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Prevalence and risk factors for wheeze, forced expiratory volume in one second and bronchoconstriction in young children living in Havana, Cuba: A population-based cohort study

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Abstract

Asthma has not been extensively studied in low- income and middle- income countries, where risk factors and access to treatment may differ from more affluent countries. **Objectives** To identify the prevalence of asthma and local risk factors in Havana. **Method:** Population- based cohort design of children 6-7 years old living in Havana, Cuba, recruited from primary care centres at age 12–15 months. Data on wheeze in the past 12 months, asthma treatment and environmental exposures collected regularly until the age of 6 years, when spirometry with reversibility test was conducted. **Results** 1106 children provided data at the age of 6 years old. Prevalence of wheeze in the previous 12 months was 422 (38%), and 294 (33%) of the study population had bronchodilatation of 12% or more in FEV_1 after administration of inhaled salbutamol. In the previous 12 months, 182 (16%) of the children had received inhaled corticosteroids, 416 (38%) salbutamol inhalers and 283 (26%) a course of systemic steroids. Wheeze in the first year and a family history of asthma were associated with bronchodilatation to inhaled salbutamol (1.94% and 1.85, respectively), paracetamol use in the first year was associated with wheeze at 6 years (OR 1.64). There were large differences in FEV_1 , bronchodilatation and risk of wheeze across different geographical areas. **Conclusions** Asthma is common in young children living in Havana, and the high prevalence of systemic steroids administrated is likely to reflect the underuse of regular inhaled corticosteroids.

Keywords: dengue, IgG, infection, children, Cuba, lung function

I. INTRODUCTION

Asthma is a global disease that affects approximately 11% of 6 year old children,[1] but with marked regional differences in prevalence.1 The aetiology of asthma is complex, and involves a range of environmental exposures that are likely to have differential impacts at different ages over the human lifetime.[2–7]

The early years of childhood is a particularly important period as this is when the lungs and immune system are developing rapidly, and lung function in children is a key determinant of health in adulthood.[8] The role of infection in early life in the development of allergic disease remains unclear.[9]

The main hypothesis of interest was that infection with parasites,[10] Helicobacter pylori,[11] dengue[12] or systemic inflammation [13] may be associated with wheeze or bronchoconstriction. Exposure to environmental tobacco smoke and paracetamol had previously been observed to be positively associated with wheeze[14] or atopic dermatitis[15] symptoms, respectively, and so the association of these exposures with wheeze and bronchoconstriction were also studied. Finally, as growth from in utero onwards may also be related to development of asthma and growth of the lungs,[16] anthropometric measures from birth onwards were also considered. The study design is a prospective population- based study of an existing cohort of children followed from approximately 1 year of age for 5 years.

The aim is to determine the prevalence of wheeze in young children living in Cuba, and to identify modifiable risk factors for wheezing, reduced lung function and reversible bronchoconstriction.

II. METHOD

I. Study population

The study population is a cohort of 1956 children aged 12–15 months who were randomly selected from the general population from four municipalities across Havana in 2010 and 2011.[14 15 17]

The response rate of those who were eligible to participate initially was 96%.[14].

II. Data collection

Data were collected by a standardized questionnaire that was administered by a member of the study team at baseline and subsequently at 2 years, 3 years and 5 years later. This included a number of health and lifestyle questions that were answered by the parent or guardian and particular attention was paid to parental/guardian reported wheeze in the past 12 months using the methodology developed for the ISAAC epidemiological studies of asthma, [18] use of asthma medication in the past 12 months and exposure to environmental tobacco smoke. The child's weight, height and mid- arm circumference in both arms were collected at each study visit. Historical baseline data including birth weight and height were collected from the primary care centre records. At each annual follow- up study the participants' guardians were asked if the child had received a medical diagnosis of dengue infection in the previous year and a blood sample was collected from children to measure circulating eosinophil levels. This sample was stored at −20°C and subsequently defrosted and analysed for dengue IgG serology to generate an antibody index, [19] serum IgE,[17] highly sensitive C- reactive protein (hsCRP, SpinReact, Spain),[20] toxoplasmosis IgG antibodies [21] and toxocariasis IgG antibodies (DRG Instruments, Germany). A faecal sample was also collected at each review and stored at −20°C, and later examined for H. pyloriusing the

faecal antigen test (SpinReact, Spain) and intestinal parasites using the Kato- Katz test (Campiñas Medical COMI, Brazil).

Lung function

Forced expiratory volume in 1 s (FEV_1) and forced vital capacity were measured in accordance with American Thoracic Society/European Respiratory Society criteria 22 using spirometers (CareFusion Micro I) calibrated each day to allow for local climatic change. The best value of FEV_1 within a threshold of repeatability of 200 mL was used as the final value. Aerosolised salbutamol (300 µg) was then administered via a spacer and after 15 min lung function was measured again to quantify airway reversibility. In children who provided a postbronchodilator FEV_1 that was less than the baseline value, they were considered as having no reversibility to bronchodilator as this was likely to be due to fatigue.

Skin prick test

Skin prick testing was used to determine allergy to mite, cat, grass, cockroach, fungus, mosquitos, wheat and soy (allergens from Diater, Argentina except mite allergen from Biocen, Cuba). For each test a drop of allergen solution was placed on the skin and a lancet used to break the skin. After 15 min, the skin weal was measured at its maximum diameter, and also perpendicularly, and a mean value generated. The final skin prick test result was calculated by subtracting the saline result from the allergen. A value of ≥3 mm was used to define a positive atopic result for each allergen, and atopy was defined as any positive skin prick test.

III. Statistical analysis

The main outcome variables were FEV_1, per cent increase in FEV_1 after to inhaled salbutamol and wheeze in the past 12 months. The main exposure variables were grouped into three categories:

1. Prior exposures: wheeze in the first year of life, family history of asthma, nursery attendance, birth weight, birth height, duration of breastfeeding, blood IgE and eosinophils at 1 year old; faecal H. pyloriantigen at 2 and 3 years old; blood hsCRP, dengue IgG serology, eosinophils, toxoplasmosis serology, IgE at 3 years old and any prior medical diagnosis of dengue infection.
2. Cross- section exposures: number of smokers living in the home, current weight, current height, mean arm circumference, municipality of residence.
3. Biomarkers of current infection and inflammation: H. pylori stool antigen, toxoplasmosis IgG serology, dengue IgG serology, blood hsCRP, eosinophils, IgE, toxocariasis serology and atopy. Less than 2% of children has current gastro- intestinal parasite infection and these data were not analysed further.

Statistical analysis used linear and logistic regression adjusting for sex and age in months as a priori confounding factors, and also adjusted for clustering by municipality of residence. As height was associated with FEV_1, all analyses of this outcome measure also adjusted for height to ensure that the analyses were not confounded by somatic growth. $\chi 2$ tests were used to explore differences in categorical exposures for binary outcome measures. All analyses used Stata V.14 statistical software.

III. RESULTS

Data were available for 1106 children, of whom 422 (38%) had reported wheeze in the previous year. Wheeze in the first year of life was reported in 514 (46%) current participants, while there was a prevalence of wheeze in the first year of life of 42% (358 children) for those who did not participate in the study at the age of 6 years (p=0.055). 930 (83%) children provided lung function data, and of these 903 (99%) children had their reversibility to salbutamol measured. The mean FEV_1 was 1.13 L (SD 0.31), and 294 (33%) had an increase in FEV_1 of more than 12% after administration of aerosolised salbutamol. 883 (26%) of the current study population were reported to have received systemic steroids in the previous 12 months (table 1).

Table 1. Description of study population

	Total (N=1106)	Provided FEV_1 (N=913)
Male sex (%)	575 (52)	473 (52)
Mean age, months (range)	74 (63 to 83)	74 (64 to 83)
Mean FEV_1, L, (sd)	-	1.13 (0.31)
Mean bronchodilation after salbutamol, % (sd)	-	13.4 (20.1) N=903
Wheeze in the past 12 months (%)	422 (38)	356 (39)
Received inhaled steroids in the 12 months before (%):		
Year 1	89 (8)	68 (7)
Year 2	176 (17)	153 (18)
Year 3	203 (18)	163 (18)
Year 5	182 (16)	150 (16)
Received salbutamol inhaler in the previous 12 months (%):		
Year 5	416 (38)	345 (38)
Received IV or oral steroids in the 12 months before (%):		
Year 1	295 (27)	244 (27)
Year 2	418 (40) N=1052	345 (38) N=870
Year 3	407 (37)	333 (36)
Year 5	283 (26)	240 (26)

Risk factors for wheeze in the past 12 months at 6 years old

Both wheeze (OR 1.89; 95% CI 1.65 to 2.16) and paracetamol use (OR 1.64; 95% CI 1.14 to 2.35) in the first year of life along with a family history of asthma (OR 1.66; 95% CI 1.40 to 1.97) were associated with wheeze at 6 years. A positive H. pylori faecal antigen test at age 2 years was negatively associated with wheeze in the past 12 months (OR 0.57; 95% CI 0.40 to 0.82), but this association was not observed for H. pylori at the age of 3 years or 6 years. The number of smokers in the household was a strong risk factor for wheeze in the past 12 months (p<0.001 for trend), with homes with two or more smokers having an OR of the child having wheeze in the past 12 months of 2.08 (95% CI 1.71 to 2.54) compared with those homes with no smokers. The municipality of residence was associated with wheeze in the past 12 months (p=0.04, χ 2 test), with children living in Cerro municipality having the highest risk of wheeze (OR 1.72 compared with Arroyo Naranjo; 95% CI 1.61 to 1.84). These differences were not substantially modified by adjusting for the number of smokers in the home (Table 2).

Table 2 Association of exposures with wheeze in past 12 months

Total number=1106	**No (%, SD)**	**OR of wheeze (95% CI)**
Prior exposures		
Any wheeze in first year of life	514 (46)	**1.89 (1.65 to 2.16**)
Family history of asthma	614 (56)	**1.66 (1.40 to 1.97**)
Paracetamol in first year of life	256 (23)	**1.64 (1.14 to 2.35**)
Mean birth weight, N, kg (SD) n=1104	3.31 (0.51)	0.87 (0.75 to 1.01)
Mean birth height, cm (SD)	50.2 (2.4)	0.95 (0.89 to 1.00)
Age=1 year		
Mean log IgE, n=885	3.38 (1.47)	1.06 (0.88 to 1.27)
Mean log eosinophils, n=856	−2.11 (1.05)	0.93 (0.77 to 1.13)
Age=2 years		
Helicobacter stool +ve, n=1067	40 (4)	**0.57 (0.40 to 0.82)**
Age=3 years		
Mean log CRP, SD, n=986	−2.07 (2.70)	1.01 (0.95 to 1.07)
Log dengue IgG, n=865	−0.44 (2.00)	0.99 (0.96 to 1.02)
Helicobacter stool +ve, n=951	58 (6)	1.01 (0.64 to 1.60)
Mean log eosinophils, n=1039	−1.77 (1.23)	**0.91 (0.86 to 0.96)**
Toxoplasmosis serology +ve, n=966	565 (58)	1.15 (0.82 to 1.64)
Mean log IgE, n=986	3.70 (1.53)	1.14 (0.98 to 1.31)
Medical diagnosis of dengue infection	93 (8)	1.40 (0.91 to 2.14)
Current exposures		
Male sex	575 (52)	**1.35 (1.00 to 1.82**)
Age (months), (range)	74 (63 to 83)	**0.97 (0.96 to 0.99**)
Number of current smokers in house vs 0 smokers 546 (49)		
1	322 (29)	**1.61 (1.22 to 2.12)**
≥2	238 (22)	**2.08 (1.71 to 2.54)**
Municipality of residence		p_{TREND} <0.001
Arroyo Naranjo	455 (41)	**0**
Cerro	139 (13)	**1.72 (1.61 to 1.84)**
Habana del Este	307 (28)	**0.86 (0.84 to 0.88)**
La Lisa	205 (19)	**1.24 (1.21 to 1.27)**
		p=0.04
Current infection and blood assays		
Helicobacter stool antigen +ve, n=756	11 (1)	1.45 (0.63 to 3.33)
Toxoplasmosis +ve, n=759	487 (64)	0.97 (0.70 to 1.34)
Mean log dengue IgG serology, n=758	1.67 (1.53)	0.95 (0.90 to 1.01)
Log CRP, n=757	−0.83 (1.41)	0.99 (0.86 to 1.15)
Mean log eosinophils, n=868	−1.62 (1.45)	1.02 (0.90 to 1.15)
Mean log IgE, n=759	4.51 (0.97)	**1.27 (1.15 to 1.41)**
Toxocariasis +ve, n=673	64 (9)	0.96 (0.70 to 1.33)
Any atopy* (n=857)	52 (6)	0.81 (0.43 to 1.53)

Results in bold font have a probability of <0.05. CRP, C- reactive protein.

Risk factors for decreased FEV_1 at 6 years old

Table 3 Association of exposures with FEV_1

Total number=903	**No (%, SD)**	**FEV_1, mL (95% CI)**
Prior exposures		
Mean birth height, cm (SD)	**50 (2)**	**11 (5 to 18)**
Age=1 year		
Mean log IgE, n=456	3.44 (1.39)	−19 (−50 to 12)
Mean log eosinophils, n=451	−2.14 (1.04)	−13 (−56 to 30)
Age=2 years		
Helicobacter stool +ve, n=589	29 (5)	−78 (−270 to 115)
Age=3 years		
Mean log CRP, SD, n=614	−2.16 (2.71)	2 (−9 to 12)
Log dengue IgG, n=545	−0.43 (2.00)	7 (−10 to 25)
Helicobacter stool +ve, n=775	51 (7)	−39 (−132 to 54)
Mean log eosinophils, n=652	−1.78 (1.26)	22 (−5 to 49)
Toxoplasmosis serology +ve, n=606	362 (60)	48 (−46 to 143)
Mean log IgE, n=614	3.68 (1.57)	8 (−21 to 37)
Medical diagnosis of dengue infection	78 (9)	−27 (−59 to 5)
Current exposures		
Male sex	468 (52)	36 (−23 to 96)
Wheeze in past 12 months	353 (39)	−62 (−160 to 35)
Mean weight, kg, n=902 (range)	**23.5 (11 –51)**	**11 (3 to 18)**
Current height, cm, n=903 (range)	**119 (90 –175)**	**8 (2 to 14)**
Mean arm circumference, cm n=901	**18.4 (2.4)**	**12 (1 to 24)**
Municipality of residence		
Arroyo Naranjo	**371 (41)**	**0**
Cerro	**119 (13)**	**74 (31 to 117)**
Habana del Este	**247 (27)**	**048 (39 to 57)**
La Lisa	**166 (18)**	**−95 (−126 to −64)**
		p<0.001
Current infection and blood assays		
Helicobacter stool antigen +ve, n=685	10 (1)	−10 (−228 to 207)
Toxoplasmosis +ve, n=688	437 (64)	8 (−49 to 65)
Mean log dengue IgG serology, n=687	1.63 (1.56)	−5 (−24 to 14)
Log CRP, n=686	−0.87 (1.38)	−9 (−37 to 20)
Mean log eosinophils, n=785	−1.61 (1.47)	−5 (−41 to 31)
Mean log IgE, n=688	4.52 (0.97)	−12 (−87 to 63)
Toxocariasis +ve, n=667	57 (9)	−15 (−125 to 95)

Any atopy* (n=818)	52 (6)	−54 (−182 to 74) adjusted for sex, age in months, current height and clustering by municipality

Results in bold font have a probability of <0.05.
* Any allergen skin prick test >3 mm larger than saline control.
CRP, C- reactive protein; FEV_1, forced expiratory volume in 1 s.

A number of measures of somatic growth were positively associated with FEV_1 at 6 years. These were birth height (14 mL /cm height at birth; 95% CI 6 to 23), current height (11 mL /cm; 95% CI 5 to 18), current weight (11 mL /kg; 95% CI 3 to 18) and current mean arm circumference (12 mL /cm; 95% CI 1 to 24). Municipality of residence was strongly associated with current FEV_1 (p<0.001), with children living in La Lisa having the lowest lung function (−95 mL compared with Arroyo Naranjo, 95% CI −126 to −64). These differences were not substantially modified by adjusting for the number of smokers in the home. No measures of infection or inflammation were associated with lung function (Table 3)

Table 4 Association of exposures with bronchodilatation after inhaled salbutamol

Total number=903	**No (%, SD)**	**% change in FEV_1 (95% CI)**
Prior exposures		
Any wheeze in first year of life	417 (46)	**1.94 (0.81 to 3.08)**
Family history of asthma	510 (56)	**1.85 (0.14 to 3.57)**
Age=1 year		
Mean log IgE, n=455	3.42 (1.39)	**1.68 (0.54 to 2.82)**
Mean log eosinophils, n=449	−2.13 (1.04)	−0.16 (−2.54 to 2.21)
Age=2 years		
Helicobacter stool +ve, n=586	28 (5)	−6.41 (−14.94 to 2.10)
Age=3 years		
Mean log CRP, SD, n=615	−2.12 (2.71)	−0.28 (−0.88 to 0.32)
Log dengue IgG, n=550	−0.43 (2.01)	−0.38 (−1.50 to 0.74)
Helicobacter stool +ve, n=776	51 (6)	−1.40 (−7.30 to 4.51)
Mean log eosinophils, n=653	−1.78 (1.26)	−0.39 (−4.45 to 3.68)
Toxoplasmosis serology +ve, n=607	362 (60)	−0.45 (−7.06 to 6.16)
Mean log IgE, n=615	3.68 (1.57)	0.23 (−1.81 to 2.27)
Medical diagnosis of dengue infection	78 (9)	−0.58 (−8.55 to 7.38)
Current exposures		
Male sex	466 (52)	2.22 (−0.28 to 4.71)
Age (months), (range)	74 (64– 83)	−0.13 (−0.47 to 0.20)
Wheeze in past 12 months	353 (39)	3.61 (−5.80 to 13.02)
Mean current weight, kg, n=893 (range)	24 (11 –51)	−0.23 (−0.54 to 0.08)
Current height, cm, n=893	119 (90– 175)	−0.08 (−0.50 to 0.34)
Mean arm circumference, cm, n=893	18.4 (2.4)	−0.14 (−0.81 to 0.54)
Municipality of residence		
Arroyo Naranjo	368 (41)	0
Cerro	119 (13)	**−1.34 (−2.56 to −0.11)**
Habana del Este	249 (28)	**−0.07 (−0.46 to 0.31)**
La Lisa	167 (18)	**6.24 (5.56 to 6.91)** P=0.002
Current infection and blood assays		
Helicobacter stool antigen +ve, n=684	10 (1)	8.89 (−9.17 to 26.96)

Toxoplasmosis +ve, n=687	438 (64)	−0.47 (−3.34 to 2.39)
Mean log dengue IgG serology, n=686	1.64 (1.56)	0.30 (−1.44 to 2.03)
Log CRP, n=685	−0.87 (1.40)	0.37 (−1.64 to 2.38)
Mean log eosinophils, n=782	−161 1.47)	0.99 (−0.48 to 2.46)
Mean log IgE, n=686	4.52 (0.98)	0.64 (−0.18 to 1.45)
Toxocariasis +ve, n=666	58 (9)	−1.03 (−5.29 to 3.23)
Any atopy* (n=816)	52 (6)	−2.75 (−10.15 to 4.60)

Adjusted for sex, age in months and clustering by municipalit y.
Results in bold font have a probability of <0.05.
*Any allergen skin prick test >3 mm larger than saline control.
CRP, C- reactive protein; FEV_1, forced expiratory volume in 1 s.

Risk factors for bronchodilatation after inhaled salbutamol at 6 years old

Any wheeze in the first year of life was positively associated with bronchodilatation (1.94%; 95% CI 0.81 to 3.08) as was a family history of asthma (1.85; 95% CI 0.14 to 3.57), but there was no relation with wheeze in the past 12 months (3.61; 95% CI −5.80 to 13.02). Children with a higher birth weight had a lower risk of bronchodilatation (–2.67%; 95% CI −4.49 to −0.84). IgE at the age of 1 year was positively associated with a higher risk of bronchodilatation (1.68%; 95% CI 0.54 to 2.82), but not IgE at age of 3 years or 6 years. The numbers of smokers living in the child's home was not associated with bronchodilation, but the municipality of residence was again a strong determinant of current bronchodilatation (p=0.002), with children living in La Lisa having the highest increase in FEV_1 after administration of inhaled salbutamol at 6 years old (6.24% compared with Arroyo Naranjo; 95% CI 5.56 to 6.91). These differences were not substantially modified by adjusting for the number of smokers in the home (Table 4).

VI. CONCLUSSIONS

Asthma is common in young children living in Havana, and the high prevalence of the use of systemic steroids probably reflects the underuse of regular inhaled corticosteroid prophylaxis treatments leading to the requirement for rescue treatment for wheezing. As societies urbanize, environmental air pollution may increase from a variety of sources. Cuba's economy has been inversely affected due to historical and political events, 33 and it remains under an economic embargo from the USA that has negatively impacted on healthcare. 34 This makes providing regular inhaled corticosteroids to all children who need them challenging. However, other low- income and middle-income countries also have difficult economic and environmental circumstances, and if these observations are replicated elsewhere, then this represents an important global public health issue.

IV. REFERENCES

1. Pearce N, Aït- Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International study of asthma and allergies in childhood (Isaac). Thorax2007;62:758–66.
2. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. J Allergy Clin Immunol 2017;140:895–906.

3. Edwards MR, Strong K, Cameron A, et al. Viral infections in allergy and immunology: how allergic inflammation influences viral infections and illness. J Allergy Clin Immunol 2017;140:909–20.
4. Prescott SL. Effects of early cigarette smoke exposure on early immune development and respiratory disease. Paediatr Respir Rev 2008;9:3–10.
5. Lewis SA, Antoniak M, Venn AJ, et al. Secondhand smoke, dietary fruit intake, road traffic exposures, and the prevalence of asthma: a cross- sectional study in young children. Am J Epidemiol 2005;161:406–11.
6. Litonjua A, Gold D. Early- Life exposures and later lung function. Am J Resp Crit Care Med2016;193:110–1.
7. Schultz ES, Hallberg J, Bellander T, et al. Early- Life exposure to traffic- related air pollution and lung function in adolescence. Am J Respir Crit Care Med2016;193:171–7.
8. Sly PD, Bush A. From the cradle to the grave: the early- life origins of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2016;193:1–2.
9. Postma DS, Weiss ST, van den Berge M, et al. Revisiting the Dutch hypothesis. J Allergy Clin Immunol2015;136:521–9.
10. Feary J, Britton J, Leonardi- Bee J. Atopy and current intestinal parasite infection: a systematic review and meta- analysis. Allergy 2011;66:569–78.
11. Amberbir A, Medhin G, Abegaz WE, et al. Exposure to Helicobacter pylori infection in early childhood and the risk of allergic disease and atopic sensitization: a longitudinal birth cohort study. Clin Exp Allergy 2014;44:563–71.
12. Mabalirajan U, Kadhiravan T, Sharma SK, et al. Th(2) immune response in patients with dengue during defervescence: preliminary evidence. Am J Trop Med Hyg2005;72:783–5.
13. Fogarty AW, Jones S, Britton JR, et al. Systemic inflammation and decline in lung function in a general population: a prospective study. Thorax2007;62:515–20.
14. Venero- Fernández SJ, Suárez- Medina R, Mora- Faife EC, et al. Risk factors for wheezing in infants born in Cuba. QJM2013;106:1023–9.
15. Suarez- Medina R, Venero- Fernandez S, Mora Faife E, et al. Risk factors for eczema in infants born in Cuba. BMC Dermatology 2014;14:6.
16. Shaheen SO, Sterne JA, Montgomery SM, et al. Birth weight, body mass index and asthma in young adults. Thorax1999;54:396–402.
17. Fundora- Hernández H, Venero- Fernández SJ, Suárez- Medina R, et al. What are the main environmental exposures associated with elevated IgE in Cuban infants? a population- based study. Trop Med Int Health2014;19:545–54.
18. TISoAaAiCIS C. Worldwide variations in the prevalence of asthma symptoms: the International study of asthma and allergies in childhood (Isaac) Steering Committee. Eur Resp J1998;12:315–35.
19. Vircell dengue ELISA IgG. Available: http://wwwperamedcom/peramed/docs/G1018_ENpdf [Accessed 14 Apr 2016].
20. Josefina Venero- Fernández S, Fundora- Hernández H, Batista-Gutierrez L, et al. The association of low birth weight with serum C reactive protein in 3- year- old children living in Cuba: a population-based prospective study. Am. J. Hum. Biol.2017;29:e22936.

21. Garcia F, Venero Fernandez S, Fundora Hernández H, et al. Seroprevalencia de anticuerpos IgG anti- Toxoplasma gondii en infantes de la habana. Parasitaria. In Press 2015:73.
22. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J2005;26:319–38.

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