

# Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy

To the Editors:

The paper by BRUSSEE *et al.* [1] describes the first large survey of the fraction of exhaled nitric oxide ( $F_{eNO}$ ) in a young population. The authors should be congratulated for undertaking such a study in an age range where great patience and persistence are required to obtain data.

BRUSSEE *et al.* [1] reported only a marginal increase in  $F_{eNO}$  among atopic and asthmatic children compared with the nonatopic nonasthmatic children studied. One explanation for the large overlap in the distribution of  $F_{eNO}$  in children with and without asthma or atopy could be that, at this age, the difference is simply smaller than in older children. There are three methodological issues that may have reduced the ability of the study to detect differences in  $F_{eNO}$  between groups, and I would be grateful if the authors would clarify these issues.

First, in the study, the mean  $F_{eNO}$  from two exhaled breath samples was reported, unless the individual values varied by  $>10$  ppb. Current guidelines recommend that paired on-line  $F_{eNO}$  values should be within 5% of each other [2], but these criteria may be too stringent in young children whose  $F_{eNO}$  values are low relative to older children. How did the authors determine the criteria for their recent study [1]? As the difference between paired values increases, the criteria used in this study will result in  $F_{eNO}$  reflecting allergic airway inflammation less accurately; for example, paired values of 4 ppb ("low") and 12 ppb ("high") would be reported as 8 ppb ("average"), but which, if either, value was "correct"? If stricter criteria were applied (for example, only considering paired measurements within 5 ppb of each other), were  $F_{eNO}$  values more discriminating between atopic and nonatopic children, even though fewer data points are analysed?

Secondly, this group has previously reported that paired measurements using this technique were within the limits of agreement [3]. Did the authors also find good reproducibility between the paired  $F_{eNO}$  values in the study of 4-yr-old children [1]? Finally, the authors have previously reported [2] that ambient nitric oxide of  $<20$  ppb influenced the  $F_{eNO}$  values using the apparatus from the recent study [1]. I note that in the recent study, children inhaled through a charcoal nitric oxide filter, and that measurements were not taken on days when ambient nitric oxide exceeded 20 ppb. The authors report that, when analyses were limited to children where ambient nitric oxide levels were  $<10$  ppb at the time of testing, similar results to the whole population were obtained [1].

Thus, ambient nitric oxide does not appear to have substantially influenced the relationship between the fraction of exhaled nitric oxide and asthma/atopy, but I would appreciate

it if the authors could clarify whether ambient nitric oxide influenced the fraction of exhaled nitric oxide.

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## REFERENCES

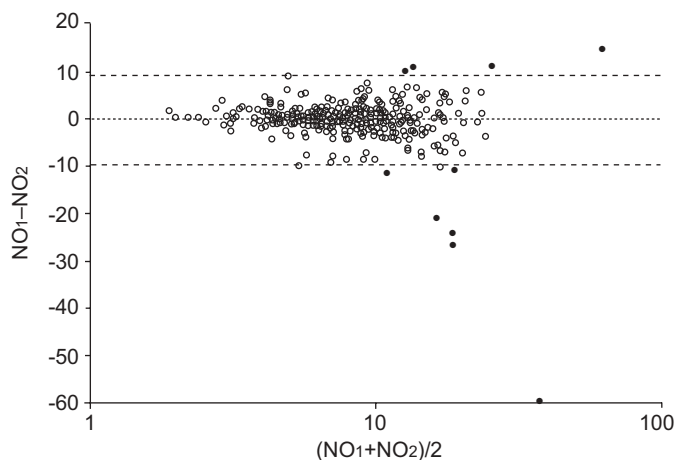
- 1 Brussee JE, Smit HA, Kerkhof M, *et al.* Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. *Eur Respir J* 2005; 25: 455–461.
- 2 Baraldi E, de Jongste JC, Force ET. Measurements of exhaled nitric oxide in children. *Eur Respir J* 2001; 20: 223–237.
- 3 Pijnenburg MW, Lissenberg ET, Hofhuis W, *et al.* Exhaled nitric oxide measurements with dynamic flow restriction in children aged 4–8 yrs. *Eur Respir J* 2002; 20: 919–924.

DOI: 10.1183/09031936.05.00035705

From the authors:

We would like to thank S. Turner for his interest in our work, and we are pleased to comment on the methodological issues raised.

The first issue deals with the reproducibility of the fraction of exhaled nitric oxide ( $F_{eNO}$ ) measurement within a child. In our study [1], we observed a good correlation between the first and the second  $F_{eNO}$  measurements from the children (Spearman  $r=0.73$ ;  $p<0.001$ ). Also, in the majority of the children, the mean difference between the duplicate  $F_{eNO}$  measurements was  $<5$  ppb (89%), whereas, in a small minority of children, the difference was  $>10$  ppb (2%; fig. 1). To find a reasonable balance between the reproducibility of the measurement on the one hand, and the maintenance of sufficient numbers of children on the other hand, we chose to include all children for whom the difference between the duplicate  $F_{eNO}$  measurements was within 10 ppb. Separate analyses of children for whom the duplicate measurements were within 5 ppb produced similar results. For example, in the total study population, the geometric mean  $F_{eNO}$  values in ppb (95% confidence interval) for children with and without a doctor's diagnosis of asthma were 9.4 (7.6–11.7) and 7.6 (7.3–8.0), respectively ( $p=0.06$ ), instead of 10.0 (8.3–12.1) and 7.9 (7.5–8.2), respectively ( $p<0.05$ ), when duplicate samples were within 10 ppb from each other. With respect to atopy, these numbers were 9.1 (8.0–10.4) and 7.4 (7.0–7.9), respectively ( $p<0.05$ ), for samples within 5 ppb, and 9.4 (8.4–10.5) and 7.7 (7.2–8.1), respectively ( $p<0.05$ ), for samples within 10 ppb. So, when more stringent



**FIGURE 1.** Bland Altman plot of the agreement between the duplicate fraction of exhaled nitric oxide ( $F_{eNO}$ ) measurements, indicating the mean difference between the duplicate  $F_{eNO}$  measurements (.....) and the mean difference  $\pm 2SD$  (----). The open and solid circles indicate the children for whom the difference between duplicate  $F_{eNO}$  measurements was  $<10$  ppb or  $>10$  ppb, respectively. The x-axis is logarithmic.

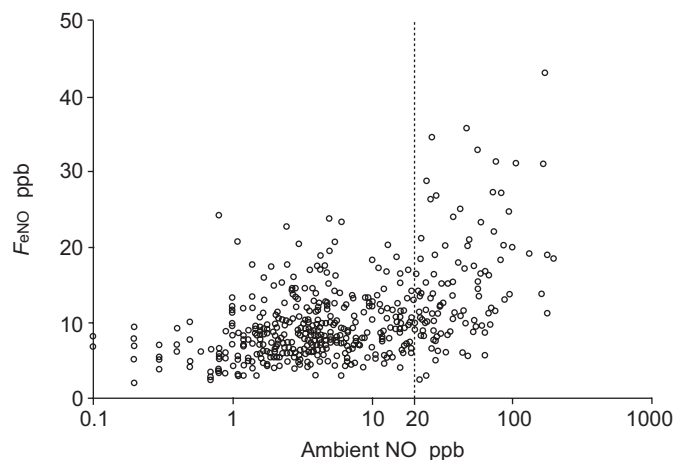
criteria were applied, the  $F_{eNO}$  values were not more discriminative between children with and without asthma or atopy.

With respect to the ambient nitric oxide values, we have examined their effect on exhaled nitric oxide. Since there was no significant influence of ambient nitric oxide levels  $<20$  ppb on the fraction of exhaled nitric oxide values in our study population (figs 2 and 3), we decided to include all children with ambient nitric oxide levels  $<20$  ppb in the analyses. When the analyses were repeated, including only those children for whom the ambient nitric oxide values were  $<10$  ppb, similar results were observed.

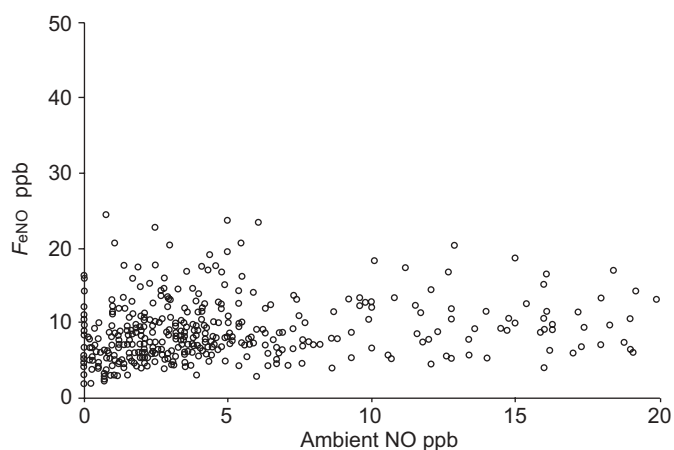
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**FIGURE 2.** The influence of ambient nitric oxide (NO) levels on the fraction of exhaled nitric oxide ( $F_{eNO}$ ) values in the study population. The x-axis is logarithmic.



**FIGURE 3.** The influence of ambient nitric oxide (NO) levels  $<20$  ppb on the fraction of exhaled nitric oxide ( $F_{eNO}$ ) levels in the study population.

## REFERENCES

- 1 Brussee JE, Smit HA, Kerkhof M, *et al.* Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. *Eur Respir J* 2005; 25: 455–461.

DOI: 10.1183/09031936.05.00050405

# Predictive value of BAL cellular analysis in differentiating pulmonary tuberculosis and sarcoidosis

To the Editors:

In a recent issue of the *European Respiratory Journal*, WELKER *et al.* [1] assessed the utility of bronchoalveolar lavage (BAL) cell counts and CD4/CD8 ratios as a test panel for the

differential diagnosis of interstitial lung diseases (ILDs), and reported that their usage significantly modified the pre- versus post-test probability of a correct diagnosis. The diagnostic gain appeared particularly high in sarcoidosis, a disease where distinctive findings such as low BAL neutrophil counts, higher