

Month of birth and childhood atopic diseases in the tropics

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The relationship between the month of birth and prevalence of diagnosed asthma, asthma-like symptoms (wheezing, nocturnal cough, and exercise wheezing), rhinitis, and eczema was investigated in four cohorts each of primary schoolchildren and secondary school (high school) adolescents in Singapore by questionnaire survey. Significantly increased prevalence rates of diagnosed asthma and asthma-like symptoms were observed in certain birth months of the year for two adolescent cohorts, while significant association between birth month and presence of symptoms of rhinitis was found in a cohort of 6–7-year-olds. However, when demographic factors were taken into consideration by multivariate analysis, only the association between asthma, asthma-like symptoms, and birth month remained significant in one of the adolescent cohorts. There was, therefore, only a weak association between the month of birth and atopic disease in our schoolchildren. The overall seasonal trends, however, did show two main seasons (March–May and September–November) associated with higher prevalence of these diseases.

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A previous study documented the existence of seasonal variation in acute asthma exacerbation among children in Singapore (1). Distinct peaks in acute asthma frequency were observed in January–February, May, and August each year. Although not as pronounced as those reported in temperate countries (2–4), the consistent seasonal pattern of peaks in acute asthma despite a tropical climate is of particular interest. It is an indication of “seasons” of potential environmental trigger factors. These triggers may also act as inducers of atopic disease. Exposure to allergens in early life has been shown to be an important factor in sensitization and the development of allergic disease (5). Investigators elsewhere have noted a relationship between asthma and birth during the pollen season (6, 7), and between allergic rhinitis and birth months of November–May in Sweden (6). In this study, we set out to examine whether the month of birth was associated with the development of atopic disease in our childhood population.

Material and methods

Data from two questionnaire surveys were evaluated. The first study, carried out in 1987 (8), used

the modified American Thoracic Society and the Division of Lung Diseases (ATS-DLD), of the National Heart, Lung, and Blood Institute, USA, respiratory symptom questionnaire (9). The second was carried out in 1994 (10) and used the International Study on Asthma and Allergies in Childhood (ISAAC) protocol (11). The data from three cohorts each of primary schoolchildren (ages 6–8, 9–10, and 11–13 years) and secondary school (high school) adolescents (ages 13–14, 15–16, and 17–19 years) of the 1987 survey, and two cohorts of schoolchildren (ages 6–7 and 12–15 years) of the 1994 survey were analyzed (Table 1).

In both surveys, the prevalence of diagnosed asthma and asthma-like symptoms (wheezing, nocturnal cough, and exercise wheezing), rhinitis (except for primary schoolchildren of 1987 study), and eczema (except for the adolescent cohort of 1987 study) were evaluated. The questions used in both surveys to define these atopic diseases were not identical but similar (Appendix 1).

These prevalence figures were then analyzed in relation to the month of birth of the children surveyed. For each cohort, the prevalence of each allergic disease was cross-tabulated with the month of birth by the PROC FREQ procedure of the

statistical package SAS (Version 6.08) (12) and analyzed for statistical significance with the chi-square test.

For cohorts which showed significantly ($P < 0.05$) higher prevalence rates in certain months of birth, the data were analyzed further in a multivariate manner. Cox's proportional hazards model (PROC PHREG procedure), with the assumption of a constant risk period, was used to determine the statistical significance of the prevalence rate ratios (relative risk) of the particular birth month after controlling for demographic factors (sex, ethnic origin, and socioeconomic status as defined by the type of housing). Each demographic factor was included in a separate model to avoid problems with collinearity and to characterize better these demographic influences on the association between the month of birth and the presence of atopic diseases.

Additionally, a rank test was used to evaluate the presence of particular month(s) with higher prevalence rates than the others. The monthly rates within each cohort were initially ranked from one (for the lowest) to 12 (highest). The data were then tabulated in a table with n columns, n (one representing each cohort) and 12 rows, r (representing the 12 months). The ranks in each row were then summed across the table, giving the 12 overall monthly scores, M_j . To test the null hypothesis of no month with significantly increased prevalence rates over the other months, the test statistic, T , was approximated to the chi-square distribution with $(r-1)$ degrees of freedom, and where $T = 12 \sum_{j=1}^r \{M_j - [n(r+1)/2]\}^2 / \{nr(r+1)\}$. The analysis was carried separately for each atopic condition (asthma, asthma-like symptoms, rhinitis, and eczema).

Various other statistical techniques have been proposed to detect cyclical trends, particularly for acute events such as hospitalization rates or emergency room visits (13–16). These methods usually consist of estimation of the amplitude of seasonal variations and the time at which the maximum occurs in a postulated simple harmonic fluctuation. However, the simple tests, e.g., that proposed by Hewitt et al. (14), have rather low power to detect a seasonal trend, unless it has a fairly large amplitude. Furthermore, they do not allow one to estimate parameters of the simple harmonic curve even if a significant departure from the null hypothesis is indicated. The later tests, e.g., that proposed by Walter & Elwood (16), are more complicated. Nevertheless, with the use of computers, such statistical techniques are no longer disadvantageous, as has been demonstrated previously by another study in the tropics (17).

Thus, to determine whether clustering of disease occurs around particular birth periods, the test for

seasonality of events with a variable population at risk, as proposed by Walter & Elwood (16), was adopted. Briefly, in this test, the population at risk was taken to be the total number of subjects surveyed with a given month of birth. If the number born in month i with a particular disease is n_i , and the total number of births for that month is m_i , then the total number of subjects with the disease is $N = \sum n_i$ and the total number surveyed is $M = \sum m_i$. By the method proposed by Edwards (13), the data are represented by weights $\sqrt{n_i}$ placed around a unit circle at points corresponding to the sector mid-points at angles θ_i to an arbitrary diameter. There are altogether 12 sectors (months), each represented by approximately $\pi/6$ rad. The moment about the diameter of all the weights is $\sum (\sqrt{n_i} \sin \theta_i)$, and the sample center of gravity of the system $(\bar{x}, \bar{y})$ is given by $\bar{x} = \sum_{i=1}^k (\sqrt{n_i} \cos \theta_i) / W$, and $\bar{y} = \sum_{i=1}^k (\sqrt{n_i} \sin \theta_i) / W$, where $W = \sum \sqrt{n_i}$, the total weight.

The expected values of $\bar{x}$ and $\bar{y}$ are given by

$$\begin{aligned} E(\bar{x}) &= \mu_{\bar{x}} = \sum_i (\sqrt{m_i} \cos \theta_i) / \sum_i \sqrt{m_i}, \text{ and} \\ E(\bar{y}) &= \mu_{\bar{y}} = \sum_i (\sqrt{m_i} \sin \theta_i) / \sum_i \sqrt{m_i} \end{aligned} \quad (1)$$

The variance of the coordinates of the sample center of gravity are

$$\begin{aligned} \text{Var}(\bar{x}) &= \sigma_{\bar{x}}^2 = \sum_i \frac{1}{4} \cos^2 \theta_i / (\sum_i \sqrt{m_i} / M)^2, \text{ and} \\ \text{Var}(\bar{y}) &= \sigma_{\bar{y}}^2 = \sum_i \frac{1}{4} \sin^2 \theta_i / (\sum_i \sqrt{m_i} / M)^2 \end{aligned} \quad (2)$$

The test statistics used is $[(\bar{x} - \mu_{\bar{x}}) / \sigma_{\bar{x}}]^2 + [(\bar{y} - \mu_{\bar{y}}) / \sigma_{\bar{y}}]^2$, which on the null hypothesis is distributed as χ^2 with two degrees of freedom. The direction of the maximum rate on the postulated simple harmonic curve is given by $\theta_m = \tan^{-1} [(\bar{y} - \mu_{\bar{y}}) / (\bar{x} - \mu_{\bar{x}})]$. As previously, the analysis was done separately for each atopic condition.

Results

Table 1 shows the demographic profile of the different cohorts surveyed. There were significantly higher female-to-male ratios in four of the six cohorts in the earlier survey. Similarly, there was a higher proportion of Chinese than the other ethnic groups and lower socioeconomic groups (as reflected in the type of housing) in the earlier survey than the later (in particular, the 12–15-year-old cohort of the 1994 ISAAC survey).

The prevalence of allergic disease in the children of these cohorts is shown in Table 2. Rhinitis (30.8% and 50.9%) and asthma-like symptoms (30.6–36.3%) were more prevalent than symptoms of eczema (10.5–12.3%). Since the protocols and questionnaires for both surveys were not identical, temporal comparisons were not made.

Table 1. Demographic profile of study population

Cohort	1987 survey						1994 survey	
	6–8 years*	9–10 years	11–13 years	13–14 years	15–16 years	17–19 years	6–7 years	12–15 years*
Year of birth	1979–81	1977–8	1974–6	1973–4	1971–2	1968–70	1987–8	1979–82
Total surveyed	2941	1855	1354	2195	2409	2016	2030	4208
%								
Sex								
Male	55.8	46.2	35.1	40.4	45.2	50.8	52.5	55.5
Female	43.9	53.3	64.3	59.2	54.3	48.5	46.7	44.3
Not stated	0.3	0.5	0.3	0.4	0.5	0.7	0.9	0.2
Ethnic origin								
Chinese	89.8	90.3	88.3	84.8	85.4	88.2	84.8	78.0
Malay	4.4	3.8	6.4	10.3	8.4	4.0	9.1	14.4
Indian	3.7	3.6	3.4	2.5	4.0	5.3	3.3	5.1
Others/not stated	2.1	2.3	1.9	2.4	2.2	2.5	2.7	2.5
Type of housing**								
Public housing	58.1	63.3	67.8	64.6	66.7	70.1	61.0	81.1
Condominium	18.6	15.6	13.2	17.2	14.2	12.4	13.6	7.6
Landed house	18.6	17.2	14.9	14.5	16.8	15.0	21.4	9.0
Not stated	4.7	3.9	4.1	3.7	2.3	2.5	3.9	2.3

*Cohort with similar year of birth.

**Type of housing: majority of Singaporeans up to family income ceiling of S\$8000 per month stay in government-built Housing Development Board (HDB) flats (public housing). Those beyond this income ceiling usually own private condominiums or have landed property (terrace homes, bungalows, etc.).

Table 3 shows the prevalence of allergic diseases among these Singapore children and adolescents tabulated by their birth months. Significantly increased (doctor-diagnosed) asthma prevalence rates were observed in certain months of the year in the 17–19-year-olds (born in 1968–70) ($\chi^2=21.21$; 11 degrees of freedom, $P<0.05$). Similar results were also observed when the data for

asthma-like symptoms were analyzed ($\chi^2=22.57$; 11 degrees of freedom; $P<0.05$). In addition, the data for the 15–16-year-olds (born in 1971–2) also showed significant association between birth month and the presence of asthma-like symptoms ($\chi^2=21.29$; 11 degrees of freedom; $P<0.05$). With rhinitis, the 6–7-year-old cohort of the 1994 ISAAC study showed the presence of significantly

Table 2. Prevalence of allergic diseases among Singapore children and adolescents by cohort

Cohort	1987 survey						1994 survey	
	6–8 years*	9–10 years	11–13 years	13–14 years	15–16 years	17–19 years	6–7 years	12–15 years*
Year of birth	1979–81	1977–8	1974–6	1973–4	1971–2	1968–70	1987–8	1979–82
Total surveyed	2941	1855	1354	2195	2409	2016	2030	4208
%								
Protocol	ATS-DLD	ATS-DLD	ATS-DLD	ATS-DLD	ATS-DLD	ATS-DLD	ISAAC	ISAAC
Respondent	Parent	Parent	Parent	Self	Self	Self	Parent	Self
Asthma**	16.5	15.2	13.0	8.5	9.0	11.3	18.5	20.7
Asthma symptoms†**	36.3	35.1	32.0	26.4	30.6	31.8	30.8	34.8
Rhinitis†**	NA	NA	NA	16.8	14.0	16.7	30.8	50.9
Eczema†**	7.9	5.7	5.3	NA	NA	NA	10.5	12.3

ATS-DLD: American Thoracic Society and Division of Lung Diseases of the National Heart, Lung, and Blood Institute, USA, respiratory symptom questionnaire (9).

ISAAC: International Study on Asthma and Allergies in Childhood protocol (11).

NA: not available.

*Cohort with similar year of birth.

**As different questionnaires and protocols were used for the 1987 and 1994 surveys, respectively, operative definitions used for these allergic diseases may be different and, as such, temporal comparison may not be accurate.

†Asthma symptoms – wheezing, nocturnal coughing, and exercise wheezing.

‡Operative definition of doctor diagnosis of “hay fever” and eczema was used in earlier, 1987 (ATS-DLD-based) survey, while presence of “blocked/running nose, or sneezing without flu” and “itchy rashes” were used to determine prevalence of rhinitis and eczema, respectively, in later, 1994 (ISAAC-based) survey.

Table 3. Birth month and prevalence of allergic diseases among Singapore children and adolescents

Allergic condition/cohort (birth year)	Prevalence of allergic disease (%) by month of birth												Chi-square test <i>P</i> value
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
Asthma													
1987 study													
6–8 years (1979–81)*	20.1	14.5	15.2	14.8	16.6	19.5	15.0	13.0	17.1	19.1	16.8	15.5	NS
9–10 years (1977–8)	12.8	12.8	18.5	13.6	14.3	20.0	16.4	15.0	12.6	16.7	17.3	12.0	NS
11–13 years (1974–6)	13.3	10.3	13.7	15.4	8.8	14.5	9.3	15.1	16.5	14.0	14.4	11.0	NS
13–14 years (1973–4)	5.9	5.2	10.0	6.8	9.2	8.8	8.7	6.1	8.5	11.6	7.8	12.1	NS
15–16 years (1971–2)	10.1	8.5	12.2	12.1	7.7	10.0	6.7	8.0	9.4	4.0	12.7	7.0	NS, <i>P</i> =0.06 <i>P</i> =0.03
17–19 years (1968–70)	13.7	13.5	15.6	11.0	15.0	11.5	10.2	7.3	3.8	8.5	12.8	9.4	
1994 study													
6–7 years (1987–8)	15.6	16.2	19.4	21.0	20.5	19.2	20.9	16.7	22.6	18.3	19.3	13.6	NS
12–15 years (1979–82)*	21.7	24.8	20.0	21.9	21.1	19.0	19.3	18.2	21.2	21.4	20.8	22.5	NS
Asthma symptoms (wheeze, nocturnal cough, exercise wheeze)													
1987 study													
6–8 years (1979–81)*	35.3	35.0	31.7	40.3	35.1	37.8	35.6	33.7	36.3	39.8	38.5	34.0	NS
9–10 years (1977–8)	30.1	33.0	31.3	37.5	31.0	37.1	35.2	34.5	34.6	43.4	36.1	34.8	NS
11–13 years (1974–6)	34.8	31.3	30.3	40.7	29.4	33.7	21.4	35.1	31.3	31.9	30.1	30.4	NS
13–14 years (1973–4)	17.0	24.5	25.3	29.5	29.4	26.4	27.4	20.3	25.6	30.2	28.3	28.8	NS
15–16 years (1971–2)	27.9	32.1	34.2	35.0	29.0	31.0	27.9	37.1	29.8	21.9	35.5	26.2	<i>P</i> =0.03
17–19 years (1968–70)	31.2	33.0	33.7	28.7	42.1	32.3	24.8	29.7	26.8	31.4	40.7	25.3	<i>P</i> =0.02
1994 study													
6–7 years (1987–8)	32.5	30.3	38.7	36.5	39.2	36.2	37.2	34.3	41.2	36.9	37.6	26.4	NS
12–15 years (1979–82)*	34.0	36.8	34.8	30.6	34.7	31.6	33.4	33.6	34.6	38.0	35.7	37.2	NS
Rhinitis													
1987 study													
13–14 years (1973–4)	15.3	18.7	20.7	23.3	15.8	14.9	14.4	13.8	20.6	16.4	12.8	16.8	NS
15–16 years (1971–2)	11.7	12.7	15.3	13.1	13.2	17.1	15.4	17.0	13.6	13.5	13.8	10.3	NS
17–19 years (1968–70)	15.6	16.1	19.2	18.7	19.7	13.3	11.0	16.1	15.9	20.4	15.9	17.3	NS
1994 study													
6–7 years (1987–8)	27.5	30.3	39.3	36.5	39.8	31.4	28.3	26.3	36.7	35.7	32.7	29.1	<i>P</i> =0.04
12–15 years (1979–82)*	48.7	50.2	54.2	47.8	50.2	52.3	54.2	48.5	49.5	53.2	57.0	50.5	NS
Eczema													
1987 study													
6–8 years (1979–81)*	7.3	6.3	12.3	9.0	7.1	5.9	6.3	6.6	8.1	9.9	6.6	9.8	NS
9–10 years (1977–8)	8.7	5.4	5.4	5.3	3.9	5.4	5.6	5.3	8.4	3.2	6.6	5.0	NS
11–13 years (1974–6)	9.6	3.8	6.0	7.0	5.7	3.8	2.3	2.7	3.8	7.5	3.6	4.4	NS
1994 study													
6–7 years (1987–8)	5.6	3.5	5.9	5.5	4.0	2.7	5.2	4.0	5.5	4.4	5.0	6.4	NS
12–15 years (1979–82)*	13.8	12.4	12.8	14.8	12.7	14.9	16.6	10.4	13.5	13.9	15.2	13.1	NS

*Cohort with similar year of birth.

NS: not significant.

increased birth-month prevalence rates in certain months over the others ($\chi^2=20.40$; 11 degrees of freedom; $P<0.05$).

Using the method described by Walter & Elwood (16), significant ($P<0.05$) seasonality was observed in the same years and diagnostic groups, as shown in Table 3 (data not shown). Additionally, the data comparing the birth month and presence of asthma

diagnosis among the 15–16-year-olds (born in 1971–2), which did not show significant association by cross-tabulation ($P=0.06$), showed significant seasonality via this test ($\chi^2=12.6$; two degrees of freedom; $P<0.01$).

When the data were analyzed in a multivariate fashion controlling for the individual demographic influences (sex, ethnic origin, and socioeconomic

status), the association between birth month and asthma or asthma-like symptoms remained significant for the 17–19-year-olds (born in 1968–70). However, for the 15–16-year-olds (born in 1971–2), the association between birth month and asthma-like symptoms was rendered not significant after controlling for ethnic group ($P > 0.05$). With rhinitis, the association between birth month and prevalence rates among the 6–7-year-old cohort of the 1994 ISAAC study was not significant when controlled for sex.

The mean percent variation of the birth-month disease prevalence rates from the overall cohort prevalence rates for (a) asthma, (b) asthma symptoms (wheeze, nocturnal cough, exercise wheeze), (c) rhinitis, and (d) eczema are shown in Fig. 1. With the rank test, none of the four monthly variation series showed statistically significant increases. However, the four disease trends showed that there were two main periods (March–May and September–November), with exceptions in certain birth years, where the birth-month prevalence rates were generally higher than the cohort prevalence rates. This was confirmed further by the estimation of θ_m , direction of the maximum rate (in degrees) on the postulated simple harmonic curve, calculated by the method described by Walter & Elwood (16). The estimated θ_m for asthma diagnosis for the 1971–2 and 1968–70 cohorts were 85° (corresponding to the month of March) and 302° (November), respectively. With asthma symptoms, the estimated θ_m for the same two cohorts were 309° and 323° , respectively (both corresponding to maximums in the month of November).

Discussion

This study focused on the possible association between the month of birth and the prevalence of atopic diseases among Singapore children and adolescents. The results indicated that birth season is not as strongly associated with the development of atopic diseases in the Singapore population as in other studies done in the temperate climates (18–22). In the temperate environment, studies suggest that exposure to allergens at certain periods soon after birth may be associated with a greater tendency for the development of hypersensitivity. In addition, evidence of antigen priming *in utero* has come from studies demonstrating the presence of T cells with specific proliferative responses to environmental allergens in cord blood (23–25). These allergen-specific T-cell responses in cord blood were also shown to be related to maternal exposure during pregnancy to high environmental aeroallergen load (23).

The weak or absent association between season of birth and development of atopic disease in the

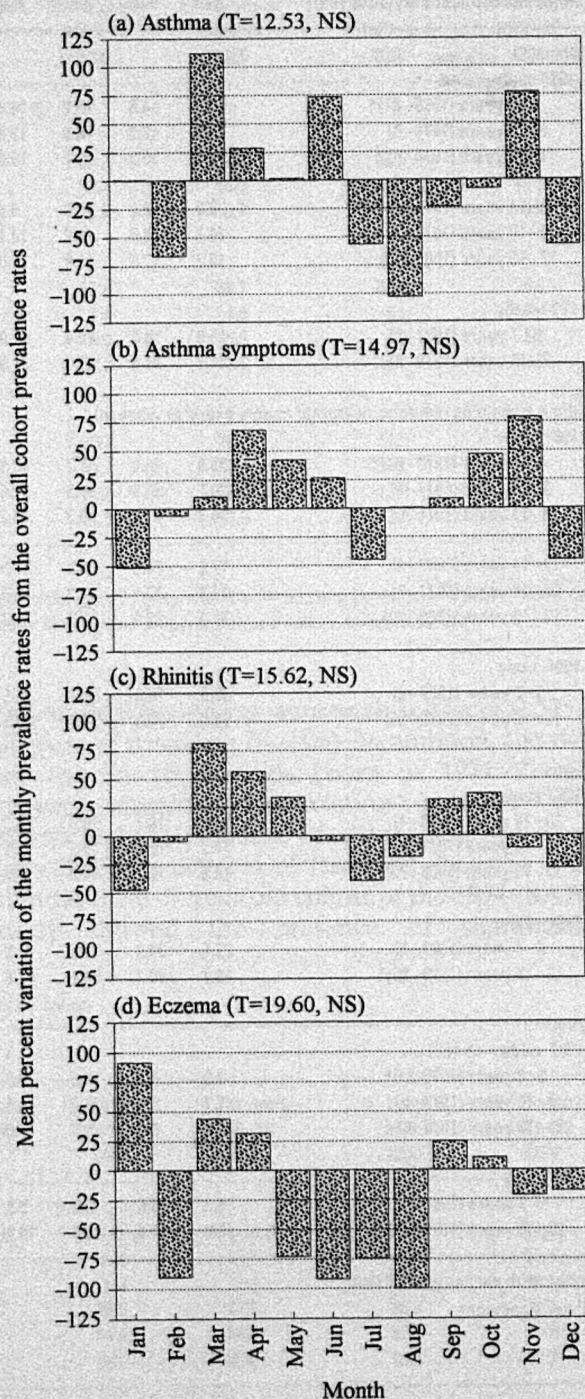


Fig. 1. Mean percent variation of birth-month disease prevalence rates from overall cohort prevalence rates for (a) asthma, (b) asthma symptoms (wheeze, nocturnal cough, exercise wheeze), (c) rhinitis, and (d) eczema. Rank test was not statistically significant in all cases (NS: not significant). However, four disease trends showed that there were two main periods (March–May and September–November), with exceptions in certain birth years, where the birth-month prevalence rates were generally higher than cohort prevalence rates.

tropics could be due to the relatively constant environment year round. However, our recent data showed that airspora in the tropics might not be as constant as previously assumed. Variations in airspora have been observed (26–27) and have also been associated with acute asthma exacerbation trends in children (January–February, May, and August) (1). In this study, *in utero* antigen priming may contribute to the association of birth “seasons” with development of atopic disease (March–May and September–November), which is a month or two after the months of increased airspora allergen load (January–February, May, and August).

Although positive associations between the month of birth and atopic disease were found in this study, these associations were weak and confounded by demographic factors. The effect of ethnic origin may be related to each group’s preference for the time or season of birth. For example, the Chinese tend to avoid births during the “hungry ghost festival” (August–September), and the Malays have predetermined preferences on the months of birth due to the influence of Ramadan (the fasting month). Since asthma is differentially associated with ethnic groups in the Singapore population (28), the observed association of asthma with the season of birth may also be related to these ethnic preferences for birth periods.

The results in this study also reflect the inconsistency shown by other studies relating to birth month and atopic diseases (6, 7, 18–22). Different cohorts may experience different environmental stimuli possibly influencing the development of atopy. In addition, the effect of age at the time of investigation may be particularly important, as accumulating environmental experiences can progressively outweigh the influence of the month of birth (19, 22). This may explain why there was no birth-month effect on rhinitis in the older age groups, while an association was found in the younger 6–7-year-old cohort. Similarly, greater variability in the birth-month prevalence rates was observed in the younger age groups than the older cohorts (with the exception of asthma), and this may again be due to the cumulative effect of age.

In conclusion, the data obtained showed only a weak association between birth month and the development of atopic diseases in the Singapore environment. However, these associations may be related to the seasonal peaks in the airspora load in Singapore.

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Appendix 1. American Thoracic Society and Division of Lung Diseases of the National Heart, Lung, and Blood Institute, USA (ATS-DLD) respiratory symptom questionnaire, and International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire used to define asthma, asthma symptoms, rhinitis, and eczema

ATS-DLD questionnaire*:		ISAAC questionnaire**:
Core questions for cough, wheezing, and asthma:		
For secondary school (high school) adolescents:	For primary schoolchildren:	For primary and secondary schoolchildren:
Do you usually cough during the day or at night? Yes/No.	Does your child usually have a cough apart from cold? Yes/No.	Have you ever had wheezing or whistling in your chest at any time in the past? Yes/No.
Does your chest ever sound wheezy or whistling: occasionally apart from a cold? Yes/No. most days or nights? Yes/No.	Does his/her chest ever sound wheezy or whistling: occasionally apart from a cold? Yes/No. most days or nights? Yes/No.	In the last 12 months, has your chest sounded wheezy during or after exercise? Yes/No.
Have you ever had an attack of wheezing that has made you feel short of breath? Yes/No.	Has your child ever had an attack of wheezing that caused him/her to be short of breath? Yes/No.	In the last 12 months, have you had a dry cough apart from a cough associated with a cold or chest infection? Yes/No.
Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? Yes/No.	Does your child ever get attacks of wheezing after he/she has been playing hard or exercising? Yes/No.	Have you ever had asthma? Yes/No.
Have you ever had asthma? Yes/No.	Has a doctor ever said that your child had asthma? Yes/No.	
Was it confirmed by a doctor? Yes/No.		
Core question for rhinitis: Have you ever had hay fever (allergic rhinitis)? Yes/No.	—	Have you ever had a problem with sneezing, or blocked nose when you did not have a cold or flu? Yes/No.
Was it confirmed by a doctor? Yes/No.		Have you ever had hay fever? Yes/No/Don't know.
Core question for eczema: —	Did a doctor ever say that this child had eczema (skin rash) before the age of 2 years? Yes/No.	Have you ever had an itchy rash that was coming and going for at least 6 months? Yes/No. Have you ever had eczema? Yes/No/Don't know.

*These questions were directed at the secondary school (high school) adolescents, who self-completed the questionnaire; questions for primary schoolchildren were completed by the parents.

**These questions were directed at 12–15-year-olds, who self-completed the questionnaire; questions were modified for 6–7-year-olds, whose parents completed the questions.

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