

Correspondence

The mediating effect of microbial colonization on the effect of cesarean section delivery

To the Editor:

van Nimwegen et al¹ report an intriguing set of results concerning the role of intestinal microbiota colonization in the relationship between mode and place of delivery on childhood risk of allergic disease. The possibility of cesarean section being a potential cause of asthma has received considerable attention,^{2,3} and although other hypotheses have been posed,⁴ the most often cited explanation for this association is reduced colonization with microbiota from the maternal gut and vagina.⁵ The authors observed that, of the measured microbiota, only colonization by *Clostridium difficile* was related to the risk of allergic disease. It is worth noting that this observation is slightly different from the initial interpretation of the hygiene hypothesis,⁶ which suggested that lack of colonization rather than increased colonization by particular organisms increased the risk of allergic disease. In fact, none of the organisms measured in this study were associated with a protective effect against allergic disease, possibly because of the lack of statistical power.

The claim that *C difficile* might cause allergic disease needs to be tempered. Although some previous reports have suggested higher rates of colonization by *C difficile* in patients with allergic disease,⁷ it remains possible that colonization by *C difficile* is simply a marker for other exposures that have allowed this opportunistic bacterium to colonize the infant's gastrointestinal tract. Colonization by *C difficile* might be a marker for other exposures (eg, high exposure to cleaning products or lack of exposure to pets, rural environment, or probiotics/prebiotics) or innate factors (deregulation of the immune system) that lead to increased risk of both colonization to *C difficile* and increased risk of allergic disease. Furthermore, colonization by *C difficile* might be a marker for reduced colonization by other protective microbiota. This could not be fully addressed in the Child, Parent and Health: Lifestyle and Genetic Constitution (KOALA) study because the relative abundance of each bacterium was not measured.¹

On the basis of a mediation analysis, the authors state that, "Notably, mediation was not only found for vaginal home delivery but also for cesarean section compared with vaginal hospital delivery in association with both asthma and eczema." Among those children born in the hospital, when compared with vaginal delivery, cesarean section delivery was associated with an increased risk of colonization by *C difficile* in the first month of life, and *C difficile* colonization at this age was associated with an increased risk of development of asthma at age 6 to 7 years (Fig 1). Given the direction of these associations, delivery by means of cesarean section should be related to increased risk of asthma in the child in this study (Fig 1), but the results show they are not related. The only ways that this pattern of results is possible is if (1) cesarean section (in the absence of colonization with *C difficile*) is associated with reduced risk of asthma, (2) the association between cesarean section delivery and asthma risk is negatively confounded by a third factor that has not been taken into account, or (3) *C difficile* is not a mediator of the relationship between cesarean section and asthma risk (ie, the *C difficile*–asthma association is noncausal). These possibilities do not appear to have been adequately addressed within the article and are particularly important because the vast majority of children in the westernized world are delivered within a hospital setting (<http://www.uptodate.com/contents/planned-home-birth>). Could the authors please comment on this and present the association between mode of delivery (in children born in hospital) and risk of asthma if colonization by *C difficile* did not occur? To our knowledge, the potential for delivery by means of cesarean section to be protective against allergic disease has not previously been suggested.

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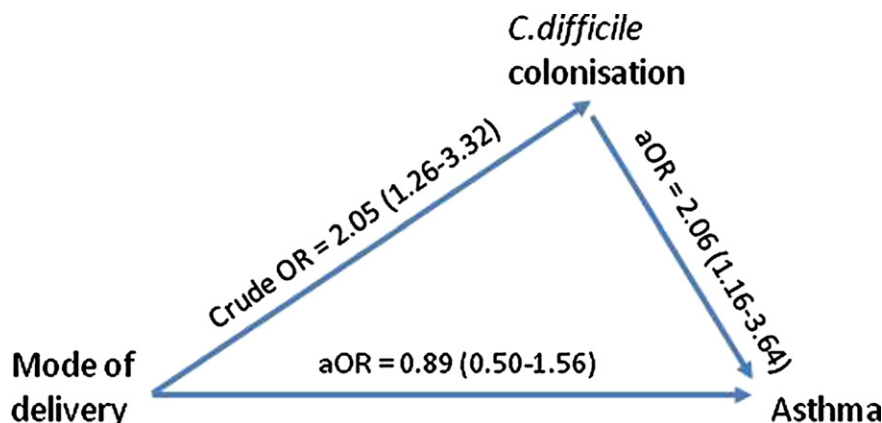


FIG 1. Associations between mode of delivery, *C difficile* colonization, and risk of asthma observed in the KOALA study in children born in the hospital. The association between mode of delivery and risk of *C difficile* colonization is based on colonization rates for vaginally hospital-born (27.2% of 382) and cesarean section-delivered (43.4% of 99) children (as per page 950 and Table I). aOR, Adjusted odds ratio; OR, odds ratio.

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