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ORIGINAL RESEARCH

High Serum Allergen-Specific IgE of House Dust Mite in Predicting the Risk of Comorbidity in Children with Allergic Conjunctivitis

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Purpose: To investigate the patterns of allergens in allergic conjunctivitis (AC) and the association with allergic comorbidity.

Methods: This retrospective cross-sectional study enrolled 2972 children with AC. Clinical data, including sex, age, allergic comorbidities (allergic asthma, allergic rhinitis, and atopic dermatitis), and serum allergen-specific immunoglobulin E (sIgE), were collected from the electronic medical record (EMR). The categorical variables were compared with the chi-square test. The characteristics of allergens in children of different ages and comorbidities were analyzed by trend chi-square. The sensitivity level of HDM associated with AC and comorbidities was assessed by odds ratios (ORs) with 95% confidence intervals of logistic regression analysis.

Results: A total of 2972 children (2015 boys and 957 girls) with AC were included in the study. The mean age was 3.78 (0.5~12) years. The most common allergen was house dust mite(HDM) (43.41%). With age, the positive rate for inhaled allergens gradually increased, and the positive rate for ingested allergens decreased. With the number of comorbidities increasing, the positive rates of sensitization were 38.33%, 74.51%, 80.72%, and 89.05%, and the incidence of polysensitization was 44.66%, 56.48%, 59.54%, and 74.59%, respectively. With the increase of HDM-sIgE level, the number of comorbidities and the risk increased gradually.

Conclusion: HDM is the most common allergen in AC children of different ages. High levels of HDM-sIgE may be a predictor for allergic comorbidities. Children with polysensitization and high levels of HDM sIgE will be an important target population for future intervention in other allergy-related disease prevention.

Keywords: allergic conjunctivitis, specific IgE, allergic comorbidity, house dust mite, children

Background

Allergic conjunctivitis (AC) is a disease caused by allergic hypersensitivity of conjunctivitis to allergens. The prevalence of AC in children varies from 13.0% to 43.60% in different regions and ethnicities, with an increasing prevalence.[1] Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the two most common forms of AC,[2] and are associated with IgE-mediated hypersensitivity reactions. Allergic conjunctivitis can cause a series of complications, such as dry eye, keratitis, and limbal stem cell damage, leading to vision loss and affecting visual development.[3] Allergic conjunctivitis recurrence is also closely related to tic disorders and other neuropsychiatric symptoms, and behavioral abnormalities.[4] In addition, children with AC are more likely to suffer from a greater number of allergic comorbidities such as allergic rhinitis (AR), food allergy, and atopic dermatitis than normal subjects. The presence of comorbidities is related to poor quality of life.[5]

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Although AC seriously affects the visual quality and quality of life of children, less attention has been paid to this entity compared to other allergic diseases, leading to clinical underestimation or underdiagnosis. It is known that the relationship between the occurrence of allergy-related diseases and allergen sensitization is complex. The allergens and allergic symptoms vary with age. Inhaled allergens have been linked to allergic rhinitis and/or asthma, while ingested allergens have been linked to atopic dermatitis. In practice, ophthalmology is often the first department for "red eyes"or "rubbing eyes" in children. The diagnosis of pediatric AC by ophthalmologists often precedes the AR and AA diagnosis. Early identification of allergens and early prevention are important clinical measures to reduce the incidence of other comorbidities. However, in traditional studies, AC was usually regarded as a concomitant disease of allergic rhinitis. Few studies investigate children with AC to investigate the association of other allergic comorbidities and risk factors.

Therefore, in this study, we retrospectively analyzed AC children who underwent allergen-specific immunoglobulin E(sIgE) tests for screening sensitization to common ingested and inhaled allergens to investigate the characteristics of allergens and the association with allergic comorbidities.

Methods

Study Design

This retrospective cross-sectional study was conducted between January 2017 to December 2022 in Chongqing, China. The study was performed in compliance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University, Chongqing, China.

Subjects and Data

The children aged 12 or younger who were clinically diagnosed with AC are enrolled and divided into 4 subgroups: infancy (0.25~1 years), early childhood (1~3 years), preschool age (3~6 years), and school-aged children (6~12 years). Information on the specialist's diagnosis history of allergic asthma, allergic rhinitis, and atopic dermatitis was obtained from the electronic medical record (EMR) system. Allergic conjunctivitis in the current research was diagnosed by well-trained ophthalmologists. The clinical diagnostic criteria included clinical symptoms such as ocular itching, eye discharge, foreign body sensation, ocular pain, or photophobia, and the signs of conjunctival hyperemia or papillae.[6] Comorbidities of allergic conjunctivitis refer to other allergic diseases, including diagnosed AR, diagnosed AA, and diagnosed AD. Children without allergen test results in EMR were excluded from this study.

Specific IgE Testing

Serum sIgE was measured by the inhalation and food allergen-specific IgE antibody detection kit (EUROLINE Atopy, Medical Experimental Diagnostics Inc, China). Inhaled allergens include house dust mites (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cat dander, pollen tree, ragweed, mugwort, cockroach, mould, dog dander, and *Humulus lupulus*. Ingested allergens include milk, egg white, beef, soybean, freshwater fish mixture (salmon, bass, carp), crab, marine fish mixture (cod, lobster, scallops), peanut, mutton, and shrimp. The test result was considered positive if the concentration of sIgE was ≥0.35 kU/L. Sensitization was classified into 0–6 levels according to concentration: level 0 (<0. 35 kU/L), level 1 (0. 35–0. 69 kU/L), level 2 (0. 70–3.49 kU/L), level 3 (3. 50–17. 49kU/L), level 4 (17. 50–49. 99 kU/L) level 5 (50. 00~99. 99 kU/L) and level 6 (≥100. 00 kU/L). Sensitization to only one allergen was defined as monosensitization, and sensitization to two or more allergens was defined as polysensitization.

Statistical Analysis

Data were analyzed using SPSS version 18.0 software (SPSS, Inc., Chicago, IL, USA). Values for continuous variables are presented as the mean ± the standard deviation. The quantitative data between the groups were compared using Student's *t*-test. The categorical variables were compared with the chi-square test. The characteristics of allergens in children of different ages and comorbidities were analyzed by trend chi-square. The sensitivity level of HDM associated with AC and comorbidities was assessed by odds ratios (ORs) with 95% confidence intervals of logistic regression

analysis. Variables with a statistical significance of P <0.01 in the univariate analysis were included in the multivariate model. Statistical significance was defined as P <0.05.

Result

A total of 2972 children with a clinical diagnosis of AC were included in the study. The mean age was 3.78±1.65 years, ranging from 0.25 to 12 years. There were 2015 males and 957 females (M: F =2.11:1). Allergic rhinitis (AR) was the most common comorbidity for AC(62.48%), followed by allergic asthma (AA), atopic dermatitis (AD). The positive rate of sIgE was 68.71%, in which 29.54% of children were monosensitisation and 39.17% were polysensitisation, respectively. The general characteristics of the children are shown in Table 1. Although the incidence of AC was significantly higher in boys than in girls (2.11:1), there were almost no significant differences in sensitivity to allergens between the genders (Supplementary Table 1).

In terms of total participants, the most common inhaled allergen in children with AC was house dust mite (HDM) (43.41%), followed by cat dander (6%), ragweed (4.1%), and pollen tree (4.1%). The most common ingested allergens were milk, egg white, and beef, with positive rates of 19.48%, 18.61%, and 15.48% respectively. The details of the positive distribution of allergens are described in Table 2.

In AC patients without other allergic comorbidities, the most common allergen was HDM (39.63%), followed by milk (19.81%), egg whites (18.89%), beef (15.62%), and soybean (7.61%). In AC patients with other allergic comorbidities, HDM was the most common allergen. The positive rates of HDM in AC patients with AA, AR, and AD were 44.73%, 45.11%, and 45.04%, respectively. The positive rates of HDM in AC patients with AA+ AR, AA+ AD, and AR+ AD were 45.84%, 47.83%, and 47.80%, respectively. The positive rate of HDM in AC patients with AA, AR, and AD was 47.93% (Supplementary Table 2).

Among children of different age groups, there were some differences in sensitivity to allergens. The chi-square test showed that with the increase of age, the positive rate of inhaled allergen increased, while the positive rate of ingested allergen decreased, except in the baby group (Supplementary Table 3).

Trend chi-square analysis found the positive rate of inhaled allergens increased gradually with age, such as HDM, cat dander, pollen tree, ragweed, mugwort, and *Humulus lupulus*. Milk and white egg were the most commonly ingested allergen in the baby group, but the positive rate decreased gradually with age. HDM was the most common allergen in all age groups. The sIgE-positive rate of HDM was 38.35% in the infant group, 47.00% in the young children group, 53.09%

Table 1 Demographic and Clinical Characteristics of the Study Population

	n	%
Sex		
Boys	2015	67.80
Girls	957	32.20
Age(months)		
3~12	1695	57.03
12~36	651	21.90
48~72	469	15.78
72~144	157	5.28
Comorbidity		
Allergic Asthma (AA)	866	29.14
Allergic rhinitis (AR)	1857	62.48
Atopic dermatitis (AD)	610	20.52
Allergens sIgE		
Negative (n,%)	930	31.29
Positive (n,%)	2042	68.71
Monosensitisation (n,%)	878	29.54
Polysensitisation (n,%)	1164	39.17

Table 2 Positive Distribution of sIgE of Different Allergens

Inhaled Allergens (n=2972)			Ingested Allergens (n=2972)		
Species	**n**	**%**	**Species**	**N**	**%**
HDM	1290	43.41	Milk	579	19.48
Cat dander	181	6.09	Egg white	553	18.61
Pollen tree (Poplar, Willow, Elm)	122	4.10	Beef	460	15.48
			Soybean	224	7.54
Ragweed	122	4.10	Freshwater fish	188	6.33
Mugwort	116	3.90	Crab	188	6.33
Cockroach	82	2.76	Marine fish	186	6.26
Mould	59	1.99	Peanut	125	4.21
Dog dander	58	1.95	Mutton	116	3.90
Humulus lupulus	56	1.88	Shrimp	100	3.36

in the preschool group, and 54.14% in the school-age group. The details of the positive distribution at different age groups were shown in Table 3. There were no significant differences in sensitivity to HDM between the genders and in different seasons (Supplementary Table 3).

With the number of comorbidities increasing, the positive rates of sensitization were 38.33%, 74.51%, 80.72%, and 89.05%, and the incidence of polysensitization was 44.66%, 56.48%, 59.54%, and 74.59%, respectively. Trend chi-square analysis found the sIgE positive rate and polysensitization increased significantly with the number of comorbidities ($\chi^2_{trend} = -5.28$, $P_{trend} < 0.0001$) (Table 4).

Considering HDM was the most common allergen in all age groups, the sensitivity level of HDM for the risk factor of comorbidity was analyzed by multivariate regression. As shown in Table 5, compared with AC children without allergic comorbidity, the risk of one comorbidity in level-1 HDM sensitivity was 102.993 times that in level-0 sensitivity(95% CI=14.343–739.546, P<. 0001). The risk of one comorbidity in level-5 HDM sensitivity was 197.828 times that in level-

Table 3 Positive Distribution of sIgE at Different Age Groups

Allergens	3~12m (n=1695)	12~36m (n=651)	48~72m (n=469)	>72m (n=157)	χ2trend	Ptrend
HDM	650(38.35)	306(47)	249(53.09)	85(54.14)	−6.6362	<0.0001***
Cat dander	90(5.31)	38(5.84)	43(9.17)	10(6.37)	−2.3812	0.0173
Elm/Willow/Poplar	53(3.13)	28(4.3)	26(5.54)	15(9.55)	−4.0664	<0.0001***
Ragweed	60(3.54)	26(3.99)	23(4.9)	13(8.28)	−2.6585	0.0078**
Mugwort	52(3.07)	26(3.99)	26(5.54)	12(7.64)	−3.4611	0.0005***
Cockroach	44(2.6)	18(2.76)	10(2.13)	10(6.37)	−1.3597	0.1739
Dog dander	37(2.18)	9(1.38)	9(1.92)	3(1.91)	0.6061	0.5445
Mould	29(1.71)	13(2)	10(2.13)	7(4.46)	−1.8744	0.0609
Humulus lupulus	23(1.36)	12(1.84)	16(3.41)	5(3.18)	−2.9618	0.0031**
Milk	451(26.61)	88(13.52)	32(6.82)	8(5.1)	11.3508	<0.0001***
Egg white	381(22.48)	105(16.13)	60(12.79)	7(4.46)	7.0393	<0.0001***
Beef	275(16.22)	96(14.75)	40(8.53)	49(31.21)	−0.2293	0.8186
Soybean	128(7.55)	44(6.76)	37(7.89)	15(9.55)	−0.5848	0.5587
Marine fish	98(5.78)	34(5.22)	42(8.96)	12(7.64)	−2.0656	0.0389*
Crab	92(5.43)	41(6.3)	41(8.74)	14(8.92)	−2.8433	0.0045**
Peanut	75(4.42)	17(2.61)	22(4.69)	11(7.01)	−0.7314	0.4646
Mutton	91(5.37)	15(2.3)	9(1.92)	1(0.64)	4.5744	<0.0001***
Freshwater fish	123(7.26)	32(4.92)	24(5.12)	9(5.73)	1.9105	0.0561
Shrimp	50(2.95)	19(2.92)	24(5.12)	7(4.46)	−2.0676	0.0387*

Notes: *P<0.05 **P<0.01 ***P<0.001.

Table 4 Positive Rates of sIgE in Children with Different Comorbidities

	AC (n=660)	AC+1 comobidity (n=1428)	AC+2 comobidities (n=747)	AC+3 comobidities (n=137)	χ2trend	Ptrend
Allergen (-) n (%)	40 (61.67)	364 (25.49)	144 (19.28)	15 (10.95)	−17.0672	<0.0001***
Allergens (+) n (%)	253(38.33)	1064(74.51)	603(80.72)	122(89.05)		
Monosensitisation n (%)	140(55.34)	463(43.52)	244(40.46)	31(25.41)	−5.2767	<0.0001***
Polysensitisation n (%)	113(44.66)	601(56.48)	359(59.54)	91(74.59)		

Note: ***P<0.001.

Table 5 The Risk of Allergic Morbidities at Different Level of HDM Sensitivity

The number of comorbidity	HDM sensitivity	OR	95% CI	P value
One comorbidity	Level 1	102.993	14.343–739.546	<0.0001
	Level 2	92.152	12.821–662.365	<0.0001
	Level 3	105.703	14.724–758.841	<0.0001
	Level 4	136.419	19.039–977.502	<0.0001
	Level 5	197.828	27.668->999.999	<0.0001
Two comorbidities	Level 1	123.24	16.967–895.18	<0.0001
	Level 2	146.063	20.165->999.999	<0.0001
	Level 3	175.732	24.323->999.999	<0.0001
	Level 4	273.864	38.078->999.999	<0.0001
	Level 5	330.878	46.076->999.999	<0.0001
Three comorbidities	Level 1	305.667	38.9->999.999	<0.0001
	Level 2	305.667	38.9->999.999	<0.0001
	Level 3	371.166	47.796->999.999	<0.0001
	Level 4	720.492	95.31->999.999	<0.0001
	Level 5	633.08	83.425->999.999	<0.0001

0 HDM (95% CI=27.668->999.999, P<. 0001). The risk of two comorbidities in level-1 HDM sensitivity was 123.24 times that in level-0 sensitivity(95% CI=16.967–895.18, P<. 0001). The risk of two comorbidities in level-5 HDM sensitivity was 330.878 times that in level-0 HDM (95% CI=46.076->999.999, P<. 0001). The risk of three comorbidities in level-1 HDM sensitivity was 305.667 times that in level-0 sensitivity(95% CI=38.9->999.999, P<. 0001). The risk of three comorbidities in level-5 HDM sensitivity was 633.08 times that in level-0 HDM (95% CI=83.425->999.999, P<. 0001). The results showed that with higher HDM sIgE titers, the risk of more comorbidities was significantly higher.

Discussion

The incidence of allergic conjunctivitis is increasing in children, which seriously affects eye health and quality of life. Changes in sensitization patterns are considered to be an important factor in the prevalence of allergic disease in children.[7] From infants and young children to adolescents, allergic symptoms and sensitization patterns change as the immune system develops. Early detection of allergens could facilitate allergy-related disease prevention in children. The quantitative value of sIgE levels was found to have a better ability to predict later allergic rhinoconjunctivitis and asthma.[8] However, it is unclear the pattern of allergens sIgE in children with AC and the association with other allergic comorbidities. In this retrospective cross-sectional study, we found the positive rate of sIgE was 66.69% in children with AC. The most common allergen was HDM in all age groups. With age, the positive rate of inhaled allergens increased, while the positive rate of ingested allergens decreased. The

frequency of positive sIgE and polysensitization increased significantly with the increase in the number of co-morbidities. The risk of comorbidities increased with high HDM-sIgE levels.

In the present study, the positive rate of sIgE was 66.96% in children with AC. Allergic rhinitis(AR) is the most common comorbidity (62.48%), followed by allergic asthma(AA) (29.14%) and allergic dermatitis(AD) (20.52%). The co-occurrence of AR and AC is higher than that of other allergic diseases. The ocular mucosa has a large surface area. It is therefore one of the most accessible sites allowing direct antigen deposition, leading to the initiation of the allergic cascade.[9] In terms of anatomical and physiological functions, the nasolacrimal duct as a drainage system maintains the connection between the conjunctiva and the nasal mucosa, and the conjunctiva can be regarded as the top of the respiratory system in fact. Since the conjunctiva exposure area covers several hundred square millimeters, the surface of the conjunctiva is a large exposure for inhaled allergen. Therefore, AC should be considered an integral part of respiratory allergic disease as "one airway, one disease".

HDM, the most important source of indoor allergens is recognized as the most important allergen of respiratory allergic diseases.[10] In our current study, HDM was also the most commonly allergen in AC children. The sensitivity distribution of different age groups had obvious changes. In the baby group (0.25~1-year-old), there was no statistical difference between the positive rates of inhalation (44.42%) and ingestion allergens (43.66%). After 1-year-old, with the increase of age, the positive rate of inhaled allergen increased, while the positive rate of ingested allergen decreased. Milk and white egg were the most common ingested allergen in the baby group (0.25~1-year-old), but the positive rate decreased gradually with age. The IgE positivity rate for inhaled allergens (most notably HDM) tended to increase with age. There was a decreasing trend in IgE positivity at the age of ingested allergens, such as milk and egg whites. The trends in allergens we observed were consistent with the results of previous studies.[8,11] After the child is born, the sequence of exposure to allergens is food, indoor and outdoor. As age increased, the sensitisation to food allergens decreased,[12] and sensitization to inhaled allergens increased.[13]

In addition, HDM was the most common allergen in all age groups, from infancy, early childhood, and preschool age to school-aged children. This result partly differs from previous studies. Allergies to milk and eggs most commonly occur before the age of 2–3 years, while sensitization to inhaled allergens occurs in later childhood and increases with age.[13,14] Milk allergies are most common in the first year of life, while allergies to inhaled allergens mostly occur later.[15] This difference may be related to the living environment in which the study subjects live. HDM occurs in homes in humid regions worldwide, but its densities vary tremendously between regions.[16] The population in this study came from southwest China, which is in the inland area of China, with an average annual temperature of 16–18°C and an average relative humidity of 70%~80%. The environmental relative humidity is a key climatic factor in determining mite prevalence.[17] Previous studies confirmed that HDM growth and allergen production occur more rapidly in moist and warm places.[16,18] The regional characteristics of southwest China can explain the high HDM allergy among children aged 0.25–3 years in our study. Therefore, for AC children living in regions with high humidity and temperature, adequate attention should be paid to the isolation measures of HDM allergy in infants and young children, which is as important as the prevention of ingested allergy.

We found a strong correlation between a higher frequency of polysensitization and more comorbidities in AC children. Polysensitization is common in children[19] and it is the expression of a distinct clinical, more severe, atopic phenotype and is associated with a significantly poorer quality of life.[19,20] Previous studies have found polysensitization in children was a significant independent risk factor for rhinoconjunctivitis.[12] A study in a pediatric population showed that children with polysensitization had higher symptom scores and severe clinical outcomes compared with monosensitization.[21] In addition, we report here the positive rate of sIgE was positively correlated with the number of comorbidities, from 38.33% of no comorbidity to 89.05% of three co-morbidities. The greater the number of co-morbidities in children with AC, the higher the rate of allergen positivity. In children with polysensitization, careful follow-up of the clinical symptoms of comorbidities and prompt treatment, in addition to the treatment of AC, can provide better relief of the clinical symptoms of allergic disease.

The results of this study revealed the risk of comorbidities increased with the increase of HDM-sIgE level. Recent studies have shown that sensitization to HDM is the start of sensitization to aero-allergens and polysensitization. Sensitization to dust mite at an early age may be a predictor for the development of polysensitization in children.[12]

A population-based study found inhalant allergen sensitization and allergic predisposition increased the risk of allergic diseases.[22] The early-life dust mites' exposure was associated with increased asthma risk.[23] In a multinational epidemiological study of asthmatics and non-asthmatics, HDM was the antigen most consistently associated with asthma or increased bronchial reactivity.[24] In a cross-sectional research of HDM-allergic patients, 95.8% had rhinitis, and 45.6% had asthma.[25] AR patients had a higher HDM-sIgE than asymptomatic subjects.[26] The quantity of HDM-sIgE was significantly correlated with the amount and frequency of longitudinal fractional exhaled nitric oxide (FeNO) increases in atopic asthmatic patients.[27] The level of sIgE HDM was higher in persistent asthma than in intermittent asthma.[28] These findings provided a possible explanation for the relationship between the high HDM-sIgE level and the risk for more comorbidities. Our finding reveals that a high-level of HDM sIgE may be a predictor for other allergic comorbidities in children with AC.

There are several limitations to this study. Firstly, this study is based on a retrospective study of EMR, which may result in selection bias. Children without allergen test results in EMR were excluded from this study. Research design is the main factor that causes the selection bias. Secondly, this is a single-center study in southwest China. Because the pattern of sensitization to specific allergens appears to depend on the geographic region,[29] it cannot be absolutely applicable to other regions and populations. A sample of multicenter data could be used to clarify this issue in the future. Thirdly, we did not test the local IgE for the tear fluid, and there is no direct evidence of ocular local HDM sensitization. Considering that other allergic comorbidities may be associated with systemic sensitization, we examine and analyze the pattern of serum sIgE. Serum sIgE can simultaneously demonstrate the sensitization of HDM in the conjunctiva and other organs (nose, skin, and respiratory tract). Previous studies have found a correlation between tear IgE and serum IgE. The total tear IgE score was correlated with the total and specific serum IgE levels in seasonal allergic conjunctivitis.[30] Specific IgE was detected in sera as well as in tears of allergic patients and tear-derived allergen-specific IgE exerted similar specificities to the corresponding IgE from serum in patients with allergic rhinoconjunctivitis.[31] The relationship between the total and specific IgE in the tear and allergic comorbidities could be clarified in further studies. Lastly, the results only found the association between HDM-sIgE levels and comorbidities in children with AC but did not clarify the underlying mechanism. Further research needs to be designed to reveal the causal relationship and the mechanisms involved.

Despite these limitations, the present study indicates a strong correlation between a higher frequency of polysensitization and more comorbidities. HDM is the most common allergen in AC children of different ages. High-level of HDM-sIgE may be a predictor for allergic comorbidities. In clinical practice, children with polysensitization and high-level of HDM sIgE will be an important target population for future intervention in other allergy-related disease prevention.

Availability for Data and Material

All data generated or analysed during this study are included in this published article.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University, Chongqing, China (2023-322). We obtained written informed consent from legal guardians for all participant.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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