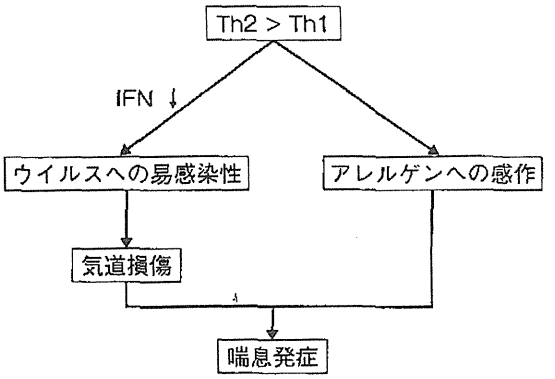

図2　Th2優位による喘息発症

告もある[6]。また，フィトヘマグルチニン(PHA)刺激による臍帯血単核球からのIFN－γ産生量が多い児では，生後1年間のウイルス感染症の罹患回数が少なく，逆にIFN－γ産生量が少ないとウイルス感染を起こしやすいことが示されている[7]。

このように，Th2が優位な状況があると，ウイルス感染やアレルゲン感作により喘息を発症しやすくなるといったストーリーも存在すると考えられる(**図2**)。

ウイルス感染とダニ感作の関係については，BALB/cマウスによる実験[8]で，幼若マウスにインフルエンザAを感染させその後チリダニ抗原を曝露すると，末梢血好酸球やダニ特異的IgEが増加するとともに気道の基底膜肥厚や気道への好酸球浸潤をきたすこと，さらにそのマウスが成熟期に至ると基底膜のコラーゲン沈着が増加し，リモデリングが持続していることが報告された。これらの結果から，動物実験の段階ではあるが，ウイルス感染とアレルゲン曝露が相互作用すること(allergen virus interaction)により，喘息が発症する可能性が示唆された。

3．低肺機能による喘息の発症―ビタミンDの関連

上記の2つと異なり，まず肺機能が低いことが喘息発症の原因とする考え方もある。新生児期に肺機能(t_{PTEF}/t_E)を測定し10年間フォローした研究では，新生児期に肺機能が低値であった児では，そうでなかった児に比して10歳の時点で喘息症状を有している率が有意に高いことが報告され[9]，また2012年に報告されたコペンハーゲンのコホート研究[10]では，7歳時に喘息である群の肺機能は，非喘息群に比して生下時から低値であったと報告されている。さらに，van der Xalmは生後2ヵ月以内に測定した気道抵抗が平均より高い群では，低い群に比べその後RV感染によって喘鳴を呈した割合が有意に高かったことから，RVが関係した喘鳴は新生児期の肺機能低下を示す最初のサインではないかと述べている[11]。

小児の肺機能低下の原因として，妊娠中の母親の喫煙[12]が以前より言われているが，最近ビタミンDの不足も原因の一つではないかと注目されている。BALB/cマウスの実験では，母体の妊娠中のビタミンD摂取不足が児の肺の発達を抑制すること[13]が報告されている。ビタミンD不足は，肺の成熟抑制やそれに伴う肺機能低下ばかりでなく，抗菌ペプチドであるカテリジン産生が低下するために気道感染症に罹患しやすくなり，これらの結果として喘息発症に関連するといわれている[14]。事実，臍帯血の25(OH)D欠乏がRSVによる細気管支炎に関連する[15]ことや，ビタミンDの4ヵ月間の補給によりインフルエンザや喘息発作の発生率が減少した[16]との報告もある。さらに，臍帯血中25(OH)Dが50 nmol/L未満の児では，正常域にある児に比して一般的なアレルゲンに感作されやすいとの報告がある[17]。そこで，われわれは9～10歳の小児約1000人についてビタミンD濃度を測定するとともに，ISAACの問診票を用いて喘息やその他のアレルギー疾患の有無を調査したところ，約2/3の児がビタミンD不足であったが，ビタミンD濃度とアレルギー疾患の有症率には一定の関連はみられなかった(**表1**)[18]。欧米では，この年齢の小児でもビタミンD不足がアレルギー疾患の発症や増悪に関与するとの報告もあり，わが国でも低年齢児を含めたより大規模な調査が必要と思われる。

表1　わが国の小児におけるビタミンD濃度とアレルギー疾患の関連(文献18)

25OH Vit D3 (ng/mL)		Current asthma			Any allergic diseases		
		n(%)	Adjusted OR	95% CI	*n*(%)	Adjusted OR	95% CI
<20	*n*=109	10(9.2)	1.06	0.51-2.21	35(32.1)	0.73	0.46-1.18
≧20-<30	*n*=563	63(11.2)	1.22	0.80-1.88	202(35.9)	0.93	0.71-1.22
≧30	*n*=443	41(9.3)	1		169(38.1)	1	

OR：odds ratio, CI：confidence interval
ORs were determined for each 25OH vitamin D3 category with respect to the reference group (≧30 ng/mL)
*Adjusted for gender, obesity (dichotomous, BMI 95 th), parental history of asthma, parental smoking, pet owing, and early kindergarten (dichotomous, before age 1 year)

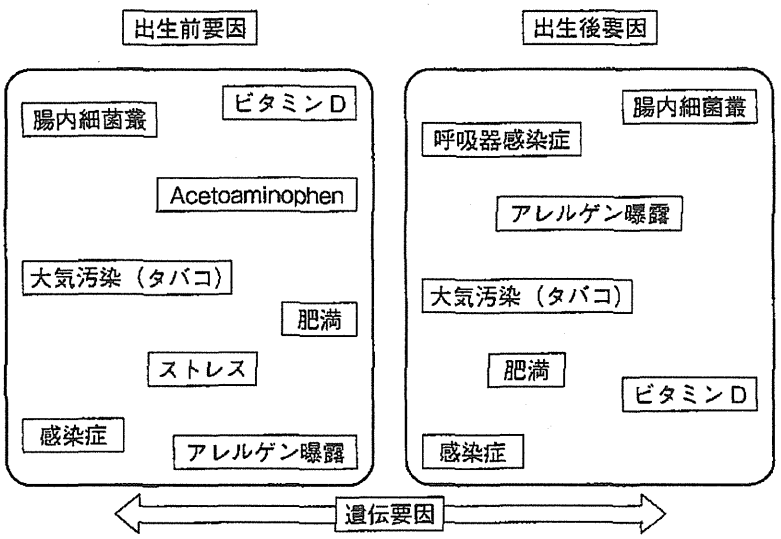

図3　喘息の発症機序

4. 小児の喘息発症における母体の影響

小児の喘息発症に対する妊娠中の母体の影響は大きいと考えられる。Barker仮説[19]では，小さく生まれた分だけ早く成長しようとするために成人病になりやすい(early adaptation mechanism)といわれており，喘息についても，妊娠19～34週の胎児において発育が悪く，生後6ヵ月までに発育がよかった群では，他の群に比して3歳の時点で最も喘鳴をきたしやすかったとの報告がある[20]。また，胎内での発育状態ではなく，生後3ヵ月までの発育がよかった群で4歳時点での喘鳴症状が多かったとする報告もある[21]。いずれにしても生後の急速な発育は将来の肥満と関係するといわれており，肥満と喘息の関係とも合致する[22, 23]。

ま と め

小児の喘息の発症には環境や遺伝の問題，さらにそれらに対するエピジェネティックな関与，そして胎内および生後の成長の問題などが複雑に関与している[24]。そして少しずつではあるが，関連因子が明らかになってきている(図3)。

現在，環境省で全国10万組の小児とその両親

を対象に，小児の健康と環境に関する全国調査「エコチル調査」が行われている。欧米では関与が明らかになっている肥満，ビタミンD，大気汚染の問題がわが国でもあてはまるのか，また，妊娠中の黄砂やスギ花粉の曝露の影響など，新たな予防や治療に有用な結果をもたらすものと期待される。

文　献

1) Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354:541-5.
2) Saga R, Mochizuki H, Tokuyama K, et al. Relationship between bronchial hyperresponsiveness and development of asthma in wheezy infants. Chest 2001;119:685-90.
3) Jakson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178:667-72.
4) Guilbert T, WSingh AM, Danov Z, et al. Decreased lung function after preschool wheezing rhinovirus illnesses in children at risk to develop asthma. J Alergy Clin Immunol 2011;128:532-8.
5) Lodge CJ, Lowe AJ, Gurrin LC, et al. House dust mite sensitization in toddlers predicts current wheeze at age 12 years. J Alergy Clin Immunol 2011;128:782-8.
6) Soto-Quiros M, Avila L, Platts-Mills TA, et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. J Alergy Clin Immunol 2012;129:1499-505.
7) Copenhaver CC, Gern JE, Li Z, et al. Cytokine response patterns, exposure to viruses, and respiratory infections in the first year of life. Am J Respir Crit Care Med 2004;170:175-80.
8) Al-Garawi A, Fattouh R, Botelho F, et al. Influenza A facilitates sensitization to house dust mite in infant mice leading to an asthma phenotype in adulthood. Mucosal Immunol 2011;4:682-94.
9) Haland G, Carlsen KC, Sandvik L, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. N Engl J Med 2006;355:1682-9.
10) Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. Am J Respir Crit Care Med 2012;185:1183-9.
11) van der Xalm MM, Uiterwaal CS, Wilbrink B, et al. The influence of neonatal lung function on rhinovirus-associated wheeze. Am J Respir Crit Care Med 2011;183:262-7.
12) Stick SM, Burton PR, Gurrin L, et al. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 1996;348:1060-4.
13) Zosky GR, Berry LJ, Elliot JG, et al. Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Respir Crit Care Med 2011;183:1336-43.
14) Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. Curr Opin Allergy Clin Immunol 2009;9:202-7.
15) Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics 2011;127:e1513-20.
16) Urashima M, Segawa T, Okazaki M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr 2010;91:1255-60.
17) Rothers J, Wright AL, Stern DA, et al. Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. J Alergy Clin Immunol 2011;128:1093-9.
18) Ito Y, Adachi Y, Yoshida K, et al. No association between serum vitamin D status and the prevalence of allergic diseases in Japanese children. Int Arch Allergy Immunol 2013;160:218-20.
19) Barker DJP, Hales CN, Fall CH, et al. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1993;36:62-7.
20) Pike KC, Crozier SR, Lucas JS, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years.Thorax 2010;65:1099-106.
21) Sommenshein-van der Voort AMM, Jaddoe VW, Raat H, et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. Am J Respir Crit Care Med 2012;185:731-7.
22) Okabe Y, Itazawa T, Adachi Y, et al. Association of overweight with asthma symptoms in Japanese school children. Pediatr Int 2011;53:192-8.
23) Okabe Y, Adachi Y, Itazawa T, et al. Association between obesity and asthma in Japanese preschool children. Pediatr Allergy Immunol 2012;23:550-5.
24) Duijts L. Fetal and infant origins of asthma. Eur J Epidemiol 2012;27:5-14.

Environ Health Prev Med (2014) 19:81–88
DOI 10.1007/s12199-013-0356-4

SHORT COMMUNICATION

Indoor particle counts during Asian dust events under everyday conditions at an apartment in Japan

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Received: 8 June 2013 / Accepted: 21 July 2013 / Published online: 10 August 2013

Abstract
Objective Asian dust storms originating from arid regions of Mongolia and China are a well-known springtime phenomenon throughout East Asia. Evidence is increasing for the adverse health effects caused by airborne desert dust inhalation. Given that people spend approximately 90 % of their time indoors, indoor air quality is a significant concern. The present study aimed to examine the influence of outdoor particulate matter (PM) levels on indoor PM levels during Asian dust events under everyday conditions.
Methods We simultaneously monitored counts of particles larger than 0.3, 0.5, 1, 2, and 5 μm using two direct-reading instruments (KC-01D1 airborne particle counter; Rion), one placed in an apartment room and another on the veranda, under everyday conditions before and during an Asian dust event. We also examined how indoor particle counts were affected by opening a window, crawling, and air purifier use.
Results An Asian dust event on 24 April 2012 caused 50- and 20-fold increases in PM counts in outdoor and indoor air, respectively. A window open for 10 min resulted in a rapid increase of indoor PM counts up to 70 % of outside levels that did not return to baseline levels after 3 h. An air purifier rapidly reduced PM counts for all particle sizes measured.
Conclusions It is important to account for occupant behavior, such as window-opening and air purifier use, when estimating residential exposure to particulate matter.

Keywords Indoor air · PM2.5 · PM10 · Dust storm · Asian dust

Introduction

Asian dust events are well-known spring phenomena in East Asia that originate from the deserts of Mongolia and China. Asian cities experience yellow air on several days in the spring when the dust is blowing. The dust includes quartz, an amorphous and crystalline silica known to cause respiratory disease in people with occupational exposure or high levels of exposure from living close to deserts [1–4] and inflammation in the lungs of rats in experimental studies [5–8]. Further, dust particles contain chemicals derived from air pollutants, such as sulfate (SO_4^{2-}) and nitrate (NO_3^-), as well as microbial agents, including bacteria, fungi, fungal spores, and viruses, that sometimes survive long-distance transportation [9–11]. The impact of airborne dust may be exacerbated by these potential allergens and pathogens.

Epidemiological studies also provide increasing evidence of adverse health effects from airborne desert dust inhalation. Hospitalization risk increases significantly for asthmatic children [12], as do emergency ambulance dispatches [13] after Asian dust events in Japan. Non-accidental mortality and cardiovascular mortality also increase significantly after

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Asian dust events in Taiwan [14]. A Korean study, where the influence of desert dust was not necessarily specifically investigated, also shows that particulate matter (PM) number as well as mass concentration are significantly associated with respiratory and cardiovascular disease-related mortality among the elderly [15].

Given that people spend approximately 90 % of their time indoors [16], indoor air quality is a significant concern. In Japan, the season for Asian dust events coincides with one of the most comfortable periods of the year. Our preliminary investigation (unpublished data) revealed that approximately half of the pregnant women in Kyoto, Japan, opened windows every day during April 2012 (1794 respondents/2107 queried).

We investigated how indoor PM counts (larger than 0.3, 0.5, 1, 2, and 5 μm, respectively) are influenced by various factors, including window/door openness, activity (crawling), and air purifier use, under everyday conditions in an apartment in Japan on days with Asian dust events.

Methods

Monitoring situation

We monitored PM counts in a room on the 10th floor of an apartment building in a residential area of Kyoto. There is a 100 m distance from the apartment building to the nearest two-way road. The building is a reinforced concrete structure built in 2001, 11 years before this study.

The apartment is a 4LDK with 86 m^2 floor area, occupied by two adults and an 11-year-old girl. None of the occupants are at home during the daytime and all three are non-smokers. The floor is wooden and shoes are strictly prohibited in the rooms in accordance with Japanese culture. The monitored room of the apartment has a 22 m^2 floor area and is shown in Fig. 1. The door in the monitored room was kept closed throughout the study period except when occupants went in or out, but there is a 0.8 cm-wide space at the bottom of the door even when it is closed. An air purifier was constantly used in the living/dining room during the observational period (2 m^3/min airflow) and was moved to the monitored room for the experiment.

The study period was composed of an observational period and an experimental period. An observational period was composed of a control period and an Asian dust period (Fig. 2). In the experimental periods, we performed experiments of opening windows (20 cm, 10 min) or air-purifier use to see how these factors affect the PM counts indoors. We also performed an experiment of crawling (a researcher, 160 cm height, crawled on the floor for 10 min) to see if dust fallen on the floor affects the indoor air again because of activities.

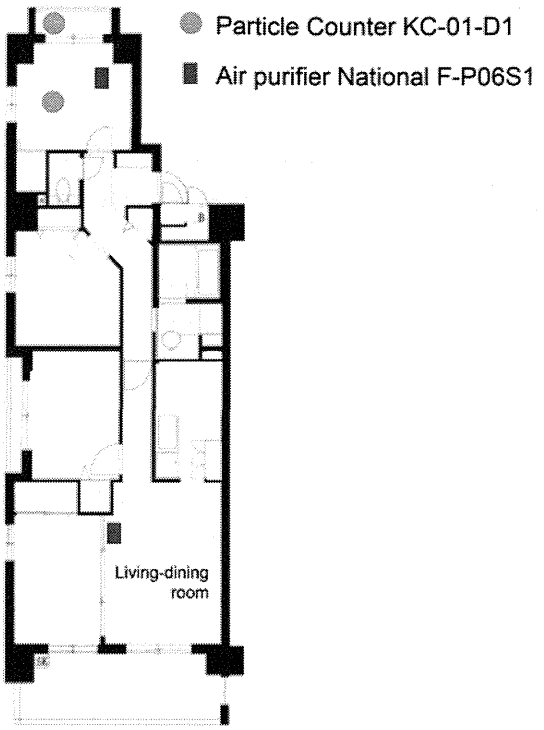

Fig. 1 Floor plan of the monitored apartment. Two particle counters (*solid circles*) were used. One was placed 20 cm above the floor in the monitored room and the other was placed 120 cm above the veranda floor. An air purifier (*solid rectangle*) was placed in the living-dining room during the observational period and moved to the monitored room for the experiment

Monitoring equipment

The direct-reading instrument used to measure particle size and count was a Rion KC-01-D1 airborne particle counter. The machine simultaneously counts particles larger than 0.3, 0.5, 1, 2, and 5 μm. We concurrently monitored the indoor PM counts 20 cm above the floor, and outdoor PM counts 120 cm above the veranda floor (Fig. 1). The flow rate was 0.5 L/min, and particle counts were measured every 2 min.

Room variables recorded during the study period included the following: window (open/closed), room door (open/closed), air conditioner (on/off), ventilation system (on/off), cooking in the apartment (yes/no), and the number of persons present during the testing.

Information regarding desert dust concentration was provided by light detection and ranging (LIDAR) with a polarization analyzer in Osaka [17, 18], which distinguishes soil dust (non-spherical particles) from atmospheric pollutants (spherical particles) by measuring the extent of scattered reflected light [19, 20]. We used the data for an altitude of 135 m. Suspended particulate matter (SPM; PM7) was measured at an air quality monitoring station in Kyoto located approximately 5 km from the apartment building.

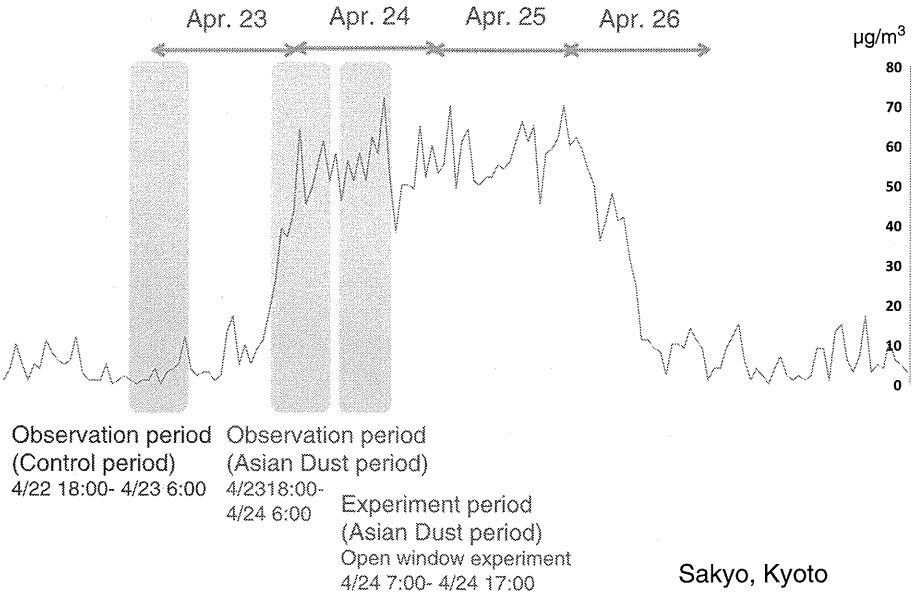

Fig. 2 Local SPM measurements during the control and Asian dust periods

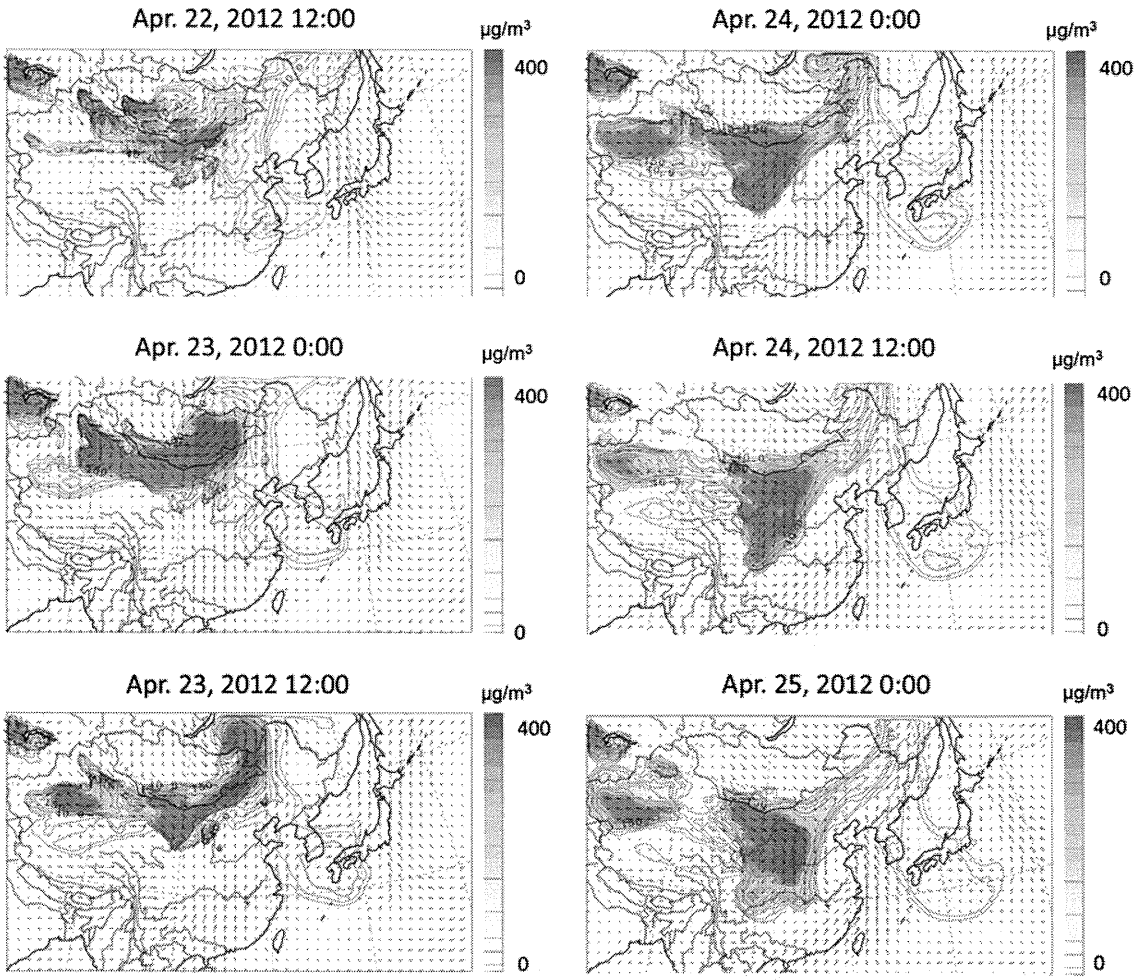

Fig. 3 Asian dust distribution prediction by the Chemical Weather Forecast System [17]. The Asian dust clouds were predicted to arrive in Kyoto at noon on 23 April 2012

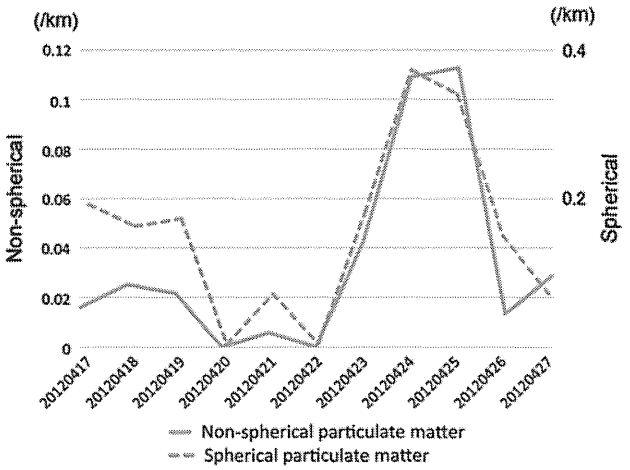

Fig. 4 Estimation of non-spherical and spherical particle concentrations by light detection and ranging (LIDAR) [21]

Results

Forecast and station data during the study period (22–25 April 2012)

The Chemical Weather Forecast System (CFORS) predicted the arrival of an Asian dust cloud in Kyoto at noon on 23 April (Fig. 3) [21, 22], and LIDAR in Osaka measured high concentrations of soil dust during the same period (Fig. 4) [17, 18].

SPM measured by the Atmospheric Environmental Regional Observation System at a local site in Kyoto, 5 km from the apartment, increased from the afternoon of 23 April until the morning of 26 April (Fig. 2).

Notably, CFORS predicted increased sulfate in the air during the same period (Fig. 5) [21], and an increase in the spherical particulate matter was observed by LIDAR

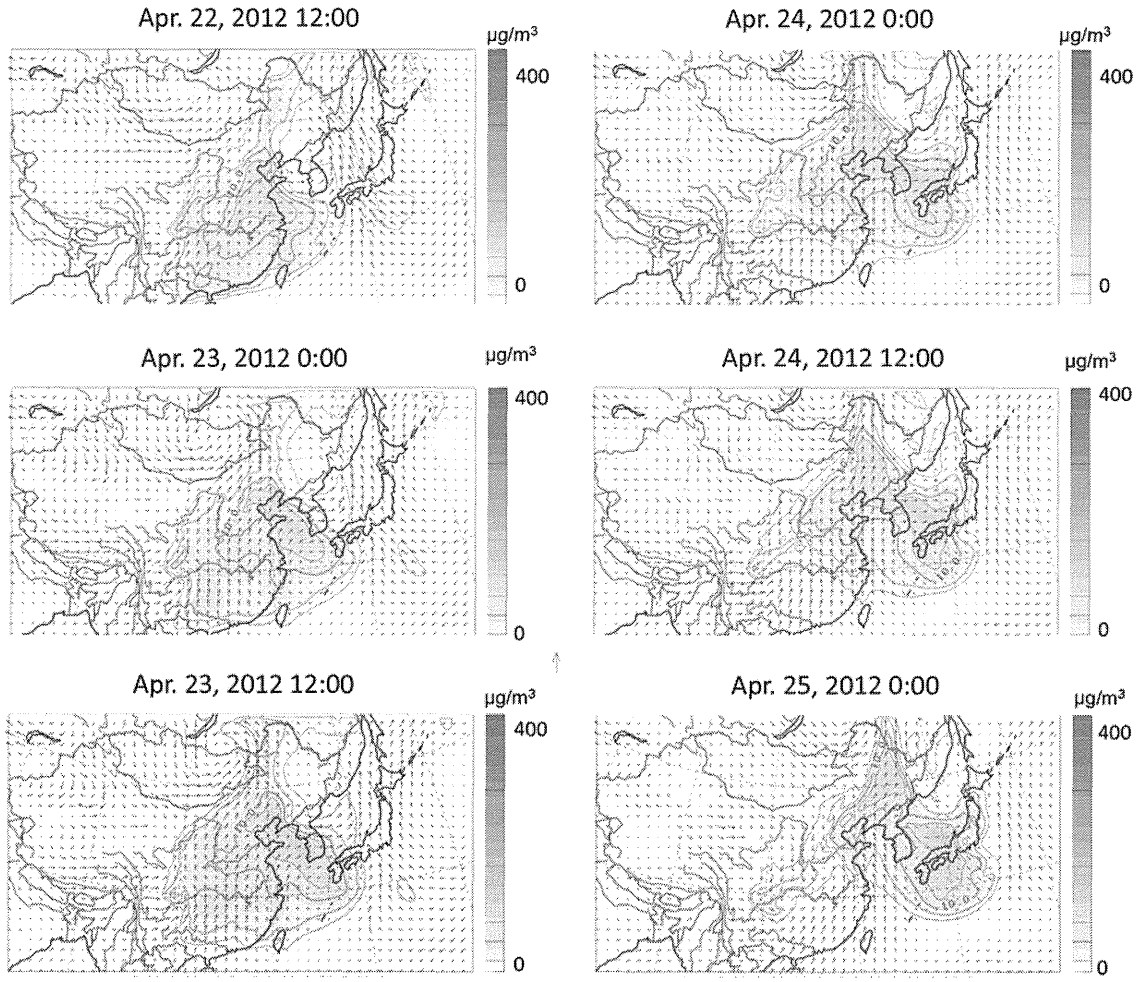

Fig. 5 Sulfate distribution prediction by the Chemical Weather Forecast System [17]

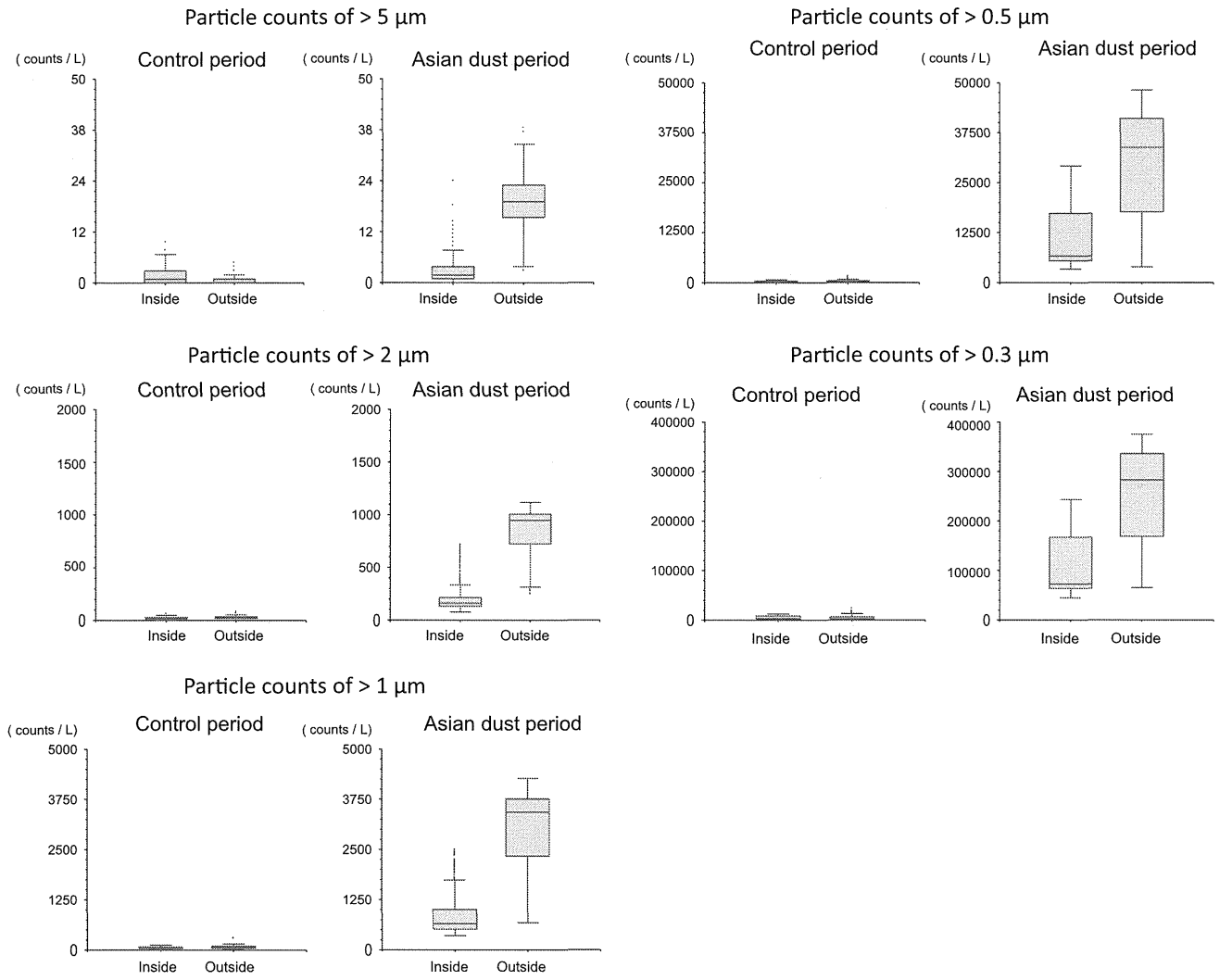

Fig. 6 Comparison of particle counts/L inside and outside during control (*left*) and Asian dust (*right*) periods

during this Asian dust event (Fig. 4) [17], which was considered to be trans-boundary air pollution flying simultaneously with Asian dust.

Indoor and outdoor PM counts (/L) before and during dust storms

Figure 6 shows indoor and outdoor air PM counts (/L) before and during a dust storm with closed windows, without air-conditioner use in the monitored room, and without cooking throughout the study period. A room door was opened twice during each period and the apartment door was opened twice for short periods of time (several seconds) during each period. Before the dust storm, the PM (particles > 0.3 μm) counts were very low both indoors and outdoors (indoors: mean 5186/L, range 921–12 670/L; outdoors: mean 4779/L, range 1154–23 637/L). During the dust storm, the indoor PM (particles > 0.3 μm) counts increased approximately 20-fold, while the outdoor PM counts increased approximately 50-fold (indoors: mean 115 340/L, range 44 737–243 399/L; outdoors: mean 250 867/L, range 65 152–375 367/L; Fig. 6). Indoors, smaller PM levels seemed to be more influenced by outdoor PM levels than larger PM levels (Fig. 6).

Factors that affect indoor PM counts

Figure 7 shows the time course of PM counts through the experiments. Opening a window (20 cm) for 10 min resulted in a rapid increase in PM counts up to 70 % of outdoor levels. Smaller PM sizes remained longer in room air, as high as 50 % of outdoor levels for PM greater than 0.5 and 0.3 μm even after 3 h. A researcher's crawling caused an increase in counts of PM larger than 1 μm. An air purifier (non-HEPA filter, 3 m^3/min airflow) reduced PM counts for all sizes in 30 min. With the air purifier on, window opening (20 cm) for 10 min still caused elevation of PM counts up to 50 % of outdoor levels, but counts for all sizes rapidly returned to baseline levels after closing the window.

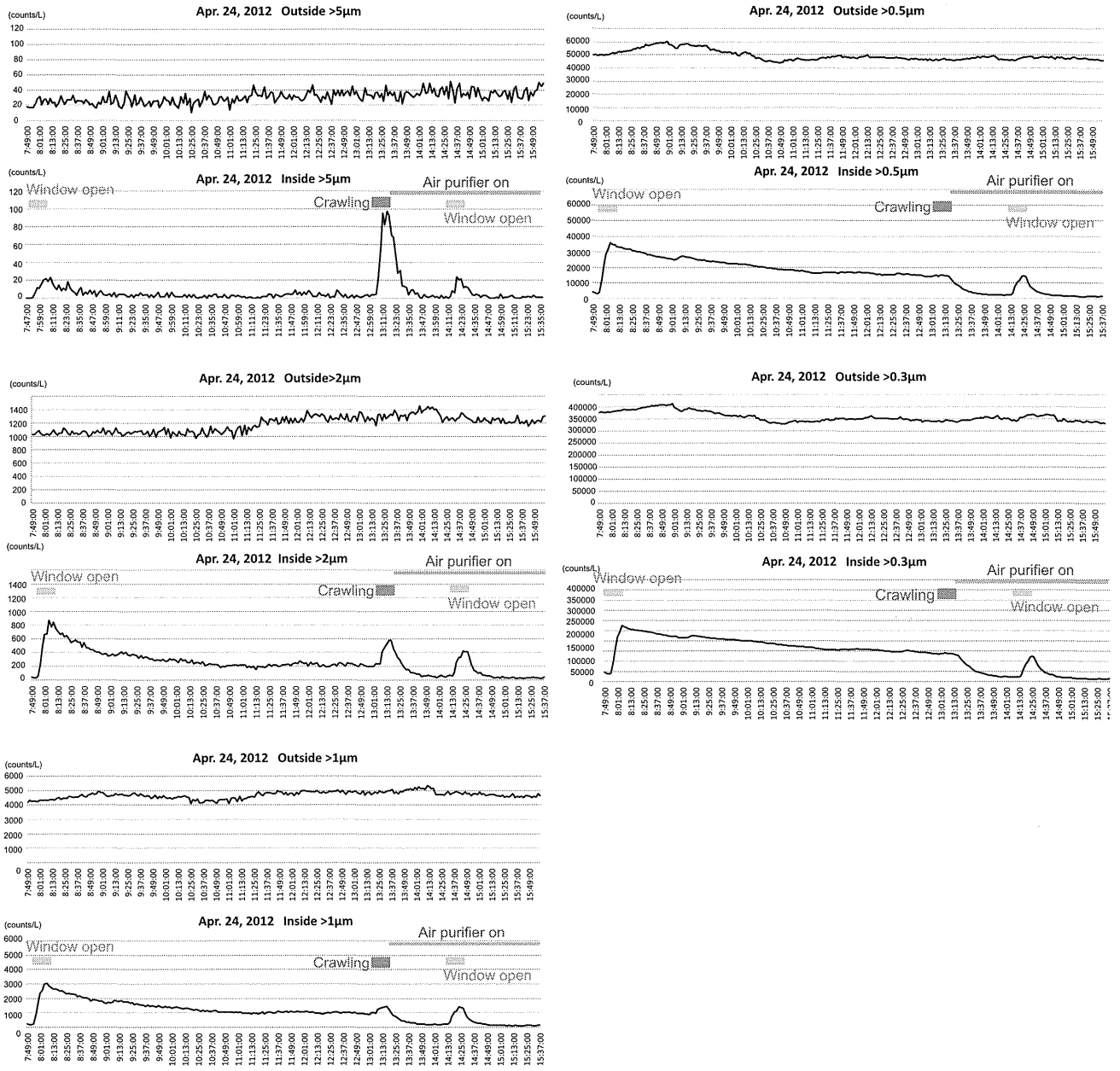

Fig. 7 PM counts/L in outdoor (*upper*) and indoor (*lower*) air under various conditions

Discussion

This study measured indoor and outdoor particle counts during an Asian dust event under everyday conditions. An Asian dust event on 24 April 2012 caused a 50-fold increase in PM counts outdoors and a 20-fold increase indoors in an apartment room in Japan. As far as we know, there is one report regarding PM changes in indoor air during Asian dust events at an office building in Taipei [23]. This report showed that indoor PM2.5 and PM10 increased threefold during the dust storm while outdoor PM2.5 and PM10 increased 1.7-fold. The ventilation systems in this high-rise building utilize air from outside, and the authors concluded that this was likely the primary reason that air particle concentrations inside the building were significantly affected by outside air pollutants during dust storms. The ventilation system in our apartment was used once for 20 min, 2 h before observation began. We speculate that, in addition to this ventilation, the occupants opening doors and their movements into and out of the rooms were the main routes for PMs entering the monitored room.

The PM increase observed in this study was larger than in the Taipei study. One explanation for this is that

the baseline count was very low in our study (mean SPM during the control period was 1.7 μg/m^3, range 0–5 μg/m^3) compared to the control period in Taipei (PM2.5 and PM10 were 45 and 70 μg/m^3, respectively). Second, in this study, air pollution other than desert dust was also observed during the Asian dust period; CFORS predicted sulfate aerosol arrival in our Asian dust period and LIDAR observed spherical as well as non-spherical particulate matter during this time period. Accordingly, the observed PM count increase is considered to be a mixture of desert dust and other air pollution. Finally, this study and the Taipei study may have also differed in the original scale of the Asian dust storms observed.

An open window (20 cm) for 10 min resulted in a rapid increase of indoor PM counts up to 70 % of outside levels, which was maintained for 3 h after closing the window. An air purifier rapidly reduced the PM counts for all particle sizes larger than 0.3 μm.

Previous reports have often noted that air change rates in occupied houses are highest when weather conditions are mild, and several investigators have speculated that this is due to increased window-opening behavior under mild conditions. Iwashita and Akasaka measured ventilation rates using gas tracers and questionnaire surveys assessing indoor environment and residents' behavior, and concluded that 87 % of the total air change rate was due to occupant behavior [24]. United States researchers quantitatively confirmed that having a single window open can increase air change rates [25].

This study's PM observations indoors and outdoors during an Asian dust event are consistent with the previous reports above and suggest the importance of accounting for occupant behavior, such as window-opening and air purifier use, when estimating residential exposure to particulate matter.

In conclusion, Asian Dust arrival caused a 50-fold increase in PM counts outdoors and a 20-fold increase indoors under everyday conditions on 24 April 2012, in Kyoto, Japan.

A window open for 10 min resulted in a rapid increase of indoor PM counts up to 70 % of outside levels that was maintained for 3 h. An air purifier rapidly reduced PM counts for all particle sizes larger than 0.3 μm.

The results suggest it is important to account for occupant behavior, such as window-opening and air purifier use, when estimating residential exposure to particulate matter.

Acknowledgments We thank Dr. Nobuo Sugimoto for providing LIDAR data, the Kyoto City Environmental Protection Guidance Division for SPM data, Dr. Itsushi Uno for CFORS images, and Mr. Tadashi Hioki for fruitful discussion. This research was supported by the Environment Research and Technology Development Fund (C-1152) of the Ministry of the Environment, Japan.

Conflict of interest The authors declare no conflict of interest.

References

1. Griffin DW. Atmospheric movement of microorganisms in clouds of desert dust and implications for human health. Clin Microbiol Rev. 2007;20:459–77.
2. Valiante DJ, Schill DP, Rosenman KD, Socie E. Highway repair: a new silicosis threat. Am J Public Health. 2004;94:876–80.
3. Eagan TM, Gulsvik A, Eide GE, Bakke PS. Occupational airborne exposure and the incidence of respiratory symptoms and asthma. Am J Respir Crit Care Med. 2002;166:933–8.
4. Kassimi FA, Majed SA, Hajjaj MS. Silicosis in a Himalayan village population: role of environmental dust. Thorax. 1991;46:861–2.
5. Ichinose T, Yoshida S, Sadakane K, Takano H, Yanagisawa R, Inoue K, et al. Effects of Asian sand dust, Arizona sand dust, amorphous silica and aluminum oxide on allergic inflammation in the murine lung. Inhal Toxicol. 2008;20:685–94.
6. He M, Ichinose T, Yoshida S, Yamamoto S, Inoue K, Takano H, et al. Asian sand dust enhances murine lung inflammation caused by *Klebsiella pneumoniae*. Tox App Pharm. 2012;258:237–47.
7. Murphy SA, Be'rube'a KA, Pooleya FD, Richards RJ. The response of lung epithelium to well characterised fine particles. Life Sci. 1988;62:1789–99.
8. Mancino D, Vuotto ML, Minucci M. Effects of a crystalline silica on antibody production to T-dependent and T-independent antigens in Balb/c mice. Int Arch Allergy Appl Immunol. 1984;73:10–3.
9. Chen PS, Tsai FT, Lin CK, Yang CY, Chan CC, Young CY, et al. Ambient influenza and avian influenza virus during dust storm days and background days. Environ Health Perspect. 2010;118:1211–6.
10. Kobayashi F, Kodanikuchi K, Kakikawa M, Maki T, Yamada M, Tobo Y, et al. Direct samplings, separated culture, and identifications of Kosa bioaerosols over Noto Peninsula, Suzu City (Japanese). Earozoru Kenkyu. 2010;25:23–8.
11. Maki T, Susuki S, Kobayashi F, Kakikawa M, Tobo Y, Yamada M, et al. Phylogenetic analysis of atmospheric halotolerant bacterial communities at high altitude in an Asian dust (KOSA) arrival region, Suzu City. Sci Total Environ. 2010;408:4556–62.
12. Kanatani KT, Ito I, Al-Delaimy WK, Adachi Y, Mathews WC, Ramsdell JW, et al. Desert dust exposure is associated with increased risk of asthma hospitalization in children. Am J Respir Crit Care Med. 2010;182:1475–81.
13. Ueda K, Shimizu A, Nitta H, Inoue K. Long-range transported Asian Dust and emergency ambulance dispatches. Inhal Toxicol. 2012;12:858–67.
14. Chan CC, Ng HC. A case-crossover analysis of Asian dust storms and mortality in the downwind areas using 14-year data in Taipei. Sci Total Environ. 2011;410–411:47–52.
15. Cho YS, Lee JT, Jung CH, Kim YS. Relationship between particulate matter measured by optical particle counter and mortality in Seoul, Korea, during 2001. J Environ Health. 2008;71(2):37–43.
16. Lunden MM, Thatcher TL, Hering SV, Brown NJ. Use of time- and chemically resolved particulate data to characterize the infiltration of outdoor PM2.5 into a residence in the San Joaquin Valley. Eiviron. Sci Technol. 2003;37:4724–32.
17. http://soramame.taiki.go.jp/dss/kosa/en/index.html.
18. Sugimoto N, Lee CH. Characteristics of dust aerosols inferred from lidar depolarization measurements at two wavelengths. Appl Opt. 2006;45:7468–74.
19. Shimizu A, Sugimoto N, Matsui I, Arao K, Uno I, Murayama T, Kagawa N, Aoki K, Uchiyama A, Yamazaki A. Continuous

observations of Asian dust and other aerosols by polarization lidar in China and Japan during ACE-Asia. J Geophys Res. 2004;109:D19S17. doi:10.1029/2002JD003253.
20. Sugimoto N, Uno I, Nishikawa M, Shimizu A, Matsui I, Dong X, Chen Y, Quan H. Record heavy Asian dust in Beijing in 2002: observations and model analysis of recent events. Geophys Res Lett. 2002;30(12):1640. doi:10.1029/2002GL016349 2003.
21. http://www-cfors.nies.go.jp/~cfors/.
22. Uno I, Carmichael GR, Streets DG, Tang Y, Yienger JJ, Satake S, et al. Regional chemical weather forecasting system CFORS: model descriptions and analysis of surface observations at Japanese island stations during the ACE-Asia experiment. J Geophys Res. 2003;108(D23):8668.
23. Kuo H-W, Shen H-Y. Indoor and outdoor PM 2.5 and PM 10 concentrations in the air during a dust storm. Build Environ. 2010;45:610–4.
24. Iwashita G, Akasaka H. The effects of human behavior on natural ventilation rate and indoor air environment in summer—a field study in southern Japan. Energy Build. 1997;25:195–205.
25. Howard-Reed C, Wallace LA, Ott WR. The effect of opening windows on air change rates in two homes. J Air Waste Manage Assoc. 2002;52:147–59.

Allergology International. 2013;62:337-341
DOI: 10.2332/allergolint.12-OA-0519

ORIGINAL ARTICLE

Translation and Linguistic Validation of the Allergy-CONTROL-Score™ for Use in Japan

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ABSTRACT

Background: Symptom and medication scores are recommended to measure the primary outcome on allergies. The Allergy Control Score was proved to be a valid and reliable instrument to assess allergy severity in clinical trials and may be used in observational studies of respiratory allergic diseases in many countries. We translated the Allergy Control Score and adapted it for use in Japan.

Methods: We translated the original English version into Japanese according to the Mapi approach to linguistic validation: conceptual definition, forward translation by two native Japanese speakers, reconciliation, back-translation by an independent translator, review in consultation with original developer, and pilot testing on 12 patients of an allergy clinic and 3 volunteers with seasonal/non-seasonal allergic rhinitis and/or asthma.

Results: Two of the ten back-translated items needed slight modifications and some words were revised. In the pilot test, the average time required to complete the questionnaire was 55 seconds for the section on symptoms and 25 seconds for the section on medication. All participants were able to self-complete the questionnaire.

Conclusions: By applying the Mapi approach to linguistic validation, we ensured a close match between the Japanese and English versions of the Allergy Control Score. The Allergy Control Score Japanese version is accessible and acceptable to persons with respiratory allergic symptoms in Japan.

KEY WORDS

allergic rhinitis, asthma, Japanese, questionnaire

INTRODUCTION

Symptom and medication scores are recommended to measure the primary outcome of clinical trials on respiratory allergies,[1] and their use is proposed by international regulatory agencies, such as the European Medicines Agency (EMEA).[2] However, validated symptom and medication scores assessing respiratory allergy symptom are currently not available in Japan. The Allergy Control Score (ACS) was developed and has been used successfully in multiple clinical trials in Europe[3-5]; it was validated by assessing reproducibility, discrimination capacity, and feasibility in healthy controls and patients with respiratory allergies.[6] Convergent reliability analysis indicated a highly significant correlation between ACS and global allergy severity ($P < 0.0001$), quality of life ($P < 0.0001$), and allergy-related medical consultations ($P < 0.0001$). Scores were highly related to pollen counts. ACS showed a good retest reliability ($r = 0.81$; $P < 0.0001$) and discriminated well between patients with allergy and healthy controls with a sensitivity of 97% and a specificity of 87%. Study participants evaluated the feasibility as excellent. The ACS was proved to be a valid and reliable instrument to assess allergy severity in clinical trials and observational studies of

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Conflict of interest: KTK is an advisor for Bayer Health Care. BTS is employed by Eisai. DH is employed by Allergopharma. YA received lecture fees from GlaxoSmithKline and MSD. The rest of the authors have no conflict of interest.

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Received 10 November 2012. Accepted for publication 6 March 2013.

respiratory allergic diseases.

The objective of the present study was to develop a translated Japanese version of the ACS, with subsequent linguistic validation among Japanese persons with respiratory allergies.

METHODS

MAPI STANDARD LINGUISTIC VALIDATION PROCESS

The Mapi approach to cross-cultural adaptation was referenced and used in this study.[7] The Mapi Research Institute is an international research organization that engages in translating and validating health-related QOL questionnaire for cross-cultural use.[8] More than 350 instruments into over 110 languages have been translated and validated internationally there.[8] We followed their 'standard linguistic validation process', which deals with questionnaire developed in English and needed in another language and/or culture. The Mapi Institute itself was not involved in this study.

'The standard linguistic validation process' of the Mapi Research Institute is composed of the following stages:

- Conceptual definition: the developer of the ACS and the researcher managing the linguistic validation process (the consultant) reviewed all items of the questionnaire to clarify the concepts involved;
- Forward translation: the original instrument was translated into Japanese by two translators, a medical professional and a lay person, both native Japanese speakers proficient in English. The consultant re-conciliated the two translations and established a consensus version;
- Backward translation: the consensus version was back-translated into English by an independent translator who was a native speaker of English and had never seen the original version of ACS. The consultant compared the back translation and the original version and examined any discrepancies between them. These were reviewed by the developer of ACS to produce the pilot version;
- Pilot testing: the Mapi approach pilot testing comprises 2 stages that take place in parallel: cognitive debriefing, where the pilot version is tested with a small sample from the target population (5-10 subjects) to assess its relevance, clarity and intelligibility; and a clinician's review, where an expert clinician reviews and offers feedback on the pilot version.
- Proofreading: two rounds of proofreading ensured the instrument was free of typing, spelling and grammatical errors. This was done, as recommended, by the consultant and one translator.

PILOT TESTING PARTICIPANTS AND PROCEDURE

The study protocol was approved by the Kyoto University Ethics Committee Review Board. The subjects gave a written informed consent and patient anonymity were preserved using documents and methods approved by the ethical review committee.

We recruited subjects with seasonal/non-seasonal allergic rhinitis, allergic conjunctivitis, and/or asthma in Kyoto at a clinic and elementary school. Eligibility criteria included a) suffering from seasonal/non-seasonal allergic rhinitis and/or asthma, and b) not being a medical professional. A letter that included information on the project was given to each participant by their physician (at a clinic), or by the investigator (at an elementary school). Once written consent was given, each participant filled out the following:

- Background information: age, sex, and allergic disease history.
- Pilot version of ACS symptom and medication parts. ACS symptom part consisted of 10 items that covered 3 domains: nasal, eyes, and bronchial symptom. Scores range from 0 to 3 : 0 = absent (no sign/symptom evident); 1 = mild (sign/symptom clearly present, but minimal awareness; easily tolerated); 2 = moderate (definite awareness of sign/symptom that is bothersome, but tolerable); 3 = severe (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping). ACS medication part consisted of 2 items; brand name of medication, and dosage on the day.
- Eleven questions on accessibility (e.g., 'Did you find any of the items difficult to understand?'), the content validity and the acceptability of the questionnaire (e.g., 'Do you think you would score high on this questionnaire if you have severe allergic symptom?' 'How difficult was it to respond to the questionnaire?' 'Do you have any suggestions on the questionnaire?).

DATA ANALYSIS

Descriptive analyses were used to assess the quality of the translations. Time to complete and the percentage of missing data were calculated to assess how accessible and acceptable the questionnaire was to participants. We also assessed the accessibility/acceptability/validity of the questionnaire using a feasibility questionnaire given to participants post-pilot. Participants' reactions to the ACS questionnaire items were observed to assess whether they misread any of them, asked for clarification, or needed prompting to answer them. The calculation of the J-ACS was done as described in the original publication of the ACS.[6]

RESULTS

CONCEPTUAL DEFINITION

The consultant reviewed all instructions, items and

Table 1 Answers to feasibility questions

Feasibility Questions	*n*	0	1	2	3
Do you have any items difficult to understand? (0 = no, 1 = yes)	15	15	0	0	0
Do you have any items difficult to answer? (0 = no, 1 = yes)	15	12	3		
Do you think the items are easy to answer overall? (0 = yes, 1 = no)	15	15	0		
How strenuous was it to respond to the questionnaire? (0 = not at all, 4 = very much)	15	13	2	0	0
How unpleasant was it to answer to the questions? (0 = not at all, 4 = very much)	15	15	0	0	0
Do you think you will have higher score at the questionnaire on the day you have severe allergic symptom? (0 = yes, 1 = no)	15	14	1		
I appraised the content of the questionnaire altogether: (0 = very easy, 4 = very difficult)	15	15	0	0	0
How much did you have to think to answer the single questions? (0 = very little, 1 = little, 2 = some, 3 = much)	15	4	10	1	0
How comprehensible is the instruction on filling out questionnaire? (0 = very easy, 4 = very difficult)	15	13	2	0	0
How comprehensible is the instruction on the application of medication? (0 = very easy, 4 = very difficult)	15	9	6	0	0
Do you have any suggestions to the questionnaire? (0 = no, 1 = yes)	15	15	0		

response choices of the ACS with the developer of the instrument to ensure conceptual clarity.

TRANSLATIONS

The original ACS was translated into Japanese by two native Japanese-speakers. The consensus version of these two translations was then back-translated into English. The back-translated version was compared with the original ACS. The items used in the questionnaire were easily translated, and our results were promising: Eight of the 10 back-translated items were identical to the consensus version and another 2 slightly differed ('watering' to 'tears' and 'itching' to 'ticklishness'). Accordingly, in consensus with original developer, we re-transferred the two, which were then back-translated essentially identical to the original version but with slightly different in wording; 'teary eyes' and 'itchiness (feeling itch)'. Six of the 7 direction sentences were essentially identical in meaning but slightly different in wording. One direction sentence was slightly modified, but the difference was due to the back-translator's error.

PILOT TEST

Clinician's Review

The clinician reviewed the translated ACS and confirmed that the translated version of ACS was appropriate for Japanese patients with respiratory allergies. However, the clinician proposed giving more examples in instruction to make the questionnaire more user-friendly. In fact, the pilot testing revealed that the instructions regarding items related to medications were not very easily comprehensible (Table 1). In consensus with the original developer, we added more examples to the instructions (Supplementary Fig. 1).

Cognitive Debriefing

We administered the first version of J-ACS that included translated items with no diary-styled items to 9 subjects. We then administered the second version of J-ACS that included the diary style to 6 subjects.

Participants' characteristics—Fifteen subjects with seasonal/non-seasonal allergic rhinitis, and/or asthma were recruited from an allergy clinic and from parents at an elementary school in Kyoto. Participants comprised 2 men and 13 women, with an age range of 16-60 years (mean 41 years, median 40 years). All participants had allergic rhinitis, eight (53%) of which were seasonal, three (20%) with allergic conjunctivitis, and two (13%) with asthma. All subjects completed the questionnaire only once, observed by the investigator at the clinic or at the school. The one-day part of the diary-styled questionnaire was completed within 3 minutes (range: 40-123 seconds, mean 80 seconds; 55 seconds for symptom part and 25 seconds for medication part).

Accessibility and acceptability of the ACS—All subjects were able to self-complete the questionnaire. They all found the questionnaire easy to answer overall and all replied that no items were difficult to understand. Two participants commented that the questionnaire was "slightly strenuous" while the other 13 participants chose "not strenuous at all". Three participants chose that they felt one item was difficult to answer; one felt it was slightly difficult in judging if a symptom was tolerable; another pointed out that he could not judge if he should take into account his cold symptom (sneeze). Because the second version of ACS included a field to comment in that allowed the users to describe their irrelevant symptoms (i.e., cold), we believe the second version of the J-ACS resolves all of the above concerns.

In addition to the above, one participant did not remember her medication name used on that day, but commented that she would have noted the medication if she knew that she was going to be asked. Again another participant did not specify her medication but commented that she could fill in the part once she returned home. The problem of forgetting the name of one's medication could be resolved if the participant was made aware of the need to know this

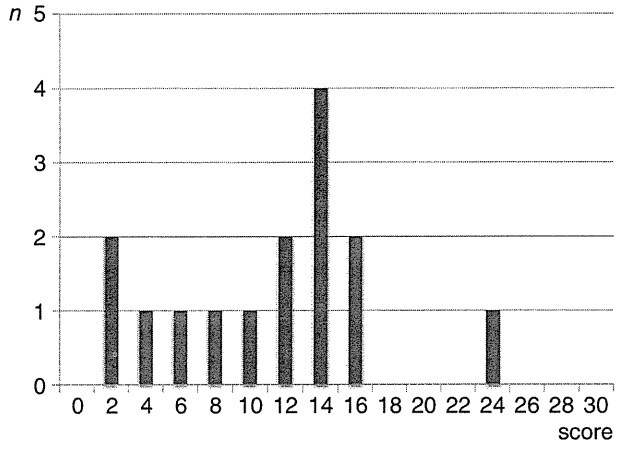

Fig. 1 Distribution of J-ACS scores.

information prior to filling out the questionnaire.

Content validity—No items needed specific clarification. All but one subject commented that it was easy to describe changes in severity of their allergic symptom if the questionnaire once administered daily. One patient with severe seasonal allergic rhinitis commented that she suffered intolerable allergic symptoms daily during the spring, and some of her symptom scores were fixed at 3 during the season, suggesting a ceiling effect. However, once she was explained that ACS uses the total score of all symptoms and medications used on the day, she agreed that her score accurately reflected her symptom severity on the day. Her clinician commented that she suffered from severe seasonal allergic rhinitis, and that her case was an outlier. In fact, the scores of the questionnaire were well distributed across response categories, and this patient had the highest score of all the participants (Fig. 1).

DISCUSSION

This study linguistically validated the Allergy Control Score for use with Japanese people with respiratory allergic symptoms. The Mapi Institute guidelines was referenced and used. Two native Japanese-speakers, a medical professional and a layperson, translated the instrument into Japanese. An independent translator back-translated the consensus version of these two translations into English to check equivalence with the original ACS. We tested the pilot version of the Japanese ACS on 15 subjects with respiratory allergic symptom to evaluate its accessibility, acceptability and content validity. Fifteen subjects recruited to the study, all agreed to take part and all were eligible, making the overall response rate (100%). The accessibility of the J-ACS to subjects with respiratory allergic symptoms is supported by the fact that all respondents were able to complete the questionnaire within 3 minutes. The responses were well distributed across response categories (Fig. 1), suggesting the questionnaire items would discriminate well between respondents. Although an extremely severe patient pointed out a ceiling effect in the symptom score, she later recognized that her medication score would be added to the total score and that the J-ACS can discriminate everyday changes in symptoms among severe patients. Initial support for content validity for this questionnaire was supported by the fact that no one requested to add information to the questionnaire.

A limitation of this pilot study is its small sample of participants. Although we followed the sample size suggested by the Mapi guidelines (n = 5-10), we did not carry out quality controls of data that require large samples sizes, such as estimating Cronbach's alpha. Further validation is needed for use in clinical research aimed to evaluate symptoms of allergic diseases in Japan.

In Japan, nearly 40% of the population is reported to have allergic rhinitis.[9] Some patients do not regularly consult a physician even though aware of their allergic symptoms. We included such patients in cognitive debriefing, and we did not observe any specific problems in answering the questionnaire. We believe our results can be generalized not only to patients at clinics but also to those with respiratory allergic symptoms who do not regularly consult a physician.

Using the Mapi approach to linguistic validation, this study ensured a close match between the original and Japanese ACS. The Japanese ACS is accessible and acceptable to persons with respiratory allergic symptom in Japan.

ACKNOWLEDGEMENTS

We thank Ms Akiko Tsuchida of Academic Research Communications for her help in formatting the questionnaire. This work was partly supported by the Environment Research and Technology Development Fund (C-1152) of the Ministry of the Environment, Japan.

SUPPLEMENTARY MATERIALS

Supplementary Figure 1 is available online.

REFERENCES

1. Canonica GW, Baena-Cagnani CE, Bousquet J *et al.* Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;**62**:317-24.
2. European Medicine Agency. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. London, 20 November 2008. Doc. Ref. CHMP/EWP/18504/2006. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf.
3. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A; Study Group. Efficacy and safety of preseasonal-

specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005;**60**:801-7.
4. Pfaar O, Klimek L. Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2008;**100**:256-63.
5. Klimek L, Mewes T, Wolf H, Hansen I, Schnitker J, Mann WJ. The effects of short term immunotherapy using molecular standardized grass and rye allergens compared with symptomatic drug treatment on rhinoconjunctivitis symptoms, skin sensitivity, and specific nasal reactivity. *Otolaryngol Head Neck Surg* 2005;**133**:538-43.
6. Häfner D, Reich K, Matricardi PM, Meyer H, Kettner J, Narkus A. Prospective validation of 'Allergy-Control-SCORE™': a novel symptom-medication score for clinical trials. *Allergy* 2011;**66**:629-36.
7. Acquadro C, Conray K, Giroudet C, Mear I. *Linguistic Validation Manual for Patient-Reported Outcomes (PRO) Instruments.* Lyon: Mapi Research Institute, 2004.
8. Kartsona A, Hilari K. Quality of life in aphasia: Greek adaptation of the stroke and aphasia quality of life scale-39 items (SAQOL-39). *Eura Medicophys* 2007;**43**:27-35.
9. Okubo K, Kurono Y, Fujieda S *et al.* Japanese guideline for allergic rhinitis. *Allergol Int* 2011;**60**:171-89.

Rhinitis has an association with asthma in school children

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ABSTRACT

Background: *A relevant relationship exists between the upper and lower airway, indicating the concept of a unified airway. This study aimed to evaluate whether rhinitis has an association with asthma in children.*

Methods: *A cross-sectional nationwide survey was performed among children 6–7, 13–14, and 16–17 years old, using the International Study of Asthma and Allergies in Children (ISAAC) questionnaire in Japan. According to the responses to the ISAAC core questions, a child who had experienced nasal symptoms in the past 12 months in the absence of a cold was defined as having current rhinitis.*

Results: *After excluding 11,475 children because of incomplete data, 136,506 children were analyzed. Even after adjusting for demographics, sex, and obesity, children with current rhinitis were more likely to have asthma (adjusted odds ratio [OR], 3.10 [95% CI, 2.92–3.30] in children aged 6–7 years; OR, 3.76 [95% CI, 3.45–4.10] in children aged 13–14 years; and OR, 3.59 [95% CI, 3.33–3.88] in children aged 16–17 years). Children whose daily activities were more impaired by rhinitis symptoms had a significantly higher prevalence of severe asthma. The adjusted ORs for severe asthma among asthmatic children whose daily activities were severely impaired by rhinitis symptoms were 3.66 (95% CI, 2.29–5.85) in children aged 6–7 years, 2.55 (95% CI, 1.64–3.96) in children aged 13–14 years, and 1.87 (95% CI, 1.24–2.82) in children aged 16–17 years compared with asthmatic children whose daily activities were not impaired at all.*

Conclusion: *There was a close association between rhinitis and asthma in young children to adolescents. Asthma should be examined in children with rhinitis symptoms.*

(Am J Rhinol Allergy 27, e22–e25, 2013; doi: 10.2500/ajra.2013.27.3846)

A close association between allergic rhinitis and asthma has been established.[1,2] There are many similarities in the pathogenesis of both disorders.[3–5] For example, Th2 cells and allergic inflammatory cells, such as eosinophils and mast cells, infiltrate the nasal mucosa of subjects with allergic rhinitis and the bronchial mucosa of subjects with asthma. A nasal allergen challenge leads to the increased responsiveness of the lower airways in asthmatic subjects comorbid with allergic rhinitis.[6] Similarly, bronchial allergen challenge leads to the nasal inflammation in nonasthmatic allergic rhinitis patients.[7]

In adults, it has been shown that allergic rhinitis has a major impact on asthma morbidity and that treatment of rhinitis helps to improve asthma control. A *post hoc* analysis of data from a clinical trial showed that the presence of comorbid allergic rhinitis in adult patients with asthma resulted in a higher rate of asthma attacks and more emergency department visits compared with patients with asthma alone.[8] A nationwide study of Japanese adults patients with asthma showed that >60% of patients had rhinitis and that asthma control was significantly impaired in patients with rhinitis compared with patients without rhinitis.[9] It has also been reported that treating allergic rhinitis in patients with comorbid asthma significantly lowered the risk of asthma-related emergency department visits and hospitalizations.[10] In children, a recent cross-sectional survey in 203 children with asthma showed that the presence of rhinitis was associated with poor asthma control.[11] However, there have been no large population-based surveys regarding association between rhinitis and asthma in children.

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Presented in part at the 68th annual meeting of American Academy of Allergy, Asthma. and Immunology, Orlando, Florida, 2012

Funded by the Japanese Ministry of Health, Labor and Welfare

The authors have no conflicts of interest to declare pertaining to this article

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To evaluate whether rhinitis has an association with asthma in children, we analyzed the data of a cross-sectional population-based nationwide survey that was performed using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. The effect of the severity of rhinitis on the prevalence of asthma was also evaluated.

METHODS

Study Population

This study was a cross-sectional and questionnaire-based survey performed in 6- to 7-, 13- to 14-, and 16- to 17-year-old school children in Japan from April through July 2008. To perform a nationwide survey, schools were randomly selected from all of the prefectures. The total number of children recruited was 179,218, corresponding to ~2% of the pediatric population, according to the data of the National Institute of Population and Social Security Research. This study protocol was approved by the Institutional Review Board of the National Center for Child Health and Development.

Questionnaire

The survey used a Japanese version of the ISAAC questionnaire,[12] which was distributed among teachers of the participating schools. The questionnaires for children 6–7 years old were completed by their parents, and those for older children were answered by the children. The questionnaire also included questions regarding the living area, gender, height, and weight of the participants.

Current rhinitis was defined as a positive answer to the question, "In the past 12 months, have you (or your child) had a problem with sneezing, or a runny, or a blocked nose when you (or he/she) did not have a cold or the flu?" The severity of rhinitis was graded according to the answer to the question, "In the past 12 months, how much did this nose problem interfere with your (or your child's) daily activity"; not at all, a little, a moderate amount, or a lot. Current asthma was defined as answering positively to the question, "In the past 12 months, have you (or your child) had wheezing or whistling in the chest during the past 12 months?" Among children with current asthma, the severity of asthma was estimated with a combination of

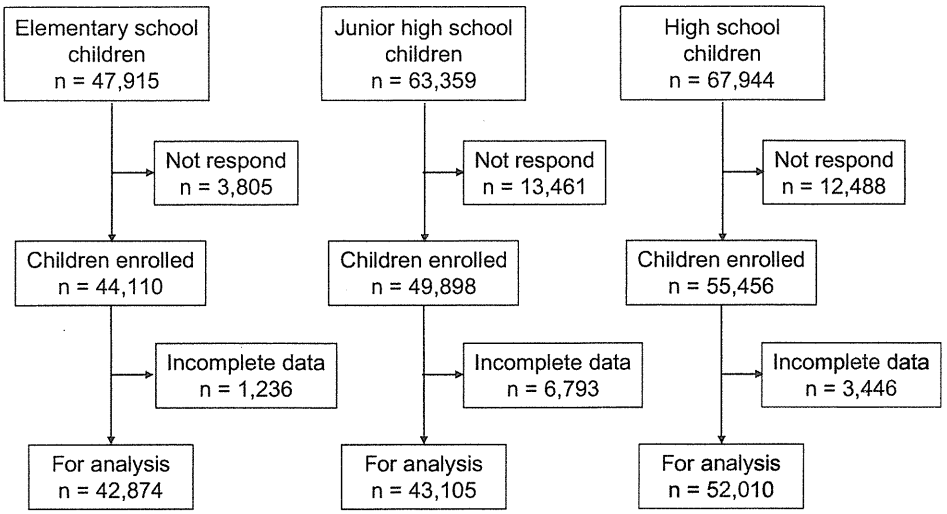

Figure 1. Participants in the cross-sectional and questionnaire-based survey.

three questions assessing the severity of asthma: "How many attacks of wheeze have you (or your child) had during the last 12 months? (none, 1 to 3, 4 to 12, or more than 12)"; "In the last 12 months, how often, on average, has your (or your child's) sleep been disturbed due to wheezing? (never, less than one night per week, or one or more nights per week)"; and "In the last 12 months, has wheezing been severe enough to limit your (or your child's) speech to only one or two words at a time between breaths?" Current severe asthma was defined as four or more asthma attacks, when sleep was disturbed for one or more nights per week, or when there had been an episode of speech limitation in the past 12 months.

Statistical Analyses

The χ^2-test was used to compare the differences in the prevalence of current symptoms between groups. A logistic regression analysis was performed to estimate the effects of rhinitis and other confounding factors, such as living area, gender, and obesity, on asthma prevalence. Multivariate analysis was used to evaluate the association of degree of impairment of daily activities caused by nasal symptoms with prevalence of current asthma and current severe asthma. A value of $p < 0.05$ was considered to be statistically significant. All of the analyses were performed using the statistical package SPSS for Windows, Version 17.0J (SPSS, Inc., Chicago, IL) and R Version 2.13.1 (available online).

RESULTS

Of the 179,218 children, 149,464 replied to the questionnaire (response rate, 92.1% in children aged 6–7 years; 78.8% in children aged 13–14 years; 81.6% in children aged 16–17 years). After excluding incomplete data, 139,506 questionnaires were analyzed (Fig. 1). Current rhinitis was found in 44.2–60.1% of the children (Table 1). In children aged 6–7 years, the prevalence of current rhinitis was lower and the prevalence of current asthma was higher than in older children. Significantly more boys had current rhinitis and asthma compared with girls in children aged 6–7 years, whereas these gender differences were not statistically significant in older age groups.

There was a higher incidence of asthma in children with current rhinitis compared with children without rhinitis (20.8% versus 7.7% in children aged 6–7 years, 13.5% versus 4.0% in children aged 13–14 years, 12.4% versus 3.8% in children aged 16–17 years; Table 2). Even after adjusting for living area, gender, and obesity, which are known to have effects on the prevalence of asthma,[13] rhinitis was still associated with asthma (adjusted odds ratio [OR], 3.10 [95% CI, 2.92–3.30] in children aged 6–7 years; OR, 3.76 [95% CI, 3.45–4.10] in children aged 13–14 years; and OR, 3.59 [95% CI, 3.33–3.88] in children aged 16–17 years). Among asthmatic children, severe asthma was also more prevalent in children with current rhinitis than in children with no rhinitis (10.9% versus 6.1% in children aged 6–7 years, 15.6% versus 9.5% in children aged 13–14 years, 15.0% versus 10.1% in children aged 16–17 years; Table 2). Again, even after adjusting for confounding factors, having rhinitis was still a significant risk factor for having severe asthma (adjusted OR, 1.94 [95% CI, 1.55–2.44] in children aged 6–7 years; OR, 1.70 [95% CI, 1.29–2.24] in children aged 13–14 years; and OR, 1.54 [95% CI, 1.22–1.95] in children aged 16–17 years).

More than 80% of the children with current rhinitis answered that their daily activity was impaired by rhinitis symptoms (data not shown). Children whose daily activities were more impaired by rhinitis symptoms had a significantly higher prevalence of current asthma even after adjusting for confounding factors (Table 3). The adjusted ORs for asthma among children whose daily activities were impaired a lot were 1.75 (95% CI, 1.50–2.04) in children aged 6–7 years, 2.54 (95% CI, 2.20–2.94) in children aged 13–14 years, and 2.21 (95% CI, 1.91) in children aged 16–17 years compared with children whose daily activities were not impaired at all. Furthermore, among asthmatic children, a higher degree of impairment of daily activities caused by rhinitis symptoms was associated with increased severity of asthma after adjusting for confounding factors (Table 3). The adjusted ORs for severe asthma among asthmatic children whose daily activities were impaired a lot were 3.66 (95% CI, 2.29–5.85) in children aged 6–7 years, 2.55 (95% CI, 1.64–3.96) in children aged 13–14 years, and 1.87 (95% CI, 1.24–2.82) in children aged 16–17 years compared with children whose daily activities were not impaired at all.

DISCUSSION

Many studies have indicated that allergic rhinitis and asthma are common comorbidities in children.[14–16] However, only a few epidemiological population-based surveys have evaluated this association in young children to adolescents. In this large population-based nationwide survey evaluating >100,000 children aged 6–7, 13–14, and 16–17 years, we reconfirmed a close association between rhinitis and asthma in Japanese school children. Even after adjusting for confounding factors affecting the prevalence of asthma, having rhinitis was a significant risk factor for having current asthma and severe asthma. Furthermore, among asthmatic children, a greater degree of impairment of daily activities caused by rhinitis symptoms was associated with higher prevalence of severe asthma.

Asthma and allergic rhinitis have similar pathophysiological manifestations; therefore, they are considered to be a single syndrome: chronic allergic respiratory syndrome.[3,4] Supporting this concept, the

Table 1 **Baseline characteristics of the study participants**

	Total	Boys	Girls	*p* Value*
Children aged 6–7 yr	42,874	21,861	21,013	
Current rhinitis	18,930 (44.2)	10,592 (48.5)	8338 (39.7)	<0.001
Current asthma	5798 (13.5)	3435 (15.7)	2363 (11.2)	<0.001
Current severe asthma	542 (1.3)	332 (1.5)	210 (1.0)	<0.001
Children aged 13–14 yr	43,105	21,080	22,025	
Current rhinitis	25,891 (60.1)	12,668 (60.1)	13,223 (60.0)	0.906
Current asthma	4195 (9.7)	2098 (10.0)	2097 (9.5)	0.135
Current severe asthma	613 (1.4)	297 (1.4)	316 (1.4)	0.839
Children aged 16–17 yr	52,010	26,815	25,195	
Current rhinitis	27,148 (52.2)	14,222 (53.0)	12,926 (51.3)	<0.001
Current asthma	4311 (8.3)	2264 (8.4)	2047 (8.1)	0.192
Current severe asthma	598 (1.1)	307 (1.1)	291 (1.2)	0.935

Data represent number (percentage).
χ^2-analysis for evaluating gender differences.

Table 2 **Association of current rhinitis with asthma**

	All Children			Children with Current Asthma		
	Prevalence of Asthma (%)	AOR*	95% CI	Prevalence of Severe Asthma (%)	AOR*	95% CI
Children aged 6–7 yr						
No rhinitis#	7.7	1		6.1	1	
Current rhinitis	20.8	3.10	2.92–3.30	10.9	1.94	1.55–2.44
Children aged 13–14 yr						
No rhinitis#	4.0	1		9.5	1	
Current rhinitis	13.5	3.76	3.45–4.10	15.6	1.70	1.29–2.24
Children aged 16–17 yr						
No rhinitis#	3.8	1		10.1	1	
Current rhinitis	12.4	3.59	3.33–3.88	15.0	1.54	1.22–1.95

**Adjusted for living area, sex, and obesity.*
#Reference group in regression.
AOR = adjusted odds ratio.

Table 3 **Association of the impairment of daily activities due to rhinitis symptoms with asthma**

	Children with Current Rhinitis			Children with Current Rhinitis and Asthma		
	Prevalence of Asthma (%)	AOR*	95% CI	Prevalence of Severe Asthma (%)	AOR*	95% CI
Children aged 6–7 yr						
Not at all#	17.2	1		5.7	1	
A little	20.2	1.23	1.10–1.37	10.0	1.73	1.13–2.65
Moderate	22.8	1.44	1.27–1.64	12.3	2.31	1.48–3.60
A lot	26.7	1.75	1.50–2.04	18.0	3.66	2.29–5.85
Children aged 13–14 yr						
Not at all#	8.4	1		9.4	1	
A little	12.4	1.57	1.37–1.80	13.2	1.47	0.95–2.27
Moderate	15.0	1.96	1.71–2.26	16.4	1.88	1.21–2.91
A lot	18.5	2.54	2.20–2.94	21.1	2.55	1.64–3.96
Children aged 16–17 yr						
Not at all#	8.4	1		12.8	1	
A little	11.2	1.41	1.23–1.62	12.8	1.10	0.73–1.65
Moderate	13.3	1.70	1.48–1.96	14.4	1.26	0.84–1.91
A lot	16.5	2.21	1.91–2.60	19.8	1.87	1.24–2.82

**Adjusted for living area, sex, and obesity.*
#Reference group in regression.
AOR = adjusted odds ratio.

degree of nasal eosinophil infiltration is inversely correlated with spirometry parameters and bronchial hyperreactivity in allergic rhinitis patients without asthma.[17] In this study, a child who had experienced nasal symptoms in the past 12 months in the absence of a cold was defined as having current rhinitis. It has been reported that rhinitis with itchy–watery eyes (rhinoconjunctivitis) is the symptom combination most closely relating to objective indicators of allergic sensitization in European children.[18,19] Therefore, some children with

current rhinitis might be nonallergic, although we did not evaluate allergic sensitization. Recently, it has been shown that asthma is associated with not only allergic rhinitis, but also nonallergic rhinitis.[20] A birth cohort study conducted in Denmark showed that asthma coexisted equally in 7-year-old children with allergic and nonallergic rhinitis.[21] In the same cohort, Chawes *et al.* indicated that in 6-year-old children, there was an association between upper and lower airway patency, which was measured with acoustic rhinometry and spirometry, respectively, and that this association was independent of allergic sensitization.[22] It has been suggested that neuronal mechanisms, T cells, and innate immunity may play a role in nonallergic rhinitis and contribute to asthma symptoms.[20] Additional studies will be needed to understand the mechanisms of a link between the upper and lower airway beyond allergy-driven mechanisms.

In >80% of children with rhinitis, their daily activities were impaired. Children whose daily activities were more impaired by nasal symptoms had a significantly higher prevalence of current asthma in children with rhinitis. Furthermore, among asthmatic children, a higher degree of impairment of daily activities because of rhinitis symptoms was associated with increased severity of asthma. Consistent with our data, a cross-sectional study of 3225 patients with allergic rhinitis aged 10–50 years revealed that the severity of allergic rhinitis influenced the development of asthma.[23] The treatment of allergic rhinitis helps to improve the control of asthma. A nested case–control study of patients with both allergic rhinitis and asthma aged ≥6 years old revealed that treatment with either nasal corticosteroids or oral antihistamines was associated with a significant reduction in the risk of asthma-related emergency room visits and hospitalizations.[24] These results suggest that rhinitis should be examined in patients with asthma and that rhinitis could be a marker of the poor control of asthma.

One of the limitations of our study is that the cross-sectional study does not allow for the determination of whether rhinitis precedes the development of asthma or *vice versa*. A prospective cohort study in which 1314 healthy children had been followed from birth to 13 years old showed that allergic rhinitis until the age of 5 years was a predictor for developing wheezing between the ages of 5 and 13 years old, but nonallergic rhinitis was not a risk factor for future wheezing onset.[25] Additional studies will be needed to evaluate the role of atopy in the development of asthma in children with rhinitis. Another limitation of this study was that we failed to account for several important confounding factors, such as parental tobacco smoking, socioeconomic status, medications for rhinitis and asthma, and atopic status. These factors might affect the association between rhinitis and asthma. Additional limitation is that self-reported questionnaires have a tendency toward overdiagnosis, although the ISAAC questionnaire has been widely used in many epidemiological studies. This might explain rather higher prevalence of asthma and rhinitis in our population.

In conclusion, there was a close association between rhinitis and asthma in young children to adolescents. As recommended by the Allergic Rhinitis and its Impact on Asthma,[26] asthma should be examined in children with rhinitis symptoms. Additional studies will be needed to understand the mechanisms underlying the association between the upper and lower airway.

ACKNOWLEDGMENTS

The authors thank the children and their parents who participated in this survey. They also thank Dr. Kumiko Kanatani from the Department of Health Informatics, Kyoto University School of Public Health, for consultation regarding statistical analysis.

REFERENCES

1. Marseglia GL, Merli P, Caimmi D, et al. Nasal disease and asthma. Int J Immunopathol Pharmacol 24:7–12, 2011.
2. Feng CH, Miller MD, and Simon RA. The united allergic airway: Connections between allergic rhinitis, asthma, and chronic sinusitis. Am J Rhinol Allergy 26:187–190, 2012.
3. Togias A. Rhinitis and asthma: Evidence for respiratory system integration. J Allergy Clin Immunol 111:1171–1183, 2003.
4. Marple BF. Allergic rhinitis and inflammatory airway disease: Interactions within the unified airspace. Am J Rhinol Allergy 24:249–254, 2010.
5. Suh DI, Lee JK, Kim JT, et al. Bronchial hyperresponsiveness in preschool children with allergic rhinitis. Am J Rhinol Allergy 25: e186–e190, 2011.
6. Corren J, Adinoff AD, and Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. J Allergy Clin Immunol 89:611–618, 1992.
7. Braunstahl GJ, Kleinjan A, Overbeek SE, et al. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. Am J Respir Crit Care Med 161:2051–2057, 2000.
8. Bousquet J, Gaugris S, Kocevar VS, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: A subgroup analysis of the investigation of montelukast as a partner agent for complementary therapy. Clin Exp Allergy 35:723–727, 2005.
9. Ohta K, Bousquet PJ, Aizawa H, et al. Prevalence and impact of rhinitis in asthma. SACRA, a cross-sectional nation-wide study in Japan. Allergy 66:1287–1295, 2011.
10. Crystal-Peters J, Neslusan C, Crown WH, et al. Treating allergic rhinitis in patients with comorbid asthma: The risk of asthma-related hospitalizations and emergency department visits. J Allergy Clin Immunol 109:57–62, 2002.
11. de Groot EP, Nijkamp A, Duiverman EJ, and Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. Thorax 67:582–587, 2012.
12. Kojima N, Ohya Y, Futamura M, et al. Exercise-induced asthma is associated with impaired quality of life among children with asthma in Japan. Allergol Int 58:187–192, 2009.
13. Okabe Y, Itazawa T, Adachi Y, et al. Association of overweight with asthma symptoms in Japanese school children. Pediatr Int 53:192–198, 2011.
14. Aït-Khaled N, Pearce N, Anderson HR, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. Allergy 64:123–148, 2009.
15. de Andrade CR, da Cunha Ibiapina C, Goncalves Alvim C, et al. Asthma and allergic rhinitis co-morbidity: A cross-sectional questionnaire study on adolescents aged 13–14 years. Prim Care Respir J 17:222–225, 2008.
16. Sun HL, Yeh CJ, Ku MS, and Lue KH. Coexistence of allergic diseases: Patterns and frequencies. Allergy Asthma Proc 33:e1–e4, 2012.
17. Ciprandi G, Vizzaccaro A, Cirillo I, et al. Nasal eosinophils display the best correlation with symptoms, pulmonary function and inflammation in allergic rhinitis. Int Arch Allergy Immunol 136:266–272, 2005.
18. Charpin D, Sibbald B, Weeke E, and Wüthrich B. Epidemiologic identification of allergic rhinitis. Allergy 51:293–298, 1996.
19. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 8:161–176, 1997.
20. Bousquet J, Fokkens W, Burney P, et al. Important research questions in allergy and related diseases: Nonallergic rhinitis: A GA2LEN paper. Allergy 63:842–853, 2008.
21. Chawes BL, Bonnelykke K, Kreiner-Moller E, and Bisgaard H. Children with allergic and nonallergic rhinitis have a similar risk of asthma. J Allergy Clin Immunol 126:567–573, 2010.
22. Chawes BL, Kreiner-Moller E, and Bisgaard H. Upper and lower airway patency are associated in young children. Chest 137:1332–1337, 2010.
23. Valero A, Pereira C, Loureiro C, et al. Interrelationship between skin sensitization, rhinitis, and asthma in patients with allergic rhinitis: A study of Spain and Portugal. J Investig Allergol Clin Immunol 19: 167–172, 2009.
24. Corren J, Manning BE, Thompson SF, et al. Rhinitis therapy and the prevention of hospital care for asthma: A case-control study. J Allergy Clin Immunol 113:415–419, 2004.
25. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. J Allergy Clin Immunol 126:1170–1175, 2010.
26. Cruz AA, Popov T, Pawankar R, et al. Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. Allergy 62:S1–S41, 2007. □