

The difference between groups and individuals

To the Editor:

We are in complete agreement with de Blic et al¹ regarding the need to explore noninvasive methods of assessing structural airway changes in asthma. This need is greatest in children, given that bronchoscopy with endobronchial biopsy (EB) is an invasive procedure.² However, we would urge caution in the interpretation of the findings presented in the authors' recent article.

In their study, de Blic et al¹ demonstrated a weak but statistically significant correlation between bronchial wall thickening (BWT) on high-resolution computed tomography (HRCT) and reticular basement membrane (RBM) thickness in EB. Thus, they showed an association between BWT score and RBM thickness for the group of subjects studied. However, examination of the data in Fig 1 of their article, illustrating the relationship between BWT score and RBM thickness, shows that subjects with a similar BWT score (eg, 10) may have very different values for RBM thickness (ranging from 5 to 11.5 μm). Similarly, subjects with a similar RBM thickness (eg, 6 μm) may have a BWT score anywhere between 2 to 25. Therefore, while there may be an association between BWT and RBM thickness for the group, the data demonstrate that BWT score is a poor predictor of RBM thickness for an individual. It is worth reiterating the general point, often disregarded, that the requirements are much more stringent for a measurement to be useful in the management of an individual than to be of possible interest in demonstrating mechanistic associations.

The authors conclude that more sophisticated HRCT scanners may prove to be more useful in the future. This could be the case, but critical examination of their data is not encouraging. As things currently stand, we would urge caution in using BWT score on HRCT scan as a surrogate marker for RBM thickness measured in EB.

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Reply

To the Editor:

In their correspondence, Saglani et al¹ argue that our bronchial wall thickening (BWT) score is a poor predictor of reticular basement membrane (RBM) thickness. We did not intend to replace bronchial biopsy by high-resolution computed tomography (HRCT) scan to evaluate airway inflammation/remodeling. Our messages are that we need to develop noninvasive techniques to evaluate such abnormalities and that HRCT scan may be one of them. The relationship we found between biopsy and BWT score was not strong, and we wrote that "the corresponding coefficient of determination of the change in BWT score explained by change of RBM thickening was 11%." This was probably related to a lack of power, and certainly we need more patients and more accuracy signs with new generations of computed tomography scan.

Saglani et al¹ state that in the figure from our article, patients with the same BWT score may have different values for RBM. This is not surprising, because parameters contributing to BWT score are not limited to RBM thickness, and conversely, RBM thickening is not the only character of airway remodeling. The author's group has shown that even in children with severe asthma, RBM may be not thickened.²

We do not assume that BWT score on HRCT scan is a surrogate marker of RBM thickness, but it might be used as a noninvasive approach to examining airway structural changes. Again, we need to develop such procedures even if there is no extremely strong relationship.

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Viral specimen collection by parents increases response rate in population-based virus studies

To the Editor:

Recently, Lemanske et al¹ described an impressive study in the Journal with regard to the role of viral respiratory infections in the development of wheezing and allergic diseases in childhood.

In a prospective cohort study in 285 high-risk newborns, nasopharyngeal mucus samples for viral diagnostics were collected at 5 scheduled clinic visits in the first year of life. In addition, parents were asked to notify the study coordinator during times of acute respiratory illnesses to schedule an extra visit with nasopharyngeal sampling. A total of 1668 nasal specimens were obtained, 1102 during scheduled clinic visits and 566 during sick visits.

Hence, the study by Lemanske et al¹ reports $566/285 = 1.99$ respiratory viral episodes per infant per year, which is considerably lower than expected rates from other studies.²

We argue that the study design might have influenced the response rate of parents during periods of respiratory symptoms. Nowadays, parents might be too busy to call the study coordinator, leading to underreporting of viral episodes. Parents might also simply forget to call the study coordinator, which possibly leads to bias to periods with more severe symptoms.

We tested this hypothesis in the Wheezing Illnesses Study Leische Rijn (WHISTLER) study currently being conducted in The Netherlands.³ In this study, infants are followed from birth through the first year of life with daily questionnaires about respiratory symptoms. We asked parents of 50 children to participate in a 6-month pilot study into the diagnosis of viruses during periods of upper or lower respiratory tract infections. A random half of the parents were asked to call the study coordinator to schedule a sick visit at home (group A), and the other half of the parents were asked to take a nasopharyngeal mucus sample from their child themselves and to send it to the study center by mail (group B). All samples were analyzed using PCR techniques for respiratory syncytial virus, rhinovirus, enterovirus, corona OC43/229E, human metapneumovirus influenza type A and B, adenovirus, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. During the observation period, the 2 groups had an equal number of symptomatic periods according to their diaries (respectively, 49 vs 47 periods in group A and B). In group A, 12 sick visits with sampling were obtained (24% of periods), and in group B, 24 samples were obtained (43% of periods; $P = .07$). No differences between the groups were observed for severity of symptoms or for viral recovery rate (respectively, 67% vs 80%; $P = .44$).

We conclude that study design can improve the response rate in population-based virus studies. As much as 76% of symptomatic periods can be missed when parents have to call a study coordinator for virus sampling. This will importantly influence the numbers on prevalence of virus infections in population-based studies. Our data show that these numbers can be significantly reduced to 57% if parents are asked to sample their children themselves, without any loss of viral recovery rate.

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Reply

To the Editor:

We appreciate the comments by Dr van der Zalm et al¹ regarding our recently published findings that demonstrate the importance of rhinovirus infections during infancy and their relevance to long-term wheezing outcomes in early childhood.² The authors comment on our reporting of 1.99 viral infections per child per year during infancy, which is low compared with other published findings, and suggest that underreporting of illnesses contributed to this low value. In fact, the major reason for the relatively low illness rate was that the study was designed to obtain nasal lavage samples only for moderate to severe respiratory illnesses. The initial hypothesis for the Childhood Origins of Asthma (COAST) project was that respiratory syncytial virus (RSV) infections were the major influence on subsequent wheezing outcomes, and our protocol for nasal sampling was developed to maximize our ability to document RSV illnesses while minimizing coordinator time procuring specimens during minor illnesses that were less likely to affect long-term respiratory outcomes. We therefore instructed our families to call on the basis of the nature and the severity of the child's symptoms, and mild respiratory symptoms were not systematically sampled. Importantly, however, despite targeting our scoring system to document RSV illnesses during infancy, moderate to severe outpatient rhinovirus illnesses (with or without wheezing) were the most important predictor of subsequent wheezing in early childhood.

To expand on the data reported in our article regarding the incidence of illness rates during infancy in our cohort, we have performed some additional calculations. There were a total of 538 moderate to severe (score 5+) illnesses in the first year of life. The number reported in the paper (566) includes multiple nasal washes for the same illness.