lower birth rank is also a reflection of the fecundity of one’s parents. All of these factors are aspects of heritability and not intrauterine effects. Subsequent analysis of the menopause relation assessing the age of the mother at birth instead of the number of siblings provided a better fit, corroborating our hypothesis on the role of oocyte age as a more likely explanation for the effects detected previously (3).

We wonder whether examining birth order effects from this oocyte-age perspective by the age of the mother at birth could also explain the results presented by Karmaus et al. or explain them even better. Their data allow computation of the ages of the parents at birth and testing of the proposed hypothesis on maternal age at birth. A similar study by Ball et al. (4) lacked the necessary information with which to test the hypothesis.

Age at (first) birth is rising in westernized countries. Thus, this hypothesis would fit equally the observed increase in atopic problems as family size declines, reducing the average number of siblings. For menopause, we have hypothesized that the intrauterine milieu may not be the relevant factor but that age of the oocyte at conception, reflecting the genetic stability of nuclear and mitochondrial DNA, could be the underlying heritable phenomenon. We hypothesize that this might be an alternative explanation for the results presented by Karmaus et al. (1). If maternal age at birth provided a better fit in the data set of Karmaus et al., this oocyte hypothesis would also predict higher levels of atopic problems among children born through the use of assisted reproductive techniques and among children with trisomies.

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THE AUTHORS REPLY

We appreciate the observations of Drs. Maziak (1), Bernsen and van der Wouden (2), and van Noord (3). The innovative character of recent research on asthma etiology is challenging. Mechanistically based hypothesis-driven research, highly respected in the United States, has not stimulated the detection of the sibling effect, since the mechanisms are still unknown and detection is based purely on epidemiologic findings. The world of intuition is less restricted, and there is little chance of being counterintuitive; however, there is a greater likelihood of being countermechanistic when challenging the paradigm of the infection hypothesis.

We thank Wasim Maziak (1) for debating our “counterintuitive” interpretation or, as we would see it, our countermechanistic view. We stated in our paper (4) that the association between infections and asthma might be spurious. Given that the majority of infections in childhood are viral (5, 6), exposure to the same virus may cause an apparent infection in one child (a child with a Th1 helper 1 (Th1) pattern of response at birth) and an upper respiratory tract infection with wheezing in the other (a child with a Th2 helper 2 (Th2) response at birth). The immune systems of children who experience only infection are likely to identify and eliminate the infectious agent. Those children who start out with wheezing are more likely to develop asthma (7, 8). Consequently, it becomes apparent that children with infections may have less asthma, but children with wheezing have more. Given this scenario, infections may not be protective, but the type of infection is a marker of a Th1- or Th2-biased immune response. Accordingly, the alleged protective effect of infections has not been observed consistently in different studies (8–12). However, we would need other data to address this question.

Roos Bernsen and Johannes van der Wouden (2) emphasize two points: first, the assumption that fetomaternal interactions may underlie the association between birth order and atopy has been hypothesized before; and second, the age of the mother should be controlled for as a confounding factor. With regard to the previously proposed hypothesis, Bernsen and van der Wouden refer to an editorial (13) that addressed a paper cowritten by two of the current authors (J. M. and W. K.) (14). The original paper emphasized prenatal immunologic interactions between the mother and the fetus that may underlie the so-called sibling effect. In support of our earlier hypothesis (14), we were able to present empirical data to address this issue in our recent paper (4).

It is correct that maternal age and the number of offspring are related. However, controlling for maternal age has two aspects, a statistical aspect and a biologic aspect. Statistical considerations include the following. Maternal age at the birth of the child ranged from 16.4 years to 43 years. We grouped the variables into three nearly equidistant groups. Maternal age and the birth order of the offspring were associated (table 1). The information presented in table 1, which corresponds to table 2 in our paper (4), is stratified by maternal age group (16–23 years, 24–33 years, and ≥34 years) and shows a nearly identical association between the birth order of the child and cord blood immunoglobulin E level (<0.2, ≥0.2–<0.5, and ≥0.5 kilounits/liter). For the three age groups, the prevalence of immunoglobulin E levels greater than or equal to 0.5 kilounits/liter is reduced in those children who start out with wheezing are more likely to develop asthma. Those children who start out with wheezing are more likely to develop asthma. Therefore, it is correct to say that infections may not be protective, but the type of infection is a marker of a Th1- or Th2-biased immune response.
Regarding biologic considerations, we are not aware of any study indicating that aging explains a reduction in maternal immunoglobulin E levels. However, age is a marker for other biologic processes, and it is preferable to include a potential indicator of the potential biologic process, that is, number of pregnancies, in the model. This is why we did not include age. Regarding pregnancies, it has been suggested that successive pregnancies decrease atopy in the mother and thus reduce the risk of atopy in subsequent offspring (15). Additionally, regarding our speculation of an endocrine effect, there may be several biologic mechanisms involved that increase the tolerance of the mother with an increasing number of pregnancies, including fetomaternal cell trafficking and the possibility of microchimerism (15).

Paulus van Noord also suggested statistical control for maternal age (3). However, the direction of his proposed mechanism—the aging of oocytes until conception and a related increase in adverse effects on the fetus—is the opposite of what we detected. Our results indicated that the incidence of allergic sensitization is higher among firstborns and lower among second- and thirdborn children.

We epidemiologists teach our students to consider epidemiologic explanations (time order, selection bias, the impact of third variables, etc.) first, before biologic mechanisms. Thus, we must first understand the epidemiology of the protective sibling effect (16) before we focus on mechanisms. There are a sufficient number of data sets from different parts of the world to address the most urgent questions and to guide epidemiologists in obtaining additional understanding. Therefore, we suggest that further collaboration and debate is necessary to understand the epidemiology of the so-called sibling effect.

**REFERENCES**


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