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Non-atopic persistent asthma in children

Henderson and colleagues¹ interestingly describe six different wheezing phenotypes among which persistent wheeze is, they say, less associated with atopy than intermediate or late-onset wheeze (but with similar lung function deficits, suggesting a mixture of structural airway abnormalities and atopic wheeze).

We would like to emphasise the fact that children with persistent asthma without allergic sensitisation (ie, non-atopic persistent asthma (NAPA)) constitute a phenotype of its own that should be accounted for separately, since its clinical features differ noticeably from atopic persistent asthma (APA).

At our reference centre for paediatric asthma in a north-eastern region of Italy, there were 14 patients with NAPA out of 1280 seen in the last 5 years (1%). In this series, 12/14 patients with NAPA (84.7%) had clinical features of moderate and severe persistent asthma vs 304/1266 patients with APA (24%, $p < 0.001$); 8/14 patients with NAPA (57%) required hospital admission compared with 130 patients with APA (10%, $p < 0.001$). The transition from first wheezing (usually viral) and persistent asthma symptoms was much faster in patients with NAPA than in those with APA (mean (SD) 0.5 (0.8) years vs 3.6 (2.4) years; $p = 0.001$). Moreover, only one of the patients with NAPA had a clinical history of atopic dermatitis compared with 785 (63%) of those with APA.

Just as children with APA and adults with “intrinsic” asthma, children with NAPA do have intense eosinophilic inflammation of the respiratory airways.¹ In agreement with this finding, inhaled steroids were an effective treatment in our patients.

Despite its low incidence, this infrequent—although not very rare—paediatric asthma phenotype should not be missed in large epidemiological cohort studies. Nothing is known about which treatment is best for NAPA and—even more importantly—

nothing is known about the natural history of this severe disease.

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Competing interests: None.

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Authors' reply

We thank Dr Ventura and colleagues for their interest in our paper and for drawing attention to the phenomenon of non-atopic persistent asthma (NAPA). We agree that non-atopic airway inflammation is a potential mechanism for modification of early life influences on airway development. In our paper we highlighted the strong positive association of persistent wheeze with atopy¹ but, as shown in table 2, the prevalence of atopy in this group was 42%. As persistent wheeze comprised 7% of the total population, non-atopic persistent wheeze would be expected to occur in around 4% of this unselected population-based sample. This contrasts with the prevalence of NAPA of 1% reported by Ventura and colleagues from their specialist clinic population in Italy and raises important questions about comparing results from different population samples. It is not clear from their letter how Ventura and colleagues defined persistent asthma but, without frequent early life measures, it would be difficult to disentangle intermediate onset (62% atopic) from persistent wheeze in our model. As both these phenotypes were very strongly associated with persistent wheezing and with physician-diagnosed asthma in later childhood, such misclassification could alter the inferences of their respective associations with objective markers of atopy and airway function. Ventura *et al* make some interesting observations about the early life course of NAPA which are highly relevant to our attempts to

disentangle the course of early childhood wheezing trajectories. Clearly, there are more complexities to emerge from approaches to defining the various sub-phenotypes of asthma, and detection of rare phenotypes—even in relatively large population samples—remains a challenge. The trade-off between population size and the intensity of detailed phenotyping with relevant biomarkers that is feasible in very large epidemiological surveys exemplifies some of these difficulties, although the application of non-invasive markers of inflammation in this setting shows some promise.² There is a need to understand the variation of phenotypes within asthma and how these relate to clinical and pathological end points. A greater understanding of genetic determinants of components of the asthma phenotype,³ harmonisation of outcomes between studies and exploration of environmental interactions with genetic variants will hopefully reveal modifiable targets for disease treatment and prevention.

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CORRECTION

doi:10.1136/thx.2007.084814corr1

T Sandström, F J Kelly. Traffic-related air pollution, genetics and asthma development in children. *Thorax* 2009;**64**:98–99. Reference 6 in this editorial is incorrect, it should be Salam MT, Lin P-L, Avol EL, *et al.* Microsomal epoxide hydrolase, glutathione S-transferase P1, traffic and childhood asthma. *Thorax* 2007;**62**:1050–7.