

Correspondence

Reply

To the Editor:

We appreciate the comments by Lowe et al¹ on our article entitled “Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy.”²

The authors suggest that we “claim that *C. difficile* might cause allergic disease.”¹ In our article the only strong causal claim concerns the role of delivery: “The findings of mediation by *C. difficile* strengthen the evidence for a causal role of birth mode on atopic manifestations through influencing the GM composition.” The term “birth mode” in this sentence might be confusing because it was meant to refer to both birth mode and place.

Although the gastrointestinal microbiota (GM) composition in neonates is far less complex than in adults, it still contains numerous genera and species not examined in our study. We therefore fully agree that *C. difficile* might reflect other shifts in the GM composition.

This is exactly why we called for “studies that extensively profile the whole neonatal GM composition....” As long as no specific changes can be pinpointed, *C. difficile* remains a possible causal candidate, however.

We do not consider it very likely that *C. difficile* is a marker of other environmental exposures because we previously demonstrated that of a broad range of potential determinants, mode and place of delivery were by far the strongest determinants of *C. difficile* colonization.³ Other determinants of *C. difficile* were included as covariables in the mediation analysis (eg, infant feeding) or considered as exclusion criteria (antibiotic use and prematurity) for the present study.

The main conclusion of our article was the effect of birth place on childhood allergies, although we did indeed find significant mediation for birth mode (cesarean section) as well.

The question on cesarean section raised by Lowe et al¹ is legitimate, but their Fig 1 does not represent the right results because it is based on the whole study population. The mediation analyses presented in our article were confined to the subsets of subjects with complete data on all 3 primary variables considered in each model (ie, mode of delivery, *C. difficile*, and study outcomes). Fig 1 in this letter presents the correct results.

In this subset cesarean section is associated with an increased risk for asthma (adjusted odds ratio [aOR], 1.13 [95% CI, 0.50-2.58]), whereas in the entire population this association had an opposite direction (aOR, 0.89 [95% CI, 0.50-1.56]), with none being statistically significant in both cases. One might raise the question of whether this can be attributed to selection bias in this subset. However, the results for home delivery with asthma were comparable between the overall population and this subset (aOR, 0.59 [95% CI, 0.40-0.89] and 0.51 [95% CI, 0.27-0.95], respectively). Additionally, the OR for the association of cesarean section with asthma in this subset falls well within the CI of this association in the total study population. It is thus more likely the result of unstable estimates because of the low sample size. Presenting this association if colonization by *C. difficile* did not occur, as requested, therefore provides no additional insight because numbers will decrease even further (only 3 asthma cases among 42 cesarean section–delivered infants).

In conclusion, the positive associations of both the “a” and “b” paths (Fig 1) are evident. The findings for cesarean section and

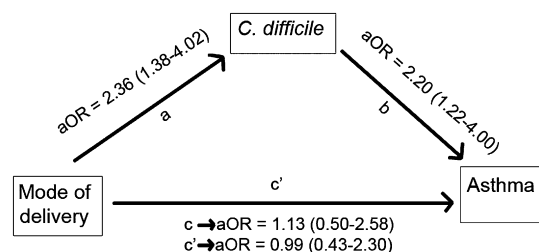


FIG 1. Associations between mode of delivery (cesarean section vs hospital delivery), *C. difficile* colonization, and risk of asthma in the KOALA (Child, Parent and Health: Lifestyle and Genetic Constitution [in Dutch]) Birth Cohort Study in children born in the hospital confined to the subset of study participants with complete data on the 3 primary variables. Note that the a*b product used standardized coefficients in mediation analyses because in logistic regression a variable used as predictor has a different scale from when it is used as an outcome.

asthma within this subset are not contradictory to these findings. However, as the authors suggest, there might still be additional mediations, including negative ones, at stake for the associations between cesarean section and asthma. The suggestion of additional operative pathways is valid for this but also any of the associations investigated, a point that we have also stressed in the conclusions of our study.

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