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Invited Review Article

Epidemiological aspects of allergic conjunctivitis

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ABSTRACT

The prevalence of ocular allergies has been increasing worldwide for the past several decades. The geographical distribution and hot spots of rhinoconjunctivitis have been documented in a global survey by the International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC indicated that Africa, Latin America, and Japan were notable for their high prevalence of rhinoconjunctivitis. The outcomes of follow-up studies of regional differences and the characteristics of allergic conjunctivitis are summarized in this review.

Currently, comorbid diseases and socioeconomic and environmental factors, including climate and air pollution, are proposed to contribute to the regional differences in the prevalence of allergic conjunctivitis. Of them, rhinitis has been shown repeatedly to be significantly associated with allergic conjunctivitis. Their mechanistic aspects on association with the prevalence of systemic allergic diseases have been reviewed by examining the birth cohort or in vitro analyses.

A vision threatening form of ocular allergy, vernal keratoconjunctivitis, is prevalent in the African countries and Japan. Of the proposed associated factors, air pollution was shown to contribute not only to aggravating the symptoms but also to the increase in the incidence of its severe forms. Its mechanistic aspects are discussed in this review in the context of comorbid diseases.

Background

During the past several decades, the prevalence of ocular allergic diseases has been increasing worldwide. Ocular allergic diseases are known to cause significant reductions in the work and educational productivity and the overall quality of life. This can impose enormous economic costs which need to be addressed in health and welfare policies. However, detailed epidemiological information is still lacking or fragmented for ocular allergic diseases. Considering their potential impact on global health care, the factors associated with ocular allergic diseases need to be analyzed at the global and regional levels. However, a large number of countries or regions remain un-surveyed or unavailable for epidemiological surveys for the possible exacerbating factors for ocular allergic diseases.

Even though the increase in the prevalence of allergic conjunctivitis is worldwide, the exact prevalence is highly variable depending on the country and even in different regions of the same country. These variations appear to reflect the highly heterogeneous nature of the diseases, and also on the differences in the ethnicities, allergen species, and environmental risk factors.

In this review, we shall summarize the currently available data on the prevalence of ocular allergic diseases in different regions, countries, and worldwide. We shall review how ocular allergic diseases may be associated with allergen sensitization and environmental risk factors. In addition, we shall discuss their associations with comorbid factors and diseases. We shall also describe the limitations of the currently available data in understanding how we

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can interpret the variations and the effects of the exacerbating factors.

Currently, Asia is one of the regions with the highest prevalence of allergic conjunctival disease. Among the Asian countries, Japan is a hot spot with a high prevalence, and comprehensive information is available to analyze the effects of environment factors on the prevalence. Therefore, we shall focus on the epidemiological aspects of ocular allergic diseases in Japan.

Global prevalence of allergic conjunctivitis

In spite of the relatively abundant literature on the prevalence and incidence of systemic allergic diseases, including asthma, the available data on allergic conjunctivitis have been scarce. In the USA, the population level of allergic conjunctivitis was determined by a large-scale survey called The National Health and Nutrition Examination Survey (NHANES) III in 1988–1994. In the NHANES, 33,994 participants were interviewed with health-related questions as well as their socioeconomic and demographic status. Based on this dataset, 40% of the population age >17-years were reported to have ocular allergic symptoms, and they were classified as having allergic conjunctivitis.[1] Importantly, the ocular allergic symptoms were often accompanied by nasal symptoms. The prevalence of the allergic rhinoconjunctivitis was estimated to be 30% of the cohort, and it was more prevalent in younger individuals. Interestingly, the identified symptoms of allergic conjunctivitis could be retained for >50 years old subject.

The burden of rhinoconjunctivitis on medical resources was also shown for allergic subjects on an outpatient basis. In the Alergologica-2005 study in Spain, heavy users of allergy health care resources who were <14-years-of-age were analyzed. Of these, the most frequent disease was rhinoconjunctivitis (44.7%) followed by asthma (40.5%).[2]

The worldwide prevalence of allergic diseases is an important issue from the standpoint of health care delivery and the need to determine the global health associated factors. However, such analyses are technically demanding, and it requires enormous resources to perform such studies compared to focusing on one nation. More specifically, the standardization of the disease identification and diagnosis can become major obstacles for meaningful analyses. To overcome this difficulty, the framework of the International Study of Asthma and Allergies in Childhood (ISAAC) commenced from two multi-national projects and developed to a global scale survey after attracting world-wide scientific networks.[3–5] ISAAC was designed to analyze the geographical distribution and time trend of allergic diseases. ISAAC used a questionnaire to unify the diagnosis, which was agreed to in 1991. The questionnaire asked for disease symptoms and not the diagnosis or labeling. It is still widely used with modifications. One of the strengths of ISAAC was that it used disease symptoms based on standardized methods to allow for comparisons between different countries and even data obtained at different times.

The Phase 1 ISAAC was conducted between 1993 and 1997, and Phase 3 of ISAAC was conducted between 2002 and 2003 on 1,059,053 children from 98 countries. The results of ISSAC Phase 3 showed that the average overall prevalence of rhinoconjunctivitis was 14.6% for 13- to 14-year-old children (Fig. 1).[5]

The results of the ISSAC study provided the first global picture of allergic diseases including rhinoconjunctivitis, and its prevalence was reported highly variable depending on the country and region of the country (Fig. 1). The highest prevalence was observed in Africa (18.0%) and Latin Africa (17.3%), while the lowest was Northern & Eastern Europe (9.2%).[5] The large variations in the prevalence were also observed in different regions of the same country. For example, large cities in Asian Pacific region, including Ho Chi Minh City (Vietnam), Bangkok (Thailand), and Hong Kong (China) had higher prevalence rates compared to adjacent area or cities (Fig. 1). The observed high heterogeneity within the region may have been affected by inherent sampling bias including preferred selection of the participating cities. However, the outcomes suggest that the prevalence needs to be carefully monitored on a country or regional basis. Importantly, a global increasing trend of rhinoconjunctivitis has been found. Compared to the results of the Phase 1 study, the prevalence of rhinoconjunctivitis in 6- and 7-year-old children and 13- and 14-year-old children was found to have increased almost globally in the Phase 3 study. The increase was also observed for eczema in 6- and 7-year-old children.

After the completion of ISSAC Phase 3, there were a limited number of reports that estimated the prevalence of allergic conjunctivitis on a countrywide basis. Population-based surveys for allergic conjunctivitis are summarized In Table 1.

In Palermo, Italy, randomly selected school children of 10- to 17-years-of-age were surveyed using the SIDRIA and ISAAC questionnaires in 2005–2006. This cross-sectional study determined that the prevalence of rhinoconjunctivitis was 20.5%, while the prevalence of rhinitis with or without conjunctivitis was 38.7% (N = 2150). Thus, 52.9% of the children with rhinitis also had conjunctivitis. The comorbidity of conjunctivitis was more highly associated with the presence of asthma than rhinitis alone (odds ratio (OR) of rhinoconjunctivitis, 5.23; rhinitis, 2.28).[6]

The results of the French INSTANT Study used a population-based, cross-sectional design, and it found that the prevalence of allergic rhinoconjunctivitis was 16.5% while that of allergic rhinitis was 31.7% in 2006 (N = 4019).[7] In Karachi (Pakistan), school children ages 5- to 19-years-of-age were surveyed in 2008, and the prevalence of allergic conjunctivitis was 19.2% (N = 818).[8]

In Japan, the prevalence of rhinoconjunctivitis is known to be high, and it is typically caused by cedar and cypress pollen. To understand the changes in the trend of the prevalence, school children in Kyoto ages 7- to 15-years were surveyed in 1996 and again 2006 with a questionnaire (N = 13,215). The lifetime prevalence of allergic conjunctivitis was 30.0% in 2006 which was an increase from the 24.5% in 1996. Similarly, the lifetime prevalence of allergic rhinitis also increased from 21.8% in 1996 to 29.0% in 2006. Thus, both disorders have a similar increase in the high prevalence. Moreover, the proportion of severe symptom cases of allergic conjunctivitis or rhinitis appeared to be increasing.[9]

A large population-based survey was conducted as the West Japan Study of Asthma and Allergies in Childhood (WJSAAC). The WJSAAC study surveyed elementary school children ages 6- to 12-years-of-age focusing on west Japan through 1992, 2002, and 2012.[10] The prevalence of allergic conjunctivitis was 17.5% in 2012. Of these, those with active current allergic conjunctivitis was 11.4% and those with remitted allergic conjunctivitis was 6.14% (N = 33,902). In contrast, the prevalence of rhinitis was higher; active allergic rhinitis was 28.1% and remitted allergic rhinitis was 6.4%. The prevalence of the active allergic conjunctivitis had increased from 6.7% (1992, N = 46,718) to 9.8% (2002, N = 36,228). In 2002, the prevalence of active allergic rhinitis was 28.1% which was an increase from 15.9% in 1992.

In Africa, different regions are hot spots with high prevalence of allergic conjunctivitis. In Kumasi Metropolis of Ghana, a cross-sectional community-based study using a questionnaire and slit-lamp examinations was conducted on 5- to 16-year-old school children in 2011–2014. The reported incidence of allergic conjunctivitis was 39.9% (N = 1571).[11] In Kuwait, the prevalence of

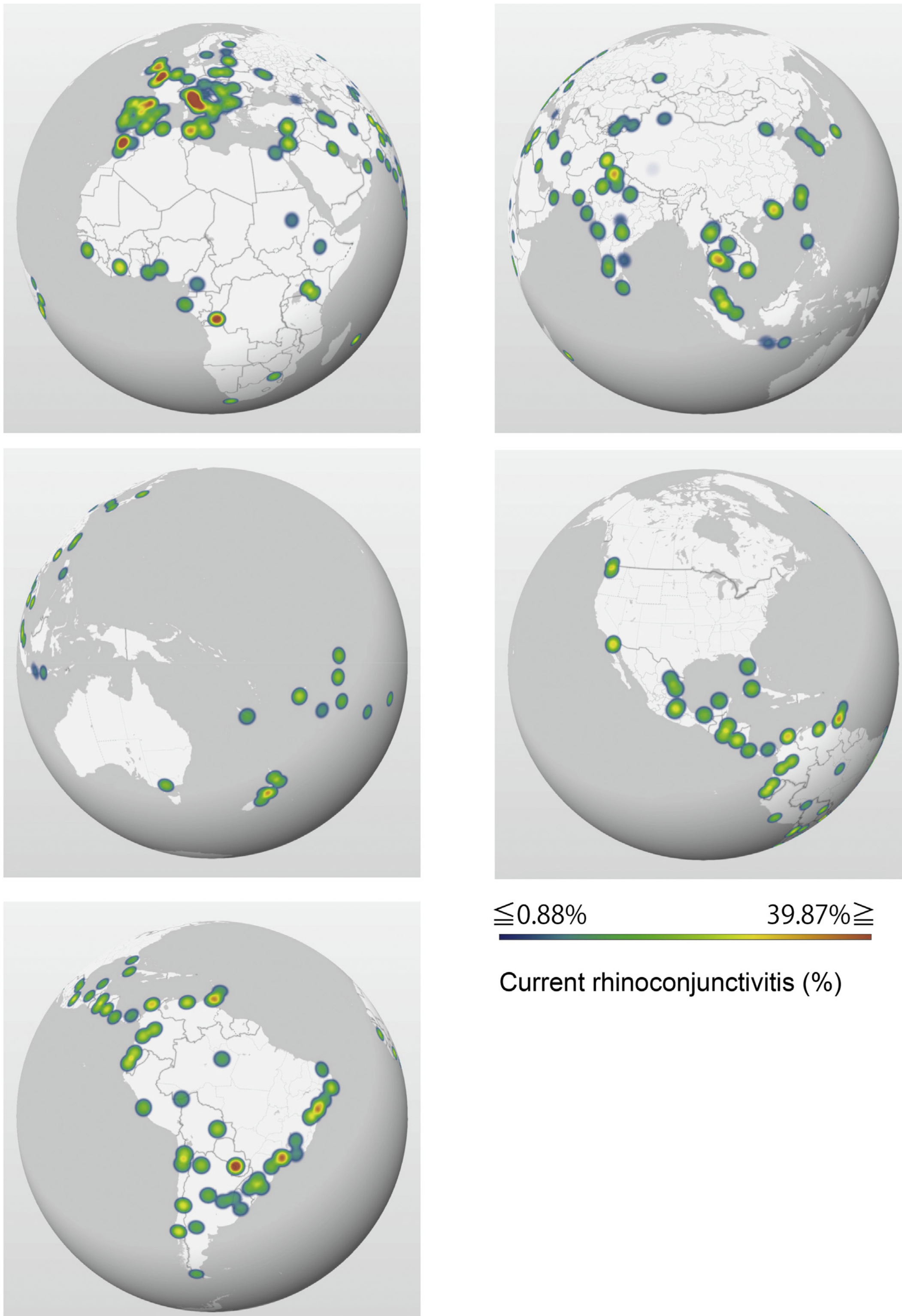

Fig. 1. Global distribution of rhinoconjunctivitis of 13- to 14-year-old subjects between 2002 and 2003. The prevalence from the ISAAC Phase 3 data are mapped for global distribution. Data source of mapping is the reference.[5]

Table 1
Prevalence of allergic conjunctivitis by population based-studies.

Title/Investigator	Year	Area	Disease	Prevalence	age	n	Survey methods	Reference
NHANES	1988–1994	USA	allergic conjunctivitis	40.0%	>17 years	33,994	Interview	1
ISAAC phase 3	2002–2003	98 countries	rhinoconjunctivitis	14.6%	13- to 14-years	1,059,053	ISAAC questionnaire	5
Bremond-Gignac D *et al.*	2002	Italy	vernal keratoconjunctivitis	0.02–0.3%	all ages	NA	questionnaire for 776 ophthalmologists	24
		Finland	vernal keratoconjunctivitis	0.007–0.08%				
		Sweden	vernal keratoconjunctivitis	0.01–0.09%				
		Netherland	vernal keratoconjunctivitis	0.006–0.05%				
		France	vernal keratoconjunctivitis	0.007–0.03%				
		Norway	vernal keratoconjunctivitis	0.003–0.02%				
Cibella F *et al.*	2005–2006	Palermo, Italy	rhinoconjunctivitis	20.5%	10- to 17-years	2150	SIDRIA and ISAAC questionnaires	6
INSTANT Study	2006	France	rhinoconjunctivitis	16.5%	>18 years	4019	Interview	7
ASK study	2006	Kyoto, Japan	allergic conjunctivitis	30.0%	7- to 15-years	13,215	questionnaire	9
De Smedt SK *et al.*	2007	Rwanda	vernal keratoconjunctivitis	4.0%	7- to 14-years	3041	Ophthalmological examination	20
Baig R et Al	2008	Karachi, Pakistan	allergic conjunctivitis	19.2%	5- to 19-years	818	Ophthalmological examination	8
Kassahun FB *et al.*	2008	Ethiopia	vernal keratoconjunctivitis	5.2%	5- to 20-years	792	Ophthalmological examination	21
Kumah DB *et al.*	2011–2014	Kumasi Metropolis, Ghana	allergic conjunctivitis	39.9%	5- to 16-years	1571	Ophthalmological examination	11
WJSAAC	2012	Japan	allergic conjunctivitis	17.5%	6- to 12-years	33,902	ATS-DLD questionnaire	10
Duke RE *et al.*	2014	Nigeria	vernal keratoconjunctivitis	18.1%	4- to 15-years	1226	Ophthalmological examination	19
Hayilu D *et al.*	2015	Ethiopia	vernal keratoconjunctivitis	5.8%	under 18-years	737	Ophthalmological examination	22
Ziyab AH *et al.*	2016–2018	Kuwait	rhinoconjunctivitis	28.6%	11- to 14-year	3864	ISAAC questionnaire	12
Miyazaki D *et al.*	2017	Japan	Seasonal allergic conjunctivitis	45.4%	all ages	3004	questionnaire	25
			perennial allergic conjunctivitis	14.0%				
			atopic keratoconjunctivitis	5.3%				
			vernal keratoconjunctivitis	1.2%				
Alemayehu AM	2018	Ethiopia	vernal keratoconjunctivitis	11.1%	under 18-years	578	Ophthalmological examination	23

rhinoconjunctivitis in 11- to 14-year-old children was 13.5% while that of rhinitis was 28.6% in 2016–2018 (N = 3864).[12]

Study design and prevalence

Published studies have reported different prevalences of allergic conjunctivitis. The use of a questionnaire for symptoms-based surveys is an efficient way to analyze a large number of participants. In this context, the ISAAC studies which used the same standardized questionnaire, allowed unified assessments of the time trends of the global prevalence in different regions or countries. This use of a questionnaire also minimized the bias derived from communication problems arising from different investigators or respondents with different cultural backgrounds or languages. In addition, the ISAAC questionnaire simply questioned the symptoms and not the disease label such as allergic conjunctivitis or eczema. This avoided a labelling bias due to different diagnostic criteria or clinical practice in the different countries. However, in interpreting the results of the prevalence of allergic diseases, it is necessary to be cautious on how the disease was defined or labelled.

The calculated prevalence obtained from the questionnaire-based surveys may not reflect the true differences made by more accurate diagnostic protocol. For example, the ISAAC questionnaire first defined allergic rhinitis by the nasal symptoms in the absence of a cold. This was followed by a question for rhinoconjunctivitis asking if itchy and watery eyes were present in the past 12 months. Rhinoconjunctivitis is only labeled after rhinitis is present. Thus, this will underestimate the prevalence of isolated allergic conjunctivitis. In addition, ISAAC only estimated the current prevalence and not the life-time prevalence.

Prevalence of seasonal allergic conjunctivitis and perennial allergic conjunctivitis

Survey studies showed that the prevalence of allergic conjunctivitis is high and probably increasing in spite of regional differences.[13] The importance of allergic conjunctivitis derives from its high prevalence which causes a socio-economic burden.

Allergic conjunctivitis is classified as seasonal allergic conjunctivitis (SAC) or perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), or giant papillary conjunctivitis.

When a symptom-based questionnaire was used, these subtypes of allergic conjunctivitis were not accurately diagnosed and their prevalence was not correct. To estimate the prevalence of these subtypes, ophthalmological examinations for diagnosis is generally required. Because of this, outpatient visit-based surveys have been used to evaluate the prevalence of the subtypes of ocular allergic diseases. The prevalence of the subtypes is also different depending on the region or design of the studies.[14] In Japan, the highest prevalence of SAC reported was 81.2% (N = 1079) and in Italy, it was 55% (N = 3685).[15,16] In Thailand, PAC was the most frequent allergic disorder at 81.8% (N = 445).[17] However, we need to be cautious in interpreting these outcomes because their study design can often cause overestimation and does not provide true prevalence in the general population.

In Japan, an internet-based survey was conducted for ophthalmologists and their families in 2017 to estimate the prevalence of ocular allergic diseases throughout Japan in the general population (N = 3004).[18] The findings showed that the prevalence of SAC was as high as 45.4%. This prevalence was followed by PAC at 14.0%.

Geographically, the prevalence of SAC and allergic rhinitis was high in the central region of Japan (Fig. 2, Fig. 3).[19] SAC in Japan is caused mainly by cedar pollen, however the pollen dispersion is highest in the Tohoku (northeastern) district (Fig. 3). Thus, obvious discrepancies in the regional differences of SAC and pollen dispersion are observed. Pollen dispersion in Japan is nation-wide, and prevalent at any location with more than certain levels of pollen. This suggests that the effects or requirement of other exogenous factors to increase pollen sensitization, which may serve as adjuvant-like mechanism, leading to increased prevalence .

PAC has a distinctive distribution, and its prevalence is high in the Hokkaido, Kanto, and Hokuriku districts of Japan. It was higher in large cities (Fig. 2).[19] PAC is well known to be associated with house dust or mite sensitization. However, there remain no clear epidemiological evidence to explain its association with allergen sensitization.

Prevalence of atopic keratoconjunctivitis and vernal keratoconjunctivitis

The severe forms of allergic conjunctivitis can impose significant visual morbidity. AKC and VKC are such diseases, and they may cause devastating visual complications. AKC is typically adult onset, and associated with eczema and can cause corneal alterations and severe conjunctival inflammation. VKC typically has a childhood onset and is characterized by proliferative lesions in the bulbar and tarsal conjunctiva including giant papilla formation. VKC is classified as the limbal or tarsal types and the mixed type. Both can lead to corneal shield ulcers in its severe forms which require intensive medical management.[19] Both diseases are difficult to differentially diagnosis because AKC can have a childhood onset[20] and present as similar ocular signs and symptoms in its severe forms.

The prevalence of AKC or VKC also differed depending on the studies. Using patient-based surveys, the ratio of VKC to that in all ocular allergic patients was 10.6% in Thailand and AKC was 4.7% in 1998–2000 (N = 445).[17] In Japan, the ratio of VKC in ocular allergic patients was 3.8% and that for AKC was 4.4% in 2002–2003 (N = 1079). A 2006 Brazilian study found a very high ratio of 38.6% for VKC and 38.6% for AKC (N = 207).[21] These values were 9% and 7% in Italy in 2012 (N = 3545).[15,16] However, it is not certain whether the large variations in the ratio may reflect actual prevalence differences because these estimates are not only derived from different surveyed years and regions, but also by sampling bias, availability of medical resources, and cultural differences.

The prevalence of VKC has been determined in a population-based surveys that emphasized the severity of its symptoms and signs.[22–26] It was found that male subjects were more affected than female subjects with VKC. New onsets were mainly reported in

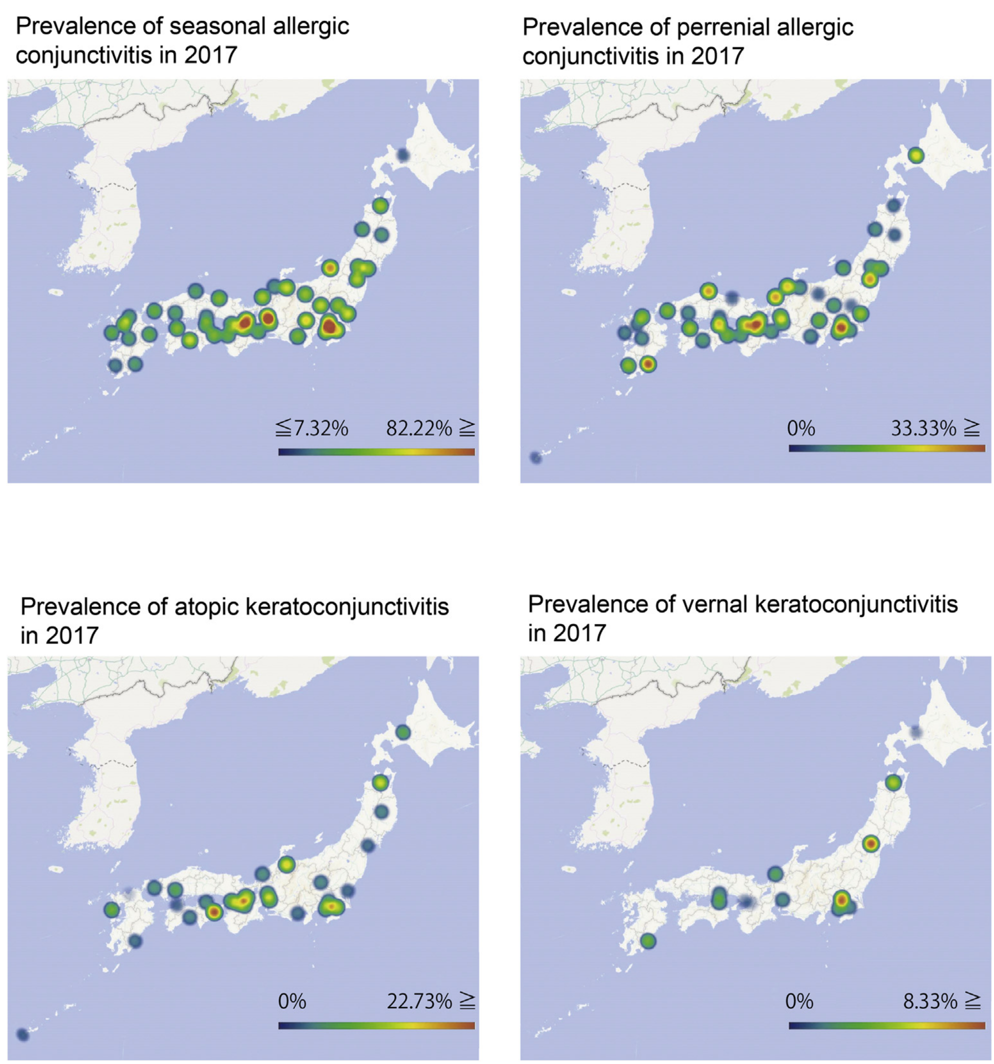

Fig. 2. Distribution of prevalence of allergic conjunctivitis and its subtypes in 2017 in Japan. Geographical distribution of prevalence data.[18]

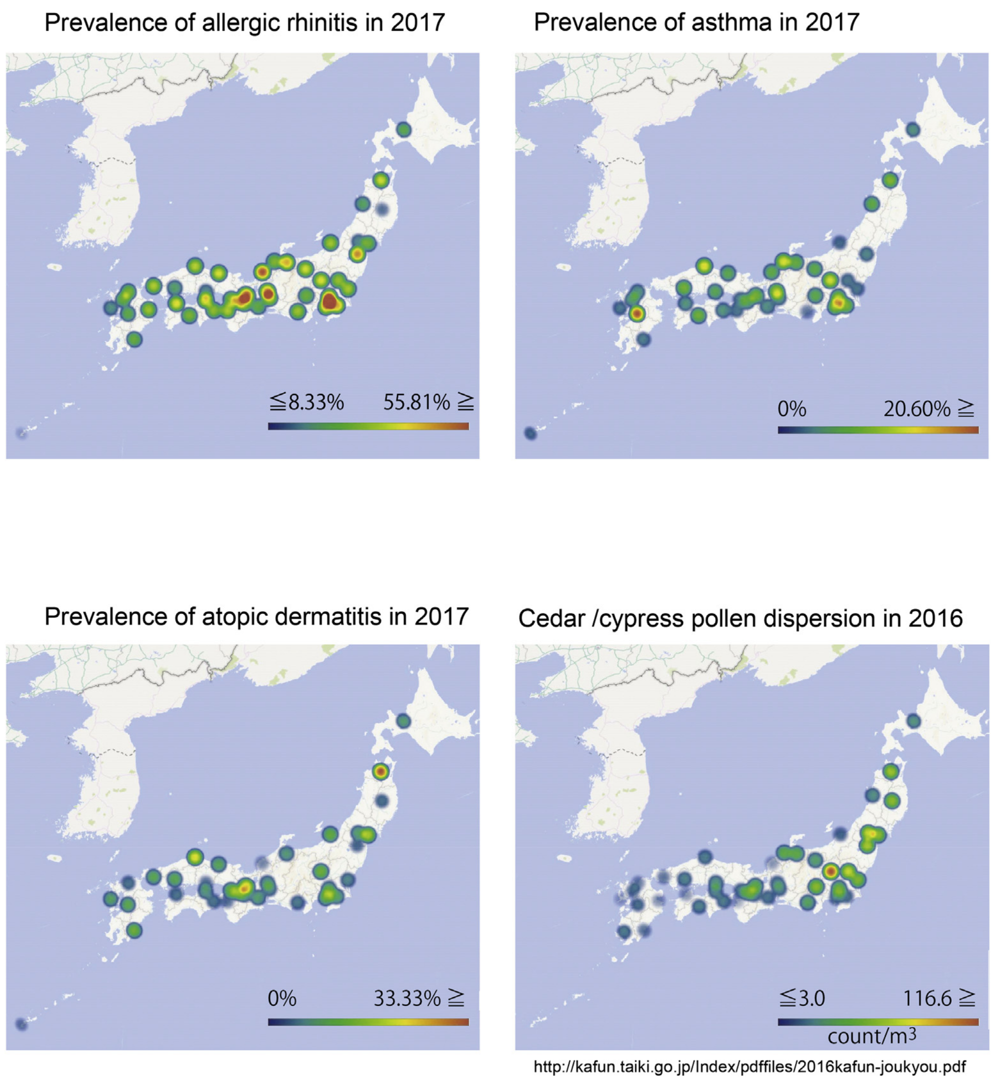

Fig. 3. Distribution of prevalence of systemic allergic diseases and cedar/cypress pollen dispersion in 2017 in Japan. The distribution of the prevalence data[18] are mapped. The cedar and cypress pollen count was obtained from http://kafun.taiki.go.jp/Index/pdffiles/2016kafun-joukyou.pdf.

young subjects, however new onsets beyond the age of 20-years were also present.[27] Of the subtypes of VKC, the tarsal and mixed type were most prevalent.

The prevalence of VKC varied greatly depending on the regions of the world. High prevalence rates were reported especially for regions with warm dry climates, e.g., the middle Eastern countries, central and south Africa, and Mediterranean countries. In contrast, western European Union nations had low prevalences of VKC.

Generally, an accurate diagnosis of the disease subtypes, including VKC and AKC, requires ophthalmological examinations. Ophthalmological examination-based surveys have been conducted mainly in African countries. In Nigeria, a high prevalence of 18.1% for VKC was reported in 2014 for school children of 4- to 15-years-of-age (N = 1226).[22] In Rwanda, a prevalence of VKC was 4% for school children 7- to 14-years-of-age (N = 3041) in 2007.[23] In Ethiopia, the prevalence of VKC for school children 5- to 20-years-of-age was 5.2% (N = 792) in a 2008 survey.24 In a 2015 survey, the prevalence was 5.8% for children under 18-years-of age in Ethiopia (N = 737).[25] The most recent survey in Ethiopia indicated an increase in the prevalence to 11.1% in 2018 (N = 578).[28]

To estimate the prevalence of ocular allergic diseases in European countries, a questionnaire-based survey was conducted for ophthalmologists in the European countries in 2002.[26] Several assumptions were made including that all the VKC patients were referred to ophthalmologists, and the prevalence of VKC was estimated to be 0.02–0.3% for Italy, 0.007–0.08% for Finland, 0.01–0.09% for Sweden, 0.006–0.05% for Netherland, 0.007–0.03% for France, and 0.003–0.02% for Norway. There is agreement on these low VKC prevalence levels, however the assumptions in the prevalence calculations may lead to an underestimation of the actual prevalence. For example, symptomatic but undiagnosed patients were not considered unless they visited ophthalmologists.

In Japan, an internet-based survey conducted for ophthalmologists and their families in 2017 indicated that in general population the prevalence of AKC was approximately 5.3% and that for VKC was 1.2% (N = 3004).[18] In Tokyo or Osaka, AKC and VKC had an especially high prevalence (Fig. 2). The increased prevalence of AKC and VKC, not limited to SAC or PAC, suggests influence of factors common to large cities, including socioeconomical factors or air pollution.

Factors associated with prevalence of ocular allergy and comorbidity

The prevalence of allergic conjunctivitis appears to have increased globally. Moreover, regional differences of allergic conjunctivitis prevalence are high. The ISAAC studies identified factors which affected the prevalence of allergic disease including rhinoconjunctivitis. Those that were proposed were socioeconomical factors, diet, temperatures, climate, and pollen dispersion.

As was reported in the ISAAC study, rhinoconjunctivitis is more prevalent in low latitudinal regions of the world (Fig. 1). Indeed, the results of the ISAAC studies indicated that climate factors can contribute to the prevalence of rhinoconjunctivitis. The climate-related factors including low latitudinal location, high mean annual temperature, and low annual outdoor humidity were significantly associated with higher prevalence of allergic rhinoconjunctivitis symptoms.[29] Dietary factors may also affect the prevalence. For example, a decrease in the prevalence of allergic rhinoconjunctivitis, eczema, and wheeze was shown to be associated with the intake of calories from cereal and rice, and proteins from cereals, nuts, starch, and vegetables.[30]

The hygiene hypothesis conceptualized that childhood exposure to microorganisms will protect also against ocular allergy. The ISAAC study examined the association of allergic diseases and microbial exposure, which was evaluated using the tuberculosis notification rate as a surrogate. An increase in tuberculosis notification rate was significantly associated with a decrease in the prevalence of asthma and rhinoconjunctivitis, confirming the validity of the hygiene hypothesis.[31]

The socioeconomic environment may also affect the induction and exacerbation of various aspects of ocular allergies directly and indirectly. The gross national product/capita can be used to assess the socioeconomic factors. The ISAAC study showed that the gross national product/capita was positively associated with atopic symptoms but not rhinoconjunctivitis in <14-year-old children.[32]

In contrast, pollen exposure was not significantly associated with allergic rhinoconjunctivitis but there was an inverse but weak significant association of grass pollen count with allergic rhinitis.[33]

Association of prevalence of allergic diseases and air pollution

A significant association of allergic diseases with air pollution is well known. Air pollution not only aggravates symptoms of allergic diseases, but also causes onsets in new individuals.[34,35] Air pollution is classified as gaseous or particulate pollution, and traffic-related air pollution (TRAP) as their mixtures. Air pollution can impact the global prevalence of allergic diseases.

The gaseous pollution include nitrogen oxides, ozone, SO_2, and CO. Of these, the oxidizing agents including nitrogen oxides and ozone are well recognized as important allergy associated pollutants. Nitrogen oxides are formed by photochemical reactions and are enhanced in warm conditions or during the summer months. These oxidizing agents not only damage the mucosal surface presumably by promoting allergen penetration, but also induce neutrophilic inflammation and promotes Th2/Th17 cytokine induction.[36,37]

Ambient particulate matters (PMs) are emitted by the combustion of fossil fuels or by natural sources such as volcanic eruptions and wildfires. The PMs are categorized by their diameter; PM10, PM2.5, and ultrafine PMs. PM2.5 is sized as <2.5 μm, and they easily penetrate into conducting airways because of their size. The PM10s are 2.5–10 μm sized aerosols that contain coarse suspended materials. The PM10s vary in their contents depending on the source. PM10 may typically contain allergenic material including pollen, fungal spores, or dust as well as metallic or polycyclic aromatic hydrocarbons. They can serve as allergens or adjuvants. In addition, PM pollution is often associated with increased levels of nitrogen oxides or ozone as irritant or barrier damaging compounds.[34]

The global association of allergies to air pollution was also analyzed using the ISAAC data.[38] The city level of PM10 which was estimated using the World Bank model was assessed for their association with allergic diseases. However, the modeled PM10 failed to show significant associations with the prevalence of rhinoconjunctivitis, asthma, and eczema.

A birth cohort study is a more suitable design to assess the associations between allergies and environmental factors. Recent metanalysis including many birth cohort studies showed that the development of asthma was significantly associated with prenatal exposure to NO_2, PM2.5, PM10, and black carbon particles.[35] The analyses used age stratification for adjustment. The results were confirmed by sensitivity analysis,[35] however a high heterogeneity in the effect of size was observed for nitrate oxides and some for PM2.5 and PM10.

There are some explanations on why the globally-conducted ISAAC study did not find significant associations between the prevalence of allergies and exogenous factors. If one needs to analyze effects of exogeneous risk factors, the analysis requires the estimation of the prevalence which is typically obtained by cohort studies. The prevalence may also be assessed for associations with environmental factors, however, the prevalence of symptoms within a defined short period, e.g., 12 months, as was used in the ISAAC study, was not appropriate. This mainly allowed an analysis of the exacerbation of latent allergy.

Association of ocular allergy with air pollution

Air pollution can induce or aggravate symptoms of allergic conjunctivitis. This was shown by cross sectional studies that showed an increase in the outpatient visits associated with an increase in air pollutants. These studies were mainly conducted for urban cities individuals including Deagu (Korea, 2006–2014),[39] Lombardia (Italy, 2013),[40] Taiwan (2007–2009),[41] and Tokyo (Japan, 2017)[42] where the prevalence of allergic conjunctivitis was moderate to high. These findings can be interpreted as a stimulation of allergen recall responses. Among them, the PM10-association with conjunctivitis appeared consistent with what was found in Daegu, Lombardia, and Taiwan studies. In the Tokyo study, PM2.5 was shown to be significantly associated with visits for allergic conjunctivitis.[42] The Taiwan study also showed a significant association with NO_2, SO_2, and O_3.[41]

These findings indicated that the acute exacerbation of ocular symptoms was affected. However, they do not directly indicate a significant association with the prevalence of the disease. Significant associations of the prevalence with pollutants were shown using cross sectional studies in Africa and Japan where the prevalence of VKC is high. In the Ethiopian study for subjects under age of 18, the use of kerosene and firewood for cooking (Odds ratio (OR) = 6.25) and dust exposure (OR = 10.0) were significantly associated with VKC (N = 737).[25] Another recent Ethiopian study showed that dust exposure (OR = 3.38) and close animal contact (OR = 3.45) were significantly associated with VKC (N = 578).[28]

In a Japanese study, NOx (OR = 1.72, per quintile) and PM10 (OR = 1.54 per quintile) were shown to be significantly associated with the prevalence of VKC (N = 3004).[18] AKC was also significantly associated with the NO_2 levels (OR = 1.23 per quintile). SAC was associated with PM10 and oxidants, however their relative contribution was small considering the very high prevalence of SAC. Thus, air pollution can especially affect the severe forms of ocular allergic diseases.[18]

Molecular mechanisms affected by air pollution

A birth cohort study design is an efficient way to determine the associations of new onsets of allergies to pollutants, however this has not been conducted for ocular allergic diseases. Instead, birth cohort studies conducted for systemic allergic disease has revealed the mechanistic aspects on how air pollution may induce allergic disease. The French EDEN mother-child cohort study showed that maternal exposure to PM10 was associated with decreased $CD4^+$ and $CD25^+$ T cells in the cord blood of newborns. Thus, PM10 exposure may possibly decrease the regulatory function of her child.[43] In the Swedish birth cohort study (BAMSE), nitrogen oxides exposure during the first year of life was shown to be associated with increased pollen sensitization in later years.[44] Meta-analysis of birth cohort studies showed that early childhood exposure to PM2.5, but not to NO_2, was strongly associated with sensitization to outdoor aeroallergens.[45] Collectively, air pollutants can affect the allergen sensitization although high variations were observed among the studies and cohorts. This may suggest a global increase of ocular allergic diseases.

Summary

The prevalence of allergic conjunctivitis is region-dependently high and appears to be increasing worldwide. The heterogeneity may be explained not only by allergen sensitization but also by differences in ethnicity, climate, diet, socioeconomical factors, and type of air pollutants. Among the systemic allergic diseases, allergic rhinitis is the most commonly-associated type, and it had similarly high prevalence. Global knowledge of the prevalence of severe forms of ocular allergic diseases remains scarce, however, reports from high prevalent region for allergic conjunctivitis suggests that air pollutants may be associated with the increase together with increased sensitization.

Conflict of interest

Honoraria: DM, Lecture fees from Santen, Japan, Senju Pharmaceutical, Japan; KF, JS, Lecture fees from Santen, Japan; AF, Lecture fees from Santen, Japan, Senju Pharmaceutical, Japan, and Novartis, United States; KN, Lecture fees from HOYA, Japan, Alcon, United States, Pfizer, United States, Novartis, United States, Kowa, Japan, Senju Pharmaceutical, Japan, Mitsubishi Tanabe, Japan, Eisai, Japan, Abbvie, United States, and Santen, Japan; EU, Lecture fees from Santen, Japan, Senju Pharmaceutical, Japan. Research funding: KN, Santen, Japan, Abbvie, United States, Mitsubishi Tanabe, Japan, and Eisai, Japan; AF, Santen, Japan and Novartis, United States; JS, Takanashi, Japan; NE, Santen, Japan, Senju Pharmaceutical, Japan, and Novartis, United States. The rest of the authors have no conflict of interest.

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