

LETTER TO THE EDITOR

Reduced asthma susceptibility from early childhood exposure to residing in developing country

To the Editor,

Asthma and other allergic diseases cause significant disease burdens worldwide, with recent escalation particularly conspicuous in industrialized countries (1). Lai et al. analyzed results from Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC), measuring global prevalence and severity of asthma symptoms in children, and demonstrated that asthma symptoms tend to be more prevalent in affluent countries, as the 'Hygiene Hypothesis' suggests (2).

Reported by Strachan in 1989 (2), the 'Hygiene Hypothesis' maintains that higher prevalence of allergic disease in industrialized countries could be due to improved hygiene and health care, altering exposure patterns to infectious agents, parasites, and endotoxins in early life, and predisposing the immune system toward atopic response (3). Implications arise that developing countries lack budgets for advanced health care and infrastructure, creating disparate access to hygienic facilities, pharmaceuticals, and treatments, yet asthma prevalence in children is lower.

As both genetic susceptibilities to allergic disease and environmental factors are suspect, with disease prevalence differing among countries, migrating population analyses can help differentiate causes.

Immigrant health studies for industrialized countries have shown allergic disease less prevalent among non-native residents (4). A systematic review of the association between migration status and asthma by Cabieses et al. (5) in 2014 reported that most studies analyzed allergy prevalence in populations migrating from developing to industrialized countries.

In contrast, we focused on families native to industrialized Japan, who migrated to a developing host, Thailand. We explored if a history of residing in developing countries for at least 6 months under age 5 reduced asthma prevalence in a population largely of Japanese descent. Countries listed as Official Development Assistance (ODA) recipients by the Organization for Economic Co-operation and Development (OECD), were defined as developing countries (6). In this study, we designated this history of residing in developing countries as 'OECD-ODA under-five exposure'.

In June 2009, an anonymous, self-administered questionnaire was distributed to students of grades 1–9 (ages 6–14) at the Thai Japanese Association School in Bangkok, which teaches Japanese curriculum in Japanese. Parents were provided with written study objectives and assured the study was voluntary, without academic repercussions. Information on outcomes, predictors, and covariates from birth was collected. Questionnaires were answered by caregivers at home and collected at school.

During the survey period, with 2511 students, about 90% had one or both parents Japanese, with families originating

from developed or developing countries. Born in Japan, Thailand, or elsewhere, like the Philippines or United States, years of early childhood in developing or industrialized countries varied.

Parent reporting of physician-diagnosed asthma was the study's main outcome of interest, and age of asthma diagnosis by physician the primary end-point. OECD-ODA under-five exposure was the primary predictor of interest. We asked in what cities children resided at least 6 months, place of birth, and relevant dates.

Other independent variables included questionnaire items: number of siblings and age first commencing daycare, as well as histories of family smoking, having pets, breastfeeding, and major infectious diseases. Infectious diseases were categorized as either lower respiratory, with effects differing from infections in other organs, or other. Hereditary characteristics were controlled by three variables: prevalence of siblings' allergic diseases, prevalence of parents' allergic diseases, and parents' familial national background and ethnicity. Descriptive statistics of continuous variables were presented as mean with standard deviations and 95% confidence intervals (CI), with categorical variables presented as number and percentages.

We tracked each student's month of birth, with months of asthma diagnosis by physician or return of questionnaire as administrative censoring date, whichever came first. The cohort's rate of physician-diagnosed asthma was calculated as number of events per follow-up months. Using the Cox proportional hazards regression model to assess the association between development of physician-diagnosed asthma and time-varying OECD-ODA under-five exposure, we included the above variables that hold the proportional hazard (PH) assumption to the adjusted models.

As the Hygiene Hypothesis suggests the preventive effect of infections or unhygienic environments on asthma in 'early childhood', the main analysis considered only environmental factors under age 5. So, new exposures to a developing country, pets, family smoking, infectious diseases, daycare, or kindergarten were ignored after age 5. Questionnaires missing key variable data were excluded. A history of exclusive breastfeeding throughout the first 3 months, *BF_dummy* (1 = true, 0 otherwise), is time-varying until 3 months, and then, time-unvarying.

SAS (Version 9.4; SAS Institute, Inc., Cary, NC, USA) was used for all analyses, and a two-sided p-value <0.05 was considered statistically significant. The Research Ethics Board at Juntendo University Hospital, Tokyo, Japan, approved the study.

Overall, 2008 parents (80%) returned the questionnaire, with 1824 used for analyses and 184 excluded for missing key data.

In Table 1, asthma diagnoses were affirmed for 248 (13.6%) before the survey, with mean age of diagnosis at age

Table 1 Population characteristics of asthma study cohort

		Total		
		(n = 1824)		
		n		[95% CIs]
		Mean	(SD)	(%)
Outcome measure				
Physician-diagnosed asthma		248		13.6%
Age at diagnosis (months)		36.7	(25.5)	[33.5–39.9]
Primary predictor of interest				
History residing in developing countries under age 5		680		37.3%
No history residing in developing countries under age 5		1144		62.7%
Age of first experience residing in developing countries (months)		70.7	(45.2)	[68.6–72.8]
	Min-max	0–176		
Other characteristics				
Age (months)	Mean	118.9	(28.4)	[117.6–120.2]
Gender	Boy	905		49.6%
	Girl	919		50.4%
Number of older siblings	0	1113		61.0%
	1	622		34.1%
	2	78		4.3%
	>3	11		0.6%
Number of younger siblings	0	851		46.7%
	1	823		45.1%
	2	138		7.6%
	>3	12		0.7%
History of smoking status in family who resided with child when younger than age 5	Mother	86		4.7%
	Father	738		40.5%
	Other	65		3.6%
History of having pets under age 5	Dog	0	1643	90.1%
		1	141	7.7%
		>2	40	2.2%
	Cat	0	1619	88.8%
		1	204	11.2%
		>2	1	0.1%
	Other furred animal	0	1667	91.4%
		1	147	8.1%
		>2	10	0.5%
Age of exclusive breastfed (months)	Mean	9.3	(9.3)	[9.0–9.7]
Exclusively breastfed until at least 3 months old		1493		81.9%
Age when first attended daycare/kindergarten (months)		37.3	(11.6)	[36.8–37.9]
History of infectious diseases before age 5	Lower respiratory infection	0	1755	96.2%
		>1	69	3.8%
	Other infectious diseases	0	1792	98.2%
		>1	32	1.8%
Family history of allergic diseases	Mother	754		41.3%
	Father	752		41.2%
	Siblings	453		24.8%
Familial national background or ethnicity	Both parents Japanese	1483		81.3%
	One parent Japanese	167		9.2%
	Other	174		9.5%

36.7 months. A total of 680 (37.3%) had developing country exposure under age 5, and 1144 (62.7%) had exposure after age 5. Mean age for moving to developing countries was 77 months old, with the oldest 176 months (age 14 years,

8 months), and the youngest newborn. A total of 255 (13.9%) students were born in developing countries.

Table 2 shows cohort event rates per 1000 person-months and OECD-ODA under-five exposure. There were 215 and 33

Table 2 Asthma incidence rate for full cohort and by exposure to residing in developing countries before age 5

	Person-month*	Number of asthma cases [†]	Incidence rate [‡]	Crude rate ratio [§]
Overall	198,371	248	1.25	
Exposed [¶]	56,913	33	0.58	0.38
Unexposed**	141,458	215	1.52	

*Person-months of follow-up calculated from the month of birth to month of asthma diagnosis for students diagnosed with asthma by physicians, or to month of return of questionnaire for students never diagnosed with asthma.

[†]Asthma cases defined as physician-diagnosed asthma.

[‡]Incidence rate defined as number of asthma cases per 1000 person-months.

[§]Crude rate ratio is incidence rate in exposed group/incidence rate in unexposed group.

[¶]Children in exposed group defined as children with history of residing in developing countries before age 5 for at least a period of 6 months.

**Children in unexposed group defined as children with no history of residing in developing countries before age 5 for at least 6 months.

cases of physician-diagnosed asthma during 141,458 and 56,913 person-months of follow-up, with and without OECD-ODA under-five exposure, respectively. The absolute event rate was 1.25 overall, with rates of 0.58 with OECD-ODA under-five exposure, and 1.52 otherwise, yielding a crude rate ratio of 0.38.

Table 3 shows results from unadjusted and adjusted Cox proportional hazards models. Number of young siblings, age first commencing daycare, and prevalence of mothers' allergic diseases violated the proportional hazards assumption and were therefore excluded from the adjusted model. We estimated that children with OECD-ODA under-five exposure had a 67% risk reduction of physician-diagnosed asthma (hazard ratio, 0.33; 95% Confidence Interval [CI]: 0.23–0.47, *p*-value <0.01) in the unadjusted model and a 58% reduction (hazard ratio, 0.42; 95% CI: 0.28–0.61, *p*-value <0.01) in the adjusted model, compared to children not having OECD-ODA under-five exposure (Appendix Fig. A1). The adjusted models did not violate the PH assumption.

In our retrospective observational study, we found that OECD-ODA under-five exposure strongly associated with asthma development in ensuing years. Five rationales for why our study is innovative beyond previous immigrant asthma susceptibility studies (4) are as follows:

First, we collected each child's detailed history of countries where they had resided, designating the difference in prevalence of asthma between those with OECD-ODA under-five exposure and those otherwise. Many studies categorized immigrants as 'foreign-born' (4), examining the difference in asthma prevalence between native and immigrant populations. However, immigrants could have come from a country where hygienic conditions were similar to their host country. In our study population, although all were Japanese-speaking

Table 3 Results from cox proportional hazards models

	Hazard Ratio	95% CI*		p value
Crude	0.33	0.23	0.47	<0.01
Adjusted [†]	0.42	0.28	0.61	<0.01

*Confidence intervals.

[†]Model included control variables: gender; smoking status in the family; history of having pets; history of breastfeeding (as BF_dummy, equals 1 if children exclusively breastfed during first 3 months after birth and 0 otherwise); history of infectious diseases; prevalence of siblings' allergic diseases; and parents' familial national background and ethnicity. The number of siblings; age commencing attendance at daycare; prevalence of mothers' allergic diseases violated the proportional hazards assumption and were excluded from the adjusted model.

children living in Thailand at survey time, 5.5% were born outside of Japan or Thailand. Additionally, among those not born in Thailand, 28.9% had OECD-ODA under-five exposure. Therefore, in our study, 'foreign-born' does not necessarily signify whether a student lived under hygienic conditions during the critical period of early childhood.

Second, we collected information on the parents' ethnic or national origin so that we could control for genetic susceptibility to asthma. We believe self-reporting was appropriate to this study.

Third, the systematic review by Cabieses et al. (5) asserts the direction of migration to and from developing and high-income countries in the analysis reveals useful epidemiological patterns of allergic diseases. Garcia-Marcos et al. (7) analyzed ISAAC Phase Three for the prevalence of asthma and allergies for migration patterns flowing both directions between affluent and non-affluent countries. Results showed that birth outside the current country of residence was associated with lower asthma prevalence only for affluent countries. Whereas ISAAC did not collect place of birth or history of countries where each child resided, our study accumulated detailed information. Also in our study, most Japanese-speaking families originated from a country with a higher prevalence of allergic diseases and migrated to Thailand, with a lower prevalence of allergic diseases.

Fourth, in studies targeting migrating populations, language in questionnaires or interviews could often be problematic (4) because recent immigrants might misunderstand questions. Our Japanese-language survey was given to parents of children in a school conducted in Japanese, minimizing misunderstandings.

Lastly, previous studies reported lower rates of asthma and allergic disease for immigrants than non-immigrants in the host population. However, results could be due to a 'healthy migrant effect', that is, those with relatively lower morbidity are more likely to migrate (7). Our study controlled for this effect as all of our target population was immigrant.

We conducted a series of sensitivity analyses. First, as a more-sensitive, but less-specific outcome, patients were asked whether they had suffered labored breathing or bouts of

wheezing (characteristic whistling sounds in breathing, like 'hyuu hyuu' or 'zhhh zhhh', using Japanese onomatopoeic conventions) more than three times in one season. Second, unlike the main analyses, we identified children who resided in a developing country at an older age as having under-five exposure. Third, a combination of bouts of wheezing and physician-diagnosed asthma was used as an outcome, paired with a history of residing in developing countries. Fourth, our analysis enrolled students into the study cohort at age 5 if they had not previously developed asthma. This analysis aimed to remove confounding effects from employing Cox proportional hazards analysis with time-varying exposures and covariates.

Sensitivity analyses results were consistent with the main analysis: children with OECD-ODA under-five exposure had a lower risk of developing asthma compared with children without. The fourth sensitivity analysis was not statistically significant due to a reduced number of events, but still suggested a protective association (Hazard ratio, 0.77; 95% CI: 0.37–1.60) (Appendix Table A1).

As Garcia-Marcos et al. (7) demonstrated from the ISAAC study, only immigrants to affluent countries had lower prevalence of asthma compared to the native population, suggesting that reduced risk of asthma is not due to simply 'being immigrants'. Thus, we hypothesized that histories of countries where immigrants had resided would provide important interpretations to the difference in asthma prevalence between immigrant and native populations. With a high response rate of 80%, this survey provides evidence that OECD-ODA under-five exposure has a protective effect against developing asthma in ensuing years.

Several limitations of our study should be acknowledged. First, a main outcome was parental reporting of doctor-diagnosed asthma. Although used to capture asthma prevalence in previous studies (4, 8), no biochemical or biophysical

markers of asthma, such as IgE serum levels or spirometry results, were available. Additionally, we did not confirm parent reports of asthma in medical records. Misclassification of the outcome, if non-differential, may lead to estimates being biased toward the null. Second, recall bias cannot be denied. However, living in foreign countries and receiving an asthma diagnosis by physicians are memorable events. Therefore, we believe the recall bias in both outcome and predictor is small. Last, although there is a well-known complex relationship between migration status, socioeconomic status (SES), and asthma/allergy (9, 10), we were not able to collect SES information due to ethical considerations, and consequently, were not able to include it in the analysis.

In conclusion, residing during early childhood in developing countries may have a protective effect against asthma. Follow-up research to collect environmental factors, including SES, infections, or more detailed living environment could contribute to more realistic strategies in prevention and treatment of allergic diseases.

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Appendix

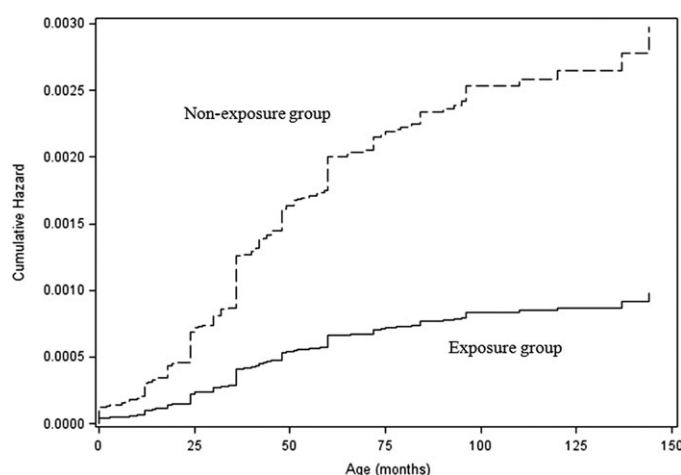


Figure A1 Person-time curve. Exposure group indicates children with a history of living in developing countries under the age of 5.

Table A1. Results from sensitivity analyses to test relationship between history of residing in developing countries during early childhood and outcomes

	Hazard Ratio	95% CIs*		p value
Sensitivity analysis 1 ^{†,‡}				
Crude	0.45	0.34	0.58	<0.01
Adjusted [§]	0.46	0.35	0.61	<0.01
Sensitivity analysis 2 [¶]				
Crude	0.15	0.11	0.22	<0.01
Adjusted [§]	0.17	0.11	0.24	<0.01
Sensitivity analysis 3 ^{†,**}				
Crude	0.04	0.03	0.06	<0.01
Adjusted [§]	0.03	0.02	0.05	<0.01
Sensitivity analyses 4 ^{††}				
Crude	0.50	0.24	1.03	0.06
Adjusted [§]	0.77	0.37	1.60	0.48

*Confidence intervals.

[†]A bout of wheezing more than three times per season is defined as susceptibility to wheezing.

[‡]Combination of susceptibility to wheezing and physician-diagnosed asthma is used as outcome of interest.

[§]Model included control variables: Gender; smoking status in the family; history of having pets; history of breast feeding (as BF_dummy, equals 1 if children exclusively breastfed during first 3 months after birth and 0 otherwise); history of infectious diseases; prevalence of siblings' allergic diseases; and parents' familial national background and ethnicity.

[¶]We simply evaluated effect of any history of residing in developing countries. Namely, children would be treated as children with a history of experience residing in developing countries if they moved to developing countries at any point in time.

^{**}Combination of susceptibility to wheezing and physician-diagnosed asthma was used as outcome of interest. Additionally, as Sensitivity Analysis 2, children would be treated as children with a history of experience residing in developing countries after they moved to developing countries.

^{††}We excluded children if they were diagnosed as having asthma by physicians during the first 5 years of life.