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

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To the Editor:

We read the manuscript by VAN MEEL *et al.* [1] with interest as they have investigated the relationship between early-life infection and both later asthma and lower lung function in school-aged children of the general population, to address an internationally recognised research gap. Using primary data from 150 090 children from 38 participating pregnancy and birth cohorts across Europe, mainly from the EU Child Cohort Network [2], the authors grouped several different types of upper (URTIs) and lower respiratory tract infections (LRTIs) separately as binary exposures and then meta-analysed the individual participant data. Specifically in reference to school-aged asthma, table 3 summarised the positive associations for early-life respiratory infection, which were highest for LRTIs within the stratum of participants without early-life wheezing (*i.e.* statistically significant 2.1- to 2.7-fold increases in the odds), followed by LRTIs with early-life wheezing (*i.e.* significant 1.4- to 1.9-fold increases in the odds), URTIs without early-life wheezing (*i.e.* significant 1.1- to 1.2-fold increases in the odds), and URTIs with early-life wheezing (*i.e.* generally non-significant 1.0- to 1.2-fold increases in the odds).

In the discussion, we were drawn to the following text which raises two methodological issues: "*Although the effect sizes for the associations of upper respiratory tract infections with asthma remained when additionally adjusted for concomitant lower respiratory tract infections (data not shown), we cannot fully rule out that this observed association is due to misclassifications of infections or concomitant infections*".

First, by investigating URTI (yes/no) and LRTI (yes/no) as two separate exposures, by design, the meta-analysis does not directly consider the asthma risk of children who have suffered from *both* an URTI and LRTI in early life. It seems biologically plausible to hypothesise that the strength of association between having an URTI in early life and school-aged asthma is stronger for children who have also suffered from a documented LRTI compared with children who had been ill with an URTI alone. Such a two-way interaction analysis would be adequately powered and, theoretically, even a three-way interaction with early childhood asthma/wheezing could be explored by investigating the statistical significance of the interaction. We note that individual types of URTIs have not been studied by this meta-analysis. However, if having "any URTI" without having a co-existent LRTI does not infer a significant asthma risk, then parents of affected children could be reassured that the overall asthma risk is not more than that expected of the general population.

Secondly, it was appropriate for the authors to acknowledge the potential for measurement error as this could lead to biased findings if the misclassification of the exposure is dependent on the outcome and *vice versa*. Although not specifically mentioned, recall bias of the children's exposure to URTIs and LRTIs was minimised by the prospective design of the cohorts originating during pregnancy or at birth. The use of parental report of doctor-diagnosed asthma for most of the cohorts included (n=27, 71%) increased outcome specificity and potential validity [3], when compared with asthma symptoms *via* validated questionnaire alone. However, the potential for misclassification of the parent-reported information across multiple infective illness exposures remains, which is likely to have been non-differential and could have attenuated the strength of some associations. Systematic measurement error that differentially misclassifies the health outcome between exposed and unexposed children is also quite possible, given the infective exposure and later asthma outcome were both self-reported by the child's parents. In other words, parents

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Further analyses to clarify the clinical and public health messages for early-life upper respiratory tract infections are suggested to better inform parents and the healthcare professionals who look after these children in the general community https://bit.ly/3xAWxz0

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who were concerned about respiratory infections in their young children would tend to either over-report or more accurately report the occurrence of asthma when their children were school-aged [4]. The direction of bias could be away from the null if more children exposed to early-life URTIs and/or LRTIs were considered to have the asthma outcome by their parents [4]. It is then of some interest that the Tasmanian Longitudinal Health Study (TAHS) found childhood bronchitis by age 7 years to be associated with doctor-diagnosed current asthma in mid-adult life (age range 51–55 years), especially for subgroups within the stratum of participants who did not have concomitant asthma and/or wheezing by age 7 years (tables 4 and E3) [5]. This similar finding used an asthma outcome that was unlikely to have been differentially reported by the participant themselves over 45 years later. The consistency of results strengthens the study message that early-life LRTIs can increase the risk for later current asthma, while potential differential misclassification of the asthma *outcome* could partially explain the URTI analysis results.

So, while we commend the authors on addressing this important research question using an exceptionally large dataset and a robust meta-analytical design, the clinical and public health messages for early-life URTIs could be made clearer by conducting a further interaction analysis to better inform parents and the healthcare professionals who look after these children in the general community.

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References

1 van Meel ER, Mensink-Bout SM, den Dekker HT, *et al.* Early-life respiratory tract infections and the risk of school-age lower lung function and asthma: a meta-analysis of 150 000 European children. *Eur Respir J* 2022; 60: 2102395.
2 Jaddoe VWV, Felix JF, Andersen AN, *et al.* The LifeCycle Project-EU Child Cohort Network: a federated analysis infrastructure and harmonized data of more than 250,000 children and parents. *Eur J Epidemiol* 2020; 35: 709–724.
3 Yland JJ, Wesselink AK, Lash TL, *et al.* Misconceptions about the direction of bias from nondifferential misclassification. *Am J Epidemiol* 2022; 191: 1485–1495.
4 Alexander LK, Lopes B, Ricchetti-Masterson K, *et al.* Sources of Systematic Error or Bias: Information Bias. *In:* The University of North Carolina, ERIC Notebook, Second Edition. Chapel Hill, Gillings School of Global Public Health, 2014.
5 Perret JL, Wurzel D, Walters EH, *et al.* Childhood 'bronchitis' and respiratory outcomes in middle-age: a prospective cohort study from age 7 to 53 years. *BMJ Open Respir Res* 2022; 9: e001212.