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Under-diagnosis of atopic dermatitis in Puerto Rican children

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ABSTRACT

Background: Little is known about atopic dermatitis (AD) among children in Puerto Rico.
Objective: To examine risk factors and identify approaches to better diagnose AD in Puerto Rican children.
Methods: Case-control study of AD among 540 children aged 6–14 years in San Juan, Puerto Rico. AD was defined as: 1) physician-diagnosed AD, 2) RAST-AD: AD symptoms plus ≥1 positive IgE to allergens, and 3) STR-AD: AD-symptoms and skin test reactivity to ≥1 allergen. Logistic regression was used for the multivariable analysis. We also evaluated the diagnostic performance of various approaches by comparing their sensitivity, specificity, positive predicted value [PPV], negative predictive value [NPV], and area under curve [AUC]).
Results: Of the 70 children with STR-AD, only 5 (7.1%) had PD-AD. In children without asthma, a positive IgE to Dermatophagoides (D.) pteronyssinus and signs of mold/mildew at home were significantly associated with 3.3 and 5 times increased odds of STR-AD, respectively. Among children with asthma, private/employer-based health insurance and a positive IgE to D. pteronyssinus were each significantly associated with approximately twofold increased odds of STR-AD. A combination of current eczema symptoms and a positive IgE to *D. pteronyssinus* yielded a sensitivity ≥70%, specificity and NPV ≥95%, PPV ≥88%, and an AUC ≥0.85 for STR-AD. Replacing a positive IgE to D. pteronyssinus with a positive IgE to ≥1 allergen slightly increased sensitivity without affecting other parameters.
Conclusions: AD is markedly under-diagnosed by physicians in Puerto Rico. This could be improved by assessing eczema symptoms and measuring IgEs to common allergens.

Introduction

Atopic dermatitis (AD) is a common allergic disease worldwide, affecting over 20% of children in high income countries and rising in prevalence in low to middle income countries.[1,2] Among participants in a U.S.-based study, ~17.1% had eczematous symptoms but only 6% were diagnosed with AD, suggesting marked disease under-diagnosis and under-treatment.[3] In Puerto Rico, where atopic asthma is a major public health problem, 24.8% of second-grade children attending two schools had parental report of symptoms of atopic dermatitis.[4]

The "gold standard" for a diagnosis of AD consists of a thorough history and physical exam, combined with allergy skin testing. Such diagnostic approach, however, may not be feasible in epidemiologic studies or in underserved areas with limited access to an allergist, such as Puerto Rico. Some epidemiologic studies rely on questionnaire-reported symptoms or a physician's diagnosis to identify AD,[5] while others use a

Abbreviations: AD, Atopic dermatitis; STR, Skin test reactivity; RAST, Radioallergosorbent test; STR-AD, Skin test reactivity atopic dermatitis; PD-AD, Physician diagnosed atopic dermatitis; BMI, Body mass index; PPV, Positive predictive value; NPV, Negative predictive value; AUC, Area under curve; ROC, Receiver operating curve.

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combination of questionnaire-based data and objectively measured allergic sensitization.[6] Since self-reported diagnosis or symptoms are subject to recall and reporting bias, the ideal criteria to detect or diagnose AD in population-based studies remains to be established.[7]

AD frequently occurs during infancy, often serving as a harbinger of other atopic diseases during childhood, including allergic rhinitis and asthma. Indeed, up to 80% of children with AD may develop or have concurrent allergic rhinitis or asthma.[8] In addition to such atopic diseases, common risk factors or co-morbidities of AD include low income,[2] obesity,[9] dust mite allergen exposure,[10] and an elevated total serum IgE.[11,12]

We hypothesized that AD would be markedly under-diagnosed among Puerto Rican children living in the island of Puerto Rico, where fewer than fifteen allergists served a population of 3.7 million people before Hurricane Maria. We further hypothesized that such under-diagnosis of AD could be reduced by obtaining a history of symptoms suggestive of eczema and measuring levels of IgE to common allergens.

In this report, we estimated and compared the prevalence of AD identified through self-reported symptoms and objectively measured allergic sensitization against that of physician-diagnosed-AD among 540 Puerto Rican children aged 6–14 years living in the metropolitan area of San Juan, PR.

Methods

Subject recruitment

From March of 2009 to June of 2010, children were recruited for a case-control study of asthma from randomly selected households in San Juan (Puerto Rico). As previously described,[15] households in the metropolitan area of San Juan were selected by a multistage probability sampling design. Primary sampling units were randomly selected neighborhood clusters based on the 2000 U.S. census. Secondary sampling units were randomly selected households within each primary sampling unit. A household was included if ≥1 resident was a child aged 6–14 years whose four grandparents were all Puerto Rican. In households with >1 eligible child, only one child was randomly selected for screening. On the basis of the sampling design, 7073 households were selected and 6401 (90.5%) were contacted. Of these 6401 households, 1111 had ≥1 child who met inclusion criteria. In an effort to reach a target sample size of approximately 700 children, we attempted to enroll a random sample (n = 783) of these 1111 eligible children. We were able to obtain parental consent for 678 of these 783 children. There were no significant differences in age, gender, or area of residence between eligible children who did (n = 678 [86.6%]) and did not (n = 105 [13.4%]) agree to participate. Of the 678 participating children, 540 (79.7%) had complete data on allergy skin testing, levels of allergen specific-IgEs, and parental report of AD symptoms, and were thus included in the current analysis.

Cases had asthma, defined as parental report of physician-diagnosed asthma and at least one episode of wheeze in the previous year. Control subjects had neither parental report of physician-diagnosed asthma nor wheeze in the prior year.

Study procedures

Study participants completed a protocol that included questionnaires, allergy skin testing, and collection of blood (for measurement of total and allergen-specific IgEs). One of the child's parents (usually [>93%] the mother) completed questionnaires about the child's general and respiratory health, socio-demographic and household characteristics, and family history of asthma and allergic diseases. Height and weight were measured to the nearest centimeter and pound, respectively.

Plasma levels of total IgE and IgEs to five common allergens (dust mite [Der p 1], cockroach [Bla g 2], cat dander [Fel d 1], dog dander [Can f 1], and mouse urinary protein [Mus m 1]) were determined using the UniCAP 100 system (Pharmacia & Upjohn, Kalamazoo, MI). For each allergen, an IgE ≥0.35 IU/ml was considered positive. Skin test reactivity (STR) to aeroallergens was assessed using a Multi Test device (Lincoln Diagnostics, Decatur, IL). In addition to histamine (positive control) and saline solution (negative control), allergen extracts from dust mites (Dermatophagoides (D.) pteronyssinus, D. farinae and Blomia tropicalis), house dust, German cockroach (Blatella germanica), cat dander, dog dander, mixed grass pollen, mugwort sage, ragweed, mixed tree pollen, mold mix, Alternaria tenuis and mouse urinary protein were applied to the skin of the forearm in a site free of eczema (Alk-Abello, Round Rock, Texas). Skin test reactivity (STR) was defined as a maximum wheal diameter exceeding the saline diluent wheal diameter by at least 3 mm.

Written parental consent was obtained for participating children, from whom written assent was also obtained. The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Juan, PR), Brigham and Women's Hospital (Boston, MA), and the University of Pittsburgh (Pittsburgh, PA).

Statistical analysis

We analyzed and compared several definitions of AD, as follows: 1) physician-diagnosed AD (PD-AD), 2) current symptoms suggestive of AD (AD symptoms), defined as a positive response to the following two questions (a) "Has your child ever had a prolonged, itchy, scaly or weepy skin rash?" and (b) "Has your child had this rash in the last 12 months?", 3) RAST-AD, defined as AD-symptoms plus at least one positive IgE to allergens, and 4) STR-AD, defined as AD-symptoms and STR to at least one allergen.

Bivariate analyses were conducted using two-sample *t*-tests (for continuous variables) and chi-square tests or Fisher's exact tests (for categorical variables). Logistic regression was used for the multivariable analysis of STR-AD. All multivariable models included age, gender, body mass index as a z-score (based on 2000 CDC growth charts[13]), and asthma. The following covariates were also included in the initial multivariable models, if associated with STR-AD at $P \leq 0.25$ in bivariate analyses: parental education (either parent completed high school vs. none), household income (<vs. ≥ $15,000/year [near the median income for households in Puerto Rico in 2008–2009[14]]),[15] type of health insurance (public vs. private or employer-based), parental history of eczema, current exposure to second-hand smoke (SHS), day care attendance in the first year of life, plasma total IgE, a positive IgE to each allergen, a positive IgE to at least one allergen, and parental report of each of the following: signs of mold or mildew in the house, sighting cockroaches, and sighting mice. Because of collinearity, the initial multivariable models included only one of the significant total or allergen-specific IgE measures (i.e. we did not include total IgE and a positive IgE to dust mite in the same model). These additional covariates remained in the final models if they were associated with AD at $P < 0.05$ or if they changed the estimate of effect (β) by ≥ 10%. For test parameters, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for STR-AD, as follows: 1) Sensitivity $= \frac{True\ positives}{True\ positives + False\ negatives} \times 100$, 2) Specificity $= \frac{True\ negatives}{True\ negatives + False\ positives} \times 100$, 3) Positive predictive value (PPV) $= \frac{True\ positives}{True\ positives + False\ positives} \times 100$, and 4) Negative predictive value (NPV) $= \frac{True\ negatives}{True\ negatives + False\ negatives} \times 100$. Receiver operating curve (ROC) was plotted as sensitivity against (1 − specificity). The area under the curve (AUC) of ROC was used to assess diagnostic performance. R program (Version 3.4.2) was used for all analyses.

Results

eTable 1 shows the comparison of the main characteristics of study participants who were (n = 540) and were not (n = 138) included in the current analysis. Compared with children who were included in the

Table 1
Characteristics of study participants.[a]

	Children without asthma (n = 254)		Children with asthma (n = 286)	
	No STR-AD[b] (n = 234)	STR-AD (n = 20)	No STR-AD (n = 236)	STR-AD (n = 50)
Age, year	10.5 ± 2.7	10.9 ± 2.7	10.0 ± 2.6	10.2 ± 2.6
Female sex	126 (53.8)	9 (45.0)	94 (39.8)	25 (50.0)
Parental educational (>high school)	183 (78.2)	18 (90.0)	188 (79.7)	43 (86.0)
Household income >$15,000	78 (34.7)	11 (55.0)	68 (29.7)	20 (40.0)
Private or employer-based health insurance	85 (36.3)	8 (40.0)	65 (27.5)	22 (44.0) *
BMI z-score	0.5 ± 1.1	0.8 ± 1.1	0.7 ± 1.2	0.7 ± 1.2
Current allergic rhinitis[c]	55 (23.7)	15 (75.0) **	145 (61.7)	45 (91.8) **
Parental history of eczema	3 (1.3)	0 (0.0)	8 (3.4)	4 (8.3)
Daycare attendance in the first year of life	43 (18.6)	6 (30.0)	55 (23.6)	13 (26.0)
Home environment				
Signs of mold or mildew	75 (32.2)	14 (70.0) **	108 (45.8)	22 (44.0)
Seeing cockroaches	187 (79.9)	13 (65.0)	181 (76.7)	41 (82.0)
Seeing mice	64 (27.4)	1 (5.0) *	66 (28.0)	16 (32.0)
Current second-hand smoke exposure	89 (38.0)	9 (45.0)	102 (43.6)	24 (48.0)
Total IgE[d] (IU/ml)	2.1 ± 0.7	2.6 ± 0.7 *	2.4 ± 0.7	2.7 ± 0.6 *
Allergen-specific IgE ≥0.35 IU/ml				
>= 1 allergen	109 (46.6)	15 (75.0) *	158 (66.9)	41 (82.0) *
Dust mite (Der p 1)	94 (40.2)	14 (70.0) *	147 (62.3)	39 (78.0) *
Cockroach (Bla g 1)	60 (25.6)	7 (35.0)	91 (38.6)	24 (48.0)
Cat (Fel d 1)	14 (6.0)	2 (10.0)	25 (10.7)	7 (14.3)
Dog (Can f 1)	31 (13.2)	6 (30.0)	47 (19.9)	14 (28.0)
Mouse (Mus m 1)	2 (0.9)	1 (5.0)	11 (4.7)	1 (2.0)

*$P < 0.05$ and **$P < 0.01$ for the comparison of subjects with and without STR-AD in each group (i.e. no asthma or asthma).
[a] Values are presented as number (%) or mean (mean ± standard deviation). Numbers might vary because of missingness.
[b] STR-AD was defined as having symptoms suggestive of atopic dermatitis and at least one positive skin test to the allergens tested.
[c] Current allergic rhinitis was defined as naso-ocular symptoms apart from colds in the prior year, plus at least one positive skin test to the allergens tested.
[d] Log_{10} transformed.

analysis, those excluded were significantly more likely to have a household income >$15,000 per year and a lower BMI z-score, but significantly less likely to be currently exposed to second-hand smoke. There were no significant differences in age, gender, type of health insurance, parental education, parental history of eczema, day care attendance in the first year of life, signs of mold or mildew in the home, or sighting pests (cockroaches or mice) between children who were and were not included in the current analysis.

The characteristics of study participants, according to whether they did or did not have STR-AD, as well as asthma, are shown in Table 1. Of the 540 participants, 70 (13.0%) had STR-AD.

Among children with asthma, those with STR-AD were significantly more likely to have private or employer-based health insurance than those without STR-AD. Among children without asthma, those with STR-AD were significantly more likely to have a parent report signs of mold or mildew in the home, but less likely to sighting mice, than those without STR-AD. Among children with and without asthma, those with STR-AD were significantly more likely to have current allergic rhinitis, an increased total IgE, and a positive IgE to D. pteronyssinus than children without STR-AD. There was no significant difference in current SHS or any other characteristic between children with and without STR-AD, regardless of asthma status.

We next calculated the proportion of subjects with STR-AD who were also diagnosed by a physician (i.e. who had PD-AD). Of the 70 subjects with STR-AD, only 5 (7.1%) also had PD-AD (Fig. 1, **Panel A**). This marked under-diagnosis of STR-AD was similar in children with and without asthma (Fig. 1, **panels B and C**).

Table 2 shows the results of the multivariable analysis of STR-AD, separately in children with and without asthma. In the analysis among children without asthma (which was adjusted for age, gender, and BMI z-score), having a positive IgE to D.pteronyssinus and parental report of mold or mildew at home were significantly associated with 3.3 times and

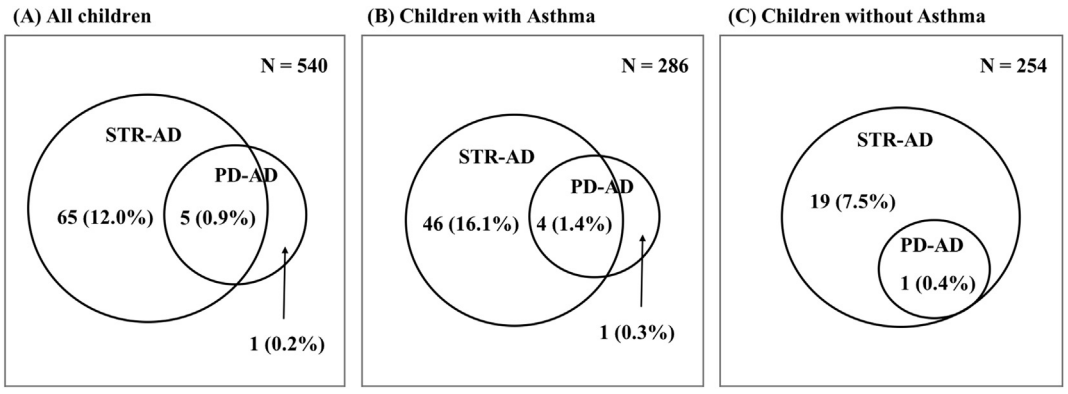

Fig. 1. Venn diagram of STR-AD and PD-AD in all children (A), in children with asthma (B) and in children without asthma (C).

Table 2
Multivariable analysis of STR-AD in children with and without asthma.[a]

	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
	OR (95%CI)		OR (95%CI)		OR (95%CI)	
No asthma (n = 254)						
Had private or employer-based health insurance	1.12 (0.41, 3.09)	0.82	1.16 (0.42, 3.20)	0.77	1.25 (0.45, 3.46)	0.67
Signs of mold or mildew	4.97 (1.77, 13.98)	0.002	5.29 (1.87, 14.98)	0.002	5.29 (1.86, 15.10)	0.002
Seeing mice at home	0.13 (0.02, 1.01)	0.05	0.12 (0.02, 0.98)	0.048	0.13 (0.02, 1.01)	0.05
Positive IgE to D. pteronyssinus	3.31 (1.17, 9.42)	0.03				
≥1 positive IgE to allergens			3.53 (1.18, 10.61)	0.03		
Total IgE[b]					2.70 (1.22, 5.99)	0.02
Asthma (n = 286)						
Had private or employer-based health insurance	2.00 (1.04, 3.86)	0.04	2.06 (1.07, 3.95)	0.03	2.26 (1.18, 4.35)	0.01
Positive IgE to D. pteronyssinus	1.98 (0.95, 4.11)	0.07				
≥1 positive IgE to allergens			2.12 (0.96, 4.65)	0.06		
Total IgE[b]					1.79 (1.08, 2.96)	0.02

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] All models were adjusted for age, gender, and BMI *z*-score.
[b] Presented per each log unit increment.

Table 3
Sensitivity, specificity, PPV, NPV and AUC under ROC for PD-AD and various predictive approaches.[a]

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95%CI)
Physician-diagnosed AD					
No asthma	5.0	100.0	100.0	92.5	0.53 (0.48, 0.57)
Asthma	8.0	99.6	80.0	83.6	0.54 (0.50, 0.58)
All	7.1	99.8	83.3	87.8	0.54 (0.50, 0.57)
Current AD symptoms and +IgE to D. pteronyssinus					
No asthma	70.0	99.6	93.3	97.5	0.85 (0.75, 0.95)
Asthma	78.0	97.9	88.6	95.5	0.88 (0.82, 0.94)
All	75.7	98.7	89.8	96.5	0.87 (0.82, 0.92)
Current AD symptoms and ≥1 positive IgE to allergens					
No asthma	75.0	99.6	93.8	97.9	0.87 (0.78, 0.97)
Asthma	82.0	97.9	89.1	96.3	0.90 (0.85, 0.95)
All	80.0	98.7	90.3	97.1	0.89 (0.85, 0.94)

Abbreviations: AD, atopic dermatitis; PPV, positive predictive value; NPV, negative predictive value; AUC, area under curve.
[a] AUC adjusted for age, gender, and body mass index (BMI) *z*-score.

5 times increased odds of STR-AD, respectively (Model 1). Similar results were obtained when a positive IgE to D. pteronyssinus was replaced with having ≥1 positive IgE to allergens (Model 2) or with total IgE (Model 3). In all three multivariable models, there was a trend for an inverse association between parental report of sighting mice and STR-AD, but such trend was non-statistically significant (models 1 and 3) or of borderline statistical significance (model 2). In the multivariable analysis of STR-AD among children with asthma (also adjusted for age, gender, and BMI *z*-score), having private or employer-based health insurance was significantly associated with approximately twofold increased odds of STR-AD (Model 1). Similar results were obtained when a positive IgE to D. pteronyssinus was replaced with either ≥1 positive IgE to allergens (Model 2) or total serum IgE (Model 3).

Table 3 shows the sensitivity, specificity, PPV, NPV and AUC of various approaches to the diagnosis of STR-AD in Puerto Rican children, which were partly based on the results of our multivariable analysis (see Table 2). PD-AD had high specificity but very low sensitivity and a low AUC for STR-AD, both in children with and without asthma. A combination of AD symptoms and a positive IgE to *D. pteronyssinus* yielded sensitivity ≥70% and specificity ≥95%, NPV ≥95% and PPV ≥88%, and an AUC ≥0.85 for STR-AD, both in children with and without asthma. Replacing a positive IgE to *D. pteronyssinus* with a positive IgE to ≥1 allergen slightly increased sensitivity (i.e. from 75.7% to 80% in all children) but had minimal impact on all other parameters (specificity, NPV, PPV or the AUC).

Discussion

We found that ~93% of cases of STR-AD among children in Puerto Rico had not been diagnosed by a physician, possibly due to limited access to healthcare (particularly allergists) in Puerto Rico.[15,16]

A previous study of AD among children ages 6–7 years who attended two schools in Puerto Rico found that the prevalence of parental report of current eczema symptoms was 24.8%,[4] and that ~70% of children with such symptoms had not been diagnosed with AD by a physician. In contrast to that study, we assessed not only eczema symptoms but also skin test reactivity to allergens and levels of total/allergen-specific IgEs in a population-based sample of school-aged children aged 6–14 years. Moreover, the response rate in the previous study (53%) was substantially lower than that in the current study.

Consistent with findings in other populations, we show that a positive IgE to common allergens such as house dust mite or an elevated total serum IgE is significantly associated with STR-AD.[6] Indeed, dust mite allergen exposure has been linked to eczematous symptoms,[2,8] and high dust mite allergen levels have been reported to be both common and associated with asthma and other allergic diseases in Latin America.[17] In contrast to our findings for total IgE and STR-AD, Perkins *et al* reported that total IgE plays little role in prediction of visible eczema at 5 years, despite a significant association between total IgE and eczema severity.[12] On the other hand, Ville *et al* showed that reductions in total IgE are associated with good treatment response and complete remission of AD[11]

Among children without asthma, we found that signs of mold or mildew in the house are associated with STR-AD. Such exposure could alter the skin barrier, a first step in AD pathogenesis.[18] However, the impact of reducing mold or mildew on AD, if any, is unknown.[19] Among children with asthma, we show that private or employer-based health insurance is significantly associated with STR-AD, likely due to improved access to healthcare.

We show that a combination of current eczematous symptoms and ≥1 positive IgE to common allergens could markedly improve the diagnostic rate of STR-AD among physicians in Puerto Rico. Indeed, such approach yielded a sensitivity of 80%, plus high: specificity, PPV, NPV, and AUC for STR-AD in all children. Of interest, replacing ≥1 positive IgE to allergens with a positive IgE to dust mite yielded a comparably high sensitivity (i.e. ≥76%) for STR-AD in all children, thus supporting a relatively simple and cost-effective approach to AD diagnosis and care in Puerto Rico.

Our study has substantial strengths, including a population-based sample of school-aged children and data on objective measures of allergic sensitization.[4] We also recognize several study limitations. First, we cannot assess temporal relationships due to the cross-sectional study

design. Second, we did not conduct direct skin examinations. However, we used a combination of STR to allergens and questionnaire-based data for our "reference diagnosis of AD". Third, selection bias and recall bias are possible in any observational study such as ours. However, selection bias is an unlikely explanation for our results, since there was no significant difference in most relevant characteristics (i.e. type of health insurance, parental history of eczema, signs of mold or mildew in the home) between children who were and were not included in our analysis. Similarly, poor parental understanding or recall of a physician's diagnosis of eczema is not probable as the sole explanation for the marked under-diagnosis of STR-AD in study subjects. Finally, we had no data on some potential confounders, such as diet.

In summary, only 7.1% of cases of STR-AD among school-aged Puerto Rican children were diagnosed by a physician, as reported by the child's parents. Physicians in Puerto Rico could improve their diagnostic accuracy for AD by inquiring about current eczematous symptoms, conducting a clinical examination of the skin, and measuring IgEs to a panel of common allergens (or, if that were non-feasible, IgE to house dust mite).

Ethics approval and consent to participate

The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Juan, PR), Brigham and Women's Hospital (Boston, MA), and the University of Pittsburgh (Pittsburgh, PA). Written parental consent was obtained for participating children, from whom written assent was also obtained.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

Dr. Celedón has received research materials from Merck and GSK (inhaled steroids), and Pharmavite (vitamin D and placebo capsules), to provide medications free of cost to participants in NIH-funded studies, unrelated to the current work. The other authors report no competing interests.

Authors' contributions

GY and JCC conceived of the study and participated in its design, and drafted the manuscript. GY, YYH, EF, and WC performed statistical analysis. EAP, ACS, MA, and GC participated in the design and coordination of the study. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2018.11.003.

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