

Original article

Comparison of local risk factors for children's atopic symptoms in Hanoi, Vietnam

Background: A 1999 study in Hanoi, Vietnam using the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire showed a high prevalence of atopic symptoms. Identifying risk factors for symptoms in these children may help in understanding the causes for these high estimates.

Methods: An ISAAC questionnaire with supplemental questions on environmental variables was distributed to 5495 school children in Hanoi and a suburban district, Dong Anh. The response rate was 65.7%.

Results: In Dong Anh, the following were among the significant age and gender adjusted associations: pig ownership [odds ratio (OR) (95% confidence interval), OR = 1.79 (1.18–2.70) for doctor-diagnosed asthma (DDA), OR = 1.72 (1.08–2.78) for doctor diagnosed hay fever (DDHF)] and farming [OR = 1.67 (1.27–2.19) for ever asthma, OR = 1.51 (1.09–2.09) for DDHF]. In multivariate models, tuberculosis (TB) was a significant predictor of atopic symptoms [Hanoi: OR = 3.09 (1.10–8.70) for DDA, Dong Anh: OR = 3.71 (1.40–9.84) for DDA, OR = 4.66 (1.88–11.57) for DDHF].

Conclusions: These findings are contrary to the 'hygiene hypothesis'. Recent immunologic and epidemiologic studies refute the inverse association between allergy and TB and may be one explanation for the positive association in this study. The positive association with pig ownership and farming may be because of exposures on farms in a developing country that may be different from exposures in farms of developed countries.

S. K. Chai¹, N. N. Nga²,
H. Checkoway¹, T. K. Takaro¹,
G. J. Redding³, M. C. Keifer¹,
L. V. Trung², S. Barnhart¹

¹Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA; ²National Institute of Occupational and Environmental Health, Ministry of Health, Hanoi, Vietnam; ³Division of Pulmonary Medicine, Department of Pediatrics, University of Washington, Seattle, WA, USA

Key words: asthma; child; developing countries; epidemiology; hay fever perennial allergic rhinitis; risk factors.

Sanders K. Chai
LUMC
Department of Parasitology
P4-35, Albinusdreef 2
2333 ZA Leiden
The Netherlands

Accepted for publication 12 November 2003

Phase I of the International Study on Asthma and Allergies in Childhood (ISAAC) demonstrated a large variability between countries in atopic symptom prevalence (1). Potential causes for this variability include environmental factors, differences in genetic susceptibility and bias because of language and perceptions leading to misclassification error.

The ISAAC survey has generated numerous published results regarding risk factors for atopy and asthma-related symptoms. Variables that demonstrate relatively consistent direct associations with symptoms include environmental tobacco smoke (ETS) (2–6), stove fuel (2, 6), parental education (7), and inverse associations with animal ownership (2, 3, 6), breast-feeding (4), and crowding (5). By and large, they confirm previous reports of associated environmental risk factors for atopy. Most of these studies were carried out in the developed world. Examining potential risk factors in a developing country may shed light on shared and

divergent risk patterns that may have environmental and/or genetic determinants.

Much of the current literature describes an increasing gradient in atopy prevalence from developing to developed countries (5, 8–10). Such findings support the hygiene hypothesis, which states that atopy is a result of reduced infectious disease burden and improved hygiene and sanitation (11). This relative lack of microbial stimulation of the immune system is what leads to sensitization to otherwise innocuous environmental antigens. Theoretically, children in the developing world, still contending with traditional environmental epitopes from microbes, fail to develop such atopic sensitivity.

Countering this model, the ISAAC survey conducted in Hanoi demonstrates a high prevalence of atopic symptoms (12). The prevalence of wheeze in last 12 months was 14.9%, ever asthma was 12.1%, and allergic rhinoconjunctivitis symptoms in last 12 months was 10.7% in a sample of public school children in Hanoi proper

($n = 969$). These estimates are more consistent with those ISAAC estimates from more developed countries than those from less-developed countries.

To better understand the nature for these high estimates, we analyzed the ISAAC data from Hanoi and from an additional suburban agrarian district Dong Anh in conjunction with supplemental questions evaluating environmental and socioeconomic factors. These questions provide the opportunity to identify risk factors for symptoms and potentially better characterize the meaning of symptoms.

Methods

Location and population

Two sites were selected for implementation of the study, central Hanoi and an outlying suburban district, Dong Anh, situated 20 km outside Hanoi. Overall, the population of Vietnam is 20% urban and has a literacy rate of 94% (13). Hanoi is the capital of Vietnam and is an urban centre with 2.5 million inhabitants. Dong Anh is a predominantly agrarian community with a growing industrial sector and a well-developed infrastructure including municipal treated water and sewage system. The study team at the National Institute of Occupational and Environmental Health (NIOEH) selected two public schools at each site. The schools contained a total of 5495 students, 5–11 years of age, 1460 in Hanoi and 4035 in Dong Anh, all of whom were considered eligible for this study.

Study design and tools

This cross-sectional survey used the parent self-administered ISAAC questionnaire (14) with supplemental questions on home environment, medical history, and social circumstances. The questionnaire was translated from English into Vietnamese, then back translated and administered to four NIOEH staff members for pilot testing and revision.

The study was conducted in November 1999 in Hanoi and in April 2001 in Dong Anh.

Teachers of all classes within the four schools distributed and collected the questionnaires to and from the students for parental self-administration and handed them over to the headmaster for secure storage until NIOEH staff pick-up.

Analysis

Normal theory test for comparison of binomial proportions was used to compare symptom prevalence rates between Hanoi and Dong Anh. Associations between potential risk factors and ISAAC symptoms were quantified as odds ratios (OR) by logistic regression adjusting for age (as a continuous variable) and gender using SPSS version 7.5 (Chicago, IL). *A priori* assumptions (based on literature review) and the age and gender adjusted OR results guided the inclusion of covariates in the multivariate logistic regression model for each site. Variables listed under the multivariate model tables (Tables 4 and 5) were all the variables included in the model regardless of their statistical significance unless otherwise noted. In the Dong Anh multivariate model, pig ownership and farming as a parental occupation were added separately due to their collinearity. The same was not performed for tuberculosis (TB) and household

TB as collinearity was found not to be significant (data not shown). Finally, regression models were generated using significantly different risk factors in the two communities as covariates and adding a dummy variable representing the community to assess the role of such covariates on any differences in symptom prevalence between Hanoi and Dong Anh. As discussed elsewhere (12), the core ISAAC questions for eczema were not amenable to the analysis carried out in this study on account of poor response rate because of what is assumed to be translational issues.

Ethical considerations

For the Hanoi sites, the on-site study team reviewed the study protocol with the headmasters, teachers, and a focus group of parents. It was decided in this review that consent would not be obtained on all participants. This protocol then received approval from the chair of the NIOEH Institutional Review Board (IRB) and director of the NIOEH and the study proceeded. The researchers at the University of Washington learned of these changes only after they had been implemented. As soon as they were informed of the changes, the implementation of the protocol was halted, and the University of Washington Human Subjects Division (UW-HSD) was notified. After review by the UW-HSD it was felt that the procedures and safeguards were culturally appropriate and the data could be used and presented.

For the Dong Anh study site, a revised human subjects protocol was generated and approved by the NIOEH-IRB and the UW-HSD. In this updated protocol, informed consent was obtained from all parents and informed assent was obtained from all children.

Results

Descriptive data

The overall questionnaire response rate was 65.7% (3610/5495) with 68.7% of respondents who completed the form being the student's mother, father, grandparent, aunt or uncle, 0.8% was an older sibling and 30.6% did not respond to this question. There was no apparent bias in responses based on the individual identified as completing the questionnaire.

Table 1 presents demographic features and other covariates for Hanoi and Dong Anh. There was a higher prevalence of TB and electric/gas stoves in Hanoi and Hanoi subjects were more likely to have received any immunizations. Dong Anh subjects were older, breast-fed more and longer, had a higher prevalence of ETS within the house, owned more animals and had parents employed as farmers and had more crowded households.

Figure 1 shows atopic symptom prevalence rates for Hanoi and Dong Anh with an overall trend for higher estimates in Dong Anh. Ever asthma, doctor-diagnosed asthma (DDA), allergic rhinoconjunctivitis symptoms in the last 12 months, and ever hay fever were all significantly higher in prevalence in Dong Anh than in Hanoi. The prevalence of ever wheeze, wheeze in the last 12 months, wheeze disturbed sleep, ever allergic rhinitis (AR) and doctor-diagnosed hay fever were not significantly different between the two sites.

Table 1. Descriptive data from Hanoi and Dong Anh

	Hanoi (response rate)	Dong Anh (response rate)
Number of respondents	969	2641
Overall response rate (total number of questionnaires distributed)	66.4% (1460)	65.5% (4035)
Average age (SD, range)*	7.6 (± 1.4 , 5–11) (90.3%)	8.4 (± 1.3 , 5–13) (87.4%)
Gender distribution	52% female (96.4%)	52% female (94.4%)
Responder identity adult (vs child, young sibling)	81.9% (83.8%)	63.8% (64.2%)
Family history of atopy (%)	23% (91.7%)	27.1% (91.2%)
History of TB (%)†	2.4% (86.7%)	1.4% (84.7%)
Household TB (%)	10.5% (97.8%)	8.0% (83.5%)
Birth order (average)*	1.5th (93.7%)	1.8th (96.0%)
Immunizations (% positive history of receiving any)†	87.1% (93.2%)	80.3% (96.0%)
Breast-feeding		
% exclusively during infancy†	55.7% (90.3%)	77.1% (97.7%)
For ≥ 12 months†	52.4% (87.5%)	63.4% (87.7%)
ETS (% with household smoker)†	39.7% (85.6%)	52.3% (98.9%)
Stove type (%)‡	47.5% (92.9%)	10.9% (96.3%)
Any animals (%)†	31.1% (79.8%)	84.6% (94.1%)
Cat	11.2%	7.6%
Dog	17.1%	47.4%
Chicken	3.6%	59.2%
Cow	0.1%	18.0%
Pig	1.0%	62.9%
Occupation (%)†	54.0% skilled labor (90.2%)	75.1% farmers (95.9%)
Education (% with $\geq$ high school diploma)	80.1% (84.8%)	76.7% (89.5%)
Household crowding (average number of people)†	3.9 (87.5%)	4.2 (91.7%)

* $P < 0.05$ comparing mean values.† $P < 0.05$ based on binomial proportions.

‡ Electric/gas vs kerosene/coal/wood/dung, straw.

Age and gender adjusted odds ratios

Age and gender adjusted ORs are given in Table 2 for Hanoi and Table 3 for Dong Anh for symptoms associated with the variables listed in Table 1. For Hanoi, there were significant ORs for maternal history (of asthma given asthma symptoms and of AR given AR symptoms), history of TB, household history of TB, and ETS, and less consistently for stove type and breast-feeding. For Dong Anh, there were significant ORs for maternal history, history of TB, household TB, stove type, pig ownership and farming as parental occupation. Less consistent ORs were seen for breast-feeding, ETS, cow ownership, any animals, education and home crowding.

Multivariate logistic regression model

The results of combined logistic regression models with number of subjects included are shown in Table 4 for

Hanoi and Table 5 for Dong Anh. For Hanoi, maternal or family history and ETS bore the most consistent associations with symptoms. History of TB and household TB were significant predictors for, ever asthma and DDA. For Dong Anh, maternal history was a consistent risk factor across all symptom categories. History of TB was as well except for wheeze in the last 12 months and allergic rhinoconjunctivitis symptoms in the last 12 months. Stove type was significant for DDA and ever hay fever. Household TB was significantly related to allergic rhinoconjunctivitis symptoms in the last 12 months and ever hay fever and education was for ever asthma respectively. Pigs and farming were not significant risk factors for any symptom or diagnosis.

To examine variables that may account for the difference in symptom prevalence between Dong Anh and Hanoi, an age and gender adjusted multivariate model was created using covariates that were significantly different in both sites regardless of their significance in the age and gender adjusted ORs. This model consisted of TB, ETS, stove type, immunizations, breast-feeding duration, breast vs formula feeding, household crowding, either animal ownership or farming as an occupation, and a dummy variable representing Dong Anh or Hanoi residence. Of the symptoms that were significantly different under crude analysis, only AR conjunctivitis in the last 12 months had prevalence estimates that were explained by the covariates included in the model. In this model, TB, ETS, and stove type were significant covariates (data not shown).

Discussion

We observed higher prevalence estimates for asthma- and allergy-related symptoms and diagnoses in suburban Dong Anh when compared with the capital city Hanoi. Notably, ever asthma and DDA, allergic rhinoconjunctivitis symptoms in the last 12 months, and ever hay fever were significantly more prevalent in Dong Anh. Our findings indicate both similarities and differences with the literature. Similarities included positive associations with maternal history of atopy in both Hanoi and Dong Anh multivariate models, and with ETS exposure in Hanoi age and gender adjusted ORs, and with unrefined fuel stove type in Dong Anh age and gender adjusted ORs. Differences with the literature included positive associations with history of TB in Hanoi and Dong Anh multivariate models and pig ownership and farming as parental occupation in Dong Anh age and gender adjusted ORs.

We analyzed Dong Anh ISAAC questions using the same method as we had with the Hanoi data in a previous publication (12) (data not shown) to examine potential relationships between symptoms. As seen in the Hanoi group, there was in Dong Anh a significant association and agreement between symptoms and physician diagnoses to

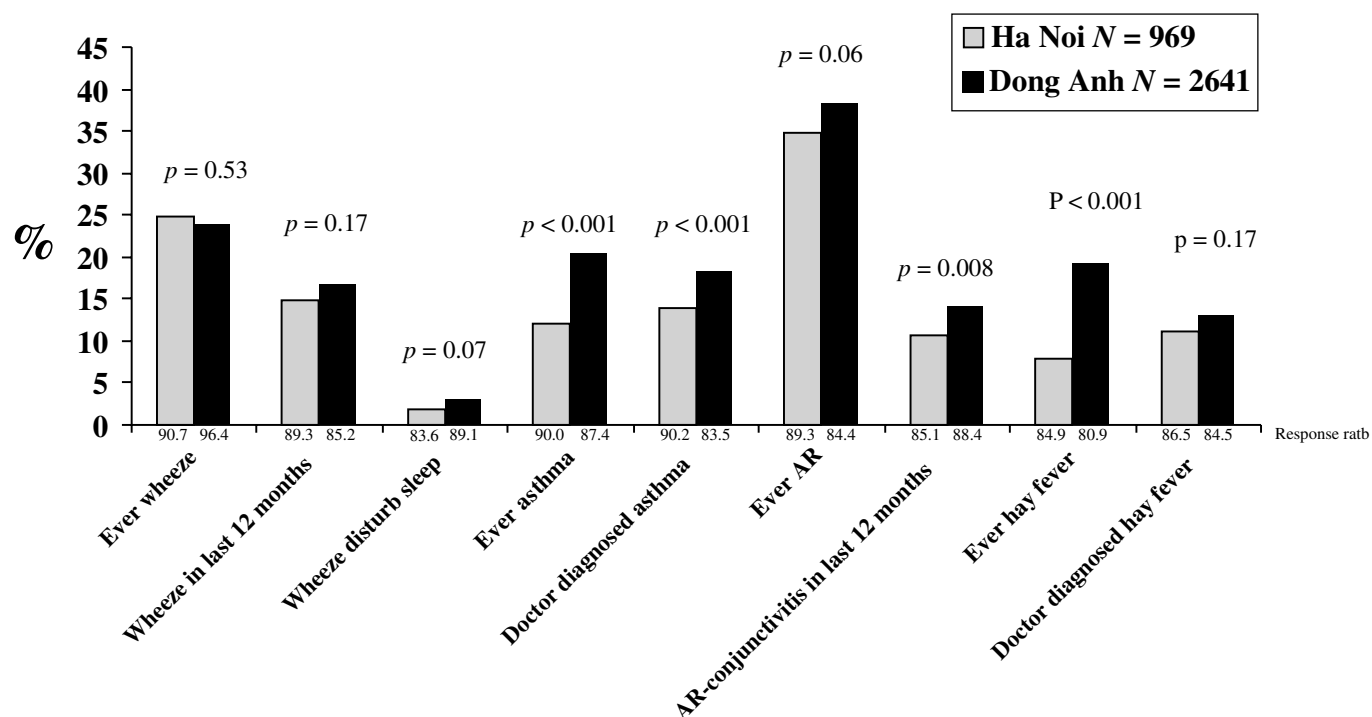


Figure 1. Comparison of asthma and allergy symptom prevalence in Hanoi and Dong Anh.

Table 2. Age and gender adjusted odds ratio for asthma and allergy symptoms – Hanoi

	Wheeze 12 months	Ever asthma	Doctor-diagnosed asthma	AR conjunctivitis 12 months	Ever hay fever	Doctor-diagnosed hay fever
Maternal history*	3.24 (1.53–6.83)	2.13 (0.97–4.68)	2.20 (1.02–4.72)	1.72 (0.93–3.20)	3.96 (2.16–7.28)	2.16 (1.21–3.86)
History of TB	3.25 (1.24–8.50)	3.90 (1.49–10.19)	3.83 (1.44–10.20)	3.57 (1.22–10.47)	2.48 (0.69–8.87)	3.53 (1.19–10.44)
Household TB	1.87 (1.09–3.22)	2.40 (1.39–4.14)	2.34 (1.38–3.96)	1.41 (0.74–2.67)	1.30 (0.62–2.73)	1.30 (0.67–2.50)
Birth order†	0.86 (0.64–1.16)	1.04 (0.76–1.42)	1.04 (0.77–1.41)	1.25 (0.86–1.80)	1.22 (0.81–1.84)	1.08 (0.77–1.50)
Immunizations‡	1.48 (0.43–5.06)	0.47 (0.18–1.21)	0.61 (0.22–1.69)	0.94 (0.27–3.22)	2.36 (0.31–17.75)	3.35 (0.45–25.04)
Breast-feeding§	0.98 (0.41–2.30)	0.75 (0.32–1.77)	1.04 (0.42–2.57)	0.79 (0.32–1.98)	0.39 (0.17–0.92)	0.61 (0.26–1.45)
Breast-feeding >12 months (vs <12 months)	0.58 (0.39–0.86)	0.89 (0.58–1.38)	1.08 (0.71–1.65)	0.67 (0.42–1.07)	0.71 (0.42–1.22)	0.92 (0.58–1.46)
Any ETS in house	2.59 (1.70–3.96)	2.12 (1.35–3.33)	1.91 (1.25–2.92)	2.61 (1.59–4.28)	1.55 (0.89–2.69)	1.42 (0.90–2.25)
Stove type¶	0.64 (0.43–0.94)	0.59 (0.38–0.90)	0.74 (0.50–1.10)	0.94 (0.60–1.48)	0.98 (0.59–1.65)	1.20 (0.77–1.87)
Any animals	1.02 (0.71–1.45)	1.01 (0.63–1.64)	1.08 (0.68–1.69)	1.11 (0.68–1.82)	1.37 (0.78–2.44)	1.23 (0.77–2.00)
Education**	1.01 (0.88–1.15)	1.00 (0.86–1.16)	0.98 (0.85–1.13)	0.92 (0.79–1.08)	0.94 (0.78–1.12)	0.99 (0.85–1.16)
Home crowding††	1.00 (0.67–1.48)	1.18 (0.69–2.02)	0.84 (0.52–1.35)	1.42 (0.78–2.56)	1.59 (0.79–3.21)	1.24 (0.78–5.15)

* Maternal history of asthma if wheeze 12 months, ever asthma or doctor diagnosis asthma; allergic rhinitis if allergic rhinitis conjunctivitis 12 months, ever hay fever or doctor-diagnosed hay fever.

† Continuous variable.

‡ Any immunizations (vs none).

§ vs exclusively formula.

¶ Electric, refined gas vs unrefined fuels including kerosene, coal, wood, dung, straw.

** Education using six-level scale (less than high school, high school, technical school, some college, college diploma, professional school).

†† ≤ 4 (vs >4 people in house).

Bold denotes statistically significant ORs.

suggest a consistent clinical entity. This consistency suggests a certain degree of reliability of ISAAC in Vietnam and further supports its validity in its application in communities with differing cultural and linguistic back-

grounds. A caveat though to consider is the response rate from the two surveys which while being consistent with one-time mailed surveys in the US (15) do not meet ISAAC criteria.

Table 3. Age and gender adjusted OR for asthma and allergy symptoms – Dong Anh

	Wheeze 12 months	Ever asthma	Doctor-diagnosed asthma	AR conjunctivitis 12 months	Ever hay fever	Doctor-diagnosed hay fever
Maternal history*	4.56 (2.89–7.21)	4.04 (2.42–6.75)	7.90 (4.89–12.77)	1.89 (1.33–2.69)	2.73 (2.00–3.73)	3.06 (2.18–4.29)
History of TB	2.42 (1.08–5.47)	9.65 (3.99–23.30)	6.60 (2.86–15.24)	2.17 (0.89–5.29)	2.78 (1.26–6.12)	5.94 (2.68–13.20)
Household TB	1.52 (1.04–2.23)	1.23 (0.84–1.80)	1.55 (1.06–2.28)	1.63 (1.09–2.45)	1.59 (1.09–2.30)	1.72 (1.14–2.59)
Birth order†	1.07 (0.94–1.20)	0.97 (0.87–1.07)	1.00 (0.90–1.12)	1.00 (0.89–1.13)	0.97 (0.88–1.08)	0.95 (0.84–1.07)
Immunizations‡	1.32 (0.94–1.86)	1.23 (0.87–1.72)	1.04 (0.74–1.48)	1.49 (1.01–2.19)	0.90 (0.65–1.24)	1.00 (0.67–1.50)
Breast-feeding§	1.24 (0.93–1.64)	1.06 (0.81–1.38)	0.89 (0.68–1.16)	0.81 (0.61–1.07)	0.89 (0.68–1.16)	0.73 (0.54–0.98)
Breast-feeding >12 months (vs <12 months)	0.90 (0.70–1.17)	1.00 (0.78–1.28)	1.12 (0.86–1.47)	0.95 (0.72–1.26)	0.91 (0.71–1.19)	0.90 (0.66–1.19)
Any ETS in house	1.20 (0.96–1.50)	1.13 (0.92–1.40)	1.33 (1.06–1.67)	1.36 (1.06–1.74)	1.22 (0.98–1.52)	1.22 (0.95–1.58)
Stove type¶	0.61 (0.41–0.90)	0.60 (0.42–0.86)	0.43 (0.28–0.65)	0.54 (0.35–0.83)	0.61 (0.42–0.89)	0.64 (0.41–0.99)
Cat	1.25 (0.84–1.88)	0.99 (0.66–1.47)	1.42 (0.97–2.08)	1.18 (0.76–1.84)	1.27 (0.86–1.87)	1.06 (0.66–1.71)
Dog	0.95 (0.76–1.20)	1.02 (0.82–1.26)	1.01 (0.81–1.27)	1.05 (0.82–1.34)	0.99 (0.79–1.24)	0.91 (0.70–1.17)
Chicken	1.26 (0.98–1.61)	1.25 (1.00–1.57)	1.23 (0.97–1.56)	0.98 (0.76–1.27)	1.06 (0.84–1.34)	1.02 (0.78–1.33)
Bird (not chicken)	0.70 (0.43–1.14)	1.11 (0.75–1.66)	1.54 (1.04–2.26)	0.72 (0.43–1.22)	0.88 (0.57–1.34)	0.96 (0.59–1.57)
Cow	1.13 (0.85–1.52)	1.19 (0.91–1.57)	1.12 (0.84–1.49)	0.89 (0.63–1.23)	1.37 (1.04–1.80)	1.26 (0.92–1.74)
Pigs	1.02 (0.71–1.48)	1.85 (1.23–2.72)	1.79 (1.18–2.70)	1.47 (0.95–2.28)	1.41 (0.95–2.08)	1.72 (1.08–2.78)
Any animal	1.05 (0.73–1.51)	1.69 (1.14–2.5)	1.67 (1.11–2.5)	0.71 (0.46–1.10)	1.25 (0.86–1.82)	1.56 (0.98–2.50)
Farmer	1.33 (1.08–1.76)	1.67 (1.27–2.19)	1.64 (1.23–2.19)	1.48 (1.09–2.02)	1.48 (1.12–1.96)	1.51 (1.09–2.09)
Education**	1.15 (1.03–1.27)	1.21 (1.09–1.33)	1.19 (1.07–1.31)	1.14 (1.02–1.27)	1.04 (0.94–1.14)	1.05 (0.94–1.18)
Home crowding††	0.98 (0.77–1.24)	0.96 (0.77–1.20)	0.76 (0.61–0.97)	0.98 (0.76–1.26)	0.96 (0.76–1.21)	0.95 (0.73–1.23)

* Maternal history of asthma if wheeze 12 months, ever asthma or doctor diagnosis asthma; allergic rhinitis (AR) if AR conjunctivitis 12 months, ever hay fever or doctor diagnosed hay fever.

† Continuous variable.

‡ Any immunizations (vs none).

§ vs exclusively formula.

¶ Electric, refined gas vs unrefined fuels including kerosene, coal, wood, dung, straw.

** Education using six-level scale (less than high school, high school, technical school, some college, college diploma, professional school).

†† ≤ 4 (vs >4 people in house).

Bold denotes statistically significant ORs.

Table 4. Multivariate logistic regression for asthma and allergy symptoms – Hanoi

	Wheeze 12 months (n = 775)	Ever asthma (n = 780)	Doctor-diagnosed asthma (n = 791)	AR conjunctivitis 12 months (n = 740)	Ever hay fever (n = 742)	Doctor-diagnosed hay fever (n = 757)
Age	1.20 (1.03–1.39)	0.99 (0.85–1.15)	0.98 (0.85–1.13)	0.94 (0.80–1.11)	0.97 (0.80–1.17)	0.93 (0.79–1.09)
Gender (female)	0.84 (0.56–1.25)	1.04 (0.68–1.60)	1.57 (1.04–2.36)	1.29 (0.82–2.05)	1.05 (0.62–1.78)	1.06 (0.68–1.65)
Maternal history*	2.84 (1.28–6.31)	1.75 (0.75–4.06)	1.73 (0.76–3.93)	1.42 (0.74–2.72)	3.59 (1.91–6.76)	1.95 (1.07–3.54)
Family history*	2.39 (1.33–4.30)	1.96 (1.07–3.61)	1.67 (0.92–3.03)	0.97 (0.53–1.76)	3.28 (1.65–6.54)	1.72 (0.87–3.41)
History of TB	2.41 (0.85–6.88)	3.13 (1.11–8.81)	3.09 (1.10–8.70)	3.01 (0.98–9.27)	1.80 (0.47–6.91)	3.02 (0.99–9.26)
Household TB	1.45 (0.82–2.57)	1.93 (1.09–3.42)	1.94 (1.11–3.39)	1.12 (0.57–2.22)	1.04 (0.47–2.32)	1.09 (0.55–2.17)
Any ETS in house	2.47 (1.60–3.79)	1.94 (1.23–3.07)	1.73 (1.12–2.66)	2.46 (1.48–4.07)	1.45 (0.82–2.58)	1.37 (0.86–2.19)

* Model based on maternal history unless not significant, in which case family history added instead (even if not significant). Other covariates are based on model with family history unless maternal history was significant. Maternal history/family history of asthma if wheeze 12 months, ever asthma or doctor-diagnosed asthma; allergic rhinitis (AR) if AR conjunctivitis 12 months, ever hay fever, or doctor-diagnosed hay fever.

Bold denotes statistically significant ORs.

The trend of higher prevalence of ISAAC symptoms in Dong Anh compared with Hanoi is contrary to reports in the literature wherein rural communities in the developing world have a lower prevalence than urban sites (8, 16). There are several potential explanations for the trend seen in our study. Adjusting the symptom prevalence estimates with those factors that were significantly different between Hanoi and Dong Anh resulted in the prevalence difference in only one symptom category (allergic rhinoconjunctivitis symptoms in last 12 months) being fully explained.

Despite the differences in demographic characteristics as suggested in Table 1, Dong Anh itself may not be sufficiently 'rural' to demonstrate the expected gradient in atopic prevalence from rural to urban found in other studies. In Dong Anh, there is a relatively high standard of living with modern housing stock and municipal infrastructure, growth of industrial facilities, substantial communication with Hanoi leading to some shared environments, and access to health care and pharmaceuticals – characteristics which all reflect elements of

Table 5. Multivariate logistic regression for asthma and allergy symptoms – Dong Anh

	Wheeze 12 months (n = 1913)	Ever asthma (n = 1769)	Doctor-diagnosed asthma (n = 1692)	AR conjunctivitis 12 months (n = 1743)	Ever hay fever (n = 1656)	Doctor-diagnosed hay fever (n = 1731)
Age	1.11 (1.01–1.21)	1.08 (0.99–1.18)	1.12 (1.02–1.23)	1.05 (0.96–1.16)	0.98 (0.89–1.07)	0.98 (0.88–1.09)
Gender (female)	1.29 (1.01–1.64)	1.25 (0.99–1.57)	1.19 (0.93–1.52)	1.00 (0.78–1.30)	1.35 (1.06–1.71)	1.23 (0.93–1.62)
Maternal history*	4.65 (2.86–7.56)	5.31 (3.19–8.84)	7.37 (4.40–12.35)	1.88 (1.29–2.74)	2.60 (1.86–3.61)	2.91 (2.03–4.19)
History of TB	1.65 (0.63–4.36)	6.54 (2.35–18.17)	3.71 (1.40–9.84)	1.47 (0.52–4.19)	2.48 (1.03–6.00)	4.66 (1.88–11.57)
Household TB	1.38 (0.91–2.11)	0.98 (0.64–1.50)	1.23 (0.80–1.89)	1.61 (1.06–2.47)	1.54 (1.02–2.31)	1.50 (0.95–2.38)
Stove type†	0.70 (0.45–1.10)	0.82 (0.54–1.23)	0.55 (0.32–0.84)	0.64 (0.40–1.04)	0.65 (0.42–1.00)	0.82 (0.50–1.34)
Pigs	0.78 (0.52–1.17)	1.32 (0.59–2.00)	1.28 (0.82–2.00)	1.24 (0.77–1.98)	1.10 (0.71–1.69)	1.54 (0.91–2.63)
Farmer‡	1.05 (0.76–1.46)	1.22 (0.89–1.68)	1.17 (0.84–1.64)	1.19 (0.83–1.70)	1.30 (0.94–1.80)	1.34 (0.92–1.96)
Education§	1.12 (1.00–1.25)	1.15 (1.04–1.28)	1.10 (0.99–1.23)	1.08 (0.96–1.22)	1.00 (0.90–1.11)	0.99 (0.886–1.13)

* Maternal history of asthma if wheeze 12 months, ever asthma or doctor diagnosis asthma; allergic rhinitis (AR) if AR conjunctivitis 12 months, ever hay fever, or doctor-diagnosed hay fever.

† Electric, refined gas vs unrefined fuels including kerosene, coal, wood, dung, straw).

‡ Farmer added in separate model without pig due to potential, collinearity, model shown is with pig for all other covariates.

§ Education using six-level scale (less than high school, high school, technical school, some college, college diploma, professional school).

Bold denotes statistically significant ORs.

urbanization. It is possible that there may be time period effects that had affected our results. The Dong Anh data were collected 2 years after the Hanoi study was conducted. Vietnam may have acquired new risk factors from rapid economic development and modernization that place its population at greater risk of developing atopy. A similar explanation has been offered to explain the rising prevalence of atopy in former East Germany after reunification (17). However, in our multivariate regression models, age was not a very robust covariate; thus a birth cohort effect is not likely. The estimates from Hanoi have a greater variability because of the smaller sample size. Finally, the interpretation of diagnostic labels, including asthma and hay fever, may be systematically different in the two areas – people (and more importantly, clinicians and medical providers) in Hanoi may have an interpretation of these terms that is different from Dong Anh residents. Potential confounding in this study due to such misclassification is discussed elsewhere (12).

Vietnam has the eleventh highest TB incidence among countries reporting to the WHO. The Vietnamese National Tuberculosis Program has resulted in a case detection rate of 75%. In addition, Vietnam is one of the few low-income countries that has reached TB control targets set by the WHO (18). Bacille Calmette-Guerin (BCG) vaccine coverage via the Extended Programme on Immunizations is > 80% in children (19). Nonetheless, childhood patterns of TB illness in Vietnam are not well defined, hence drawing conclusions regarding the association between TB and ISAAC symptoms found in this study is difficult.

This association at first appears to be counter to prevailing theories regarding the underlying immune mechanism of atopy – that TB and atopy lie at opposite sides of the T-helper (Th)1/2 balance. In the Th1 and Th2 framework, individuals have a predisposition to express either a cellular (Th1) or humoral (Th2) immune response to various environmental stimuli, most notably to infec-

tious (bacterial and parasitic) and allergic epitopes. It is generally believed that Th1 and Th2 physiologies are mutually exclusive predispositions within a given individual. Hence, TB, a Th1 type infection should be inversely associated with atopy, a Th2 type disorder. This association has been demonstrated in studies both at the ecological and physiologic level (20, 21).

While misclassification bias because of mislabeling of asthma and hay fever by respondents or other factors such as access to medical care may be an explanation for our contradictory findings, another possibility is suggested by recent studies that show an association between Th1 type and Th2 type disorders (22, 23). Other recent investigations, conducted in both TB endemic and non-endemic countries, challenge the notion of an inverse relation between TB and atopy (24). Indeed it has been shown that active TB in particular does not necessarily protect from manifesting Th2 type physiology and subsequent disease (25, 26). Individuals with such a clinical and immunologic scenario may be unable to mount the appropriate immune response to TB and are thus the ones with active disease. Hence, Th1 and Th2 type physiologies can coexist within an individual. Expressing one phenotype because of exposure to certain environmental circumstances does not preclude the potential of developing the other in another situation and may indeed indicate an inappropriate expression of the Th1/2 balance given particular immune stimulants. In addition, in the case of finding the true nature of the association between TB and atopy, BCG-induced PPD-positivity may have different immunologic significance from that caused by infection with *Mycobacterium*, which in turn is distinct from actual clinical childhood TB. TB in childhood would have been a primary infection and, if active, would have occurred most likely before school age (often considered the ‘protected years’) – the period during which immunologic development relevant to the hygiene hypothesis occurs. Recent work on T-cell

regulation in autoimmunity and allergy as well as parasite immunology are elucidating the complexity of Th1/2 balance and development.

The association of ISAAC symptoms with pig ownership and farming in age and gender adjusted ORs in Dong Anh runs counter to current studies illustrating the protective effects of farm residence on the development of atopy (27–29). These studies have found reduced risk of atopy in children brought up on farms and associated that reduced risk to higher exposure to endotoxin. However, this protective association is contradictory to occupational studies demonstrating that farm animal handlers exposed to higher levels of endotoxin have a higher risk of pulmonary illness and obstructive changes (30). Some investigators attribute this paradox to timing and dose with high levels early on in immune development having a protective effect (31, 32). If this explanation were true then one would expect protection in adult farmers who were raised on farms, but this is not always the case (30). Furthermore, most of the literature referenced above comes from studies of children and adults from the developed world. Unknown factors such as antibiotic supplementation in livestock feed, the composition of animal microbial, or farm characteristics such as crop vs animal or family vs corporate may change and modify the risk of animal exposure to developing atopy.

It is noteworthy that in our study there was no association with exposure to cows, chickens, cats and dogs in Dong Anh (although any animals tended to be a risk factor) and that no animals had a significant association with symptoms in Hanoi. With particular regard to the positive age and gender adjusted association between symptoms and pig ownership, *Ascaris suum* is a zoonotic helminth that infects pigs and until recently, was taxonomically indistinguishable from *A. lumbricoides*, a human geohelminth (33). It may be that the association

with pigs found in our study is the result of exposure to *A. suum* and subsequent (partially understood) immunologic interactions similar to those seen with *A. lumbricoides* and atopy in other human epidemiologic investigations (34). *Ascaris suum* may be acting as an immune stimulant at a subclinical level and influencing the development of atopic physiology in children appropriately exposed.

A major limitation in drawing conclusions and making conjectures about the association of these atopic symptoms with TB, pig ownership and farming is the cross-sectional, questionnaire-based nature of this study. To truly challenge the hygiene hypothesis that these results suggest, exposure must have occurred early in life when immunologic development that affects current symptoms was occurring. Hence in our case, any definitive inference on physiologic causality is not possible. In addition, more objective methods including physiologic tests (egg, skin prick test, bronchoprovocation) and exposure assessments (parasite egg microbia sampling), should be applied on this population to better characterize these symptoms and the associated risk factors described here. Such studies may provide a better understanding of the pathogenesis of atopy and the influence of environmental exposures in the developing world.

Acknowledgments

We would like to acknowledge Ta Tuyet Binh, Duong Khanh Van, Phan Han Son, Pham Ngoc Quy, and Vu Bich Hoat for their assistance in implementing this investigation.

This study was funded in part by grant numbers 3D43TW00642-05S1 from the Fogarty International Center and T32ES07262 from the NIEHS.

References

1. International Study on Asthma and Allergies in Childhood Steering Committee. Worldwide variations in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. *Lancet* 1998;**351**:1225–1232.
2. BURR ML, ANDERSON HR, AUSTIN JB, HARKINS LS, KAUR B, STRACHAN DP et al. Respiratory symptoms and home environment in children: a national survey. *Thorax* 1999;**54**:27–32.
3. MONTEFORT S, MUSCAT HA, CARUANA S, LENICKER H. Allergic conditions in 5–8-year-old Maltese schoolchildren: prevalence, severity, and associated risk factors [ISAAC]. *Pediatr Allergy Immunol* 2002;**13**:98–104.
4. ABUEKTEISH F, ALWASH R, HASSAN M, DAUD AS. Prevalence of asthma and wheeze in primary school children in northern Jordan. *Ann Trop Paediatr* 1996;**16**:227–231.
5. ANNUS T, BJÖRKSTÉN B, MAI XM, NILSSON L, RIIKJARV MA, SANDIN A et al. Wheezing in relation to atopy and environmental factors in Estonian and Swedish schoolchildren. *Clin Exp Allergy* 2001;**31**:1846–1853.
6. MELSOM T, BRINCH L, HESSEN JO, SCHEI MA, KOLSTRUP N, JACOBSEN BK et al. Asthma and indoor environment in Nepal. *Thorax* 2001;**56**:477–481.
7. DE BRITTO MC, BEZERRA PG, FERREIRA OS, MARANHÃO IC, TRIGUEIRO GA. Asthma prevalence in schoolchildren in a city in north-east Brazil. *Ann Trop Paediatr* 2000;**20**:95–100.
8. WEINBERG EG. Urbanization and childhood asthma: an African perspective. *J Allergy Clin Immunol* 1999;**105**:224–231.
9. VON MUTIUS E, FRITZSCH C, WEILAND SK, ROLL G, MAGNUSSEN H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *BMJ* 1992;**305**:1395–1399.

10. STEWART AW, MITCHELL EA, PEARCE N, STRACHAN DP, WEILANDON SK; ISAAC Steering Committee. International Study for Asthma and Allergy in Childhood, the relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC). *Int J Epidemiol* 2001;**30**:173–179.
11. STRACHAN DP. Hay fever, hygiene, and household size. *BMJ* 1989;**299**:1259–1260.
12. NG A NN, CHAI SK, BINH TT, REDDING G, TAKARO T, CHECKOWAY H et al. ISAAC-based asthma and atopic symptoms among Hanoi school children. *Pediatr Allergy Immunol* 2003;**14**:272–279.
13. UNICEF. UNICEF's State of the World's Children. New York: Oxford University Press, 1998.
14. ASHER MI, KEIL U, ANDERSON HR, BEASLEY R, CRANE J, MARTINEZ F et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–491.
15. DILLMAN DA. Mail and Telephone Surveys: The Total Design Method. New York: Wiley and Sons, 1978.
16. Italian studies on respiratory disorders in childhood and the environment, asthma and respiratory symptoms in 6–7 year old Italian children: gender, latitude, urbanization and socioeconomic factors. *Eur Respir J* 1997;**10**:1780–1786.
17. VON MUTIUS E, WEILAND SK, FRITZSCH C, DUHME H, KEIL U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998;**351**:862–866.
18. JOHANSSON E. Trust and transparency in human encounters in tuberculosis control: lessons learned from Vietnam. *Qual Health Res* 2002;**12**:473–491.
19. ANH DD, BORG DORFF MW, VAN LN, LAN NT, VAN GORKOM T, KREMER K et al. *Mycobacterium tuberculosis* Beijing genotype emerging in Vietnam. *Emerging Infect Dis* 2000;**6**:302–305.
20. VON MUTIUS E, PEARCE N, BEASLEY R, CHENG S, VON EHRENSTEIN O, BJÖRKSTÉN B et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis, and eczema. *Thorax* 2000;**55**:449–453.
21. SHIRAKAWA T, ENOMOTO T, SHIMAZU S, HOPKIN JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997;**275**:77–79.
22. KERO J, GISSLER M, HEMMINKI E, ISOLAURI E. Could Th-1 and Th-2 diseases coexist? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis: a register study. *J Allergy Clin Immunol* 2001;**108**:781–783.
23. SIMPSON CR, ANDERSON WJ, HELMS PJ, TAYLOR MW, WATSON L, PRESCOTT GJ et al. Coincidence of immune-mediated diseases driven by Th-1 and Th-2 subsets suggests a common etiology: a population-based study using computerized general practice data. *Clin Exp Allergy* 2002;**32**:37–42.
24. GRÜBER C, PAUL P. Tuberculin reactivity and allergy. *Allergy* 2002;**57**:277–280.
25. SUZUKI N, KUDO K, SANO Y, ITO K. Can *Mycobacterium tuberculosis* infection prevent asthma and other allergic disorders? *Int Arch Allergy Immunol* 2001;**124**:113–116.
26. TALREJA J, BHATNAGAR A, JINDAL SK, GANGULY NK. Influence of *Mycobacterium tuberculosis* on differential activation of helper T-cells. *Clin Exp Immunol* 2003;**131**:292–298.
27. PORTINGEN L, SIGSGAARD T, OMLAND O, HJORT C, HEEDERIK D, DOEKES G. Low prevalence of atopy in young Danish farmers and farming students born and raised on a farm. *Clin Exp Allergy* 2002;**32**:247–253.
28. DOWNS SH, MARKS GB, MITAKAKIS TZ, LEUPPI JD, CAR NG, PEAT JK. Having lived on a farm and protection against allergic diseases in Australia. *Clin Exp Allergy* 2001;**31**:570–575.
29. RIEDLER J, BRAUN-FAHRLÄNDER C, EDER W, SCHREUER M, WASER M, MAISCH S et al., ALEX Study Team. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001;**358**:1129–1133.
30. DOUWES J, PEARCE J, HEEDERIK D. Does environmental endotoxin exposure prevent asthma? *Thorax* 2002;**57**:86–90.
31. LIU AH. Endotoxin exposure in allergy and asthma: reconciling a paradox. *J Allergy Clin Immunol* 2002;**109**:379–392.
32. BRAUN-FAHRLÄNDER C. The role of the farm environment and animal contact for the development of asthma and allergies. *Clin Exp Allergy* 2001;**31**:1799–1803.
33. CROMPTON DWT. Ascaris and ascariasis. *Adv Parasitol* 2001;**48**:285–375.
34. LYNCH NR, GOLDBLATT J, LE SOUEF PN. Parasite infections and the risk of asthma and atopy. *Thorax* 1999;**54**:659–660.