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Original article

The challenge of diagnosing atopic diseases: outcomes in Cuban children depend on definition and methodology

Background: Prevalences of childhood asthma and other atopic diseases are increasing worldwide, and so is the number of diagnostic methods and definitions used. We determined the occurrence of atopic diseases in Cuban children with a range of diagnostic approaches commonly used or proposed in epidemiological studies, and compared the different outcome measures.
Methods: A total of 398 Cuban schoolchildren between 5 and 13 years of age were diagnosed by International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, clinical examination, pre- and post-exercise spirometry, and skin prick testing. All results were considered separately, as well as jointly by using scores and definitions as described in the literature.
Results: Using questionnaire-based approaches, 21–39% of the children were positive for asthma, 9–19% for atopic dermatitis, and 15–46% for rhinoconjunctivitis. With spirometry, 7% of the children had asthma. Definitions based on a combination of questionnaire and spirometry results yielded asthma rates of 5%. Of all children, 6% wheezed on clinical examination, and only one child showed clinical signs of atopic dermatitis. Eleven percent of the children had a positive skin prick test. In total, 254 children (64%) had an atopic disease as based on the ISAAC questionnaire, and 263 (66%) based on all approaches used.
Conclusion: Diagnostic outcomes on atopic diseases vary considerably depending on definition and methodology. Our results clearly demonstrate the need for consensus on diagnosing asthma and other atopic diseases in epidemiological studies. Based on the most commonly used ISAAC questionnaire, our data suggest prevalences of atopic diseases in Cuban children that rival those found in some other Latin American countries and developed nations with the highest prevalences in the world.

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Childhood atopic diseases are an increasingly important public health problem worldwide (1). They are generally reported to be higher in the developed than in the developing world. Yet, important inter- and intra-country variations exist, such as in Latin America where in some countries asthma rates are among the highest in the world while in others they are relatively low (2).

The most commonly used diagnostic method in epidemiological studies on atopic diseases in children is the International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire. The ISAAC study is an international study that examined the prevalences of atopic childhood diseases in 721 601 children aged 13–14 years and 6–7 years in 156 centers in 56 countries (3). In Latin America the participating countries were Argentina, Brazil, Chile, Costa Rica, Mexico, Panama, Paraguay, Peru and Uruguay. So far Cuba has not participated in the ISAAC study. Asthma is an important disease in Cuba, with one of the highest mortality rates in the world. (1) To our knowledge, no published data are available on other atopic diseases in Cuba.

Besides ISAAC and other questionnaires, clinical and objective markers have been used increasingly in the epidemiology of atopic diseases, such as wheeze on auscultation as well as pulmonary function testing to demonstrate airway hyperresponsiveness, and allergen skin prick tests or serum immunoglobulin-E assays to determine the presence of atopy. A considerable number of definitions for asthma and other atopic diseases have concurrently been proposed, based on one or a combination of these methods, and using different scores or algorithms.

In this study we measured atopic diseases (asthma, atopic dermatitis and allergic rhinoconjunctivitis) in Cuban children using the ISAAC questionnaire and other diagnostic methods commonly used in epidemiology. We considered the results independently as well as in combination by using scores and other approaches as

defined in the literature, and compared and evaluated the different outcomes.

Methods

Study group

The study was performed in Pinar del Rio, a province in the west of Cuba, from November 2003 to January 2004. A total of 398 children from five randomly selected primary schools were included in the study. Their age range was 5–13 years (median 8 years); 116 children (29%) were 6–7 years old. The sample consisted of 191 boys (48%) and 209 girls (52%); 206 children (52%) were from urban, 192 (48%) were from rural schools. Informed written consent was obtained from the parents of each child. The study was approved by the ethical committees of the Institute of Tropical Medicine in Antwerp, Belgium and the National Institute for Hygiene, Epidemiology and Microbiology in Havana, Cuba.

Study design

Children were submitted to a parental questionnaire, and underwent clinical examination, spirometry before and after exercise, and skin prick testing. These are commonly used methods in the epidemiology of atopic diseases in schoolchildren (4).

A parent or guardian of each child was interviewed by using an extended version of the ISAAC questionnaire. The ISAAC core questionnaire consists of eight questions about respiratory symptoms to diagnose asthma, six questions on symptoms of allergic rhinoconjunctivitis and seven questions concerning atopic dermatitis (5). Additional questions included regular intake of medication and physician's confirmation of atopic disease.

Each child was clinically examined by a physician. A thorough inspection of the skin, eyes, neck, elbows, knees and ankles (4) was performed for signs of atopic dermatitis, as well as auscultation of the lungs and heart for signs of asthma. For allergic rhinoconjunctivitis no standard clinical criteria exist.

Skin prick testing for atopy was performed using extracts of seven allergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cat dander, mixed tree, mixed grass, *Alternaria alternata*, and cockroach) produced by ALK (Nieuwegein, the Netherlands). Histamine (10 mg/ml) was used as a positive and allergen diluent as a negative control. The extracts and controls were placed on the volar side of the left forearm using separate ALK lancets. Skin response was measured after 15 min, considering a wheal of 3 mm or larger in the absence of significant reactivity of the diluent control as a positive reaction. Children with at least one positive skin reaction were considered atopic. Children taking regular short-acting antihistamines were instructed to refrain from taking them for at least 72 h prior to skin prick testing.

To demonstrate bronchial hyperresponsiveness (BHR), spirometry was performed before and 5 and 10 min after exercise (6 min free running). Children were asked to refrain from taking short-acting inhaled bronchodilators at least 8 h prior to examination (6) and not to run or play heavily prior to spirometry. Weight and body length were measured to compare spirometry results with standard curves. Forced expiratory volume in 1 s (FEV_1) was measured using a handheld computerized spirometer (spirobank; MIR, Rome, Italy) and the child in the upright position wearing a noseclip. At each time point, three to eight expiratory maneuvers were obtained according to the American Thoracic Society (ATS) guidelines (7). If at baseline the FEV_1 was lower than 70% of the predicted value, no exercise challenge was performed. After exercise, a child was considered hyper-responsive if the FEV_1 had fallen more than 15% either 5 or 10 min after running. In all three cases, the child received a bronchodilator to aid recovery, and spirometry was repeated after 20 min to make sure that the baseline values were obtained again. Pre- and post-exercise pulse as well as outside temperature and humidity were monitored according to ATS suggestions (6).

For the ISAAC questionnaire itself, answers were evaluated by using scores as defined in the literature (8–14). Only scores based on the ISAAC questionnaire were used. In addition, the results of each diagnostic method were considered both independently and in different combinations, using definitions of asthma and other atopic diseases for epidemiological studies as described in the literature (12, 15). Table 1 shows an overview of diagnostic scores and definitions for the respective atopic diseases.

Table 1. Overview of scores and definitions for asthma, allergic rhinoconjunctivitis and atopic dermatitis diagnosis as defined in the literature

Reference	Description/definition
ISAAC Steering Committee: 'current asthma' (2)	Affirmative answer to second core question of ISAAC questionnaire on asthma
Sole et al. (8): 'asthma score'	ISAAC asthma core questions are graded a score from 0 to 2; asthmatic if global score is at least 5–6 (depending on age)
Rosario and Ferrari (11): 'probable asthma'	More than four attacks of wheezing in the last 12 months, or one to three attacks plus disturbed sleep because of wheezing and/or dry cough at night and wheezy after exercise (i.e. core questions 3, 4, 7 and 8 of the ISAAC questionnaire of asthma)
Toelle et al. (15): 'current asthma'	Bronchial hyperresponsiveness plus wheeze during the last 12 months
Gruchalla et al. (12): 'probable asthma'	Positive global asthma score according to Sole et al. (8), and a post-exercise decrease in FEV_1 of at least 15%
Gruchalla et al. (12): 'rhinitis positive'	At least one affirmative answer to any of the five yes/no ISAAC core questions on rhinitis
Celedon et al. (13): 'allergic rhinitis'	Affirmative answer to the first two core questions of the ISAAC questionnaire on rhinitis
ISAAC Steering Committee, Strachan et al. (14): 'rhinoconjunctivitis'	Affirmative answer to core questions 2 and 3 of the ISAAC questionnaire on rhinitis
Vanna et al. (9): 'score rhinitis'	ISAAC core questions on rhinitis are graded a score from 0 to 2; positive for rhinitis if global score is at least 3–4 (depending on age)
ISAAC Steering Committee, Williams et al. (16): 'atopic eczema'	Affirmative answer to core questions 2 and 3 of the ISAAC questionnaire on atopic eczema
Yamada et al. (10): score atopic eczema'	ISAAC core questions on atopic eczema are graded a score from 0 to 2; positive for atopic eczema if global score is at least 3

ISAAC, International Study of Asthma and Allergies in Childhood.

Results

Parental questionnaire data were available for all children (100% response rate). The questionnaire results are shown in Table 2. The answers to the eight core questions on asthma yielded symptom percentages between 7% and 48%. Using the ISAAC definition of current asthma (an affirmative answer to the second core question on asthma 'Wheezing during the last 12 months'), 30% of the children were asthmatic. Thirty-eight percent of all children had ever been diagnosed asthmatic by a physician. Applying the score defined by Sole et al. (8) 154 children (39%) were considered asthmatic. Twenty-one percent of the children were diagnosed as asthmatic with the score for 'probable asthma' of Rosario and Ferrari (11).

For allergic rhinoconjunctivitis, the answers to the six core questions yielded percentages of symptoms between 9% and 36%. Using the ISAAC definition for allergic rhinoconjunctivitis as established by Strachan et al. (14) 15% of the children had allergic rhinoconjunctivitis. Using other scores found in the literature, allergic rhinoconjunctivitis was diagnosed in 36% (9), 46% (12), and 32% (13).

For atopic dermatitis, the answers to the seven core questions yielded symptom percentages between 8% and 26%. Using the ISAAC definition for atopic dermatitis by Williams et al. (16) 9% of the children in our study population were diagnosed as suffering from atopic dermatitis, and 3.5% were considered to be suffering from severe atopic dermatitis. Applying the score that Yamada et al. (10) used in Brazilian children, 19% had atopic dermatitis.

Another method used for diagnosing asthma was the measurement of FEV_1 before and after exercise challenge. Three children did not participate in the free running test because of physical or learning disability. Of the 395 remaining children, only 27 (7%) had an abnormal spirometry, eight with an initial FEV_1 $<70\%$ of the predicted value before and 19 with a decrease of $\geq 15\%$ after running.

Applying the definitions of Toelle et al. (15) and Gruchalla et al. (12) based on a combination of questionnaire and spirometry results, 20 (5%) and 19 children (5%), respectively, were found asthmatic.

Few children showed clinical signs of asthma or atopic dermatitis; 24 (6%) of all children wheezed on clinical examination and only one child ($<1\%$) showed clinical signs of atopic dermatitis. No clinical examination was performed for allergic rhinoconjunctivitis.

Skin prick reactivity was found against *D. pteronyssinus* (5%), *D. farinae* (2%) and against cockroach (8%). Less than 1% of the children had skin reactions to cat dander, alternaria, mixed grass and mixed tree. All children showed a positive reaction to the positive histamine control and none of them had a reaction to the negative control. In total 43 children (11%) had a positive skin reaction to at least one of the applied allergens. One hundred and one children (25%) were taking regular short-acting anti-allergic medication. Ten children ($<3\%$) had a positive skin prick test reaction and took antiallergic medication.

Table 2. Frequency of symptoms of asthma, allergic rhinoconjunctivitis and atopic dermatitis in 398 Cuban children, using the ISAAC core questionnaire (1–8), scores (9–12) and additional questions (13, 14)

Score	Asthma	*n* (%)	Allergic rhinoconjunctivitis	*n* (%)	Atopic dermatitis	*n* (%)
1	Wheezing ever	193 (48)	Nasal symptoms ever	145 (36)	Skin eruption ever	103 (26)
2	Wheezing last 12 months	119 (30)	Nasal symptoms last 12 months	134 (34)	Skin eruption last 12 months	56 (14)
3	No. asthma attacks last 12 months					
	1–3	76 (19)	With itchy-watery eyes	64 (16)	Localization of eruption on typical places	43 (11)
	4–12	21 (5)				
	>12	16 (4)				
4	No. problems at night					
	<1 per week	32 (8)	Interruption daily activities	36 (9)	Age of onset <2 years	20 (5)
	≥1 per week	47 (12)				
5	Problems with talking	29 (7)	Ever allergic rhinitis	128 (32)	Complete remission	38 (10)
6	Ever asthma	166 (42)			Trouble at night last 12 months	32 (8)
7	Problems during exercise last 12 months	54 (14)			Ever atopic dermatitis	52 (13)
8	Dry cough at night	190 (48)				
9	'Asthma score', Sole et al. (8)	154 (39)	'Score rhinitis', Vanna et al. (9)	142 (36)	'Score atopic eczema', Yamada et al. (10)	74 (19)
10	'Probable asthma', Rosario & Ferrari (11)	83 (21)	'Rhinitis positive', Gruchalla et al. (12)	184 (46)	'Atopic eczema', ISAAC, Williams et al. (16)	37 (9)
11			'Rhinoconjunctivitis', ISAAC, Strachan et al. (14)	61 (15)	'Severe atopic eczema', Williams et al. (16)	14 (3.5)
12			'Allergic rhinitis', Celedon et al. (13)	129 (32)		
13	Asthma confirmed by physician	151 (38)				
14	Medication asthma	29 (7)				

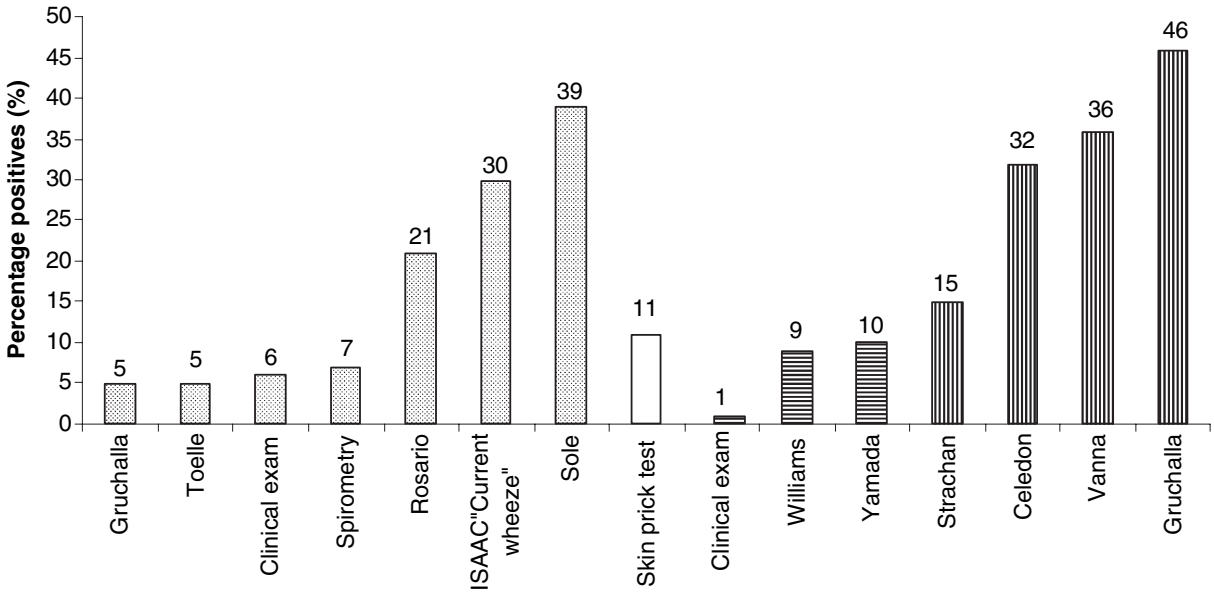

Figure 1. Percentages of asthma, atopic dermatitis and allergic rhinoconjuctivitis in Cuban children, according to each method, including the scores and definitions as described in Table 1. Dotted bars denote criteria for diagnosis asthma. Horizontally hatched bars denote atopic dermatitis. Vertically hatched bars denote allergic rhinoconjunctivitis. Blank bar denotes atopy as defined by skin prick test.

Figure 1 shows the percentages of positive children with asthma, atopic dermatitis and allergic rhinoconjunctivitis according to each method (written questionnaire as well as clinical and objective markers), using the scores and definitions as described in the literature. It is clear that percentages differ substantially according to method or definition used.

Figure 2 combines the results for the three atopic diseases, considering each child who was positive for at least one score or definition as having an atopic disease. Based on the questionnaire, 254 (64%) of all children were found to have an atopic disease: 153 (38%) could be called asthmatic, 184 (46%) had allergic rhinitis and 74 (19%) were found to have atopic dermatitis. Adding the results of the other (combinations of) methods, we found only nine (2%) more children with at least one atopic disease, thus totalling 263 (66%) children. Combining the outcomes of all methods described in this paper, including the skin prick test, a total of 278 (70%) of the Cuban children were found to have an atopic disease.

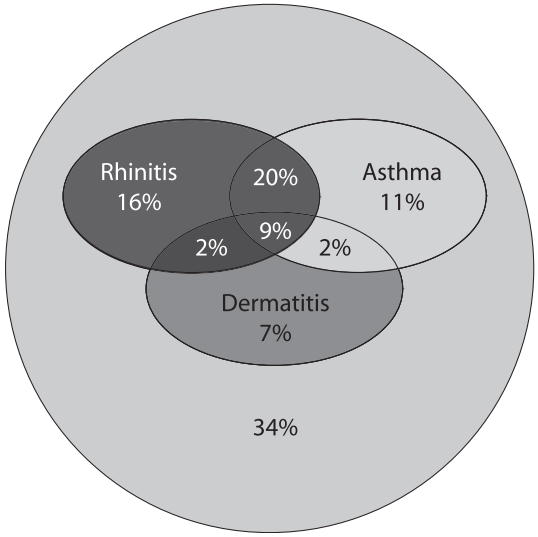

Figure 2. Proportion of children with atopic disease according to all methods as described in this study. Each child positive for at least one method, score or definition is considered as having an atopic disease. Based on any of the described methods, 263 (66%) of the children had any atopic disease, 94 (24%) had two and 34 (9%) had all three atopic diseases.

Discussion

The most referred epidemiological study of atopic diseases in children is the multicentered international study of ISAAC. In phase I of the ISAAC study the 12-month prevalence of wheezing ranged from 2.1% to 32.2% worldwide, with the highest prevalence found in 6- to 7-year olds in Costa Rica (3, 17). Applying the ISAAC asthma questionnaire to our study population in Cuba, the percentage of positives for 12-month wheeze was 30%; in 6- to 7-year olds it was 41.7% which is higher than the highest ISAAC prevalence found. Moreover, the answers to the other ISAAC core questions on asthma yielded symptom percentages in our study group which were in the same range or even higher than those found

by ISAAC and others: for example, in Peru, Panama, Brazil or Costa Rica (2, 18, 19). We are aware that our data are limited by the sample size and cannot be simply extrapolated to a national level. These comparisons should thus be made with caution. Nevertheless the ISAAC questionnaire results in our study group suggest relatively high asthma prevalences in the Cuban paediatric population.

While there is no accepted definition of asthma, the identification of asthma by questionnaire remains a contentious issue. In the ISAAC study as well as in many other studies in which the ISAAC core questionnaire is applied, the answers to the eight core questions on wheezing and respiratory symptoms are usually considered separately, with the answer on 'Have you had wheezing or whistling in the chest in the last 12 months?' being most frequently referred to as an indicator of current asthma. To our knowledge, only few authors tried to arrive at a more accurate assessment of asthma prevalence by combining the respective answers and grading each question according to their importance for the diagnosis of asthma. Applying these scores, the frequency of asthma in our study population was 21% (11) and 39% (8), both still relatively high when compared with the prevalence of asthma in other countries (11, 17, 19).

We specified the core ISAAC question 'Has your child ever had asthma?' by adding a more explicit question: 'Has your child's asthma been confirmed by a physician?' This rendered a percentage of 38%, instead of 42% when asking the core question. Physician-diagnosed asthma is often used as a standard method in asthma studies, and usually contains a combination of history and clinical examination, sometimes supplemented with physiological and laboratory tests (20). However, the precise diagnostic measures and criteria used differ considerably from one study to another. While physicians agree that certain criteria are necessary to diagnose asthma, they disagree on the combinations of factors that are needed to do so (21). According to the Cuban National Asthma Guidelines, physician diagnosis of asthma is based on clinical examination and personal and family symptom history. Objective test results are added if available (22).

In our study population the percentage of children who wheezed on clinical examination was significantly smaller than the percentage of those who wheezed in the past 12 months according to the questionnaire. Patients do not necessarily wheeze at the moment of clinical examination, which can partly explain the observed difference (20). On the other hand, it is known that questionnaires tend to overestimate prevalences (23).

Bronchial hyperresponsiveness tests are assumed to provide an objective and reliable marker of asthma, not influenced by variations in symptom perception or diagnostic trends (24). As with symptom questionnaires and clinical examination however, they are neither completely specific nor completely sensitive for asthma (25). In epidemiological studies, the most widely used methods have been inhalation challenge with methacholine or histamine, but recently there has been an increasing interest in using other challenge agents for assessing BHR in the field. We chose exercise challenge in our study because it seems more natural and acceptable to children and their parents than provocation with drugs, and more feasible in a public school setting (26). According to Toelle et al. (15) neither symptoms nor BHR alone can be used to discriminate asthma in the community. They recommended a combination of recent wheeze and BHR, based on histamine challenge. Using their definition with exercise-induced provocation, we found fewer children with current asthma than when applying BHR alone. The same percentage (5%) was found in our Cuban study population when using the definition of Gruchalla et al. (12) who proposed a diagnosis of probable asthma based on a combination of questionnaire and BHR results. On the other hand, others have stated that BHR in combination with symptom history is a very insensitive measure of asthma, and that diagnosis of childhood asthma should not be overlooked in symptomatic cases without objective evidence of BHR (25). Furthermore, Demissie et al. (27) who used a Bayesian approach for sensitivity and specificity analysis found that exercise challenge was clearly inferior to the symptom questionnaire in identifying asthmatic children in a community setting. Using BHR and/or symptom history we would have found 156 children (39%) with asthma.

Fewer studies have been performed with regard to allergic rhinoconjunctivitis. As there are no standard clinical criteria or objective tests available, symptom history is even more important here. As for asthma, some authors have suggested a score system for the diagnosis of allergic rhinoconjunctivitis (9, 12–14). Applying the ISAAC questionnaire as well as the Strachan score to our 5- to 13-year-old study population in Cuba yielded percentages that were among the highest ISAAC prevalences of allergic rhinoconjunctivitis found (14). Again, it should be noted that the little strength of our data does not allow full comparison. Symptom percentages based on the ISAAC questionnaires were thus not only high for asthma but also for allergic rhinitis. A similar association between asthma and allergic rhinoconjunctivitis has been found before (28).

In our study population the percentage of positive children with atopic dermatitis was considerably smaller than that of allergic rhinoconjunctivitis and asthma, as described by others (2). In the ISAAC study, Williams et al. (16) found prevalences of $< 2\%$ in Iran to over 16% in Japan and Sweden in 6- to 7-year olds, with a range of 7–11% in Latin America. Applying his score to our data, we found percentages of 9% (12% in 6- to 7-year olds). Thus, also for atopic dermatitis the results in our study group suggest high prevalences when compared with other countries.

Skin prick tests are frequently applied in the epidemiology of atopic diseases, although it has been described that the clinical syndromes that are commonly referred to as atopic diseases do not necessarily need to be associated with atopy on skin prick test and vice versa (29). Indeed, we found 15 children (4%) with a positive skin prick test without any symptoms or clinical signs of atopy, and 225 (57%) who had a negative skin prick test, but were positive as based on symptom questions and/or clinical examination. Combining the outcomes of all methods described in this paper, the percentage of Cuban children with at least one atopic disease was 66%, of whom 11% ($n = 28$) were reactive to the skin prick test.

Occurrences of atopic diseases in our study population vary considerably depending on the diagnostic approach. Even within one method, the ISAAC questionnaire, outcomes differ according to the score used. In general, questionnaires rendered high percentages of positives in our study population while for the other methods (exercise-induced BHR, wheeze or skin prick tests) they were much smaller. Nevertheless, every single method added extra positives to the total number of children with at least one atopic disease. For most methods, risks of overdiagnosis and/or underdiagnosis have been described (8, 11, 15).

While the number of epidemiological studies of atopic diseases is constantly growing, the discussion on measuring asthma and other atopic diseases in epidemiology seems to have rather languished. Even though various attempts towards a gold standard approach exist in the literature, a large variety of, often invalidated (combinations of), methodologies and definitions is still being used. The lack of a standardized approach hampers epidemiological research and a reliable comparison between studies (30) and we therefore plead for re-opening the discussion. At present, the most frequently used diagnostic method in epidemiological studies of atopic diseases is the ISAAC questionnaire, and based on that, our data suggest prevalences of asthma, atopic dermatitis and allergic rhinoconjunctivitis in Cuban children that rival those found in some other Latin American countries and developed nations with the highest prevalences in the world.

Conflict of interest statement

We declare that we have no conflict of interest.

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