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LETTER TO THE EDITOR

High prevalence of wheeze and atopy in rural Malagasy children

To the Editor,

Asthma and allergies in children are not only a matter of concern in affluent countries, but also increasingly so in developing countries.[1-3] Madagascar is one of the least developed countries, not only of Africa but worldwide and lower respiratory tract infections are the second most frequent cause of death in Madagascar.[4] Data from the VAVANY study were the first to suggest that in Madagascar's urban capital schoolchildren have a high prevalence of wheeze.[5,6] In order to assess the prevalence of asthma and allergies in a comparable rural setting, the Malagasy Kids with Asthma and Allergies (MAKI) Study was conducted. We hypothesized that atopic diseases are less prevalent than in an urban setting, as seen not only in more developed countries[7] but also in other sub-Saharan African countries.[8]

We conducted a cross-sectional study on 212 Malagasy children aged 8-15 years in the highlands north of the capital Antananarivo without any industry and with most of the children living in remote villages (for description of the study population see Tables S1 and S2, Supporting Information Methods). The main income source in this sparsely populated area is farming along with some limited livestock breeding. The regional mode of transportation is the oxcart, and the water supply for households is restricted to wells. At the time of our study, there was neither electricity nor mobile networks available in most of the villages. In general, asthma is unknown to people in Madagascar. Accordingly, only one child had ever had therapy with an oral salbutamol, and at the time of study, none of the children were undertaking any type of therapy. The examinations were performed in schools and healthcare centers by the same group of researchers. The questionnaire was based on items from the ISAAC questionnaire, and the core questions on wheeze were identical to the urban VAVANY study. Main outcome measures were *wheeze ever* and *current wheeze* (past 12 months). We performed skin prick tests (SPTs) with seven inhalant allergens, and atopy was defined as an average wheal diameter ≥3 mm to any allergen. Atopic and nonatopic wheeze were defined as current wheeze with or without atopy. Furthermore, spirometry and bronchodilator reversibility were tested.

In our study population, current wheeze was reported in 59 children (28.2%) and wheeze ever in 76 children (36.0%). This was significantly higher than in the urban VAVANY study, with a lifetime prevalence of wheeze of 25.2% ($P < .001$). A fairly high proportion of children was sensitized, with almost a third (27.5%) being sensitized to at least one allergen, cockroach being the allergen the children were sensitized to most frequently (20.8%), followed by *B tropicalis* (8.1%) and *D pter.* (4.3%). A total of 134 children (64.1%) reported to ever have had rhinitis symptoms without a cold, and 34.0% had current rhinitis symptoms in combination with itching or watering eyes. In contrast, skin symptoms, that is an itchy rash, were fairly rare, with only 16 children (7.9%) reporting to ever have had an itchy rash and only 11 children (5.3%) with a current itchy rash.

Wheeze was significantly associated with inhalant sensitization (OR = 2.19, 95% CI 1.13-4.23, $P = .020$ for current wheeze), the strongest effect being observed for sensitization to *D pter.* (OR = 4.77, 95% CI 1.10-20.68, $P = .037$). In total, 39% of currently wheezing children were atopic. On a population basis, atopic wheeze was almost as prevalent (13.3%) as nonatopic wheeze (19.3%). In contrast, no association with atopy was observed for rhinitis or eczema (data not shown). Nevertheless, current rhinoconjunctivitis symptoms were significantly associated with current wheeze (OR = 2.04, 95% CI 1.08-3.84, $P = .028$) and a current itchy rash with wheezing ever (OR = 8.25, 95% CI 1.70-40.00, $P = .009$). With respect to spirometry, MEF_{25-75} was significantly reduced in current wheezers (93.4 ± 29.6 vs 103.3 ± 25.2, $P = .016$), although no other lung function parameter showed similar decrements. Inhalant sensitization showed no association with any of the assessed lung function measures (data not shown).

In multivariate models with stepwise variable selection of all variables with a P-value < 0.1 in univariate analysis (Tables S3 and S4), only a few independent factors remained in the final models (Table 1). A major factor associated with wheeze both ever and current was reduced flow in small airways as assessed by the MEF_{25-75}. Ever having had a pneumonia increased the risk of wheeze, both ever and current and a higher BMI was associated with current wheezing. When trying to disentangle risk factors for atopic and nonatopic wheeze, a different pattern of risk factors was observed. The only relevant factors for atopic wheeze were BMI, with heavier children having a higher risk, and current eczema symptoms, even though not being associated with atopic sensitization themselves. Relevant factors for nonatopic wheeze were reduced MEF_{25-75}, having had a pneumonia and, in line with the hygiene hypothesis, having older siblings. Other factors potentially indicating a more hygienic, affluent

TABLE 1 Study characteristics and wheeze: adjusted odds ratios from stepwise multivariate logistic regression

	Risk for wheeze ever N = 180			Risk for current wheeze N = 187			Risk for nonatopic wheeze N = 170			Risk for atopic wheeze N = 150		
	aOR	95% CI	*P*	aOR	95% CI	*P*	aOR	95% CI	*P*	aOR	95% CI	*P*
MEF_{25-75} (in % predicted)	0.98	0.97-1.00	.011	0.98	0.96-0.99	.002	0.97	0.96-0.99	.002	–	–	–
Pneumonia	5.19	1.72-15.70	.004	4.90	1.55-15.50	.007	5.08	1.55-16.69	.007	–	–	–
BMI (in kg/m^2)	–	–	–	1.32	1.05-1.67	.019	–	–	–	1.58	1.14-2.21	.007
≥1 older sibling	0.40	0.18-0.88	.024	–	–	–	0.38	0.16-0.94	.036	–	–	–
Skin prick test												
Cockroach	–	–	–	2.82	1.22-6.50	.015	–	–	–	–	–	–
D pter.	6.52	1.09-39.02	.040	–	–	–	–	–	–	–	–	–
Current symptoms												
Nasal	–	–	–	2.25	1.03-4.89	.041	–	–	–	–	–	–
Skin	7.01	1.38-35.50	.019	–	–	–	–	–	–	5.42	1.03-28.62	.047

Abbreviations: 95% CI, 95% confidence interval; aOR, adjusted odds ratio.

or modern household, such as owning a means of transportation or wearing shoes at study date were neither associated with the wheezing outcomes, nor with any other outcomes.

In conclusion, the prevalence of wheeze was surprisingly high for a developing country.[1-3] An overview over the large span of wheezing prevalences in children aged 13-14 years in sub-Saharan African countries is best depicted by data from ISAAC centers revealing numbers as low as 5.7% in Cameroun to 13.0% in Nigeria and as high as 19.3% in Urban Cote d'Ivoire and 20.4% in Cape Town, South Africa.[1,2] Furthermore, objective assessment of atopic sensitization revealed a surprisingly high prevalence of cockroach sensitization, while house dust mite sensitization was associated with wheeze, an association so far mostly observed in the developed world.[9] However, among atopic wheezers no association with FEV_1/FVC and bronchodilator response was seen, indicators for reversible airway obstruction which would be typical for asthma. This may argue against an atopic asthma phenotype as seen in developed countries and is in line with the observation from ISAAC that the link between atopic sensitization and asthma symptoms in children increases with economic development and would thus be low in our nonaffluent population.[9] In contrast, nonatopic wheeze was strongly associated with a past history of pneumonia and showed decreased flow rates in the smaller airways suggesting that these wheezing symptoms may not be interpreted as variable airway obstruction, that is asthma, but rather as a sequelae of lower respiratory tract infections in children living in poverty and exposed to indoor air pollution. This is in line with results from a recent study in rural Bolivia, in that asthma symptoms may be more related to respiratory infections than to allergy.[10] Hence, the prevention of airway infections by means of improving living conditions is crucial for the reduction of the prevalence of wheeze in the developing world. Surprisingly, wheeze was clearly more prevalent in rural as compared to urban regions within Madagascar, as observed in the VAVANY study.[5] However, no factors associated with lifestyle or rural living showed an effect, potentially due to little variation within this poor rural environment and a sample size that might not suffice to detect effects in such a homogeneous population. Unfortunately, we have no information on a family history of allergic diseases and thus cannot disentangle the issue of heritability. Further limitations are given by the fact that difficulties may arise when working in a rural region, especially in one with such a limited set of resources. Because of these practical constraints and their impact on this study, we cannot rule out possible selection bias, misclassification, or residual confounding. Nevertheless, these findings underline that wheezing illnesses are not only an issue in industrialized countries, but also in nonaffluent countries and regions with low socioeconomic conditions, though the determinants and the underlying pathomechanisms may differ significantly.

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CONFLICT OF INTEREST

P. T. Wolff, M. Götschke, A. Rakotozanany, A. L. Robinson, and L. K. Wolff have nothing to disclose; E. von Mutius reports grants from German Research Foundation, during the conduct of the study; personal fees from OM Pharma S. A., Böhringer Ingelheim International GmbH,Peptinnovate Ltd.,PharmaVentures Ltd., and Nestlé Deutschland AG, outside the submitted work; in addition, Dr von Mutius has a patent Application number LU101064, Barn dust extract for the prevention and treatment of diseases pending, a patent Publication number EP2361632: Specific environmental bacteria for the protection from and/or the treatment of allergic, chronic

inflammatory and/or autoimmune disorders. With royalties paid to Protectimmun GmbH, a patent Publication number EP 1411977: Composition containing bacterial antigens used for the prophylaxis and the treatment of allergic diseases. Licensed to Protectimmun GmbH, a patent Publication number EP1637147: Stable dust extract for allergy protection licensed to Protectimmun GmbH, and a patent Publication number EP 1964570: Pharmaceutical compound to protect against allergies and inflammatory diseases licensed to Protectimmun GmbH. S. Illi has nothing to disclose.

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SUPPORTING INFORMATION

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