



Reply to: Early-life respiratory infections and pre-adult asthma: could there be an interaction and differential misclassification?

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Reply to J.L. Perret and co-workers:

We have read the correspondence of J.L. Perret and co-workers regarding our meta-analyses on early-life respiratory tract infections and the risk of school-age lower lung function and asthma [1] with great interest, and thank them for their critical appraisal. In their correspondence, two main comments are raised. First, whether children with upper respiratory tract infections *without* (concomitant) lower respiratory tract infections in early life would have similar odds of school-age asthma as presented, and second, whether differential misclassification of school-age asthma might have affected our findings of the association of upper respiratory tract infections in early life with school-age asthma.

First, adjusting for lower respiratory tract infections when examining the associations for upper respiratory tract infections in early life with school-age asthma indeed only partially reflects the true effect of upper respiratory tract infections solely on school-age asthma. Therefore, we have performed additional analyses to further explore the associations of both upper and lower respiratory tract infections solely and combined, with school-age asthma (table 1). With neither upper nor lower respiratory tract infection as a reference, upper respiratory tract infections solely, lower respiratory tract infections solely, and both upper and lower respiratory tract infections in the same year were all associated with an increased risk of school-age asthma (range odds ratio 1.18 to 1.42 for upper respiratory tract infections solely, 1.93 to 9.06 for lower respiratory tract infections solely and 2.60 to 6.63 for both; p-value for trend <0.01 for all ages) The odds ratio for upper respiratory tract infections solely was comparable to the odds ratio previously found in our meta-analysis for the association of upper respiratory tract infection with asthma, regardless of having lower respiratory tract infection. This implies that even upper respiratory tract infections solely in early life seem to be associated with an increased risk of school-age asthma, albeit that the size of these effect estimates were smaller than those observed for the association of lower respiratory tract infections, either solely or combined with upper respiratory tract infections, with school-age asthma. However, due to the method of data collection, we do not know whether these combined upper and lower respiratory tract infections represent a single bout of disease with an upper respiratory tract infection preceding an infection of the lower respiratory tract, or whether the upper and lower respiratory tract infections are two separate episodes within the same year. In both cases, however, the effect on asthma seems to be mostly driven by the infection of the lower respiratory tract, which is an important message for clinical practice.

Second, J.L. Perret and co-workers are correct to point out that recall bias is less likely to occur given the prospective design of the included cohorts. We cannot fully rule out that parents that are more concerned about their child's (respiratory) health are more likely to over-report the diagnosis of asthma potentially leading to misclassification. We do believe that we have minimised this as much as possible by using the validated ISAAC questionnaire by cohorts where possible [2]. Additionally, over-reporting is less likely to occur in the case of a doctor-diagnosed disease like asthma, when compared to more subjective outcomes, such as symptoms of wheezing [3].

The association of upper respiratory tract infections in early life with school-age lung function and asthma might need to be studied further in depth, for example by longitudinally examining specific viruses or detailed microbiome determination, before strong clinical certainty about their effects on respiratory health across the life course can be established. Additionally, studying the association of respiratory tract



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Upper respiratory tract infections solely in early life are associated with school-age asthma as well, although not as strongly as lower respiratory tract infections solely or both combined

<https://bit.ly/3ocwwAD>

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TABLE 1 Associations of early-life upper and/or lower respiratory tract infections with school-age asthma

	Asthma odds ratio (95% CI)
Age 6 months	
URTI solely	1.29 (1.19–1.40)**
LRTI solely	2.38 (2.14–2.65)**
Both	2.60 (2.13–3.04)**
Age 1 year	
URTI solely	1.18 (1.09–1.27)**
LRTI solely	1.93 (1.77–2.09)**
Both	2.74 (2.49–3.02)**
Age 2 years	
URTI solely	1.42 (1.33–1.53)**
LRTI solely	3.06 (2.75–3.40)**
Both	4.40 (4.03–4.80)**
Age 3 years	
URTI solely	1.33 (1.24–1.42)**
LRTI solely	4.28 (3.84–4.77)**
Both	4.51 (4.11–4.94)**
Age 4 years	
URTI solely	1.33 (1.16–1.52)**
LRTI solely	3.36 (2.80–4.01)**
Both	5.38 (4.41–6.58)**
Age 5 years	
URTI solely	1.20 (1.08–1.34)**
LRTI solely	9.06 (7.65–10.72)**
Both	6.63 (5.54–7.94)**

Values are odds ratios with 95% confidence intervals, derived from multilevel logistic regression models. **: $p < 0.01$. Models are adjusted for maternal history of asthma and atopy, ethnicity, education level, smoking during pregnancy, parity and pet keeping, and child's sex, gestational age at birth, birth weight, season of birth, breastfeeding and daycare attendance. URTI: upper respiratory tract infection; LRTI: lower respiratory tract infection.

infections and asthma later in life, as done in the Tasmanian Longitudinal Health Study, which J.L. Perret and co-workers refer to, might not only strengthen the life course effect of these respiratory tract infections in early life, but could also have statistical benefits given the reporting of exposure and outcome from a different source (the parent of the child and the child itself, respectively).

Undoubtedly, we would like to emphasise the consequent adverse effect of lower respiratory tract infections in early life on both school-age lower lung function and asthma demonstrated in our meta-analysis, and believe this to be the most important finding.

Evelien R. van Meel^{1,2} and Liesbeth Duijts^{1,2,3} on behalf of the participating authors of the meta-analysis “Early-life respiratory tract infections and the risk of school-age lower lung function and asthma”

¹The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ²Dept of Pediatrics, Division of Respiratory Medicine and Allergology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. ³Dept of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

Corresponding author: Evelien R. van Meel (e.vanmeel@erasmusmc.nl)

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Initiative for Asthma (GINA) for developing annual reports on strategies for asthma management. E.R. van Meel has nothing to disclose.

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