Asthma in urban and rural pre- and primary school children according to the latest GINA definition

To the Editor,

Asthma studies usually neglect pre-school age and are limited in both asthma diagnosis and risk factors analysis, as asthma diagnosis is often merely based on parent-reported previous diagnosis and/or parent-reported symptoms[1]. Thus, as part of INAIRCHILD project[2], this study aimed to assess childhood asthma prevalence and to evaluate whether host and environmental reported factors have an independent or combined risk effect on childhood asthma, by: i) considering a sample of the general population of pre-and primary school children from both urban and rural sites; and ii) according to the most recent Global Initiative for Asthma (GINA) guidelines[3] (i.e. history of characteristic respiratory symptoms and demonstrating variable expiratory airflow limitation by spirometry with reversibility test).

This study was approved by both the Ethics Commissions of Universidade do Porto and for Health of Centro Hospitalar Universitário de São João, Porto. Parents or guardians signed an informed consent according to the Helsinki Declaration developed by the World Medical Association. At any stage of the study, children's dissent was always respected.

Considering a general population sample of 1261 children (Supplementary Material, Figure S1), of which 516 pre- and 745 primary school children, respectively 3-5 and 6-10 years old, and 56.8% from urban and 43.2% from rural nursery and primary schools of northern Portugal involved in INAIRCHILD project[2], ISAAC-derived questionnaires allowed obtaining personal data and information on 49 reported host and environmental potential risk factors for asthma (Supplementary Material, Table S2). Questionnaires missing sex or birthdate were excluded. The method used to deal with missing reported

data was the Multivariate Imputation by Chained Equations based on logistic regression for binary variables and polytomous logistic regression for other unordered categorical variables. Missing values in the outcome were not imputed, and 20 imputed datasets were created.

Asthma was diagnosed according to the latest GINA recommendations. Bivariate and multivariate logistic regressions were used to analyse respectively individual and combined risk effects. A final ("best") multivariate logistic regression model was obtained from an automatic model selection approach. These methods were described in detail in Supplementary Material.

This is a study in a sample of the general population, which is a major strength of this study as no selection criteria for respiratory disease was considered for subjects' recruitment. In fact, as suggested by Oluwole et al. [4], this study population included children from both urban and rural sites, and results showed higher prevalence of reported asthmatic symptoms and reported asthma in urban sites as expected, as well as higher reported parental history of asthma (Table 1). Less access to medical diagnostics in rural areas and different environmental associations might explain those differences [4]. This study population also included children from different age groups, which allowed understanding variances at different childhood stages. As pre-schoolers present a number of special challenges regarding pulmonary function testing[5], asthma is usually diagnosed more robustly given the increase capability of using diagnostic adjuncts, which explains why reported asthma increased with age, although it can also be explained by the asthma prevalence continuous increase during primary school ages.[6]

Asthma prevalence was 5.5%, higher in primary school children (6.4%) than in pre-schoolers (4.4%), and higher in urban sites (6.0%) than in rural (4.8%) although neither statistically significant (*p*-value = 0.23 and 0.41, respectively). Asthma should be

correctly diagnosed as earlier in life as possible. In this study, 1.3% of children were previously undiagnosed asthmatics, providing evidence of under-diagnosed asthma in both pre- and primary school children, in accordance to what Aaron et al. [7] reviewed for school children worldwide. Also, the present study provided evidence of under-diagnosed asthma in both settings (urban and rural), confirming that asthma diagnosis merely based on reported symptoms may be underestimating the real prevalence of this disease, as previously reported in the literature.[4] Children with undiagnosed asthma may suffer poorer health-related quality of life and more school absenteeism. Thus, future studies on childhood asthma prevalence should consider populations from both urban and rural environments.

There were both host and environmental factors that had a risk effect on asthma. Results from bivariate analysis were also different from multivariate analysis (Supplementary Material, Table S3), thus enhancing the importance of studying combined risk factors instead of studying them individually. As there were two recruitment campaigns, "campaign" was included as a factor to understand potential differences in time, but non statistically significant results showed they were not relevant. The final "best" model (Figure 1) included being male, older age and having at least one asthmatic parent as main host factors, and included paracetamol administration in the previous year and antibiotics administration in child's first year of life as main environmental factors. These results were consistent with recently published findings. Bjerg et al. [8] also reported that non-environmental risk factors parental asthma and male sex had an increasing or constant importance for current asthma in 7-8 years old children in Sweden. In fact, parental history of asthma and being male have been commonly reported as risk factors for asthma in childhood.[9] Children being administered antibiotics and paracetamol during the first year of life and in late childhood were also previously reported in the literature to be

positively associated with asthma and asthmatic symptoms in children.[10, 11] In fact, early antibiotic exposure may lead to dysbiosis of the pediatric gut microbiota in the first year of life (precisely when it is highly susceptible), thus increasing the risk of developing childhood allergic disease.[12] Moreover, confounding by indication (treatment of respiratory infections with paracetamol) cannot be excluded as it was not possible to assess directly in the present study. Due to the heterogeneous nature of asthma, these results suggest that pharmacogenetics of those associations need to be further evaluated.

Surprisingly, the presence of carpet in child's bedroom revealed negative association with asthma prevalence. Although a protective effect does not seem to be a plausible explanation, in a previous study[13], which also found a similar negative association, that negative effect disappeared when restricted the analysis to participants that did not report allergy-related avoidance of a carpet. This is speculative at this stage, as the data collected in the present did not allow verifying this explanation, thus more studies are needed.

In summary, when studying childhood asthma prevalence, asthma should be clearly defined by favouring the latest clinical guidelines/recommendations, should include younger children (pre-school aged), and from both urban and rural sites. Information from the most relevant reported host and environmental risk factors should also be considered, especially sex, parental history of asthma, and early-life and current (previous year) paracetamol and antibiotics administration.

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Conflicts of interest

The authors declare they have no conflicts of interest related to the submitted work.

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