that of the firstborn. Thus, both a pregnancy after a long “dry” period and a pregnancy with a new sire may elicit similar maternal immune responses. Both possibilities need to be addressed simultaneously in future research.

We have surprisingly little knowledge of processes in consecutive pregnancies. No single study has investigated immune responses both within and between pregnancies. Regarding allergic diseases, all studies on birth order and/or interpregnancy intervals thus far are cross-sectional and do not include the simultaneous analyses of risk in consecutive offspring.
SPLITTING—DIFFERENT MECHANISMS FOR ASTHMA AND RHINITIS?

The effect of other siblings reported by Westergaard et al. (25) was analyzed in an adult female population, which indicates a stability of these effects from childhood to adulthood. However, using lifetime prevalence, the onset of rhinitis or asthma may be in childhood, adolescence, or adulthood. The authors found associations that, in some aspects, differ between allergic rhinitis and asthma with allergic rhinitis on the one hand and asthma without allergic rhinitis on the other (table 5 in Westergaard et al.) (25). They concluded that different etiologic mechanisms may be involved. However, there are two concerns with this conclusion: 1) Allergic rhinitis, determined in the Danish study, is likely to be based on immunoglobulin E sensitization triggered by pollen. Asthma that does not lead to allergic rhinitis might also be based on immunoglobulin E sensitization. This suggests that the three outcomes compared in the work of Westergaard et al. (25) do not necessarily represent different disease entities with different mechanisms. 2) Childhood asthma is a risk factor for allergic rhinitis in adolescents and adults (36). Given that the results are based on lifetime prevalence, the associations between older siblings and allergic manifestation may be confounded by exposures that took place after the inception of asthma (often in childhood) or rhinitis (often in adolescence and adulthood) but before the onset of their investigation. It may be, then, that differences among the three outcomes reported in the Danish study do not have different etiologic backgrounds but simply express different periods of onset and postonset interventions.

UNITING: FIRST PREGNANCIES, FIRSTBORNs, AND LONGER INTERPREGNANCY INTERVALs ARE RISK FACTORS FOR SEVERAL DISEASES

To understand the sibship effect, we believe that the similarities of different diseases may be more important than their differences. To further advance our knowledge, we may need to explore the similarities of the sibling effect in other diseases. There is evidence that some diseases, for example, preeclampsia and type 1 diabetes mellitus, just to mention a few, show similar patterns. Their risk is higher in firstborn or first pregnancies and/or increases with longer interpregnancy intervals (35, 37).

Preeclampsia, one of the main complications of pregnancy, occurs predominantly in first pregnancies (38, 39). For preeclampsia, paternal factors such as primipaternity, change in paternity, a maternal/paternal mismatch, or an interaction of paternity and long interpregnancy intervals have been emphasized (40, 41). In addition, it has been found that women with moderate to severe asthma are at increased risk of preeclampsia (42). There are hints of two common mechanisms. 1) As found in allergy and autoimmune disorders (43, 44), preeclampsia may be associated with a reduced count of T regulatory cells (45). 2) A role of alloantigens has been suggested in both allergy and preeclampsia. Nonpreeclampsia mothers have higher serum and placental levels of HLA-G (MHC-I, type G) (46, 47), which is less polymorphic than other MHC-I types (48) and thus has a lower potential of reacting to paternal antigens. Hence, expression resulting in higher levels of HLA-G may protect the fetus from rejection by the mother (49), contributing to a transient state of tolerance against the paternal alloantigens of the fetus (46).

Type 1 diabetes mellitus, or insulin-dependent diabetes (IDDM), is caused by immune-mediated destruction of pancreatic β cells. Studies have reported that an increase in birth order was related to a reduced risk of IDDM (50, 51). As in preeclampsia, there are suggestions that HLA is involved in the pathogenesis of IDDM (52–54).

In view of the above reports, we have to ask why different diseases, such as allergic disorders, diabetes, and preeclampsia, show a similar sibship pattern of a higher risk to the first fetus or child. Is there a common starting point for different immune disorders that produces comparable associations with regard to birth order? For instance, studies have proposed that immune responses related to alloantigens may be involved in preeclampsia, type 1 diabetes, and, more recently, allergic diseases (12). Do these diseases share a common underlying mechanism? Is there a rule of nature that first pregnancies or firstborns have an immune disadvantage? What are the protective factors in second and higher order children? Can these be used to prevent immune disease in firstborns? Or, can these differences be explained by other nonimmune factors common to firstborns?

COMPARATIVE DISEASE APPROACHES

Etiologic ideas are born from similar and differing characteristics shared by a variety of diseases (uniting and splitting). It is becoming increasingly important in epidemiology to develop comparative or interdisease approaches and to foster collaboration among basic science researchers who are focused on different diseases. Epidemiology is the science that can provide the structure between different isolated, hypothesis-driven approaches that attempt to identify disease mechanisms but miss the wider picture. Investigating the sibship effect may serve as a first opportunity to apply a comparative disease approach to better understand the prenatal and postnatal programming of different illnesses.

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