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

Citation for published version (APA):

Penders, J., Mommers, M., van Nimwegen, F. A., Stobberingh, E. E., Postma, D. S., Koppelman, G. H., Kerkhof, M., Reijmerink, N. E., Dompeling, E., van den Brandt, P. A., Ferreira, I., & Thijs, C. (2012). The mediating effect of microbial colonization on the effect of cesarean section delivery Reply. *Journal of Allergy and Clinical Immunology*, 129(2), 585-586. <https://doi.org/10.1016/j.jaci.2011.11.041>

Document status and date:

Published: 01/02/2012

DOI:

[10.1016/j.jaci.2011.11.041](https://doi.org/10.1016/j.jaci.2011.11.041)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

section to be protective against allergic disease has not previously been suggested.

Adrian J. Lowe, PhD^{a,b}
Elizabeth Williamson, PhD^{b,c}
Lennart Bråbäck, PhD^d
Caroline J. Lodge, MBBS^b
Shyamali C. Dharmage, PhD^b

From ^aMurdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, Australia; ^bthe Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, University of Melbourne, Melbourne, Australia; ^cthe Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; and ^dOccupational and Environmental Medicine, Umeå University, Umeå, Sweden. E-mail: lowe.adrian@gmail.com.

A.J.L., C.J.L., and S.C.D. are supported by the Australian National Health & Medical Research Council. C.J.L. is also supported by the Sidney Myer Foundation. L.B. and A.J.L. were supported by the Umeå SIMSAM Node "Microdata research on childhood for lifelong health and welfare" financed by the Swedish Research Council.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol* 2011;128:948-55.
2. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy* 2008;38:634-42.
3. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy* 2008;38:629-33.
4. Borgwardt L, Bach D, Nickelsen C, Gutte H, Boerch K. Elective caesarean section increases the risk of respiratory morbidity of the newborn. *Acta Paediatr* 2009;98:187-9.
5. Vael C, Desager K. The importance of the development of the intestinal microbiota in infancy. *Curr Opin Pediatr* 2009;21:794-800.
6. Penders J, Stobberingh EE, van den Brandt PA, Thijs C. The role of the intestinal microbiota in the development of atopic disorders. *Allergy* 2007;62:1223-36.
7. Linneberg A, Ostergaard C, Tvede M, Andersen LP, Nielsen NH, Madsen F, et al. IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2003;111:847-53.

Available online December 28, 2011.
doi:10.1016/j.jaci.2011.11.040

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

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.

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 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.

John Penders, PhD^{a,b}
Monique Mommers, PhD^a
Frederika A. van Nimwegen, MSc^a
Ellen E. Stobberingh, PhD^b
Dirkje S. Postma, MD, PhD^c
Gerard H. Koppelman, MD, PhD^d
Marjan Kerkhof, MD, PhD^e
Naomi E. Reijmerink, MD, PhD^{c,f}
Edward Dompeling, MD, PhD^g
Piet A. van den Brandt, PhD^h
Isabel Ferreira, PhD^{i,j}
Carel Thijs, MD, PhD^a

From the Departments of ^aEpidemiology, ^bMedical Microbiology, ^cPediatric Pulmonology, ^dClinical Epidemiology and Medical Technology Assessment, and ^eInternal Medicine, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre+, Maastricht, The Netherlands; the Departments of ^fPulmonology and ^gPediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, and ^hthe Department of Epidemiology, University Medical Center Groningen,

University of Groningen, Groningen, The Netherlands; ⁱBeatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; and ^jthe Department of Epidemiology, School for Oncology and Developmental Biology (GROW), Maastricht University Medical Centre+, Maastricht, The Netherlands. E-mail: j.penders@epid.unimaas.nl.

Disclosure of potential conflict of interest: D. S. Postma has consulted for Nycomed, GlaxoSmithKline, and AstraZeneca. G. H. Koppelman has received research support from the Netherlands Asthma Foundation, 20N-MW (BBMRI-NL), and the European Union. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Lowe AJ, Williamson E, Bråbäck L, Lodge CJ, Dharmage SC. The mediating effect of microbial colonization on the effect of cesarean section delivery. *J Allergy Clin Immunol* 2012;129:584-5.
2. van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol* 2011;128:948-55.
3. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* 2006;118:511-21.

Available online December 28, 2011.
 doi:10.1016/j.jaci.2011.11.041