

LETTERS TO THE EDITOR

RE: "DOES THE SIBLING EFFECT HAVE ITS ORIGIN IN UTERO? INVESTIGATING BIRTH ORDER, CORD BLOOD IMMUNOGLOBULIN E CONCENTRATION, AND ALLERGIC SENSITIZATION AT AGE 4 YEARS"

I read with interest the article by Karmaus et al. that was published recently in the *American Journal of Epidemiology* (1). Their finding that sibship size can influence allergic phenotype in children via prebirth factors is intriguing and actually can help explain earlier results which show that asthma is inversely related to the presence of older siblings, while early respiratory infections increase rather than decrease the risk of developing asthma (2). Karmaus et al. suggest that intrauterine factors can program the pattern of T helper 2 (Th2) and T helper 1 (Th1) cell response, with increased cord blood immunoglobulin E being a marker, and subsequently the number of infections and the risk of atopy (1). Thus, according to Karmaus et al., the negative association between infection and atopic manifestation is not causal but is more likely to be spurious (1).

My problem with such an interpretation is that it is counterintuitive. According to the Th1-Th2 model, Th1 and Th2 cytokine profiles have cross-regulating abilities; that is, interferon- γ can down-regulate Th2 responses, and interleukin-4 can down-regulate Th1 responses (3). For example, if we take a newborn with a Th2-Th1 pattern that is biased at birth towards Th2 responses, with increased cord immunoglobulin E as one of its early manifestations, this child will theoretically be more prone to allergy and to infection (his Th2 cytokines will suppress his Th1 responses to infection), and subsequently Karmaus et al.'s interpretation cannot provide an underlying mechanism by which one can explain both the effect of birth order on allergy and the negative association between infection and atopic manifestation.

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In the November 15, 2001, issue of the *Journal*, Karmaus et al. presented an interesting paper on the relation between immunoglobulin E cord blood and birth order (1). Their find-

ings indicated that an intrauterine mechanism underlies the association between birth order and atopy, as has been hypothesized previously (2, 3). However, the age of the mother could be a confounder in this relation: Of course, birth order and the age of the mother are strongly related, and it is conceivable that the immune system changes with increasing age, thus changing the mother-fetus interaction. We wonder what the results would be if the analyses were adjusted for this characteristic.

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My colleague and I read the report by Karmaus et al. (1) in the November 15, 2001, issue of the *Journal* with great interest. Apart from the effects of siblings and family size mentioned in the introduction, the authors stated in the Materials and Methods section that they also collected data on the age of the parents, allowing them to calculate the age of the mother at birth. Unfortunately, nowhere in the analysis was maternal age at birth used, either directly or to control for the effects found. We think this was a missed opportunity, as it would have allowed the authors to test a simple alternative interpretation of the so-called sibling effect.

In a 1997 study on determinants of menopause, we observed effects of birth rank for which we had no proper explanation at the time (2). Recently we realized that birth order is highly correlated with the age of the mother at birth. The age of the mother at birth reflects the age of her oocytes, from which the child is conceived. Older oocytes have a higher propensity toward aneuploidy, reflected in higher rates of spontaneous abortion and more trisomies. Having many siblings can be an indicator that one's mother was older at one's birth and that one was born from "older" oocytes than one's older siblings. Having many siblings or a