What are the main environmental exposures associated with elevated IgE in Cuban infants? A population-based study

Hermes Fundora-Hernández1, Silvia J. Venero-Fernández 1, Ramón Suárez-Medina1, Esperanza de la C. Mora-Faife1, Gladys García-García1, Ileana del Valle-Infante1, Liem Gómez-Marrero1, Andrea Venn2, Andrew W. Fogarty2 and the HINASIC Study Group*

1 Instituto Nacional de Higiene, Epidemiología y Microbiología, La Habana, Cuba
2 Nottingham Biomedical Research Unit, Division of Epidemiology and Public Health, University of Nottingham, City Hospital, Nottingham, UK

Abstract

OBJECTIVE Immunoglobulin E (IgE) plays a key role in allergy disease pathogenesis, but little is known about the environmental factors associated with higher IgE levels in infants. The aim of this study was to determine the risk factors for elevated serum total IgE infants living in Havana.

METHODS Eight hundred and seventy-seven infants provided blood samples. Data on allergic disease symptoms and a wide range of exposures were collected.

RESULTS The median IgE was 35 IU/ml (interquartile range 13–96). The risk of having an IgE level above the median was higher for children who had been breastfed for 4 months or more (adjusted odds ratio (OR) 1.28; 95% confidence interval (CI): 1.02–1.61) and for children who reported cockroaches in their home (OR 1.30; 95% CI: 1.03–1.63). The risk was lower for children whose mother was in paid employment (OR 0.73; 95% CI: 0.54–0.97 compared with those who did not), for children living in homes where gas and electricity were used for cooking (OR 0.45; 95% CI: 0.32–0.62 compared with electricity only) and for children with domestic pets at birth (OR 0.83; 95% CI: 0.70–1.00). There was no association between paracetamol use and serum IgE levels.

CONCLUSIONS Associations between gas fuel use and maternal employment indicate that IgE levels in early life are lower in children who may be living in relative affluence. The discrepancy in the effect of early exposure to pets or cockroaches may reflect differences in these allergens, or be confounded by relative affluence. Further investigation of this cohort will determine how these effects translate into the expression of allergic disease in later life.

keywords IgE, infants, risk factor, Cuba, allergy

Introduction

Allergic disease is increasing in prevalence globally and is most common in the more affluent, urbanised and economically developed countries (Asher et al. 2006). However, the aetiological factors responsible for this change remain unknown. Immunoglobulin E (IgE) is known to be an important mediator with regard to both allergic disease (Martinez et al. 1995; Rodriguez et al. 2001; Busse et al. 2011) and parasitic disease (Platts-Mills 2001; Cooper et al. 2008), and it is considered that the former may represent an aberrant response from an immune system that has evolved in coexistence with parasitic infections (Gould & Sutton 2008). Although investigators have clearly demonstrated that serum IgE is a risk factor for allergic disease in older children (Sears et al. 1991; Sporisk et al. 1995; Simpson et al. 2005), there are few population-based studies with IgE measurement in children under 2 years (Martinez et al. 1995), and hence little is known about the risk factors that modify IgE levels in this age group. Hence, environmental factors that modify serum IgE represent an important area of research as these are potentially modifiable risk factors for allergic diseases, and in particular asthma (Sears et al. 1991; Sporisk et al. 1995; Simpson et al. 2005). The study of risk factors for an elevated IgE in the early years of life is particularly important, representing the cumulative impact of the environment on the maturing immune system. The hypothesis that IgE is important in the pathogenesis of asthma has been recently supported by the development of interventions designed to reduce serum IgE in the treatment of asthma in children (Busse et al. 2011).

Cuba has an excellent health care system that delivers infant mortality rates comparable with much richer
countries (Cooper et al. 2006). The combination of good health infrastructure with limited economic growth in recent decades (as a consequence of the economic embargo on the island imposed by the USA) has resulted in a unique environment where risk factors for disease can be studied. In the recent Phase 3 of the International Study of Asthma and Allergies in Childhood (ISAAC), Cuba had one of the highest prevalences of childhood eczema among the countries studied from Latin America (Sole et al. 2010). Allergic disease is considered common in Cuba with estimates of prevalences of 32% for recent asthma symptoms and 20% for allergic rhinitis in young boys living in Habana (Venero Fernandez et al. 2009). We used a cross-sectional study design to explore the risk factors for increased IgE in a population-based study of one-year-old infants born in Havana, Cuba.

Methods

Study population

All children aged 12–15 months who were living in Havana, Cuba, between March 2010 and March 2011 and who attended one of 17 randomly selected policlinics in four municipalities in Havana, Cuba, were eligible to be selected to participate in the study (Arroyo Naranjo, Cerro, Habana del Este, La Lisa). Recruitment for the study is described in detail elsewhere (Venero Fernandez et al. 2013). The study protocol was approved by the National Institute of Hygiene, Epidemiology and Microbiology, the local Havana Scientific Committee in Cuba and the University of Nottingham Medical School Ethics Committee in the United Kingdom.

Data collection

The study was designed to identify environmental exposures that may increase the risk of asthma or allergic disease in Cuba. The baseline data collection consisted of an interviewer-administered questionnaire that collated the responses from the parent/carer about prenatal and postnatal exposures of the child, their living environment and the medical history of the family. Specific questions focussed on paracetamol exposure by the mother during pregnancy and also detailed information on exposure to individuals who smoke tobacco in the child’s living environment. Data on the height and weight at the time of the interview were also collected using the measuring equipment and weight scales available in the Policlinic. For those infants whose parents gave consent a blood sample was taken. This was frozen and subsequently analysed for serum IgE using the UMELISA assay manufactured by TecnoSuma International (Cuba) (http://www.tecnosumacom/Informacion/htm/UM2007.htm, accessed 16/1/2014; Solis et al. 1992) in a standardised manner designed to minimise measurement error. Collecting stool samples from infants in a tropical climate are challenging, and many infants were not able to provide a sample for analysis. Where possible, a stool sample was also taken and analysed for current parasite infection using the direct method with eosin and Lugol solutions following protocols from the Pedro Kouri Institute of Tropical Medicine, Havana, based on the established Kato–Katz method to identify Endolimax lana, Giardia lamblia and Entamoeba histolytica (Habtamu et al. 2011).

Data analysis

The data were entered into an electronic database, cleaned and checked for errors. All statistical analyses were carried out in Stata v12 (StataCorp, TX, USA) using the survey commands to allow for the clustered survey design. The distribution of serum IgE was not normally distributed even after log transformation. As there is no established universal definition for an increased IgE in this age group, the data were divided into above and below the median value and subsequent analyses assessed the odds of an exposure being associated with an IgE above the median value.

Bivariate analyses of all descriptive factors and exposure variables were initially performed using logistic regression and odds ratios, and associated 95% confidence intervals were computed for each exposure variable adjusting for gender and municipality, which were considered a priori confounders. Where substantial co-linearity between exposure variables was observed, e.g. between maternal education and household income, one exposure was selected for the final model to maintain model integrity. Variables that were statistically significant in this analysis ($P \leq 0.05$) were then entered into a multivariable model, and a step-wise modelling procedure followed to obtain a final model of only statistically significant ($P \leq 0.05$) variables. No further post hoc modelling was performed on the data set to maintain transparency and simplicity.

Results

Of the 1956 infants who participated in the original survey, 877 (45%) infants provided blood samples for analysis of serum IgE levels. Children who provided blood were similar to those who did not in terms of age, siblings and mothers’ age, but were slightly more likely to...
be male, have black skin, live in Habana del Este municipality, have a mother who was in paid work and have reported allergic disease symptoms than those who did not (Table 1). The median IgE was 35.00 IU/ml (inter-quartile range 13–96) and the distribution is presented in Figure 1.

In the final-adjusted analysis, there were significant differences in the risk of having higher serum IgE levels for those who lived in La Lisa (odds ratio OR: 1.51; 95% confidence intervals CI: 1.28–1.79) and Arroyo Naranjo (OR 1.44; 95% CI: 1.15–1.82) compared with those who live in Habana del Este (Table 2). Children who had been breastfed for 4 months or more had a higher risk of having increased IgE than those who were breastfed for 3 months or shorter. Those who reported cockroaches in their home also had a higher risk of having an increased IgE than those who did not (OR 1.30; 95% CI: 1.03–1.63). The presence of a mother who worked (OR 0.73: 95% CI: 0.54–0.97 compared with one who did not), cooking with gas and electricity and the presence of pets at home at the time of birth (OR 0.83; 95% CI: 0.70–1.00) were associated with a reduced risk of having elevated IgE (Table 3).

Discussion

To our knowledge, this is the largest population-based study to study the association between environmental exposures and an increased serum IgE in one-year-old infants. Our data demonstrate that being breastfed for 4 months or more and living in a home with cockroaches is associated with an increased IgE, while having pets in the home at birth, a mother who worked or living in a household that uses both gas and electricity for cooking were associated with a lower serum IgE level. Together, these indicate that IgE levels are lower among children

Table 1 Characteristics of study participants

| Variable                  | Definition of category | All children: N = 1956 | Children who did not give blood N = 1079 | Children who gave blood N = 877 | OR of increased IgE* (95% CI) |
|---------------------------|------------------------|------------------------|------------------------------------------|---------------------------------|--------------------------------|
| Mean age months, (SD)     | 13.1 (1.1)             | 13.2 (1.1)             | 13.1 (1.1)                               | 1.09 (0.97–1.24) per month      |
| Skin colour, n (%)        | White 916 (47)         | 526 (49)               | 390 (44)                                 | 1                               |
|                           | Mixed 798 (41)         | 442 (41)               | 356 (41)                                 | 0.98 (0.76–1.27)                |
|                           | Black 242 (12)         | 111 (10)               | 131 (15)                                 | 0.97 (0.58–1.65)                |
| Gender, n (%)             | Female 939 (48)        | 535 (50)               | 404 (46)                                 | 1                               |
|                           | Male 1017 (52)         | 544 (50)               | 473 (54)                                 | 1.39 (0.84–2.29)                |
| Municipality, n (%)       | Habana Este 642 (33)   | 326 (30)               | 316 (36)                                 | 1                               |
|                           | Cerro 374 (19)         | 219 (20)               | 155 (18)                                 | 0.99 (0.91–1.06)                |
|                           | La Lisa 282 (14)       | 153 (14)               | 129 (15)                                 | 1.59 (1.35–1.87)                |
|                           | Arroyo Naranjo 658 (34)| 381 (35)               | 277 (32)                                 | 1.11 (0.94–1.32)                |
| Mother with paid work, n (%) | No 780 (40)         | 469 (43)               | 311 (35)                                 | 1                               |
|                           | Yes 1176 (60)          | 610 (57)               | 566 (65)                                 | 0.75 (0.55–1.02)                |
| Any siblings, n (%)       | No 818 (42)            | 454 (42)               | 364 (42)                                 | 1                               |
|                           | Yes 1138 (58)          | 625 (58)               | 513 (58)                                 | 1.18 (1.00–1.39)                |
| Mean age of mother at birth in years (SD) | 26.7 (6.2) N = 1955 | 26.7 (6.3)             | 26.7 (6.1)                               | 0.99 (0.97–1.01) per year       |
| Family history of asthma, n (%) | No 917 (47)         | 540 (50)               | 377 (43)                                 | 1                               |
|                           | Yes 1039 (53)          | 539 (50)               | 500 (57)                                 | 1.21 (0.88–1.67)                |
| Reported eczema, n (%)    | No 1284 (66)           | 737 (68)               | 547 (62)                                 | 1                               |
|                           | Yes 672 (34)           | 342 (32)               | 330 (38)                                 | 0.89 (0.51–1.57)                |
| Reported wheeze, n (%)    | No 1084 (55)           | 612 (57)               | 472 (54)                                 | 1                               |
|                           | Yes 872 (45)           | 467 (43)               | 405 (46)                                 | 1.03 (0.64–1.67)                |
| Diagnosed allergic rhinitis, n (%) | No 677 (35)     | 383 (35)               | 294 (34)                                 | 1                               |
|                           | Yes 1279 (65)          | 696 (65)               | 583 (66)                                 | 1.09 (0.73–1.63)                |
| Parasite infection, n (%) | No 686 (96)            | 98 (97)                | 588 (96)                                 | 1                               |
|                           | Yes 26† (4)            | 3 (3)                  | 23 (4)                                   | 1.15 (0.21–6.25)                |

*Elevated IgE defined as above median value.
†Endolimax lana (six cases), Giardia lamblia (15 cases) and Entamoeba histolytica (five cases).
from relatively affluent families, suggesting that the environmental impact of differential socio-economic status is clearly evident at the age of 12–15 months.

The strengths of our data include the randomly selected population-based study from which these infants were recruited and the detailed phenotypic information collected on a number of environmental exposures. As the paucity of comparable studies in this year group demonstrates, this is a difficult population to obtain serum samples from. The relatively high number of infants who provided blood samples to allow measurement of total serum IgE is, hence, a major strength of our analysis, giving more power to detect significant associations with lifestyle risk factors. We were fortunate to have faeces samples from 712 infants in our data set. The fact that these demonstrated a very low prevalence of parasite infection is not surprising as infants of this age live in a very protected environment and would not be expected to be exposed to the contaminated water or soil, which may mediate parasite infection. There was no association observed between parasite infection and IgE levels, possibly as a consequence of this low prevalence of parasite infection. This is an important negative observation, as without it, we would speculate as to the role of parasite infection in driving the IgE immune response in our analysis.

There are a number of limitations that need to be borne in mind when critically evaluating these data. Firstly, the infants who gave blood samples were slightly different to those who did not in terms of skin colour, residential municipality, having a mother who had paid work and having eczema symptoms. We are unable to clarify why these groups were less likely to give a blood sample with the data collected as we did not ask specific questions on this issue. This does not invalidate the associations we observed within our data set, but may restrict the generalisability to other populations. Unfortunately, we do not have data on the umbilical cord IgE that has been shown to be strongly associated with serum IgE in 9-month infants in the only other population-based study of factors that impact on infant IgE that we are aware of (Holonen et al. 1991), and were thus unable to explore how the associations we have observed may be modified by serum IgE at birth, and other biological exposures that may occur in utero.

The study of environmental factors that modify serum IgE in young infants is an important area of research as at this stage in life the immune system is maturing and hence relatively plastic to external influences. There have been many studies demonstrating the association between increased serum IgE levels and a greater likelihood of asthma symptoms (Peat et al. 1996; Sherrill et al. 1999; Sunyer et al. 2000; Simpson et al. 2005), although few data sets with IgE measurements from the first 2 years of life (excluding birth). We are not aware of any other comparable population-based studies of serum IgE in infants aged 12–15 months that we can contrast our results with. Increased total serum IgE in early life is associated with an increased risk of persistent wheezing at age 6 years ($P < 0.01$) in a population-based cohort of 826 infants although no association was observed for cord blood (Martinez et al. 1995). These data from
Table 2 Univariate analysis of exposures and risk of elevated IgE

| Variable                                      | Definition of category | Number (%) or mean (SD) | OR of increased IgE* (95% CI) |
|-----------------------------------------------|------------------------|-------------------------|-------------------------------|
| Mother used paracetamol in pregnancy (%)     | No                     | 803 (92)                | 1                             |
|                                               | Yes                    | 74 (8)                  | 1.20 (0.94–1.52)              |
| Mother used aspirin in pregnancy (%)         | No                     | 800 (91)                | 1                             |
|                                               | Yes                    | 77 (9)                  | 0.65 (0.38–1.12)              |
| Infant’s mean birth weight, kg, (SD)         | N = 876                | 3.4 (0.5)               | 0.96 (0.65–1.42) per Kg       |
| Infant’s mean height at birth, cm, (SD)      | N = 876                | 50.4 (2.4)              | 0.92–1.11 per cm              |
| Infant’s mean weight, kg, (SD)               | N = 873                | 10.5 (1.6)              | 1.05 (0.92–1.19) per Kg       |
| Infant’s mean height, cm, (SD)               | N = 872                | 74.7 (3.5)              | 0.98 (0.92 1.04) per cm       |
| Caesarean birth (%)                          | No                     | 516 (59)                | 1                             |
|                                               | Yes                    | 361 (41)                | 0.92 (0.68–1.26)              |
| Respiratory distress at birth (%)            | No                     | 830 (95)                | 1                             |
|                                               | Yes                    | 47 (5)                  | 2.01 (0.85–4.75)              |
| Breastfeeding ≥4 months                      | No                     | 385 (44)                | 1                             |
|                                               | Yes                    | 492 (56)                | 1.23 (1.01–1.50)              |
| Insect sting allergy (%)                     | No                     | 387 (44)                | 1                             |
|                                               | Yes                    | 489 (56)                | 1.45 (0.92–2.29)              |
| Paracetamol use by infant including kogrip (%)| No                     | 661 (73)                | 1                             |
|                                               | Yes                    | 216 (25)                | 0.98 (0.73–1.32)              |
| State of home (%)                            | Good                   | 649 (74)                | 1                             |
|                                               | Regular                | 176 (20)                | 1.81 (0.77–4.27)              |
|                                               | Poor                   | 52 (6)                  | 1.23 (1.01–1.51)              |
| No. of rooms in house (excluding bathroom and kitchen) | 1                     | 97 (11)                 | 1                             |
|                                               | 2                     | 242 (28)                | 0.70 (0.43–1.15)              |
|                                               | ≥3                    | 538 (61)                | 0.66 (0.33–1.32)              |
| Ventilation of home (%)                      | Good                   | 696 (79)                | 1                             |
|                                               | Regular                | 125 (14)                | 1.66 (1.03–2.68)              |
|                                               | Poor                   | 56 (6)                  | 0.93 (0.53–1.63)              |
| Presence of ornamental plants (%)            | No                     | 630 (72)                | 1                             |
|                                               | Yes                    | 247 (28)                | 0.97 (0.70–1.35)              |
| Presence of bathroom in home (%)             | No                     | 99 (11)                 | 1                             |
|                                               | Yes                    | 778 (89)                | 0.93 (0.63–1.38)              |
| Mould in home (%)                            | No                     | 631 (72)                | 1                             |
|                                               | Yes                    | 246 (28)                | 1.10 (0.61–1.97)              |
| Child sleeps in cooking area                 | No                     | 792 (90)                | 1                             |
|                                               | Yes                    | 85 (10)                 | 1.08 (0.49–2.40)              |
| Cook with gas (%)                            | No                     | 39 (7)                  | 1                             |
|                                               | Yes                    | 818 (93)                | 0.72 (0.52–1.00)              |
| Cook with electricity (%)                    | No                     | 688 (78)                | 1                             |
|                                               | Yes                    | 189 (22)                | 0.75 (0.53–1.08)              |
| Mosquito nets in home (%)                    | No                     | 320 (36)                | 1                             |
|                                               | Yes                    | 557 (64)                | 0.96 (0.63–1.45)              |
| Air conditioning (%)                          | No                     | 725 (83)                | 1                             |
|                                               | Yes                    | 152 (17)                | 0.71 (0.39–1.27)              |
| Infant’s room walls painted before birth     | No                     | 411 (47)                | 1                             |
|                                               | Yes                    | 466 (53)                | 0.87 (0.63–1.20)              |
| Infant’s room walls painted after birth      | No                     | 768 (88)                | 1                             |
|                                               | Yes                    | 109 (12)                | 0.87 (0.47–1.58)              |
| Infant’s mattress                            | Used                   | 493 (56)                | 1                             |
|                                               | New                    | 384 (44)                | 1.06 (0.83–1.36)              |
Martínez et al. (1995) reported a median value of serum IgE of 3.2 to 9.9 IU/ml in a population of infants aged 9 months who were living in Tucson, Arizona in 1980 to 1984, which can be compared with our median value of 35 IU/ml for infants living in Havana, Cuba, in 2010 to 2011. Obviously, there are many explanations for the wide differential in serum IgE between these two populations, with age and geographical location constituting two possibilities.

Serum IgE is an antibody that probably has evolved in humans to protect against parasite infection (Gounnl et al. 1994; Cooper et al. 2008). Although we did not see any association between higher serum IgE levels and parasite infection, the prevalence of parasite infection was low at 4% of the study population who provided stool samples. This probably reflects the young age of the infants studied, as they will not have had much exposure to soil and dirt floors and hence not yet had the chance

### Table 2 (Continued)

| Variable                              | Definition of category | Number (%) or mean (SD) | OR of increased IgE* (95% CI) |
|---------------------------------------|------------------------|-------------------------|------------------------------|
| Infant sleeps alone                   | No (not alone)         | 396 (45)                | 1                            |
|                                       | Yes (alone)            | 481 (55)                | 1.03 (0.63–1.69)              |
| Daily use of soap                     | No                     | 27 (3)                  | 1                            |
|                                       | Yes                    | 850 (97)                | 1.26 (0.70–2.25)              |
| Use of shampoo                        | No                     | 259 (30)                | 1                            |
|                                       | Yes                    | 618 (70)                | 0.96 (0.66–1.41)              |
| No. of people in household            | 2                      | 101 (12)                | 1                            |
|                                       | 3                      | 226 (26)                | 0.63 (0.31–1.26)              |
|                                       | 4                      | 241 (27)                | 0.62 (0.25–1.54)              |
|                                       | 5                      | 146 (17)                | 0.72 (0.41–1.28)              |
|                                       | ≥6                     | 163 (19)                | 0.66 (0.27–1.62)              |
| Eats vegetables                       | No                     | 159 (18)                | 1                            |
|                                       | Yes                    | 718 (82)                | 0.87 (0.62–1.21)              |
| Eats fruit                            | No                     | 81 (9)                  | 1                            |
|                                       | Yes                    | 796 (91)                | 0.97 (0.37–2.54)              |
| Maternal smoking during pregnancy     | No                     | 815 (93)                | 1                            |
|                                       | Yes                    | 62 (7)                  | 0.94 (0.37–2.39)              |
| Mother currently smokes               | No                     | 710 (81)                | 1                            |
|                                       | Yes                    | 167 (19)                | 1.08 (0.88–1.33)              |
| Father currently smokes               | No                     | 588 (67)                | 1                            |
|                                       | Yes                    | 289 (33)                | 0.97 (0.87–1.09)              |
| Number of smokers in home             | 0                      | 436 (50)                | 1                            |
|                                       | 1                      | 223 (25)                | 1.19 (0.95–1.49)              |
|                                       | 2                      | 142 (16)                | 0.95 (0.72–1.25)              |
|                                       | ≥3                     | 76 (9)                  | 0.98 (0.68–1.42)              |
| Any grandparents smoke                | No                     | 365 (42)                | 1                            |
|                                       | Yes                    | 512 (58)                | 1.02 (0.74–1.41)              |
| Pets in home at time of birth         | No                     | 561 (64)                | 1                            |
|                                       | Yes                    | 316 (36)                | 0.86 (0.73–1.01)              |
| Pets in home now                      | No                     | 566 (65)                | 1                            |
|                                       | Yes                    | 311 (35)                | 1.03 (0.80–1.34)              |
| Rodents in home                       | No                     | 749 (85)                | 1                            |
|                                       | Yes                    | 128 (15)                | 1.12 (0.55–2.29)              |
| Cockroaches in home                   | No                     | 633 (72)                | 1                            |
|                                       | Yes                    | 244 (28)                | 1.26 (0.99–1.60)              |
| Air pollution near home               | No                     | 614 (70)                | 1                            |
|                                       | Yes                    | 263 (30)                | 0.97 (0.65–1.45)              |
| Child attended day care/nursery       | No                     | 753 (86)                | 1                            |
|                                       | Yes                    | 124 (14)                | 0.97 (0.39–2.40)              |

IQR, interquartile range; OR, odds ratio.
*Elevated IgE defined as above median value.
to be infected. Data from a rural area in Cuba reported a prevalence of any helminth infection of 22% in children (mean age of 8 years) (Wordemann et al. 2008), and this demonstrates that exposure to parasites is common in certain regions in the country, but this is not necessarily true in our urban population. However, it is likely that in the absence of parasite infection, other environmental exposures will also increase the probability of an elevated serum IgE, and this would explain the associations observed in our data.

The association between being breastfed for 4 months or more and increased IgE was unexpected as it has not been reported previously. There have been many studies of the impact of breastfeeding on the subsequent development of allergic disease and despite the undoubted health benefits of breastfeeding on child health, the impact on allergic disease is not fully understood (Wold 2006; Revalas & Katasos 2012). One of the well-recognised benefits of breastfeeding is the transfer of maternal immunity in the form of immunoglobulin A (IgA) to the infant (Hanson & Korotkova 2002) and protection against infection (AAP 2012), and breastfed infants have lower mortality attributable to infections than those who are not breastfed (Arifeen et al. 2001). Breastfeeding has been reported to be associated with a lower incidence of parasitic disease (Bilenko et al. 2008), and we speculate that one potential mechanism to explain this is the stimulation of endogenous IgE levels that may be advantageous to infant survival, particularly from an evolutionary perspective (i.e., those individuals with higher IgE levels may be more likely to thrive and survive until adulthood, increasing the chances of having offspring).

Our finding that having a pet in the home at the time of birth is associated with lower IgE is consistent with the previous observations that pet exposure in the first year of life had a lower frequency of allergic rhinitis at 7–9 years of age and of asthma at age 12–13 years (Hesselmar et al. 1999). Exposure to cat allergen in the early years of life is associated with lower risk of sensitisation and asthma (Platts-Mills et al. 2001). Unfortunately, we were unable to collect data on the type of pet living in houses of our study population, or of cat-specific IgE sensitisation, although cats are common in Cuba. There is no obvious plausible biological explanation why cooking with both gas and electricity (compared with just electricity) and having a mother who works are both also associated with lower IgE levels. We, thus, speculate that the latter may be a proxy measure of relatively increased affluence, as while we have tried to adjust for household income and socio-economic status in Cuba, it is likely that this is at best an imprecise measure due to undeclared earnings or money transfers from overseas. Previous data of women living in an urban area of the USA demonstrate that total serum IgE is inversely associated with levels of affluence (Lewis et al. 2001). Affluence may be associated with less psychological stress and better housing conditions, both factors that are associated with lower levels of allergic disease

### Table 3 Final multivariate analysis of exposures and risk of elevated IgE

| Variable                              | Definition of category | Number (%) | Number (%) with increased IgE | Adjusted OR for increased IgE* (95% CI) |
|---------------------------------------|------------------------|------------|-------------------------------|----------------------------------------|
| Gender                                | Female                 | 404 (46)   | 184 (45.5)                    | 1                                      |
|                                       | Male                   | 473 (54)   | 234 (53.7)                    | 1.35 (0.80–2.27)                       |
| Municipality                          | Habana del Este        | 316 (36)   | 150 (47.5)                    | 1                                      |
|                                       | Cerro                  | 155 (18)   | 73 (47.1)                     | 0.90 (0.80–1.02)                       |
|                                       | La Lisa                | 129 (15)   | 76 (58.9)                     | 1.51 (1.28–1.79)                       |
|                                       | Arroyo Naranjo         | 277 (32)   | 139 (50.2)                    | 1.44 (1.15–1.82)                       |
| Breastfeeding for >4 months           | No                     | 385 (44)   | 181 (47.0)                    | 1                                      |
|                                       | Yes                    | 492 (56)   | 257 (52.2)                    | 1.28 (1.02–1.61)                       |
| Mother in paid employment             | No                     | 311 (35)   | 170 (54.7)                    | 1                                      |
|                                       | Yes                    | 566 (65)   | 268 (47.4)                    | 0.73 (0.54–0.97)                       |
| Presence of cockroaches in home       | No                     | 633 (72)   | 306 (48.3)                    | 1                                      |
|                                       | Yes                    | 244 (28)   | 132 (54.1)                    | 1.30 (1.03–1.63)                       |
| Cooking source                        | Electricity only       | 59 (7)     | 34 (57.6)                     | 1                                      |
|                                       | Gas only               | 688 (78)   | 354 (51.5)                    | 1.01 (0.73–1.39)                       |
|                                       | Gas & electricity      | 130 (15)   | 50 (38.5)                     | 0.45 (0.32–0.62)                       |
| Pets at home at birth                 | No                     | 561 (64)   | 288 (51.3)                    | 1                                      |
|                                       | Yes                    | 316 (36)   | 150 (47.5)                    | 0.83 (0.70–1.00)                       |

OR, odds ratio.

*Defined as above median value.
(Wright et al. 2002; Mendell et al. 2011). The association between the presence of cockroaches in the home and an increase in the infants’ IgE levels could be another manifestation of lower affluence or alternatively a consequence of a higher burden of microbiological exposure stimulating the whole immune system, resulting in higher IgE levels. The cockroach is well recognised as an environmental exposure that is associated with increased levels of allergic disease in sensitized individuals in urban areas (Rosenstreich et al. 1997), and this may explain the association with increased IgE. Unfortunately, we do not have data on cockroach-specific IgE to clarify this issue, although recent data has reported that increased total IgE is positively correlated with allergen-specific IgE levels that included those from cockroaches (Hani 2012).

In summary, we have identified that living in a home that contains cockroaches and breastfeeding for 4 months or more are associated with higher total serum IgE, while living in a household that has pets at the time of birth, cooks with gas and electricity and having a mother that works outside the home is associated with lower serum total IgE. In probability, increased total IgE will be a consequence of a multitude of environmental exposures. As increased total serum IgE in the first year of life is associated with an increased risk of persistent wheezing at age 6 years (Martinez et al. 1995), understanding these relations will increase knowledge of the immune responses that may have evolved from protecting us against parasites to increasing our risk of allergic disease. In the future, we hope that this will allow manipulation of these aberrant biological responses for therapeutic benefit to design interventions available to prevent and treat allergic disease.

Acknowledgements

We would like to thank all of the participants and their families for making this study possible. This work was supported by the Wellcome Trust; the Nottingham Respiratory Biomedical Research Unit; and the Instituto Nacional de Higiene, Epidemiología y Microbiología, Havana, Cuba. Thanks also to all Municipality Directors and the laboratory workers who also supported the study.

References

AAP (2012) Breastfeeding and the use of human milk. Pediatrics, 129, e827–e841.
Arifeen S, Black R, Antelman G, Baqui A, Caulfield L & Becker S (2001) Exclusive breastfeeding reduces acute respiratory infection and diarrhea deaths among infants in Dhaka slums. Pediatrics 108, 667.
Asher M, Montefort S, Bjorksten B et al. (2006) Worldwide trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 368, 733–743.
Bilenko N, Ghosh R, Levy A, Deckelbaum R & Fraser D (2008) Partial breastfeeding protects Bedouin infants from infection and morbidity: prospective cohort study. Asia Pacific Clinical Nutrition Society 17, 243–249.
Busse W, Morgan W, Gergen P et al. (2011) Randomized trial of Omalizumab (Anti-IgE) for asthma in inner-city children. New England Journal of Medicine 364, 1005–1015.
Cooper R, Kennelly J & Ordunez-Garcia P (2006) Health in Cuba. International Journal of Epidemiology 35, 817–824.
Cooper P, Alexander N, Moncayo A-L et al. (2008) Environmental determinants of total IgE among school children living in the rural tropics: importance of geohelminth infections and effect of anthelminthic treatment. BMC Immunology 9, 33.
Gould H & Sutton B (2008) IgE in allergy and asthma today. Nature Reviews Immunology 8, 205–217.
Gounal A, Lambioud B, Ochli K et al. (1994) High-affinity IgE receptor on eosinophils is involved in defence against parasites. Nature, 367, 183–186.
Habtamu K, Degarege A, Ye-Ehiyo Y & Erko B (2011) Comparison of the Kato–Katz and FLOTAC techniques for the diagnosis of soil-transmitted helminth infections. Parasitology International 60, 398–402.
Hani A (2012) Concordance and relevance of total and specific IgE allergy laboratory assays at a major Jordanian hospital. International Journal of Biological & Medical Research, 3, 2199–2203.
Hanson L & Korotkova M (2002) The role of breastfeeding in prevention of neonatal infection. Seminars in Neonatology 7, 275–281.
Hesselmar B, Abern N, Aberg B, Eriksson B & Bjorksten B (1999) Does early exposure to cat or dog protect against later allergy development? Clinical and Experimental Allergy 29, 611–617.
Holonen M, Stern D, Lyle S, Wright A, Taussig L & Martinez F (1991) Relationship of total IgE levels in cord and 9-month sera of infants. Clinical and Experimental Allergy 21, 235–241.
Lewis S, Weiss S, Platts-Mills T, Syring M & Gold D (2001) Association of specific allergen sensitization with socioeconomic factors and allergic disease in a population of Boston women. Journal of Allergy and Clinical Immunology 107, 615–622.
Martinez F, Wright A, Taussig L, Holberg C, Halonen M & Morgan W (1995) Asthma and wheezing in the first six years of life. New England Journal of Medicine 332, 133–138.
Mendell M, Mirer A, Cheung K, Tong M & Douwes J (2011) Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiological evidence. Environmental Health Perspectives 119, 748–756.
H. Fundora-Hernández et al. Elevated IgE in Cuban infants

Peat JK, Toelle BG, Dermand J, van den Berg R, Britton WJ & Woolcock AJ (1996) Serum IgE levels, atopy, and asthma in young adults: results from a longitudinal cohort study. Allergy 51, 804–810.

Platts-Mills T (2001) The role of immunoglobulin E in allergy and asthma. American Journal of Respiratory and Critical Care Medicine 164, S1–S5.

Platts-Mills T, Vaughan J, Squilace S, Woodfolk J & Sorpirk R (2001) Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 357, 752–756.

Revalas A & Katusos T (2012) The effects of maternal diet and breastfeeding on children with asthma and allergy. South African Family Practice 54, 492–494.

Rodriguez G, Esquivel E, Lopez L & Gutierrez P (2001) Asociaciones entre concentraciones de immunoglobulinas en ninos, factores ambientales de riesgo y morbilidad respiratoria. Revista Cubana de Higiene y Epidemiologia 39, 101–109.

Rosenstreich D, Eggleston P, Kattan M (2000) The role of immunoglobulin E in allergy and asthma. Journal of Allergy and Clinical Immunology 104, 28–36.

Simpson A, Soderstrom L, Ahsstedt S, Murray C, Woodcock A & Custovic A (2005) IgE antibody quantification and the probability of wheeze in preschool children. Journal of Allergy and Clinical Immunology 116, 744–749.

Sole D, Mallol J, Wandalsen G, Aguirre V & Group LAIPS (2010) Prevalence of symptoms of eczema in Latin America: results of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3. Journal of Investigational Allergology and Clinical Immunology 20, 311–323.

Solis R, Urquiza H, Fernandez J, Bencomo F, Perez E & Fabre D (1992) National Cuban Program for screening for predisposition to allergic disease with the use of SUMA Technology. Proceedings of the International Conference on Improving Birth Quality and Child Upbringing, (eds J Wu & R Jan) Beijing International Academic Publishers, pp. 342–345.

Sporisk R, Ingram J, Price W, Sussman J, Honsinger R & Platts-Mills T (1995) Association of asthma with serum IgE and skin prick test reactivity to allergens among children living at high altitude. American Journal of Respiratory and Critical Care Medicine 151, 1388–1392.

Sunyer J, Torregrosa J, Anto J et al. (2000) Total serum IgE is associated with asthma independently of specific IgE levels. The European Respiratory Journal 9, 1880–1884.

Venero Fernandez S, Perez P, Ortiz D et al. (2009) Bronchial asthma and rhinitis in schoolboys from Havana City (2001–2002), Revista Cubana de Higiene y Epidemiologia 47:

http://scielo.sld.cu/pdf/hie/v47n041/hie05109.pdf (accessed 31 October 2012)

Venero-Fernandez S, Suarez Medina R, Mora Faife E et al. (2013) Risk factors for wheezing in infants born in Cuba. QJM: Monthly Journal of the Association of Physicians, 106, 1023–1029.

Wold A (2006) Why is there still confusion about the impact of breastfeeding on the risk of allergy development? Scandinavian Journal of Food & Nutrition 50, 35–41.

Wordemann M, Diaz R, Heredia L et al. (2008) Association of atopy, asthma, allergic rhinoconjunctivitis, atopic dermatitis and intestinal helminth infections in Cuban children. Tropical Medicine and International Health 13, 180–186.

Wright R, Cohen S, Carey V, Weiss S & Gold D (2002) Parental stress as a predictor of wheezing in infancy. American Journal of Respiratory and Critical Care Medicine 165, 358–365.

**Appendix**

**HINASIC study group**

The HINASIC study group (Historia Natural de la Sibilancia en Cuba/National History of Wheezing in Cuba) consists of the following individuals: National Institute of Hygiene, Epidemiology and Microbiology: Menocal-Heredia I, Caraballos-Sánchez Y, Quintana R, Rodríguez-Bertheau AM, Rosado-García FM, Carmen-Hinojosa M, Varona-Pérez P. Hospital Universitario Pediátrico Docente Centro Habana: Rivero R., Muñoz-Pérez J, González-Morfa C. Municipality of Arroyo Naranjo: Zaldívar-Ricardo D, Diburt-Amita M, Álvarez-Valdez G, Alfonso-Hernández A, Álvarez-Valdez V, Magaña-Álvarez Y, Figueroa-Barreto Z, Sardinas-Báez N, Del Toro F, Velásquez-Pérez Y, Felpeto-Fuentes M, Gainza-Bueno Y, Esquivel-Barrios GM, Suárez-Paz M, Magaña-Álvarez BJ, Carménate-Fernández A, Hidalgo-Mederos R, Hidalgo-Mederos L, Silva D, Comas-Fonseca G, Laga-Cala DM, Kessel Díaz O. Municipality of La Lisa: Llopis-Pupo I, Rudy-Colebrooke L, Loyaz-González M, Ortiz-Hernández ML, Castillo-Bu M, Betancourt-López M, Gutiérrez-Mendoza ER, Rodríguez-Trujillo N, Pozo-Herrera P, Cruz-Acosta S, Montejo-Guerra VM, Gómez-Suliman V, Vega-Enríquez Y. Municipality of Cerro: Pando CR, Cortina-Mena I, Díaz-Giraldo A, Marrero-Sosa M, Matos-Ramos C, Betancourt-Orue M, Torres Zulueta RM, Alba Monteagudo O, Valle-López M, Ferrer-Ceruto Y, Dámas-Martínez A, Peñalver-Pérez M. Municipality of Habana del Este: Castillo-Martínez S, Pérez-Pérez IM, Bravo-Hernández PL, Martínez-Hernández A, Torriente-Barzaga N, Ávila-Rodríguez I, Navarro-Ruiz M, Díaz-Hernández K, Sarduy-Flores R, Sánchez-Díaz E, Zubizarreta-Segui L, Roque-Pereira G, Corona-Carnero
H. Fundora-Hernández et al. Elevated IgE in Cuban infants

Y, Rafols-Turró M, Cobas-Espino T, Castillo-Hernández N, Tenreiro-Vilda GC, Pulido-Díaz VI, Oropesa-Varona MJ, Luís-Avilés R, Santos-Smith K, Serrano-González T, Vázquez-Lazo B, Pupo-Portal Tania, Torres-Martínez MC, Betancourt-Cabreras I, Cid-Morell Y, Suárez-Quiñones R, García-Pérez K, Griñán-Ramos JA, Calzado-Herrera Y, Rizo-Ramos MN, Verdecia G, Garcia-Sotolongo MB, Del Río-Díaz A, Abreu-Quijano JF, Romeo-Ravelo F.

Corresponding Author Silvia J. Venero-Fernández, Infanta No 1158 e/ Llinás y Clavel, Código Postal 10300, La Habana, Cuba.
Tel.: +537 878 8479; E-mail: silviavf@inhem.sld.cu