

International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life

Garcia-Marcos L, Mallol J, Solé D, Brand PLP and EISL group.
International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life.

Pediatr Allergy Immunol 2010.

© 2010 John Wiley & Sons A/S

Risk factors for wheezing during the first year of life (a major cause of respiratory morbidity worldwide) are poorly known in non-affluent countries. We studied and compared risk factors in infants living in affluent and non-affluent areas of the world. A population-based study was carried out in random samples of infants from centres in Latin America (LA) and Europe (EU). Parents answered validated questionnaires referring to the first year of their infant's life during routine health visits. Wheezing was stratified into occasional (1–2 episodes, OW) and recurrent (3 + episodes, RW). Among the 28687 infants included, the most important independent risk factors for OW and RW (both in LA and in EU) were having a cold during the first 3 months of life [OR for RW 3.12 (2.60–3.78) and 3.15 (2.51–3.97); population attributable fraction (PAF) 25.0% and 23.7%]; and attending nursery school [OR for RW 2.50 (2.04–3.08) and 3.09 (2.04–4.67); PAF 7.4% and 20.3%]. Other risk factors were as follows: male gender, smoking during pregnancy, family history of asthma/rhinitis, and infant eczema. Breast feeding for > 3 months protected from RW [OR 0.8 (0.71–0.89) in LA and 0.77 (0.63–0.93) in EU]. University studies of mother protected only in LA [OR for OW 0.85 (0.76–0.95) and for RW 0.80 (0.70–0.90)]. Although most risk factors for wheezing are common in LA and EU; their public health impact may be quite different. Avoiding nursery schools and smoking in pregnancy, breastfeeding babies > 3 months, and improving mother's education would have a substantial impact in lowering its prevalence worldwide.

**Luis Garcia-Marcos¹, Javier Mallol²,
Dirceu Solé³, Paul L. P. Brand^{4,5} and
the EISL Study Group⁵**

¹Pediatric Respiratory and Allergy Units, "Virgen de la Arrixaca" University Children's Hospital, University of Murcia, Murcia, Spain; and CIBER of Epidemiology and Public Health (CIBERSP), Murcia, Spain,

²Department of Pediatric Respiratory Medicine, Hospital El Pino, University of Santiago de Chile (USACH), ³Division of Allergy, Clinical Immunology and Rheumatology, ⁴Department of Pediatrics, Federal University of São Paulo (UNIFESP), São Paulo, Brazil, ⁵Department of Pediatric Pulmonology, Isala Clinic, Zwolle, The Netherlands

Key words: wheezing; asthma; infants; epidemiology; estudio internacional de sibilancias en lactantes

Luis Garcia-Marcos, Pabellón Docente Universitario. Campus Ciencias de la Salud, Ctra. Madrid-Cartagena, s/n. 30120 El Palmar. Murcia. Spain
Tel.: +34868888129
Fax: +34868888127
E-mail: lgmarcos@um.es

Accepted 17 April 2010

Wheezing is one of the most common respiratory causes of medical consultation and hospital admission during the first years of life, thus having a large economic impact. Although depending on the particular country, study design, and year, rates may differ; at least one episode of wheezing has been described in 25% (Australia) (1) or in 45% (USA) (2) of children during their first year. A study from New Zealand (3) reported a prevalence of 39% during the first 15 months of life. In children up to the age of 2 yr, a Dutch study found a prevalence of

30%. Other studies including older children have found prevalence rates from 22% to 42% (4–6).

Recurrent wheezing (RW), which is usually defined as three or more episodes of this condition in the previous year, is also quite frequent, accounting for 22% in one study (4) and 12% in another one (1). Additionally, this condition provokes a significant impairment of the quality of life of affected infants and their families (7). When RW occurs during the first year of life, it can cause great concern to parents and represents a treatment challenge for health personnel. Risk

factors for RW during the first year of life may vary between localities with different environmental and developmental conditions (8, 9), as occurs globally for asthma in older children and adults (10–13).

RW in infancy has been reported to be associated with several genetic and environmental factors such as asthmatic heredity, male gender, perinatal tobacco smoke exposure, respiratory infections by common viruses, pre-term birth, housing conditions, indoor air quality, outdoor air pollution, mould stains on household walls, and obesity (2, 3, 6, 14–20). Regarding protective factors, breast feeding is by far the more consistently reported one (1, 21).

At present, interpretations of the results of studies related to risk/protective factors of RW during the first year of life are rather difficult, mainly because studies include children from 1 to 5 yr and most of them are not population-based, often reporting findings on infants at high asthma risk. Moreover, with exceptions, studies have been undertaken in affluent countries. To the best of our knowledge, there is no information, obtained with standardized methods and validated questionnaires, on the potential differences and variations of risk factors for RW during the first year of life between and within affluent and non-affluent areas.

This study describes and compares the risk factors for RW, exclusively during the first year of life, and using the standardized methods (22, 23) of the “Estudio Internacional de Sibilancias en Lactantes” (EISL) (International Study of Wheezing in Infants), in a large sample of infants from centres in Latin America, Spain, and the Netherlands. Additionally, it explores the possibility that the risk factors for RW may be different for a less frequent form of wheeze.

Methods

The EISL is a multicentre, cross-sectional, international, population-based study which is carried out using standardized methods and a validated questionnaire (22–24) based on that of the International Study of Asthma and Allergies in Childhood (ISAAC) (<http://isaac.auckland.ac.nz>). It includes questions on wheezing during the first year of life and also on risk/protective factors, such as gender, family history of asthma and allergic diseases, personal history of eczema, smoking habits in the mother, nursery school attendance, breast feeding, number of siblings and persons living in the same house, mother's level of education, and pet ownership.

Subjects and sampling frame

All the primary care health clinics, either urban or rural, where infants attend for growth/development monitoring and/or vaccine administration, according to the national public health programmes in each country, and located in the geographical area corresponding to an EISL centre, were considered for recruiting infants. The recruitment period extended from January 2005 to January 2007. Parents or guardians were invited to complete the questionnaire when infants were brought for a scheduled vaccine administration or a preventive health care visit around the age of 1 yr, emphasizing that questions were related to events which occurred during the first 12 months of life of their children. Field workers and/or nurses working at the health centres were at parents' disposal if they needed help for writing and/or reading questionnaires, though they were instructed just to read and not to make interpretations of questions to avoid directing answers. Samples of at least 1000 infants – enough to significantly detect a difference in the prevalence of RW of 5% between two centres, one of them having around 20% (9), with a confidence level of 95% and a power of 80% – were required from participating centres.

Definitions

Wheezing was defined as a positive answer to the question: “Has your child had wheezing or whistling in the chest during the first 12 months of his/her life?” which was previously validated in the main languages of the study (Spanish and Portuguese) (22–24). The Dutch questionnaire was translated from Spanish to Dutch and then back translated into Spanish, following the ISAAC methods (25). RW was defined as three or more parent-reported episodes of wheezing during the first year of life. One or two wheezing episodes was termed occasional wheeze (OW).

Parental asthma and parental rhinitis was defined as father and/or mother having the disease as reported by them. Infant eczema was reported by parents when answering the question: “Has your child had an itchy rash which was coming and going in any area of his/her body, except around the eyes and nose, and the diaper area, during his/her first 12 months of life?” Common colds were also reported by parents when asked if their babies had had “short episodes of cold with runny nose, sneezing, nasal obstruction, mild cough, with or

without mild fever". Additionally, parents were asked about mother smoking during the child's pregnancy (yes/no); infant attending nursery school during the first year of life (yes/no); exclusive breast feeding (more than 3 vs. 3 or less months); number of siblings, number of persons living in the same household, existence of mould stains on its walls and presence of pets, at the time the questionnaire was taken; maximum study level achieved by the mother (primary/secondary vs. university); and ethnicity (Caucasian vs. Afro-American).

Data analysis

Descriptive statistics (SPSS v10 software (Chicago, IL, USA) was employed to show the prevalence of the main outcome variables together with that of risk factors in the different centres, and to explore potential differences between the LA and EU centres. The crude association between risk factors and outcome variables (OW and RW) was assessed by means of the odds ratio (OR) and 95% confidence intervals (95% CI). Adjusted odds ratios (aOR) and 95% CI were calculated by means of multivariate logistic regression, using generalized linear models with a binomial distribution and logistic link, with all risk/protective factors as independent variables, and OW and RW as dependent variables (Stata v7, College Station, TX, USA). Those regressions were calculated for each centre. Ethnicity was only included in those centres with at least 5% of the individuals being of Afro-American origin. Summary OR and aOR with 95% CI were calculated using the meta-analysis approach with random effects to allow for the weight of the centre (26) (Comprehensive Meta-Analysis v2; Biostat, Englewood, NJ, USA). As a way of comparing the impact of a given risk factor between LA and EU where the prevalence of those risk factors may be different, their population attributable fraction (PAF) were used. There are calculated according to the maximum likelihood, estimated from logistic regressions (27) in LA and EU independently (Stata v7) after a logistic regression model in which all subjects of LA and EU were separately included in the analysis. This was performed only for RW as dependent variable – as this is the really worrisome condition which had the strongest associations with the risk/protective factors. All factors, found statistically significant associated in the summary aOR – either for LA or for EU, were included as independent variables in the logistic regression models.

Ethical approval

The study was approved by the local Scientific Ethic Committee at each centre, and parents or guardians answered the questionnaire after signing the full-informed written consent.

Results

For this study, 16 EISL centres provided data. After excluding 771 questionnaires either without the main outcome variable (wheezing episode, yes/no) or without the number of wheezing episodes, or belonging to children younger than 12 or older than 24 months, the total number of questionnaires included in the analysis was 28687 (23624 from 11 centres in Latin America and 5063 from five centres in Europe; exclusion rate 2.6%). Response rate was higher than 70% in all centres except for Valencia (61%) and the mean age for the whole sample of infants (52.3% male) was 13.4 ± 1.7 months. The prevalence of OW and RW varied widely and was significantly higher in Latin American centres than in European centres (Table 1).

There was also high variability in the prevalence of the risk/protective factors for wheezing among centres, and for most factors the prevalence was significantly higher in LA than in EU (Table 1).

The strength of the unadjusted associations between the risk/protective factors and suffering from OW or RW during the first year of life were variable among centres, and continents. In general, OR were slightly reduced after adjustment (Tables 2 and 3) in both the outcome variables; however, none of them changed the direction of the association and only few became non-significant after adjustment, as was the case for number of siblings (LA and EU) and of persons living in the household (EU) with respect to OW; and pets for both OW and RW.

There was good consistency in the associations of well-known risk factors with higher prevalences of wheeze. However, this did not occur with some factors in some centres. For example, male gender was a risk factor for RW in most centres except in Barranquilla, Recife, Caracas, Porto Alegre and Bilbao, although the trend in those centres was in the same direction. Similarly, parental asthma was significantly associated to RW except for Valdivia, Barranquilla, Valencia, and La Coruña (Tables 2 and 3).

Suffering at least one cold during the first 3 months of life and attending nursery school were the most important and consistent risk

Table 1. Prevalence of risk/protective factors included in the study

Subjects				Risk/ protective factors (%)												
Total sample (N)	Occasional wheezing (%)	Recurrent wheezing (%)	Family history				Mother smoked during pregnancy	Colds during first 3 months	Attended nursery school	Breast feeding >3 m	Siblings (IQR)	Persons at home (IQR)	Mould stains	University studies in mother	Afro-American ethnicity	Pets at home
			Male gender	Asthma	Rhinitis	Infant eczema										
Chile																
Santiago	2988	38.6	22.0	49.7	15.1	19.9	44.2	9.0	44.7	7.4	79.7	0-2	4-6	58.6	NA	55.4
Valdivia	3075	33.4	21.1	59.2	20.3	25.1	45.1	8.7	40.0	15.2	74.3	0-2	4-5	61.2	NA	44.0
Brazil																
Fortaleza	1209	23.1	22.1	53.7	35.4	48.5	52.7	9.8	35.7	3.8	62.0	0-2	3-6	25.5	52.1	35.6
Recife	1063	18.2	25.0	53.1	40.0	35.9	58.9	12.3	39.8	26.3	59.9	0-2	3-5	32.5	54.6	30.7
Belo Horizonte	2532	22.5	27.4	50.8	41.4	52.8	59.0	13.1	36.7	11.2	63.8	0-2	3-5	33.6	46.7	48.4
Belem	3029	24.2	21.9	49.7	18.6	29.9	58.8	4.7	39.8	1.4	78.8	0-2	4-7	26.9	62.8	42.7
Porto Alegre	1016	27.0	36.3	51.7	37.7	66.4	61.1	19.6	45.1	21.5	7.1	0-2	3-5	3.9	27.5	51.6
Sao Paulo	1012	19.1	26.7	50.6	13.0	48.0	44.2	15.6	32.9	19.6	62.7	0-2	3-5	41.0	30.6	30.7
Curitiba	3003	22.5	22.6	50.7	21.0	55.8	54.1	14.0	38.8	25.1	69.5	0-2	3-5	39.5	14.1	50.7
Colombia																
Barranquilla	1688	30.1	15.9	53.6	29.9	48.7	53.4	3.5	39.5	5.4	68.8	0-2	6-8	38.3	9.7	40.7
Venezuela																
Caracas	3009	23.9	17.5	53.4	44.0	46.0	39.6	8.2	43.3	18.0	54.4	0-2	4-6	49.6	NA	37.3
Latin America Total	23624	26.8	23.7	52.4	27.7	40.9	50.9	9.9	40.1	13.3	66.2	0-2	3-6	41.1	33.3	44.2
Spain																
Valencia	886	16.7	12.1	52.8	10.4	26.4	10.6	14.7	27.5	16.2	47.6	0-1	3-4	73.3	0.5	23.2
Cartagena	1172	22.3	16.2	53.1	13.2	23.7	14.5	21.0	31.0	12.0	40.3	0-1	3-4	73.4	0.5	28.6
Bilbao	996	20.3	18.6	52.1	12.7	18.3	12.1	16.2	21.4	28.8	55.6	0-1	3-4	89.6	0.0	12.8
La Coruña	930	18.7	13.8	49.9	14.1	26.6	12.7	15.7	24.4	22.0	42.1	0-1	3-4	84.2	0.3	28.3
The Netherlands																
Zwolle	1079	14.9	13.80	51.4	13.2	44.8	22.7	9.2	43.6	40.1	45.4	0-1	3-4	97.9	0.7	56.2
Europe Total	5063	18.6	15.0	51.9	12.8	28.2	14.7	15.4	30.0	23.9	46.0	0-1	3-4	83.8	0.4	30.4
Total	28687	25.4	22.2	52.3	25.1	38.6	44.7	10.9	38.4	15.2	62.6	0-2	3-6	48.6	25.9	41.8

NA, No data available; IQR, interquartile range.

All differences between Latin America total and Europe total were highly significant ($p < 0.0001$) except for gender.

Table 2. Adjusted associations between the studied risk/protective factors and having occasional wheezing (1–2 episodes) during the first year of life (odds ratios and 95% confidence intervals in brackets, adjusted for all factors in the table)

	Family history				Mother smoked during pregnancy	Colds during first 3 months	Attended nursery school	Breast feeding >3m	Per additional sibling	Per additional persons at home	Mould stains in mother	University studies in mother	Afro- American ethnicity	Pets at home
	Male	Gender	Asthma	Rhinitis	Infant eczema									
Chile														
Santiago	1.16 (0.95–1.42)		1.55 (1.13–2.12)	1.38 (1.05–1.81)	1.47 (1.19–1.81)	1.44 (0.99–2.10)	1.64 (1.33–2.03)	1.93 (1.26–2.96)	0.84 (0.65–1.10)	1.01 (0.92–1.11)	1.04 (0.99–1.09)	1.34 (1.04–1.73)	NA	0.88 (0.71–1.08)
Valdivia	0.85 (0.72–1.01)		1.17 (0.92–1.48)	1.79 (1.45–2.21)	1.81 (1.52–2.14)	0.82 (0.59–1.13)	1.60 (1.33–1.92)	2.03 (1.57–2.63)	0.94 (0.77–1.15)	1.05 (0.96–1.14)	1.02 (0.97–1.07)	1.47 (1.21–1.77)	NA	1.24 (1.05–1.48)
Brazil														
Fortaleza	1.24 (0.91–1.69)		1.97 (1.43–2.72)	1.20 (0.88–1.63)	1.57 (1.15–2.16)	1.79 (1.06–3.01)	1.15 (0.82–1.61)	0.90 (0.38–2.17)	0.88 (0.49–0.93)	0.97 (0.86–1.09)	1.03 (0.96–1.10)	1.31 (0.85–2.02)	0.68 (0.49–0.93)	1.10 (0.80–1.52)
Recife	0.63 (0.45–0.89)		1.66 (1.17–2.37)	1.25 (0.87–1.81)	1.65 (1.15–2.37)	1.22 (0.71–2.10)	1.46 (1.02–2.09)	1.65 (1.09–2.51)	1.22 (0.85–1.75)	0.96 (0.85–1.08)	0.97 (0.89–1.07)	0.82 (0.56–1.21)	1.06 (0.74–1.52)	1.02 (0.70–1.49)
Belo Horizonte	1.32 (1.07–1.63)		1.30 (1.04–1.62)	1.48 (1.18–1.84)	1.30 (1.05–1.61)	1.26 (0.91–1.74)	1.40 (1.12–1.76)	1.58 (1.10–2.25)	0.81 (0.65–1.01)	1.04 (0.96–1.14)	1.03 (0.97–1.10)	1.08 (0.86–1.36)	1.09 (0.88–1.36)	1.01 (0.81–1.25)
Belem	1.29 (1.08–1.54)		1.24 (0.97–1.58)	1.31 (1.07–1.60)	1.38 (1.15–1.67)	1.61 (1.05–2.49)	1.31 (1.09–1.58)	2.35 (1.17–4.70)	1.11 (0.89–1.39)	0.98 (0.91–1.05)	1.04 (1.00–1.08)	1.08 (0.87–1.32)	0.89 (0.74–1.07)	1.28 (1.06–1.53)
Porto Alegre	1.22 (0.86–1.72)		1.77 (1.21–2.58)	1.03 (0.70–1.52)	1.12 (0.79–1.61)	1.36 (0.84–2.19)	1.61 (1.14–2.33)	1.61 (1.04–2.51)	0.75 (0.34–1.63)	1.16 (1.01–1.34)	0.99 (0.89–1.11)	0.91 (0.63–1.29)	0.90 (0.59–1.36)	1.05 (0.74–1.49)
Sao Paulo	1.20 (0.84–1.72)		2.05 (1.20–3.49)	1.45 (1.00–2.11)	1.41 (0.98–2.03)	2.41 (1.47–3.94)	1.80 (1.21–2.67)	1.97 (1.24–3.11)	0.91 (0.62–1.32)	1.05 (0.90–1.22)	1.03 (0.91–1.16)	1.38 (0.94–2.02)	1.26 (0.84–1.88)	1.02 (0.69–1.52)
Curitiba	1.20 (0.97–1.48)		1.21 (0.92–1.58)	1.29 (1.03–1.61)	1.31 (1.06–1.63)	0.91 (0.65–1.27)	1.48 (1.18–1.84)	1.49 (1.16–1.91)	0.96 (0.75–1.21)	1.01 (0.92–1.12)	1.01 (0.94–1.08)	1.26 (1.00–1.59)	0.88 (0.50–0.97)	0.88 (0.71–1.10)
Colombia														
Barranquilla	1.14 (0.89–1.47)		1.35 (1.00–1.83)	1.40 (1.07–1.83)	1.34 (1.04–1.74)	1.93 (0.94–3.97)	1.80 (1.39–2.33)	1.32 (0.75–2.32)	1.06 (0.80–1.40)	0.96 (0.89–1.03)	1.01 (0.97–1.06)	1.52 (1.16–1.98)	0.84 (0.50–1.40)	1.18 (0.91–1.53)
Venezuela														
Caracas	1.08 (0.90–1.30)		1.30 (1.07–1.58)	1.17 (0.96–1.42)	1.42 (1.17–1.72)	0.92 (0.65–1.30)	1.50 (1.24–1.81)	1.03 (0.81–1.33)	1.18 (0.98–1.43)	1.01 (0.94–1.08)	1.00 (0.98–1.04)	1.35 (1.10–1.66)	NA	1.00 (0.82–1.21)
Latin America	1.11 (0.99–1.24)		1.40 (1.26–1.55)	1.35 (1.24–1.47)	1.44 (1.34–1.56)	1.29 (1.06–1.58)	1.50 (1.40–1.61)	1.57 (1.33–1.86)	0.96 (0.87–1.07)	1.01 (0.98–1.04)	1.02 (1.00–1.03)	1.23 (1.11–1.37)	0.91 (0.79–1.05)	1.06 (0.97–1.16)
Spain														
Valencia	0.91 (0.61–1.35)		1.20 (0.60–2.38)	1.11 (0.69–1.80)	1.51 (0.78–2.91)	1.43 (0.84–2.45)	1.89 (1.24–2.90)	1.63 (0.98–2.72)	0.84 (0.56–1.26)	1.11 (0.82–1.51)	1.06 (0.80–1.39)	0.57 (0.16–2.07)	NA	0.96 (0.60–1.53)
Cartagena	1.55 (1.12–2.14)		2.01 (1.19–3.39)	0.88 (0.58–1.32)	1.02 (0.64–1.65)	1.67 (1.14–2.43)	1.46 (1.02–2.08)	1.23 (0.74–2.04)	0.93 (0.67–1.29)	1.07 (0.89–1.31)	0.97 (0.85–1.12)	2.09 (1.32–3.28)	NA	0.86 (0.60–1.24)
Bilbao	1.40 (0.98–2.00)		1.43 (0.82–2.50)	1.45 (0.91–2.30)	1.26 (0.73–2.18)	1.80 (1.13–2.89)	1.95 (1.29–2.95)	1.47 (0.98–2.19)	0.69 (0.49–0.98)	1.32 (0.93–1.86)	0.81 (0.62–1.07)	0.87 (0.43–1.76)	NA	0.81 (0.49–1.37)
La Coruña	2.20 (1.47–3.31)		2.13 (1.22–3.73)	1.40 (0.88–2.23)	1.71 (0.94–3.13)	2.61 (1.52–4.47)	2.36 (1.50–3.73)	2.01 (1.26–3.19)	0.69 (0.46–1.05)	0.91 (0.65–1.27)	1.08 (0.91–1.28)	0.71 (0.40–1.27)	NA	0.90 (0.57–1.41)
The Netherlands														
Europe Total	1.45 (1.12–1.87)		1.64 (1.27–2.11)	1.28 (1.01–1.62)	1.27 (1.00–1.60)	1.59 (1.14–2.23)	1.88 (1.58–2.25)	1.51 (1.24–1.84)	0.81 (0.69–0.96)	1.03 (0.89–1.19)	1.02 (0.91–1.14)	1.06 (0.63–1.79)	0.95 (0.69–1.30)	0.96 (0.79–1.16)
Total	1.18 (1.05–1.33)		1.42 (1.30–1.56)	1.34 (1.23–1.45)	1.43 (1.34–1.53)	1.37 (1.15–1.64)	1.56 (1.45–1.68)	1.55 (1.37–1.76)	0.92 (0.84–1.01)	1.01 (0.98–1.04)	1.02 (1.00–1.03)	1.22 (1.09–1.37)	0.86 (0.78–0.96)	1.05 (0.97–1.13)

NA, not available because of <5 individuals in a given cell.

6 Table 3. Adjusted associations between the studied risk/protective factors and having recurrent wheezing (3 or more episodes) during the first year of life (odds ratios and 95% confidence intervals in brackets, adjusted for all factors in the table)

	Family history					Mother smoked during pregnancy	Colds during first 3 months	Attended nursery school	Breast feeding >3m	Per additional Sibling	Per additional persons at home	Mould stains	University studies in mother	Afro-American ethnicity	Pets at home
	Male Gender	Asthma	Rhinitis	Infant eczema											
Chile															
Santiago	1.45 (1.10–1.91)	2.34 (1.60–3.40)	1.67 (1.19–2.35)	1.94 (1.47–2.56)	1.24 (0.77–2.01)	4.60 (3.48–6.08)	4.02 (2.45–6.58)	0.58 (0.42–0.81)	1.19 (1.06–1.34)	1.15 (1.08–1.23)	1.38 (0.99–1.92)	1.02 (0.76–1.37)	NA	0.89 (0.67–1.17)	
Valdivia	2.00 (1.58–2.53)	1.17 (0.88–1.57)	1.85 (1.40–2.43)	2.43 (1.95–3.04)	1.02 (0.71–1.48)	6.04 (4.76–7.66)	4.23 (3.11–5.76)	0.73 (0.57–0.94)	1.21 (1.09–1.35)	0.97 (0.90–1.05)	1.72 (1.36–2.17)	0.90 (0.71–1.15)	NA	0.66 (0.53–0.84)	
Brazil															
Fortaleza	1.70 (1.22–2.36)	2.83 (2.02–3.95)	0.77 (0.55–1.07)	1.66 (1.19–2.32)	1.73 (0.99–3.02)	2.68 (1.92–3.73)	1.38 (0.59–3.25)	0.80 (0.57–1.13)	0.97 (0.86–1.10)	1.07 (0.99–1.14)	1.65 (1.07–2.55)	0.61 (0.41–0.91)	1.16 (0.83–1.62)	1.05 (0.74–1.48)	
Recife	1.16 (0.83–1.61)	1.89 (1.36–2.63)	1.65 (1.16–2.32)	1.50 (1.08–2.09)	1.20 (0.73–1.96)	2.47 (1.78–3.42)	2.17 (1.50–3.14)	0.98 (0.71–1.37)	0.96 (0.85–1.07)	1.03 (0.95–1.11)	1.17 (0.83–1.65)	0.59 (0.40–0.87)	1.74 (1.24–2.45)	0.80 (0.56–1.15)	
Belo Horizonte	1.38 (1.11–1.70)	1.83 (1.47–2.27)	1.39 (1.12–1.74)	1.49 (1.20–1.85)	1.27 (0.92–1.74)	2.68 (2.16–3.32)	3.08 (2.22–4.27)	0.66 (0.53–0.82)	1.02 (0.93–1.11)	1.06 (1.00–1.13)	1.37 (1.10–1.71)	0.91 (0.72–1.16)	1.05 (0.84–1.29)	0.96 (0.77–1.18)	
Belem	1.51 (1.25–1.84)	1.93 (1.53–2.45)	1.86 (1.51–2.29)	1.64 (1.34–2.02)	2.04 (1.32–3.14)	2.45 (2.01–2.97)	1.55 (0.67–3.62)	0.93 (0.73–1.17)	1.01 (0.94–1.09)	1.04 (1.00–1.09)	1.15 (0.93–1.44)	0.83 (0.66–1.04)	1.43 (1.16–1.76)	1.09 (0.89–1.33)	
Porto Alegre	1.27 (0.90–1.81)	2.37 (1.63–3.44)	1.08 (0.74–1.58)	1.45 (1.01–2.10)	1.93 (1.21–3.09)	4.07 (2.82–5.88)	2.53 (1.63–3.92)	0.78 (0.36–1.66)	1.21 (1.06–1.38)	1.02 (0.92–1.13)	0.83 (0.58–1.19)	0.54 (0.21–1.40)	1.29 (0.86–1.94)	1.14 (0.79–1.63)	
Sao Paulo	1.68 (1.19–2.37)	2.29 (1.40–3.76)	1.71 (1.20–2.44)	1.74 (1.23–2.46)	2.09 (1.31–3.35)	2.90 (2.03–4.16)	2.97 (1.95–4.54)	0.65 (0.45–0.92)	1.08 (0.92–1.25)	0.97 (0.86–1.11)	1.81 (1.27–2.58)	0.92 (0.63–1.33)	1.21 (0.82–1.77)	1.34 (0.92–1.93)	
Curitiba	1.52 (1.21–1.91)	1.78 (1.36–2.32)	1.53 (1.20–1.95)	1.29 (1.03–1.63)	1.63 (1.20–2.22)	2.62 (2.08–3.29)	2.31 (1.80–2.97)	0.76 (0.59–0.97)	1.06 (0.97–1.17)	1.05 (0.98–1.12)	1.39 (1.10–1.77)	0.67 (0.52–0.86)	1.14 (0.84–1.55)	1.04 (0.83–1.31)	
Colombia															
Barranquilla	1.12 (0.80–1.55)	1.41 (0.96–2.08)	1.38 (0.98–1.96)	1.60 (1.14–2.23)	1.93 (0.79–4.70)	2.87 (2.07–3.97)	1.28 (0.61–2.69)	1.05 (0.74–1.50)	0.94 (0.86–1.03)	1.06 (1.01–1.10)	1.78 (1.27–2.49)	0.55 (0.38–0.78)	1.32 (0.74–2.35)	0.98 (0.70–1.38)	
Venezuela															
Caracas	1.20 (0.96–1.50)	2.04 (1.62–2.56)	1.55 (1.24–1.95)	1.66 (1.33–2.07)	0.97 (0.65–1.43)	2.71 (2.16–3.38)	1.91 (1.47–2.48)	0.95 (0.76–1.18)	1.01 (0.93–1.09)	1.01 (0.98–1.05)	1.19 (0.93–1.50)	0.97 (0.77–1.21)	NA	0.91 (0.72–1.14)	
Latin America Total	1.44 (1.30–1.60)	1.91 (1.67–2.20)	1.47 (1.28–1.70)	1.66 (1.48–1.86)	1.44 (1.22–1.71)	3.13 (2.60–3.78)	2.50 (2.04–3.08)	0.80 (0.71–0.89)	1.05 (1.00–1.11)	1.04 (1.02–1.07)	1.36 (1.20–1.55)	0.80 (0.70–0.90)	1.26 (1.12–1.42)	0.96 (0.86–1.07)	
Spain															
Valencia	2.26 (1.37–3.75)	1.19 (0.55–2.56)	1.37 (0.78–2.40)	3.09 (1.60–5.97)	1.17 (0.59–2.31)	3.71 (2.27–6.05)	2.31 (1.30–4.10)	0.59 (0.36–0.96)	1.52 (1.16–2.00)	0.78 (0.58–1.05)	1.26 (0.36–4.36)	0.93 (0.53–1.62)	NA	0.95 (0.55–1.66)	
Cartagena	2.00 (1.32–3.03)	3.48 (1.94–6.25)	0.72 (0.43–1.21)	1.97 (1.19–3.25)	1.87 (1.18–2.97)	3.82 (2.57–5.74)	2.10 (1.20–3.66)	0.73 (0.47–1.11)	1.09 (0.88–1.35)	1.09 (0.94–1.25)	1.54 (0.85–2.80)	0.76 (0.48–1.20)	NA	1.13 (0.73–1.75)	
Bilbao	1.47 (0.98–2.19)	2.71 (1.49–4.93)	1.16 (0.70–1.91)	2.54 (1.46–4.42)	1.42 (0.84–2.42)	2.03 (1.26–3.29)	5.69 (3.75–8.63)	0.66 (0.44–0.98)	1.50 (1.04–2.19)	1.02 (0.76–1.39)	2.79 (1.53–5.11)	3.58 (1.43–8.94)	NA	0.65 (0.31–1.34)	
La Coruña	4.22 (2.47–7.20)	1.01 (0.47–2.17)	1.28 (0.70–2.34)	1.77 (0.87–3.59)	2.89 (1.56–5.37)	3.72 (2.21–6.26)	4.15 (2.43–7.08)	1.02 (0.62–1.69)	1.23 (0.92–1.64)	0.99 (0.89–1.11)	1.07 (0.57–2.03)	1.09 (0.55–2.20)	NA	0.73 (0.41–1.30)	
The Netherlands															
Zwolle	1.57 (1.04–2.35)	1.91 (1.14–3.21)	1.78 (1.18–2.70)	2.03 (1.31–3.13)	1.00 (0.48–2.10)	2.89 (1.92–4.35)	2.29 (1.51–3.47)	0.93 (0.62–1.41)	0.99 (0.79–1.23)	1.11 (0.86–1.43)	2.68 (1.25–5.74)	NA	NA	1.15 (0.76–1.73)	
Europe Total	2.07 (1.48–2.90)	1.94 (1.26–2.99)	1.23 (0.90–1.68)	2.19 (1.72–2.80)	1.61 (1.15–2.25)	3.15 (2.51–3.97)	3.09 (2.04–4.67)	0.77 (0.63–0.93)	1.21 (1.03–1.44)	1.01 (0.93–1.11)	1.78 (1.20–2.66)	1.16 (0.68–2.00)	NA	0.98 (0.78–1.23)	
Total	1.55 (1.38–1.75)	1.93 (1.69–2.20)	1.42 (1.25–1.62)	1.73 (1.56–1.92)	1.48 (1.28–1.72)	3.14 (2.69–3.65)	2.66 (2.21–3.21)	0.79 (0.72–0.87)	1.07 (1.02–1.13)	1.04 (1.02–1.07)	1.41 (1.25–1.60)	0.83 (0.70–0.94)	NA	0.96 (0.87–1.05)	

NA, not available because of <5 individuals in a given cell.

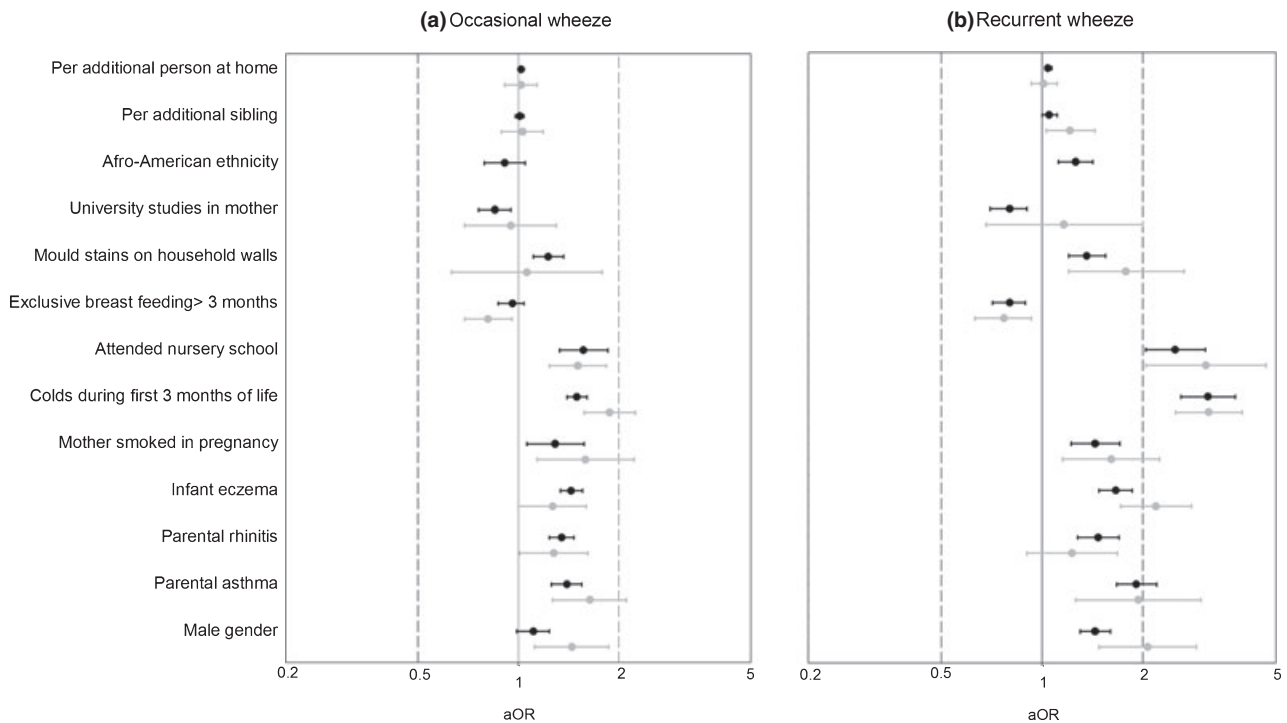


Fig. 1. Associations between the studied risk/protective factors and suffering (a), 1–2 episodes (b) 3 or more episodes of wheezing during the first year of life as expressed in adjusted (for all factors in the figure) odds ratios (aOR) and 95% confidence intervals. (Latin America dark lines, Europe light lines).

factors of all types of wheeze in all centres, in LA and EU. However, the strength of the association was much higher for RW than for OW (Fig. 1). A similar pattern was observed for gender, parental asthma, mould stains on the household walls and – inversely – for breast feeding for at least 3 months. On the contrary, the strength of the association of smoking during pregnancy, parental rhinitis, and university studies (inversely) was very similar for OW and RW. Afro-American ethnicity, siblings, and persons at home were only risk factors for RW but not for OW. Interestingly, infant eczema maintained the strength of the association throughout the two types of wheeze in EU, while this strength increased with wheeze severity in LA.

The PAF of the different independent significant risk factors for RW are shown in Fig. 2. The risk factor with the highest PAF, both for LA and for EU, was having a cold during the first 3 months of life [25.0% (23.1%–26.9%) vs. 23.7% (18.8%–28.3%), respectively]. Attending a nursery school had a very different PAF in LA and EU [7.4% (6.4%–8.3%) vs. 20.3% (16.1%–24.2%)]. Two additional risk factors that had very different PAF in LA and EU were as follows: infant eczema [15.8% (13.4%–18.1%) vs. 8.1% (5.0%–11.2%), respectively] and male gender [11.4% (9.1%–13.7%) vs. 23.8% (17.1%–30.0%), respectively].

Discussion

This study, undertaken in several centres from Latin America and Europe, shows a wide variability of strength of the risk factors for wheezing during the first year of life between centres. The variability occurs among centres in both continents, and also within a single country, suggesting the influence of regional or local environmental/ecological factors as a plausible explanation for the variation found in the magnitude of those risk/protective factors. Overall, the most important risk factors were attending a nursery school and suffering a cold during the first 3 months of life. Other risk factors common to a majority of centres/countries were male gender, smoking during pregnancy, mould stains on the household walls and atopy predisposition (parental asthma/rhinitis and infant eczema). Breast feeding tended to be a protective factor in most centres, as was university education in LA centres. The number of persons at home was a significant risk factor only for LA. Interestingly, several factors which were associated to RW were not associated to OW (number of siblings, breast feeding, mould stains – EU, and Afro-American ethnicity – LA).

The differences found in the prevalence of wheeze resembles what was described in ISAAC studies, where the prevalence of current

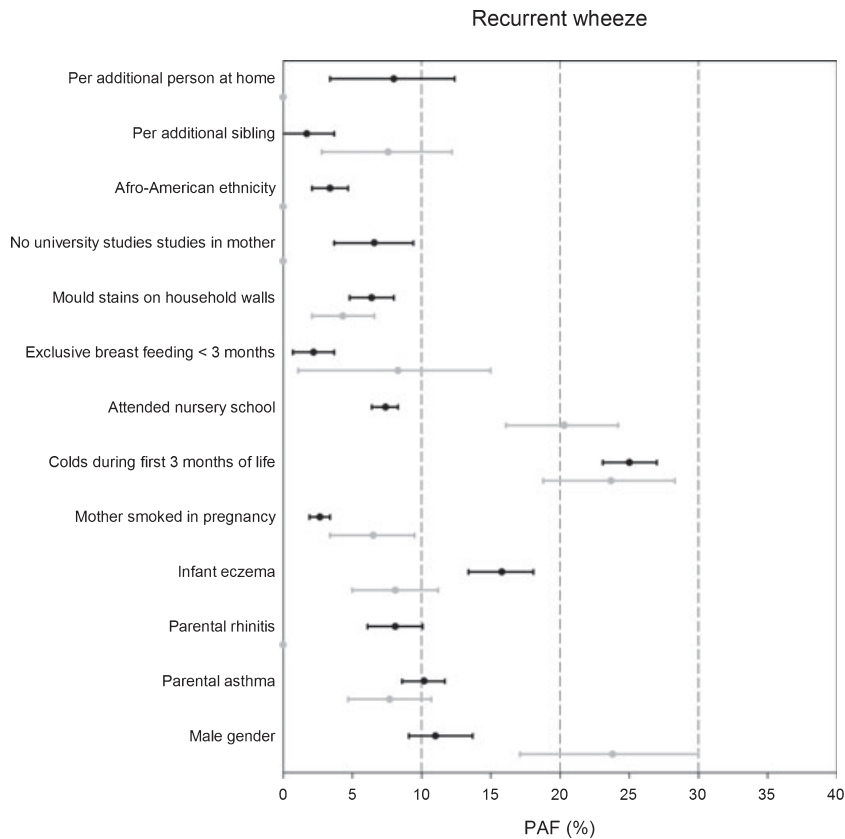


Fig. 2. Population attributable fraction (PAF) and 95% confidence intervals for recurrent wheeze of the different risk factors. (Latin America dark lines, Europe light lines).

asthma-like symptoms in children and adolescents was significantly lower in Spain and Portugal, when compared with Spanish and Portuguese-speaking countries of Latin America (28).

Racial background (independently of other factors such as education) may have a certain impact on the increased number (and perhaps on the severity) of the wheezing episodes during the first year of life, as is shown in this study where more than 30% of the participants from Brazil were of Afro-American origin. Curiously, this factor was associated to RW but not to OW. Nevertheless, other environmental factors, likely related to low socioeconomic conditions present in LA but not in EU, such as persons at home (PAF for additional person at home 8.0%) or mother without university studies in mother (PAF 6.6%), seem to play an important role for the higher prevalence of RW in LA. This indicates that improving the education level could be an important primary preventive strategy to reduce the prevalence of RW during the first year of life in LA.

Male gender – as in other studies (6, 8, 9) – was a risk factor for RW during the first months or years of life, and this was higher in EU than in

LA. In fact, PAF was double in EU (23.8%) than in LA (11.4%). Although several interactions of gender with other risk/protective factors in EU or LA are possible, and removing some of the risk factors in EU, which may be still acting in LA, could change the weight of others, there is no clear explanation for the difference.

It is of interest that the strength of the association of parental asthma/rhinitis with RW is similar in LA and EU; however, their PAF is higher in LA. This is probably related to a more frequent reported family history of asthma/rhinitis among LA mothers (almost double), which reinforces the similarity with previous ISAAC studies (2, 10, 28), showing that asthma and rhinitis are more prevalent in LA than in Spain or Portugal. A similar pattern of comparable association strength and different PAF between LA and EU was also found for mother smoking during pregnancy and infant attending a nursery school.

Breast feeding was a protective factor for LA and EU centres as groups, and PAF of not breastfeeding three or more months was not negligible (2.2% in LA and 8.3% in EU). Although the protective role of breast feeding

on infant wheezing is well known (1, 21), there was no comparative information between affluent and non-affluent countries. Although its PAF seem to be quite different between LA and EU, the confidence intervals overlap greatly.

It is worth noting how different PAF because of nursery school attendance is between LA and EU (7.4% vs. 20.2%). This would result from the addition of the somewhat greater effect in the EU centres plus the much higher use of this facility in EU: only 13.3% in LA vs. 23.9% in EU. Dampness, as in other studies (17), was a risk factor for RW in both continents, and had comparable PAF ($\approx 5\%$), even when in LA there were three times more damp houses than in EU, probably reflecting differences in available resources for household maintenance. Having one or more siblings was an independent risk factor in both continents and accounted for a non-negligible PAF in EU (7.6% vs. only 1.7% in LA). The reason for a less clear sibling effect in the LA centres might be related – at least in part – to a more widespread contact with viruses in LA, which does not make siblings necessarily an important source of infection to infants. In fact, PAF for additional persons at home was non-significant for EU but somewhat important for LA (8%).

Colds occurred in the first 3 months of life are the most important risk factor for a higher prevalence of RW. A very recent study has added some evidence to the causal relationship between viruses and early childhood wheezing (29). The impact of colds on the prevalence of OW and RW during the first year of life and on later asthma may vary depending on the ecology and virulence of common respiratory viruses, as demonstrated for the respiratory syncytial virus (30), or by the interaction of viruses with other ecological or genetic risk factors (2, 3, 6, 8, 14, 17–20), and also by protective factors such as breastfeeding (1, 21).

The potential limitations of this study include its cross-sectional nature (with the impossibility of clearly establish causal relationships), the parental reported symptoms instead of the physician's diagnosis (although validation studies with good results were carried out previously), and the non-objective measurements of several risk factors. Furthermore, the way of comparing risk factors between continents by means of PAF, although simple, has limitations and should be interpreted with caution (31). Another limitation comes from the absence of a centre in Portugal, which could have been a better comparator to Brazil than Spain or the Netherlands. However, according to ISAAC Phase I and III

(10, 11), and also the relatively comparable results of the Spanish centres with the centre in Zwolle, it might be expected that any centre in Portugal would have behaved similarly to the other European centres. Furthermore, we do not think seasonality or hemisphere had an important influence on the results, as most centres extended their recruitment time-span for one complete year. On the other hand, the main strengths of this study are that it was performed in the general population, has a large sample size, a high response rate, and includes centres with different cultural and socioeconomic statuses.

In summary, this study shows a wide variation of risk factors for the prevalence and severity of OW and RW during the first year of life among centres in LA and EU, suggesting the action of local or regional environmental/ecological factors. Furthermore, most risk factors are common for OW and RW, although the strengths of the associations are higher with RW. This study further suggests that the impact of certain risk factors (such as educational level of the mother) is higher in non-affluent localities. Suffering from a cold in the first three months of life appears, in LA and EU, as a strong predictor for RW. Despite the important variability in the risk factors among centres, interventions directed to decrease the large socioeconomic, educational, and living condition inequities in LA (32) would have a significant impact on reducing the prevalence and severity of first year wheezing in this region. On the other hand, limiting attendance to the nursery school would have a much greater impact in EU; while increasing breast feeding beyond the third month and reducing tobacco exposures, particularly during pregnancy, would decrease the prevalence of RW in different regions of the world.

Acknowledgments

We thank Mr. Anthony Carlson for his help with the written English.

Funding

Spanish “Fondo de Investigación Sanitaria” (Fund PI050480), Region of Murcia Government and Cartagena Local Health Authority (Spain).

References

1. ODDY WH, SLY PD, DE KLERK NH, et al. Breast feeding and respiratory morbidity in infancy: a birth cohort study. *Arch Dis Child* 2003; 88: 224–8.
2. BELANGER K, BECKETT W, TRICHE E, et al. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. *Am J Epidemiol* 2003; 158: 195–202.

3. GILLESPIE J, WICKENS K, SIEBERS R, et al. Endotoxin exposure, wheezing, and rash in infancy in a New Zealand birth cohort. *J Allergy Clin Immunol* 2006; 118: 1265–70.
4. BISGAARD H, SZEFLER S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol* 2007; 42: 723–8.
5. KUEHNI CE, STRIPPOLI MP, LOW N, BROOKE AM, SILVERMAN M. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clin Exp Allergy* 2007; 37: 1738–46.
6. MELEN E, KERE J, PERSHAGEN G, SVARTENGREN M, WICKMAN M. Influence of male sex and parental allergic disease on childhood wheezing: role of interactions. *Clin Exp Allergy* 2004; 34: 839–44.
7. DE JONG BM, VAN DER ENT CK, VAN PUTTE KN, et al. Determinants of health care utilization for respiratory symptoms in the first year of life. *Med Care* 2007; 45: 746–52.
8. MALLOL J, ANDRADE R, AUGER F, RODRIGUEZ J, ALVARADO R, FIGUEROA L. Wheezing during the first year of life in infants from low-income population: a descriptive study. *Allergol Immunopathol (Madr)* 2005; 33: 257–63.
9. SHERRIFF A, PETERS TJ, HENDERSON J, STRACHAN D. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3(1/2) years. *Int J Epidemiol* 2001; 30: 1473–84.
10. PEARCE N, AIT-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). *Thorax* 2007; 62: 758–66.
11. ASHER MI, MONTEFORT S, BJORKSTEN B, et al. Worldwide time 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* 2006; 368: 733–43.
12. The European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9: 687–95.
13. WEINMAYR G, WEILAND SK, BJORKSTEN B, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med* 2007; 176: 565–74.
14. EMENIUS G, SVARTENGREN M, KORSGAARD J, NORDVALL L, PERSHAGEN G, WICKMAN M. Indoor exposures and recurrent wheezing in infants: a study in the BAMSE cohort. *Acta Paediatr* 2004; 93: 899–905.
15. KUSEL MM, DE KLERK NH, HOLT PG, KEBADZE T, JOHNSTON SL, SLY PD. Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: a birth cohort study. *Pediatr Infect Dis J* 2006; 25: 680–6.
16. LEMANSKE RF JR, JACKSON DJ, GANGNON RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005; 116: 571–7.
17. CHO SH, REPONEN T, LEMASTERS G, et al. Mold damage in homes and wheezing in infants. *Ann Allergy Asthma Immunol* 2006; 97: 539–45.
18. LANNERO E, WICKMAN M, PERSHAGEN G, NORDVALL L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). *Respir Res* 2006; 7: 3.
19. TAVERAS EM, RIFAS-SHIMAN SL, CAMARGO CA JR, et al. Higher adiposity in infancy associated with recurrent wheeze in a prospective cohort of children. *J Allergy Clin Immunol* 2008; 121: 1161–6.
20. RYAN PH, LEMASTERS G, BIAGINI J, et al. Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic *J Allergy Clin Immunol* 2005; 116: 279–84.
21. SNIJDERS BE, THIJIS C, DAGNELIE PC, et al. Breast-feeding duration and infant atopic manifestations, by maternal allergic status, in the first 2 years of life (KOALA study). *J Pediatr* 2007; 151: 347–51. 351.
22. CHONG NETO HJ, ROSARIO N, DELA BIANCA AC, SOLE D, MALLOL J. Validation of a questionnaire for epidemiologic studies of wheezing in infants. *Pediatr Allergy Immunol* 2007; 18: 86–7.
23. MALLOL J, GARCIA-MARCOS L, AGUIRRE V, et al. The International Study of Wheezing in Infants: questionnaire validation. *Int Arch Allergy Immunol* 2007; 144: 44–50.
24. BIANCA AC, WANDALSEN GF, MIYAGI K, et al. International Study of Wheezing in Infants (EISL): validation of written questionnaire for children aged below 3 years. *J Investig Allergol Clin Immunol* 2009; 19: 35–42.
25. ELLWOOD P, WILLIAMS H, AIT-KHALED N, BJORKSTEN B, ROBERTSON C. Translation of questions: the International Study of Asthma and Allergies in Childhood (ISAAC) experience. *Int J Tuberc Lung Dis* 2009; 13: 1174–82.
26. NORMAND SL. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med* 1999; 18: 321–59.
27. GREENLAND S, DRESCHER K. Maximum likelihood estimation of the attributable fraction from logistic models. *Biometrics* 1993; 49: 865–72.
28. MALLOL J, ASHER MI, WILLIAMS H, CLAYTON T, BEASLEY R. ISAAC findings in children aged 14 years: an overview. *Allergy Clin Immunol Int* 1999; 11: 176–82.
29. WU P, DUPONT WD, GRIFFIN MR, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. *Am J Respir Crit Care Med* 2008; 178: 1123–9.
30. PANOZZO CA, FOWLKES AL, ANDERSON LJ. Variation in timing of respiratory syncytial virus outbreaks: lessons from national surveillance. *Pediatr Infect Dis J* 2007; 26: S41–5.
31. LEVINE B. What does the population attributable fraction mean? *Prev Chronic Dis* 2007; 4: A14.

Appendix

EISL* study group

Manuel Baeza-Bacab (México, Mérida); Álvaro Madeiro Leite, Olivia Costa Bessa (Brazil, Fortaleza), Elaine Xavier Prestes (Brazil, Belem), Emanuel Sarinho, Décio Medeiros (Brazil, Recife); Paulo Camargos, Maria Jussara Fernández-Fontes, Wilson Rocha (Brazil, Belo Horizonte); Dirceu Solé, Caroline Della Bianca (Brazil, São Paulo); Nelson Rosario, Herberto Chong (Brazil, Curitiba); Gilberto B.

Risk factors for wheezing in infants

Fischer (Brazil, Porto Alegre); Eduardo Cepeda (Colombia, Barranquilla); Oscar Aldrey, Arnaldo Capriles (Venezuela, Caracas); Javier Mallol, Viviana Aguirre, Alejandro Gallardo (Chile, Santiago); Mario Calvo (Chile, Valdivia); Luis Garcia-Marcos, Antonela Martinez-Torres, Virginia Pérez-Fernández, Manuel Sánchez-Solís (España, Murcia), Carlos

González-Díaz, Andrés González Hermosa (España, Bilbao), Angel López-Silvarrey Varela (España, La Coruña), María Morales Suárez-Varela (España, Valencia); Paul L.P. Brand, Chantal AN Visser (Zwolle, the Netherlands).

*EISL for “Estudio Internacional de Sibilancias en Lactantes” (International Study of Wheezing in Infants).