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Original Article

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). Tanihara 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-

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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 than, 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*

Table 1 Population of Japan's school children

	AGE	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
BOYS	6	889063	861930	832118	792663	773882	773657	767599	748501	722141	699064	679170	665287	633647	620041	623561	616163	610025	630095	603846	614702	609079
	7	910656	888486	861540	831759	792224	773434	773302	767397	748544	722189	698935	678924	665065	633636	620171	623424	615876	609789	629859	603601	614316
	8	954436	910356	888328	861342	831538	792013	773314	773346	767655	748776	722262	698950	679050	665293	633907	620238	623377	615829	609657	629831	603640
	9	1017088	954083	910112	888110	861138	831253	791823	773461	773631	767887	748763	722326	699059	679298	665501	634035	620275	623399	615768	609713	629768
	10	1051153	1016727	953935	909972	887853	861021	831179	791971	773670	773960	767978	748871	722419	699292	679593	665555	634073	620370	623441	615910	609768
	11	1049127	1050908	1016564	953769	909789	887726	860980	831398	792364	773970	774114	768233	748978	722681	699581	679829	665807	634203	620434	623584	615997
	12	1028886	1048099	1049890	1015635	952706	908634	886919	860406	830622	791713	773480	773831	767746	748503	722270	698939	678977	664381	632693	618464	621474
	13	991781	1028479	1048616	1049657	1015256	952084	908655	886761	859973	830830	791656	773345	773464	767788	748606	722173	698788	678828	664291	632493	618489
	14	965806	991319	1027765	1047277	1049401	1014682	952168	908401	886342	860013	830721	791658	773027	773490	767780	748373	721906	698601	678808	664083	632633
	15	874079	872231	894416	964491	983228	985701	956861	900550	862727	843482	820423	792095	755640	738475	738131	733122	715921	689328	667746	649898	636590
	16	822136	844132	841389	889458	924481	942208	941836	912297	859553	824539	807008	783643	755775	714319	697402	696508	692642	674961	651191	634663	620242
	17	674073	796099	816033	834999	859327	893221	909298	909338	881388	832112	800115	782104	758093	726837	686941	669719	669916	665605	649512	629851	614975
GIRLS	6	846880	820741	792188	754191	737750	738213	734187	715719	688300	666796	646279	634746	604038	593203	593498	586964	582233	602111	577783	586723	582629
	7	866635	846652	820465	792081	753873	737552	737990	734218	715990	688414	666761	646222	634793	604160	593334	593430	586881	582089	601955	577734	586598
	8	909605	866358	846490	820416	791802	753714	737391	738186	734455	716121	688468	666804	646363	635013	604546	593442	593530	586898	582127	602046	577603
	9	968355	909489	866271	846390	820246	791625	753734	737507	738414	734797	716320	688498	666940	646605	635314	604632	593592	593565	586963	582180	602103
	10	1001919	967957	909397	866177	846270	820084	791669	753917	737898	738694	734877	716296	688691	667219	646917	635474	604842	593581	593654	587051	582236
	11	999304	1001685	967996	909453	866155	846335	820127	791808	754164	738213	738944	735089	716586	688946	667610	647131	635568	604991	593840	593835	587196
	12	979255	999095	1001963	968094	909449	866452	846348	820352	792470	754583	738439	738780	735297	716946	689248	667660	646953	635181	604443	593051	592901
	13	944367	978936	999245	1001610	967767	909372	865936	846260	820603	792213	754582	738244	739101	735403	716936	689277	667579	647054	635284	604549	593145
	14	918772	944255	979270	999057	1001501	968073	909136	866134	846830	820785	792288	754532	738765	739350	735764	717340	689514	667866	647330	635679	604871
	15	861246	860288	883718	933879	956309	958680	929446	874610	836849	819447	797532	771258	735530	720243	721165	716080	697638	669518	647459	627939	616303
	16	831144	844084	844192	880089	913949	935093	936401	907221	855636	819759	803735	780441	752758	713764	696629	696246	690562	670218	641222	621907	604119
	17	686397	815296	828306	839178	861926	894464	914498	915656	888697	839895	805145	787991	763416	732452	693196	675298	674755	667778	647014	620596	602199

Source: Japan's Essential Statistics of School Education

Table 2 Age- and sex-specific prevalences (%) of asthma among Japan's school children

	AGE	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
BOYS	6	1.05	1.22	1.19	1.32	1.39	1.53	1.39	1.46	1.70	1.61	1.86	1.94	2.25	2.51	3.02	3.56	3.55	3.43	3.50	3.85	4.13
	7	1.05	1.44	1.03	1.26	1.33	1.24	1.40	1.21	1.40	1.55	1.71	1.86	1.91	2.11	2.82	3.15	3.24	3.21	3.29	3.67	3.86
	8	0.94	1.08	1.12	1.13	1.24	1.25	1.09	1.25	1.29	1.34	1.54	1.53	1.91	2.02	2.96	3.15	3.06	3.14	3.22	3.64	3.75
	9	1.06	0.99	1.09	1.13	1.22	1.26	1.30	1.28	1.36	1.35	1.54	1.57	1.90	2.04	2.65	3.02	2.76	2.86	3.02	3.38	3.71
	10	1.01	0.96	0.99	1.21	1.17	1.12	1.22	1.23	1.26	1.45	1.55	1.57	1.86	1.85	2.66	3.05	2.86	3.05	3.16	3.47	3.60
	11	0.99	1.18	1.08	1.18	1.24	1.29	1.21	1.17	1.41	1.21	1.57	1.61	1.67	1.91	2.57	2.87	2.83	2.79	3.07	3.35	3.57
	12	0.98	1.06	1.06	1.27	1.21	1.28	1.47	1.36	1.69	1.48	1.82	1.87	2.22	2.07	2.37	3.04	2.52	2.77	3.08	3.25	3.42
	13	0.80	0.69	0.86	0.83	0.85	1.05	1.11	1.14	1.17	1.17	1.53	1.63	1.70	1.73	1.68	2.42	2.01	2.19	2.58	2.86	2.75
	14	0.62	0.57	0.57	0.65	0.67	0.82	0.96	1.06	1.11	0.95	1.38	1.60	1.46	1.41	1.73	2.08	1.97	2.13	2.43	2.47	2.54
	15	0.40	0.35	0.39	0.56	0.57	0.53	0.62	0.71	0.85	1.09	1.15	1.07	1.14	1.19	1.38	1.84	1.81	1.83	1.77	1.49	1.94
	16	0.26	0.22	0.35	0.34	0.40	0.33	0.42	0.42	0.53	0.76	0.79	0.90	0.69	1.01	1.11	1.23	1.36	1.44	1.39	1.28	1.66
	17	0.28	0.15	0.24	0.37	0.30	0.29	0.35	0.46	0.45	0.55	0.68	0.65	0.81	0.76	0.95	1.10	1.15	1.25	1.41	1.28	1.31
GIRLS	6	0.66	0.74	0.75	0.82	0.94	0.92	0.85	0.88	1.00	0.91	1.17	1.28	1.51	1.48	2.09	2.28	2.15	2.10	2.33	2.41	2.60
	7	0.79	0.65	0.73	0.72	0.79	0.77	0.87	0.82	0.99	1.02	1.11	1.16	1.19	1.58	1.75	1.99	1.93	2.14	2.30	2.37	2.51
	8	0.60	0.91	0.67	0.70	0.85	0.79	0.76	0.81	0.94	0.99	0.98	1.08	1.22	1.13	1.69	2.06	1.88	1.91	2.25	2.07	2.31
	9	0.68	0.75	0.65	0.70	0.91	0.72	0.85	0.80	0.79	0.87	1.17	1.14	1.28	1.34	1.62	2.06	1.89	1.71	2.00	2.33	2.20
	10	0.68	0.68	0.53	0.77	0.85	0.75	0.87	0.90	0.87	0.83	0.94	0.98	1.35	1.17	1.82	1.90	1.66	1.96	2.06	2.12	2.29
	11	0.69	0.52	0.71	0.71	0.63	0.76	0.73	0.81	0.88	0.77	0.97	0.88	0.99	1.10	1.43	1.78	1.51	1.80	1.70	1.97	2.10
	12	0.60	0.64	0.77	0.72	0.75	0.89	0.87	0.83	1.19	0.91	1.14	1.25	1.34	1.36	1.44	1.74	1.62	1.67	1.84	1.89	2.02
	13	0.47	0.54	0.54	0.49	0.62	0.68	0.79	0.86	0.82	0.78	0.86	1.18	1.08	0.96	1.31	1.54	1.35	1.53	1.54	1.90	1.72
	14	0.50	0.51	0.53	0.55	0.55	0.69	0.67	0.80	0.76	0.70	1.03	1.05	1.04	0.99	1.24	1.36	1.37	1.34	1.57	1.50	1.87
	15	0.33	0.36	0.32	0.35	0.52	0.56	0.55	0.66	0.88	0.77	0.93	0.80	0.97	0.98	1.23	1.32	1.35	1.23	1.44	1.41	1.37
	16	0.22	0.14	0.22	0.25	0.29	0.41	0.37	0.49	0.56	0.63	0.59	0.65	0.69	0.96	0.89	1.16	1.09	1.25	1.08	1.29	1.17
	17	0.16	0.22	0.29	0.26	0.31	0.38	0.40	0.46	0.54	0.46	0.49	0.62	0.67	0.78	1.00	1.03	1.11	0.93	1.09	1.19	1.24

Source: Japan's School Health Survey

Table 3 Sample size and sampling rate

	School type	92	93	94	95	96	97	98	99	2000	2001	2002	2003	2004
SAMPLE SIZE	primary	528931	530494	526343	523830	520027	514428	520334	510339	507929	509617	502870	506437	498910
	junior high	394971	394994	391586	390931	391446	393575	391062	390804	386325	383589	380495	380814	375594
	senior high	246343	240184	234074	226640	222009	216389	211353	207976	208763	204132	200243	198477	197200
SAMPLING RATE (%)	primary	5.91	6.05	6.13	6.26	6.42	6.55	6.79	6.80	6.90	6.98	6.95	7.01	6.93
	junior high	7.84	8.14	8.37	8.55	8.65	8.78	8.93	9.21	9.41	9.61	9.85	10.16	10.25
	senior high	4.75	4.82	4.84	4.82	4.91	4.98	4.99	4.97	5.04	5.06	5.13	5.24	5.34

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% (∵42,199 × 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-5)th*** age), ***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***ijk***(%), can be predicted as a

Table 4 Age- and sex-specific error rates of asthma prevalence (%)

	AGE	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
BOYS	6	3.71	3.83	3.59	3.52	3.31	3.13	2.80	2.59	2.59	2.57	2.61	2.46	2.40
	7	4.02	3.84	3.69	3.56	3.50	3.38	2.90	2.74	2.70	2.70	2.64	2.54	2.47
	8	4.13	4.06	3.83	3.87	3.47	3.37	2.80	2.74	2.76	2.72	2.71	2.49	2.53
	9	4.01	3.99	3.76	3.75	3.43	3.32	2.89	2.77	2.91	2.83	2.78	2.63	2.49
	10	4.17	3.84	3.70	3.69	3.41	3.44	2.85	2.69	2.83	2.75	2.70	2.58	2.56
	11	3.89	4.20	3.66	3.59	3.53	3.33	2.86	2.74	2.77	2.84	2.75	2.61	2.56
	12	3.01	3.24	2.91	2.84	2.60	2.71	2.56	2.26	2.49	2.38	2.28	2.21	2.14
	13	3.56	3.55	3.14	3.05	2.97	2.93	2.98	2.49	2.75	2.65	2.43	2.33	2.39
	14	3.60	3.88	3.23	3.04	3.20	3.23	2.90	2.64	2.73	2.64	2.48	2.45	2.46
	15	5.36	4.75	4.68	4.95	4.86	4.78	4.43	3.86	3.91	3.96	4.06	4.44	3.89
	16	6.80	5.75	5.69	5.42	6.25	5.28	5.09	4.85	4.59	4.51	4.64	4.84	4.27
	17	7.28	6.73	6.16	6.39	5.76	6.03	5.54	5.23	5.07	4.88	4.61	4.86	4.82
GIRLS	6	4.96	5.22	4.64	4.43	4.13	4.17	3.45	3.31	3.40	3.37	3.27	3.18	3.09
	7	4.89	4.85	4.69	4.62	4.54	4.00	3.77	3.53	3.58	3.39	3.22	3.23	3.13
	8	4.95	4.83	4.92	4.71	4.45	4.61	3.80	3.47	3.61	3.57	3.32	3.38	3.29
	9	5.38	5.08	4.41	4.51	4.27	4.20	3.78	3.44	3.60	3.76	3.50	3.24	3.30
	10	5.13	5.19	4.86	4.77	4.09	4.42	3.54	3.49	3.80	3.51	3.43	3.39	3.29
	11	5.05	5.39	4.77	4.97	4.69	4.49	3.93	3.57	3.89	3.63	3.78	3.49	3.42
	12	3.68	4.23	3.77	3.56	3.43	3.42	3.36	3.06	3.18	3.13	3.02	2.96	2.85
	13	4.35	4.46	4.29	3.66	3.81	4.02	3.45	3.20	3.43	3.24	3.22	2.93	3.09
	14	4.45	4.62	3.83	3.84	3.88	3.94	3.50	3.34	3.35	3.41	3.16	3.21	2.94
	15	5.35	5.73	5.28	5.80	5.34	5.33	4.75	4.62	4.59	4.90	4.57	4.64	4.71
	16	6.63	6.34	6.60	6.39	6.26	5.41	5.68	4.99	5.13	4.86	5.31	4.88	5.15
	17	6.62	7.33	7.24	6.51	6.31	5.93	5.38	5.38	5.15	5.64	5.26	5.08	5.01

product of three functions: aging effects A(i), period effects P(j), and cohort effects C(k).

$$Rijk = A(i)*P(j)*C(k) \quad (1)$$

There is a linear relationship among i, j and k. If there are ***l*** periods and ***m*** age groups, $\boldsymbol{k = l + m - 1 = j - i + 5 + m}$. 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 Rijk 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 Rijk and compared their ability to predict aging effects (performance) on the basis of the residual sum of square (RSS), between the observed Rijk and predicted Ṙijk (an overhead dot denotes a predicted value).

Ṙijk predicted from the polynomial function of the ***l***th order is expressed as follows.

$$\dot{R}ijk = (a0*i^n + a1*i^{n-1} + \cdots + an)*C(k) \quad (2)$$

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:

$$RSS = \sum_{i=6}^{17} \sum_{j} (Rijk - \dot{R}ijk)^2 \quad (3)$$

We used Excel Solver to obtain the coefficients, a0, a1, a2 … an 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:

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

Note that the observed Rijk was 1.17%. We were able to predict the unobserved Ṙijk because of missing ***i*** and ***j*** and unobserved C(k) by fitting the cubic equation to observed Rijk (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:

$$P(ijk) = \frac{Rijk}{\dot{R}ijk} \quad (4)$$

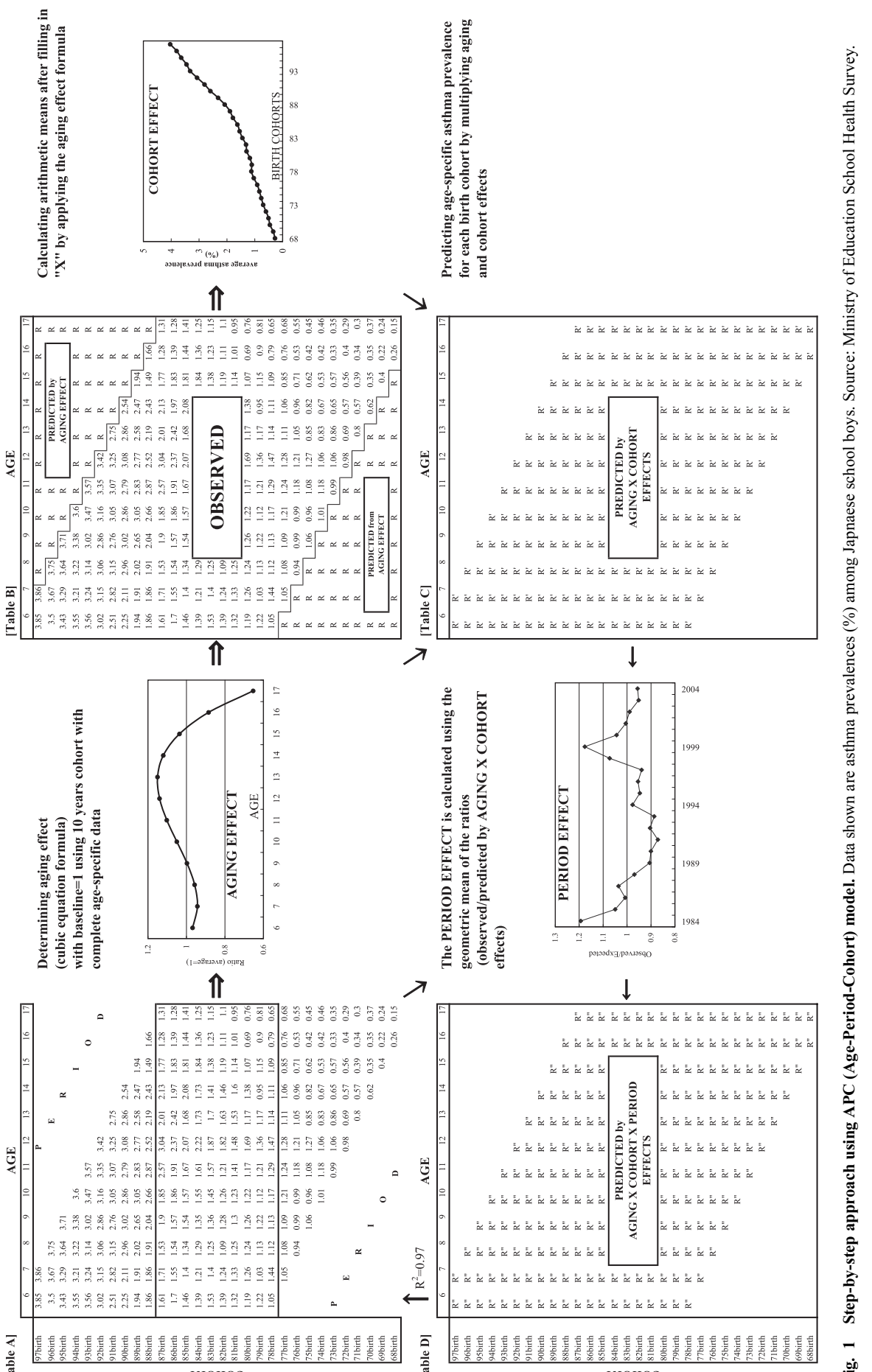

Fig. 1 Step-by-step approach using APC (Age-Period-Cohort) model. Data shown are asthma prevalences (%) among Japnaese school boys. Source: Ministry of Education School Health Survey.

Table 5 Coefficients of polynomial functions and residual sum of square (RSS) values between observed and predicted asthma prevalences

Boys	a0	a1	a2	a3	a4	RSS
1st order	–0.009	1.099				3.818
2nd order	–0.010	0.231	–0.157			2.364
3rd order	–0.002	0.066	–0.603	2.684		1.854
4th order	0.000	0.004	–0.054	0.329	0.107	2.016
Girls	a0	a1	a2	a3	a4	RSS
1st order	0.018	0.789				2.039
2nd order	–0.005	0.138	0.164			1.679
3rd order	–0.002	0.046	–0.418	2.035		1.488
4th order	0.000	0.007	–0.095	0.627	–0.736	1.575

y = a0*x^n + a1*x^(n – 1) + a2*x^(n – 2) + ⋯ + an where x is age
RSS is the residual sum of square value between observed and predicted asthma prevalences.

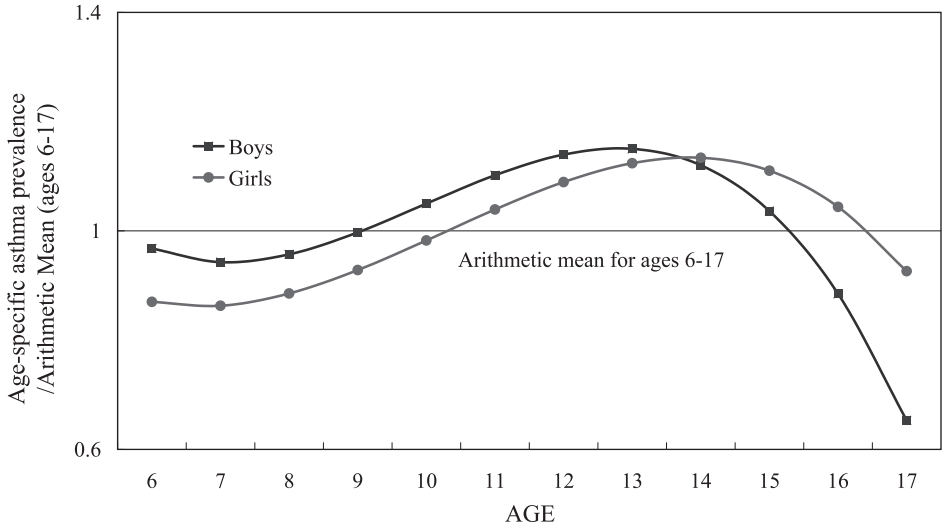

Fig. 2 Aging effects of asthma prevalence. Age-specific asthma prevalence expressed as ratio against the arithmetic mean (age 6–17). Source: School Health Survey Japan.
for boys: –0.002*i3 + 0.066*i2 – 0.603*i + 2.684
for girls: –0.002*i3 + 0.046*i2 – 0.418*i + 2.035

Ṙijk 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***.

$$P(j) = \sqrt[m]{\prod_{i}^{m}\left(\frac{Rijk}{\dot{R}ijk}\right)} \quad (5)$$

4) Performance measures

The overall performance of our model was measured using R^2 values between observed Rijk and predicted Ṙijk 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

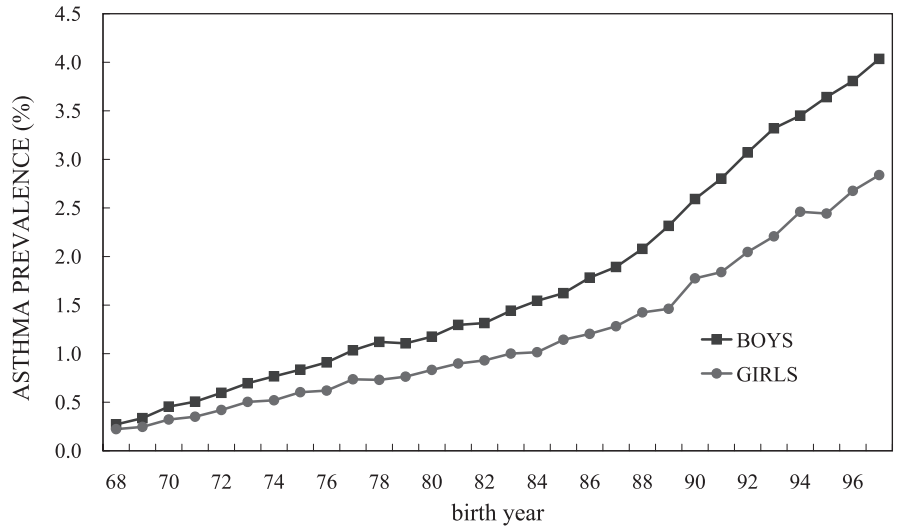

Fig. 3 Cohort effects of asthma prevalence. Arithmetic means of age-specific asthma prevalence (age 6–17) for each cohort. Source: School Health Survey in Japan.

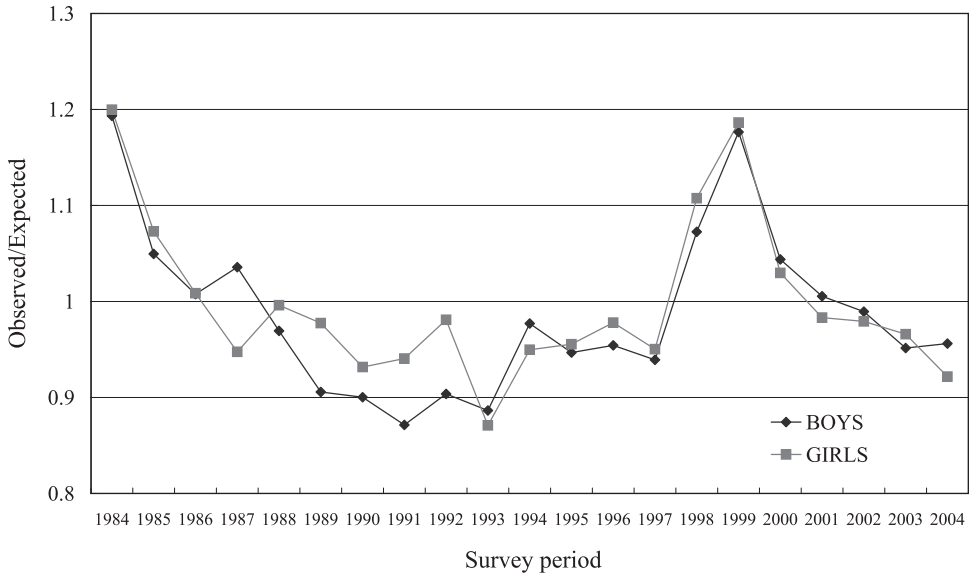

Fig. 4 Period effects of asthma prevalence. Period effects are expressed as a ratio between observed prevalence and the prevalence expected from aging and cohort effects. Source: School Health Survey in Japan.

(prevalence reported in SHSR is point prevalence).

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 R^2 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 on-going debate as to whether a new treatment has actually contributed to the decrease in asthma mortality: Suissa 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 temporarily 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.

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