

Letters to the Editor

RE: "ANTIBIOTIC EXPOSURE BY 6 MONTHS AND ASTHMA AND ALLERGY AT 6 YEARS: FINDINGS IN A COHORT OF 1,401 US CHILDREN"

Risnes et al. (1) recently evaluated the association between use of antibiotics in early life and asthma occurrence in childhood. They considered the possibility that the association, already found in several published reports (2), might be due to confounding rather than represent a causal effect. In particular, they are concerned about "protopathic bias" (3) "that applies if early asthma symptoms are the reason for antibiotic treatment" (1, p. 315). The authors suggest that "protopathic bias may be minimized by considering only antibiotic exposure that occurs several years before the onset of asthma symptoms" (1, p. 315). However, they do not present the crucial information on when wheezing symptoms started and whether antibiotics were given during wheezing episodes.

It is well known (4) that wheeze, especially in the first years of life, is chiefly triggered in susceptible persons by viral infections, for which antibiotics (owing to a difficult differential diagnosis with bacterial infections) are often prescribed. Protopathic bias is only one of the mechanisms potentially confounding the association between early use of antibiotics and subsequent development of asthma/wheezing (2).

There are several wheezing phenotypes (5). Some infants who wheeze in the first months/years of life continue to wheeze up to school age (so-called "persistent wheezers"), while others start later ("late-onset wheezers"). Taking into account specific phenotypes is crucial to evaluate the role of risk factors for wheezing in young children (6). If the children who start to wheeze early are more likely to have received antibiotics than children who start late or controls, then a non-causal (confounded) association between antibiotics and asthma at school age is expected in persistent wheezers.

In a large, unselected population of children aged 6–7 years (7), we previously demonstrated a clear gradient of antibiotic use in the first years of life in different groups of wheezing infants (persistent wheezers: 65.5%; late-onset wheezers: 40.8%). When we considered all infants who wheezed at age 6 years as a single group, we found an association between antibiotics and asthma (odds ratio (OR) = 1.57, 95% confidence interval: 1.40, 1.75) very similar to that reported by Risnes et al. (1). This figure is the composite of the very different odds ratios for late-onset wheezers (OR = 1.18) and persistent wheezers (OR = 3.06) and can be explained by confounding. In fact, the confounded association of antibiotics and wheezing in the first years of life carries on to age 6 years.

A way to minimize this effect and to obtain unconfounded associations is to exclude persistent wheezers from comparisons, considering only late-onset wheezers. Risnes et al. (1) did not collect information on the time of the start of wheezing symptoms. From their data, we can only speculate that most of their asthma cases were in fact persistent wheezers: all those

who were diagnosed between 6 months and 3 years of age and probably also some of those diagnosed after age 3 years.

In summary, we believe that the data presented by Risnes et al. (1) could be explained by confounding and cannot point to a possible causal role of early antibiotics in the development of asthma.

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