Age-Period-Cohort Analysis of Asthma Prevalence among School Children

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Abstract

Prevalence of age-dependent diseases such as asthma is confounded not only by aging effects but also by cohort and period effects. Age-period-cohort (APC) analysis is commonly performed to isolate the effects of these three factors from two-way tables of prevalence by age and birth cohort. However, APC analysis suffers from technical difficulties such as non-identifiability problems. We isolated the effects of these three factors in a step-by-step manner by analyzing Japan’s school health data collected from 1984 to 2004 focusing on asthma prevalence among school children aged 6–17 years consisting of 30 birth cohorts (entering classes). We verified the accuracy of our method showing high agreement of the observed age-, period- and cohort-specific data and the data predicted by our method. The aging effects were found to follow cubic equations whose multinomial coefficients were determined by an optimization technique. The obtained aging effect curves of age-specific asthma prevalence showed that boys reach the peak prevalence at 13 and girls at 14, declining markedly afterward. The cohort effects, defined as the arithmetic asthma prevalence means for ages 6–17 years, showed consistent upward trends for the 30 birth cohorts born in 1968–97 for both sexes. The period effects showed a consistent decline since 1984 but abruptly increased in 1999 and then declined again. We were not able to identify the exact cause of the increase in 1999, therefore, this should be examined in the future studies. Because the cohort effects show no sign of leveling off yet, asthma prevalence will likely increase in the foreseeable future.

Key words: asthma, age-period-cohort analysis, school health, cohort effect

Introduction

Asthma prevalence is said to be increasing in most developed countries (1), although Asian countries tend to have lower prevalences than western countries (2) with some sporadic reports of decline (3). Tanhara described the increasing morbidity (number of patients under treatment per population) of asthma in Japan since 1984 (4) and reported the economic impact of increasing asthma prevalence on Japan’s national medical care expenditure (5). Overall, asthma is considered as one of the most important childhood diseases in developed countries (6).

Long-term trends of prevalence over different birth cohorts are difficult to determine simply by analyzing two-way tables of prevalence broken down by age and period of survey because the obtained data are confounded by not only cohort effects but also period effects. Moreover, age-specific prevalence is inherently affected by physiological aging effects.

Environmental factors that accumulate over the long term for the same birth cohort (such as dietary habits) are referred to as “cohort effects”. Cohort effects may differ among different birth cohorts but the differences cannot be illustrated only by following the diagonals in two-way tables because the data in each cell is confounded by aging and period effects.

Aging effects are changes during the course of aging, reflecting mostly physiological and pathological characteristics of the human body and diseases. Period effects reflect temporary changes of environmental factors such as epidemics of influenza, changes in temperature, pollen density or diagnostic criteria. Because cohort effects reflect long-term cumulative environmental exposures, failure to clarify such effects properly may lead to misinterpretation of the etiology of a disease, particularly for chronic diseases such as asthma.

Epidemiologists have attempted to isolate age, period and cohort effects from typical two-way tables by “age-period-
cohort (APC)” analysis and mainly applied this method to the analyses of rare but stable data such as cancer mortality. On theoretical aspects, APC analysis has a mathematical nonidentifiability problem: because birth cohort is a linear function of age and calendar period, the APC model cannot provide separate, simultaneous estimates of these three parameters. To solve this problem, a variety of solutions had been proposed, such as the penalty function approach (7), individual records approach (8), “deviations, curvatures and drift” approach (9), and Bayesian-Poisson APC modeling (10), all of which assume certain conditions to overcome the nonidentifiability problem.

We attempted to apply APC analysis to the examination of the prevalence of asthma, a common and chronic disease with a medically reasonable condition: aging effects are held constant over the observed birth cohorts.

Materials and Methods

We dealt with asthma prevalence obtained from school health data with sufficiently large sample sizes. School health data have some advantages that enable APC analysis more affordable for the following reasons.

1) Nonoverlapping of cohorts

Pupils are enrolled to a school once; thus, making them nonoverlapping and clearly defined cohorts. Robertson and Boyle demonstrated that unique solutions are obtainable if individual records are available thereby permitting nonoverlapping cohorts (11). We were not able to obtain individual data but we were able to estimate aging effects better because of the nonoverlapping among cohorts.

2) Short time intervals of cohorts

Short time intervals (one year) enabled us to elucidate period effects better than longer time intervals. In comparison, most cancer mortality statistics are available only in five- or ten-years intervals.

3) Clear aging effect

The ages of school children are limited to 6–17 years, a period of active growth. This means that aging effects on asthma prevalence are more evident, for example, aging effects on cancer mortality in old age. This is an important precondition for our assumption that aging effects can be held constant over different cohorts.

Our model relies on the assumption that aging effect remains constant throughout different birth cohorts. The rationale behind this assumption is that the physiological aging (i.e., growing) process and susceptibility to diseases would not change over a limited time particularly during the growing period. That is, the sharp increase and decrease in asthma prevalence for ages 6–17 years may be viewed as part of the growing process. If the growth pattern of children is independent of period and cohort effects, it is possible to extract aging effects from a part of cohorts, and it is not necessary to analyze the entire cohorts at a time (note that the nonidentifiability problem arises when one tries to analyze the effects of the three factors from the entire cohorts simultaneously).

Our study involved 12 age groups (6–17 years old), 30 birth cohorts (born in 1968–1997) and 21 survey periods (1984–2004) but only the 10 central birth cohorts included the entire age groups and survey periods. The adjacent 20 birth cohorts were affected by aging and period effects not included in our study. We attempted to identify the parameters of the three effects in a step-by-step manner with the following assumptions: aging effects remain constant throughout the cohorts and can be estimated from the 10 central birth cohorts with complete age-specific data.

The data were obtained from the School Health Survey Report (SHSR) compiled and published by the Ministry of Education, Culture, Sports, Science and Technology. It is a nationwide sampling survey of the national population of school children aged 6–17 (12 age groups).

The survey is conducted as part of routine health checkups by doctors in April–June every year. The definition of asthma is “currently under treatment or presenting symptoms” and is not based on lifetime incidence. However, the diagnostic criteria are not well defined and clinical diagnosis is largely left to examining doctors.

We used the 1984–2004 data involving 30 birth cohorts born in 1968–97 (we excluded the birth cohorts born in 1967 and 1998 because they provided only one age-specific group).

Population of Japan’s school children

The age- and sex-specific populations of Japan’s school children in the years examined are shown in Table 1. The largest cohorts are those born in 1973–74 who were 10–11 years old in 1984 numbering more than one million. However, the size of recent cohorts has decreased to about 600,000, reflecting Japan’s declining birth rate. Senior high school education (ages 15–17) is not compulsory and the population size of children aged 17 years is approximately 10% smaller than that of children aged 14 years in the same birth cohort. Note that if the presence of asthma adversely affects school admission, it will underestimate asthma prevalence for senior-high-school ages.

Prevalence of asthma

The age- and sex-specific prevalences of asthma are shown in Table 2. This table is the main focus of analysis.

Sampling rate

SHSR did not include data on the sample size until the 1991 report. SHSR started to include sample size data from the 1992 report but it only provided rough aggregated numbers for three different school types (primary school, junior high school and senior high school) as shown in Table 3. Because the sample size remains rather constant, the sampling rate differs from year to year reflecting a changing population size. The smallest rate is 4.8% for senior high school in 1984 and 85, and the largest rate is 10.3% for junior high school in 2004.

Error estimate

SHSR includes no reference to error estimation after the 1994 report but did include a brief description of errors until the 1994 report: “the sampling errors are 0.05–0.07% for a prevalence of 1%, 0.16–0.21% for a prevalence of 10%, and
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Source: Japan’s Essential Statistics of School Education
Table 2  Age- and sex-specific prevalences (%) of asthma among Japan's school children

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</table>

Source: Japan's School Health Survey

Table 3  Sample size and sampling rate

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<td>secondary high</td>
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<td>394994</td>
<td>391586</td>
<td>390931</td>
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<td>390804</td>
<td>386325</td>
<td>383589</td>
<td>380495</td>
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<td>SAMPLE RATE (%)</td>
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<td>6.26</td>
<td>6.42</td>
<td>6.79</td>
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<td>6.90</td>
<td>6.98</td>
<td>6.95</td>
<td>7.01</td>
<td>6.93</td>
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</table>

Source: Japan's School Health Survey

0.27–0.34% for a prevalence of 50% depending on the sample size. These are absolute terms and can be expressed in relative terms as 5–7% for the prevalence of 1%, 1.6–2.1% for the prevalence of 10% and 0.54–0.68% for the prevalence of 50%. Because the prevalence of asthma is generally less than 1% and can be as low as 0.14% (for 16-year-old girls in 1985), it can be subject to larger sampling errors.

Although sampling rates are not available in and before the 1991 report, we attempted to estimate age- and sex-specific standard errors in and after the 1992 report. We attributed the school-specific aggregate sampling rate to age-sex groups because sampling was carried out in a stratified and systematic manner. Because asthma prevalence is generally small (the largest rate is 4.13% for 6-years-old boys in 2004), it is safe to assume a Poisson distribution in which the mean and variance are similar.

For example, the population of 6-year-old boys in 2004 was 609,079 and the sample size was estimated to be 42,199 because the overall sampling rate for primary school was 6.9%. The number of asthmatics would have been 1743 given the prevalence of 4.13% (\( \times 42,199 \times 4.13\% = 1,743 \)). Under the assumption of Poisson distribution, variance is also 1,743 and standard deviation is 41.75 (\( \sqrt{1743} \)) or 2.4% of error rate.

All the age- and sex-specific error rates are shown in Table 4. The lowest error rate is 2.4% for a prevalence of 4.13% (6-year-old boys in 2004) and the highest is 7.33% for a prevalence of 0.46% (17-year-old girls in 1993). When compared with the above brief description in the report, our estimated standard error rates are higher than the reported values. Because the prevalences of asthma in and before the 1991 report are lower than those prevalences after 1991, one expects standard error rates to be much higher than 7.33% for low prevalences in earlier years.

We used a step-by-step approach to isolate the APC effects whose outline is summarized in Fig. 1. Let \( i \) denote age (6–17 years, or \( i \)-th year), \( j \) the \( j \)-th period, and \( k \) the cohort born in the \( k \)-th year. We propose a model in which the asthma prevalence of the \( k \)-th cohort at the age of \( i \) in the \( j \)-th survey period, \( R_{jk} \), can be predicted as a

\[
R_{jk} = \beta_0 + \beta_1 i + \beta_2 j + \beta_3 k + \epsilon_{ijk}
\]
product of three functions: aging effects $A(i)$, period effects $P(j)$, and cohort effects $C(k)$.

$$R_{ijk} = A(i)P(j)C(k)$$

(1)

There is a linear relationship among $i$, $j$ and $k$. If there are $l$ periods and $m$ age groups, $k = l + m - 1 = j - i + 5 + m$. Because of this linear relationship, only two parameters out of $i$, $j$, $k$ are necessary to define $R_{ijk}$. In our study, $l=21$ and $m=12$ making $k=32$, but we excluded two birth cohorts leaving 30 birth cohorts.

We defined the three functions as follows.

1) Cohort effects, $C(k)$

We defined the cohort effects, $C(k)$ as the arithmetic asthma prevalence means of the $k$th cohort between 6 to 17 years old, for which school health data are available.

For birth cohorts born in 1978–87 for which age-specific asthma prevalence data are complete, the arithmetic asthma prevalence means can be calculated. Although these values can not be viewed as exact cohort effects because they are affected by unknown period effects, they should give good initial estimates of the cohort effects of the 10 birth cohorts.

2) Aging effect, $A(i)$

We extrapolated a polynomial function that best predicts $R_{ijk}$ from the 10 central birth cohorts born in 1978–87 for which complete age-specific asthma prevalences are available.

We applied polynomial functions of the 1st order to the 4th order to $R_{ijk}$ and compared their ability to predict aging effects (performance) on the basis of the residual sum of square (RSS), between the observed $R_{ijk}$ and predicted $R_{ijk}$ (an overhead dot denotes a predicted value).

$R_{ijk}$ predicted from the polynomial function of the $l$th order is expressed as follows.

$$R_{ijk} = (a0 + a1i + \cdots + a_ni^n)C(k)$$

(2)

Its performance is measured using the following RSS (12). Note that $j$ is not included in the formula due to the linear relationship among $i$, $j$ and $k$.

$$RSS = \sum_{i=1}^{12} \sum_{j=5}^{17} (R_{ijk} - \bar{R}_{ijk})^2$$

(3)

We used Excel Solver to obtain the coefficients, $a0$, $a1$, $a2$ ... $a_n$ to minimize RSS values, which are shown in Table 5. For both boys and girls, the polynomial functions of the 3rd order (cubic equation) yielded the least RSS and were hence deemed to be the best predictors of aging effects. The cubic equations used to predict aging effects of asthma prevalence (%) at the age of $i$, $A(i)$, are expressed as follows (Fig. 2):

- for boys: $A(i) = -0.002*i^3 + 0.066*i^2 - 0.603*i + 2.684$
- for girls: $A(i) = -0.002*i^3 + 0.046*i^2 - 0.418*i + 2.035$

For example, the asthma prevalence of boys born in 1978 at the age of 10 is predicted as:

$$R_{ijk} = A(i)C(k) = (-0.002*10^3 + 0.066*10^2 - 0.603*10 + 2.684)*1.121 = 1.177(\%$$

Note that the observed $R_{ijk}$ was 1.177%. We were able to predict the unobserved $R_{ijk}$ because of missing $i$ and $j$ and unobserved $C(k)$ by fitting the cubic equation to observed $R_{ijk}$ (shown as $R$ in Table B in Fig. 1).

3) Period effects, $P(j)$

Period effect $s$ on the $k$th cohort at the age of $i$ in the $j$th period are expressed as:

$$P(ikj) = \frac{R_{ijk}}{R_{ijk}}$$

(4)
Determining aging effect (cubic equation formula) with baseline=1 using 10 years cohort with complete age-specific data

Calculating arithmetic means after filling in "X" by applying the aging effect formula

The PERIOD EFFECT is calculated using the geometric mean of the ratios (observed/predicted by AGING X COHORT effects)

Predicting age-specific asthma prevalence for each birth cohort by multiplying aging and cohort effects

Fig. 1  Step-by-step approach using APC (Age-Period-Cohort) model. Data shown are asthma prevalences (%) among Japanese school boys. Source: Ministry of Education School Health Survey.
Table 5 Coefficients of polynomial functions and residual sum of square (RSS) values between observed and predicted asthma prevalences

<table>
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<tr>
<th></th>
<th>a0</th>
<th>a1</th>
<th>a2</th>
<th>a3</th>
<th>a4</th>
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<td></td>
<td></td>
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<tr>
<td>1st order</td>
<td>-0.009</td>
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<td>0.231</td>
<td>-0.157</td>
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<td>0.066</td>
<td>-0.603</td>
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<td>4th order</td>
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<td>0.004</td>
<td>-0.054</td>
<td>0.329</td>
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<table>
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<th></th>
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<td>Girls</td>
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<tr>
<td>1st order</td>
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<td>0.007</td>
<td>-0.095</td>
<td>0.627</td>
<td>-0.736</td>
<td>1.575</td>
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</table>

\[ y = a_0 + a_1 x + a_2 x^2 + a_3 x^3 + \cdots + a_n x^n \quad \text{where} \ x \text{ is age} \]

\[ \text{RSS is the residual sum of square value between observed and predicted asthma prevalences.} \]

Fig. 2 Aging effects of asthma prevalence. Age-specific asthma prevalence expressed as ratio against the arithmetic mean (age 6–17). Source: School Health Survey Japan. for boys: \(-0.002 + 0.066 + 0.603 + 2.684\) for girls: \(-0.002 + 0.046 + 0.418 + 2.035\)

Rijk predicted from aging and cohort effects are shown as R' in Table C in Fig. 3. The overall P(j) is expressed as the geometric mean of P(ijk) for all age groups, i.

\[ P(j) = \left( \prod_{i} \frac{R_{ijk}}{R_{i}} \right)^{1/n} \quad (5) \]

4) Performance measures

The overall performance of our model was measured using R^2 values between observed Rijk and predicted Rijk incorporating all three effects as shown by R'' in Table D in Fig. 1.

Results

The overall performance of our model demonstrated R^2 values of 0.970 for boys and 0.966 for girls, both of which were satisfactory in predicting the age-, period-, and cohort-specific asthma prevalence (R^2 value was 0.98 for both sexes even after excluding 10 birth cohorts from which the coefficients were derived).

The cohort effects of asthma prevalence, C(k), expressed as the arithmetic age-specific asthma prevalence means for the ages 6–17 in 30 birth cohorts born in 1968–97 are shown in Fig. 3. Obviously, consistent upward trends of asthma prevalence are observed for both boys and girls. The birth cohort born in 1997 is predicted to have average asthma prevalences of 4.035% and 2.839% asthma prevalence for ages 6–17 years for boys and girls, respectively.

The period effects for 1984–2004 shown in Fig. 4 showed a consistent decline since 1984 but abruptly increased in 1999 and then declined again in both sexes. The pattern is similar for both sexes, strongly suggesting that there had been temporary environmental factors responsible for the high asthma prevalence among school children in 1999.

Discussion

A national sampling survey conducted in 2005 in Japan reported annual prevalences of asthma among the 1st and 2nd graders of primary schools as 15.9% for boys and 11.3% for girls, and among the 2nd and 3rd graders of junior high schools as 8.9% for boys and 8.5% for girls (13). These figures are much higher than those reported in SHSR, but the discrepancy is explained by the difference in period vs. point prevalence.
Fig. 3 Cohort effects of asthma prevalence. Arithmetic means of age-specific asthma prevalence (age 6–17) for each cohort. Source: School Health Survey in Japan.

Fig. 4 Period effects of asthma prevalence. Period effects are expressed as a ratio between observed prevalence and the prevalence expected from aging and cohort effects. Source: School Health Survey in Japan.

The quality of data of SHSR may be evaluated by comparing them with those of other national surveys, such as the National Household Survey (NHS). Health status is surveyed every three years, the most recent of which was conducted in June 2004, almost corresponding to SHSR in 2004.

NHS provides the estimated number of people who are currently receiving medical care for various diseases broken down by sex and 5-year-age groups. According to 2004 NHS, the numbers of children aged 10–14 who were receiving care for asthma were estimated to be 82,000 for boys and 52,000 for girls. The corresponding figures of 2004 SHSR was 98,274 for boys and 59,154 for girls (calculated by applying prevalence to the population). SHSR appears to overestimate the number, but with the large sampling error of the NHS (9% error rate for the estimated size of 50,000) (14), the difference may be within permissible level. Overall, data quality of SHSR is sufficiently reliable to warrant sound analysis.

Despite technical difficulties inherent in APC analysis, our results showed a good performance of the method as evidenced by high R² values. This reflects both the strength and weakness of our method. School health data on young children show clear aging (i.e., growth) effects which are easy to estimate. We believe this is the reason why our method of estimating aging effects yielded good results. This can also be a weakness: our method may not be so accurate for the data of older populations whose aging effects are less clear and more difficult to estimate than those of children.

We proposed a valid approach in APC analysis applicable to analyzing data of school-age children. School health data include items on other diseases and health conditions, which may be analyzed similarly. Because physiological aging effects
of children should be the same across countries, our approach has generalizability, which will benefit researchers of school health or pediatrics worldwide. We demonstrated strong and consistent upward cohort effects on asthma prevalence and there remains an active debate on the cause of the global trend of increasing asthma prevalence.

Asthma and nonspecific respiratory symptoms were first attributed to air pollution, as first reported by Huber in 1954 who described “Yokohama asthma” (15) followed by Yoshida who named “Yokkaichi asthma” (16) after the name of highly polluted areas. The Japanese government established a collective civil damage compensation system known as the Air Pollution Victims Compensation Act in 1974 (17). The presumed causal relationship between air pollution and asthma was challenged by Namekata in 1987 (18), but as the ambient air condition improved, a steady decrease in the prevalence of respiratory symptoms such as cough and phlegm was observed until 1985 by Shimizu (19). However, this declining trend was reversed and an upward trend of asthma prevalence among school children was reported by Yura despite improved ambient air condition starting in 1985 (20).

Fortunately, the increasing prevalence or morbidity did not translate into increased mortality. As Tanihara reported, there have been consistent declining cohort effects on mortality indicating that asthma has become a more common but a less fatal disease. Indeed, asthma mortality for ages 5–39 years is increasingly viewed as avoidable death and has been advocated as an indicator of health care quality (21). However, there is an ongoing debate as to whether a new treatment has actually contributed to the decrease in asthma mortality: Suisa attributed Japan’s declining asthma mortality among individuals aged 5–34 to the introduction of a new drug (22) on one hand, whereas Tanihara raised the possibility of an increase in asthma mortality caused by beta2-agonists on the other hand (23).

Confusions over asthma prevalence arising from the difficulties in isolating long-term cohort effects (such as air pollution) and short-term period effects (such as change in diagnostic criteria) from stable aging effects. Various methods of APC analysis are hampered by technical difficulties, but we demonstrated a method to overcome such difficulties by isolating three factors in a step-by-step manner with satisfactory performance.

Our results demonstrated that consistently upward trends of cohort effects had been observed at least for the cohort born in 1968 for both sexes. However, such consistent upward trends have been masked by fluctuating period effects, which temporally and sharply increased in and around 1999. The exact cause of this temporary increase in 1999 cannot be determined from our analysis.

Lastly, one crucial question remains: what is the cause of the consistent upward trends of cohort effects on asthma prevalence among school children? Some speculate that environmental factors such as in-house smoking and domestic pets are potential causes, but a cross-sectional study showed no effects of these factors (24). Others suggest individual factors such as physical activities, but a thorough review of existing evidence failed to reach any definite conclusions (25). However, accumulating epidemiological evidence suggests air pollutants such as suspended particulate matter and nitrogen dioxide emitted from motor vehicles are the likely causes of the consistent increase in asthma prevalence, illustrated by a geographical difference in asthma prevalence between children living along a roadside and those living elsewhere (26). Our analysis was not able to corroborate such claims because SHSR does not provide geographical information of individual children but such causal relationship may be confirmed by a large-scale cohort study under way, namely a study on respiratory diseases and automobile exhaust (SORA) (27).

Whatever the causes, the most alarming finding of our study is that there is yet no sign of leveling off in the upward trend of cohort effects, and this trend is masked by a recent decrease in period effects after 1999. That is, younger preschoolers will continue to have higher asthma prevalences than their older siblings and we will continue to see a steady increase in the number of asthmatic children in all school ages.

Our study does call for effective treatment and precautionary measures to protect school children from potentially harmful chronic conditions.

Acknowledgement

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