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**Are asymptomatic airway hyperresponsiveness and allergy risk factors for asthma? A longitudinal study.**

*To the Editor:*

We read with interest the recent paper by Van den Nieuwenhof *et al.* [1] who reported no statistically significant association of airway hyperresponsiveness (AHR) with asthma incidence over 14 years in 123 asymptomatic adolescents 10-22 years old at baseline. They concluded that AHR is not a risk factor for the development of asthma in adulthood and that screening for AHR in adolescents to detect subjects at risk for asthma cannot be recommended. We similarly assessed the association between AHR at baseline and asthma incidence over 11.4 years among asymptomatic children (n=172, 44.2% with AHR (PD<sub>20</sub><4mg methacholine) at baseline) and adults (n=517, 31.7% with AHR at baseline) from the epidemiological study on the genetics and environment for asthma (EGEA) [2,3]. Asymptomatic adults were defined as those with a null symptomatic score according to Pekkanen *et al* [4] over the last 12 months, score based on asthma-like symptoms (wheeze with breathlessness, woken with chest tightness, attack of shortness of breath (SOB) at rest, attack of SOB after exercise, woken by attack of SOB) and already used in the EGEA study [5] and with a similar definition for children. Asthma incidence was 14.0% in children and 8.3% in adults. Asymptomatic AHR appeared significantly related with asthma incidence both in children and adults. The association remained statistically significant after adjustment for age, sex, and atopy at baseline (positive skin prick test to any of 11 allergens) and taking into account familial dependence (OR=3.39 [1.09-10.53], n=145) and in adults (OR=2.68 [1.08-6.69], n=377). Results were similar considering the same age range (10-22 years) as van den Nieuwenhof *et al.* (OR=3.16 [1.23-8.14], n=158) and remained after exclusion of atopics (OR=5.84 [1.06-32.10], n=89). Conclusions were similar (odds ratios always greater than 2) considering other definitions of asymptomatic subjects. When including any wheeze and chronic cough in the preceding list of symptoms, as van den Nieuwenhof *et al.*, AHR at baseline remains significantly associated with the asthma incidence among children (OR=3.18 ([1.08-9.37], n=142), adults (OR=2.84 [1.08-7.42], n=343), or those aged 10-22 years (OR=3.27 [1.11-9.69], n=149). Further, when asymptomatic adult subjects were defined by the absence of chronic cough, chronic phlegm, dyspnoea nor wheezing, as Brutsche *et al.* in the SAPADIA study [6], AHR was also associated to asthma incidence (OR=2.40 [1.06-5.49], n=387).

Methacholine airway hyperresponsiveness was significantly related to asthma incidence in asymptomatic subjects from the EGEA study, whatever the association of symptoms used to define asymptomatic subjects in the last 12 months and age range at baseline. Results were similar after adjusting for age, sex and atopy or restricting the analysis to those aged 10-22 as in Van den Nieuwenhof *et al.*, and even when restricting the analysis to non atopic subjects in that age range. Although no significant association of AHR with asthma incidence have been evidenced in the article of Van den Nieuwenhof *et al.*, it is interesting to note that the OR observed was greater than 2 (2.20), an association of similar magnitude than the association observed in the EGEA study. Differences likely depend on the greater statistical power in the EGEA study, but could also relate to the design of the study, which includes families of asthmatics [2]. Besides of being of prognostic significance for asthma persistence [7], AHR appears to be predictive of asthma incidence among asymptomatic subjects. Such statistical association is however insufficient to conclude that screening for asthma among asymptomatic adolescents is worthwhile, an aspect which needs specific evaluation. The main interest relies upon the understanding of various aspects of asthma expression. Specific determinants (hormonal, personal, occupational and general environment) may explain the heterogeneity of asthma expression over the lifespan. Large representative samples with repeated measurements are needed to clarify the temporality of symptoms, hyperresponsiveness and asthma diagnosis, as the expression of both symptoms and AHR are variable, in particular in the sensitive period of adolescence [7,8].

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