

Pneumonia and Wheezing in the First Year: An International Perspective

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Summary. Background: The relationship between pneumonia and recurrent wheezing (RW) and the factors associated to pneumonia in wheezing and non-wheezing infants have not been compared between affluent and non-affluent populations. Methods: The International Study of Wheezing in Infants (EISL) is a large population-based cross-sectional study carried out in Latin America (LA) and Europe (EU). We used a validated questionnaire for identifying wheeze in the first year of life. The questionnaire also inquired about pneumonia diagnosis, together with other potentially related factors. Associations between both conditions and between potential risk/protective factors for pneumonia were tested by random-effects logit model and adjusting for all factors found previously associated to RW in this cohort. Results: Pneumonia and RW were strongly associated to each other in LA and EU (aOR 5.42; 95%CI: 4.87–6.04 and aOR 13.99; 95%CI: 9.61–20.36, respectively). Infant eczema was the most consistent risk factor of pneumonia in both continents, in the whole population and also among wheezers and non-wheezers (aOR ranging from 1.30; 95%CI: 1.11–1.52 to 2.65; 95%CI: 1.68–4.18); while breast feeding for at least 3 months was the most consistent protective factor (aOR ranging from 0.60; 95%CI: 0.51–0.71 to 0.76; 95%CI: 0.69–0.84). Factors associated to pneumonia were similar between continents among wheezers, but differed considerably among non-wheezers. Conclusion: Pneumonia and RW are associated conditions sharing many risk/protective factors in EU and LA among wheezing infants, but not among non-wheezing infants. The association

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

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INTRODUCTION

Pneumonia is one of the most common causes of morbidity and death among children.^{1,2} Rates of pneumonia decrease with age, being highest in infants.^{3,4} Apart from young age,^{4–6} several risk factors for pneumonia in children have been identified in cross-sectional studies, such as measles, malnutrition,⁷ crowding at home,^{5,8} and environmental air pollution.^{9,10} Additional risk factors identified in community-based longitudinal studies in non-affluent countries include male gender, low socioeconomic status, low education, exposure to indoor air pollution and tobacco smoke, low birth weight, incomplete immunization, bottle feeding, attending nursery school, having one or more siblings, and crowding.^{4,11,12} Wheezing is a very frequent respiratory symptom during the first year of life¹³ and shares some risk factors with pneumonia in infancy, such as male gender, low education, bottle feeding, or day care attendance.¹⁴ Children with recurrent wheezing episodes have been found to be at increased risk of pneumonia, both in the preschool children¹⁵ and in the school-age period.^{16,17} Wheezing in the first year of life, although mainly triggered by viral respiratory tract infections, has been associated with bacterial colonization of the upper airways with bacteria,¹⁸ which can also cause pneumonia. Conversely, many pneumonia cases (as defined clinically and radiologically) at this age are caused by viruses.^{19,20} In a Chilean study of pneumonia in the first year of life, the only significant risk factor found was wheezing during the first 3 months after birth, and the only protective factor was exclusive breast feeding for at least 4 months.²¹

To improve our understanding of the relationship between recurrent wheezing (RW) and pneumonia and the associated risk/protective factors in the first year of life in affluent and non-affluent areas, the present paper analyzes a large population of 1-year-old infants from several countries in Latin America (LA) and Europe (EU). We hypothesize that RW and pneumonia are related conditions, which might share common risk factors, which might be different in LA and EU.

PATIENTS AND METHODS

A detailed description of the EISL (“Estudio Internacional de Sibilancias en Lactantes”) study has been

published previously.^{13,14} In short, parents of children were surveyed when attending their healthcare centers for an immunization or a routine preventive health consultation. Parents completed a questionnaire of risk factors and symptoms occurring during the first year of life of their children. The study was carried out in 14 centers in LA and eight centers in EU. Samples of at least 1,000 infants — allowing detection of a 5% difference in the prevalence of recurrent wheeze (three or more episodes) between centers, assuming mean prevalence of 20%, with 95% confidence and 80% power — were required from participating centers.

Definitions

We defined wheezing as an affirmative answer to the question: “Has your child had wheezing or whistling in the chest during the first 12 months of his/her life?” which had been previously validated in the languages of the study.^{22–24} RW was defined as having had three or more episodes of wheezing. Infants were considered to have suffered from pneumonia when parents answered positively to the question: “Has your child had pneumonia or bronchopneumonia?” Parental asthma and parental rhinitis were defined as father and/or mother having the disease as reported by them. Infant eczema was defined as an affirmative answer to 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 recorded by parents when asked whether 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 maternal smoking during the child’s pregnancy (yes/no); infant attending day care or 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 mold stains on walls and presence of pets, at the time the questionnaire was taken; and maximum education level achieved by the mother (primary/secondary vs. university). Immunization status was checked by the response to the question, “Has the child had all the scheduled immunizations so far?” Birth weight was also included in the questionnaire.

Data Analysis

In order to avoid confusion coming from infants having had one or two episodes of wheeze, they were excluded from any analysis, thus including only those with RW and those with no such symptom. Previously known statistically significant risk factors for RW in the first year of life in the present cohort¹⁴ and those listed above as identified in earlier studies, together with immunization status and birth weight (which showed some significant association with pneumonia in the exploratory bivariate analysis) were first tested for their association with having had pneumonia.

As there was a strong association between having had RW and having suffered from pneumonia, a second analysis — stratified by RW — was carried out. Children having had pneumonia with and without RW were compared separately with children free from either condition.

The associations, expressed as adjusted odds ratios (aOR), were tested by means of a random-effects logit model, using the center as the panel variable and adjusting for all factors found previously associated to RW in this cohort.¹⁴ All calculations were performed for the total population and also stratified for continent (LA and EU) by means of Stata v10.1 software package (College Station, TX, USA).

Ethical Approval

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

RESULTS

The total number of children included in the study, coming from 22 different center (Fig. 1), was 35,049. After excluding those with one or two wheezing episodes during the first year of life ($n = 8,962$) and those who could not be classified ($n = 412$) (because there was no information about the presence/absence of pneumonia [$n = 297$], the number of wheezing episodes [$n = 103$] or both [$n = 12$]), the number of children included in the analysis was 25,675. Overall, 2,768 (10.8%) had had pneumonia; the majority of whom also reported three or more episodes of wheeze (66.6%). Furthermore, a considerable proportion of children with RW also had pneumonia (30.1%). The corresponding figures for LA were 66.9% and 32.0%; for EU 62.7% and 17.1%. After adjusting for all variables listed previously, there was a very strong association between pneumonia and RW overall (aOR 5.91; 95%CI: 5.32–6.56) and also for LA (aOR 5.42; 95%CI: 4.87–6.04) and EU (aOR 13.99; 95%CI: 9.61–20.36).

In the group who did not suffer from pneumonia, the prevalence of children with RW was considerably smaller overall (18.7%) and significantly higher in LA than in EU (22.9 vs. 9.3%). Table 1 shows the demographic characteristics of the four groups of children, together with the prevalence of risk/protective factors. Figure 1 depicts the prevalence of pneumonia in each center.

Risk/protective factors for suffering from pneumonia are shown in Table 2, and these were quite similar to those previously shown to be associated to RW.¹⁴ A complete and up-to-date immunization status was associated with lower pneumonia prevalence both in LA and EU. Male gender was a risk factor in LA but did not reach statistical significance in EU despite a similar trend. We found similar associations for high (university) maternal education and for pets at home. Higher birth weight was associated to lower prevalence of pneumonia in the whole population but did not reach statistical significance in either continent separately.

Among children with RW, the factors associated to pneumonia were similar to those found for the whole population except for male gender and parental asthma, which were risk factors also in EU (Table 3).

Among children with no wheezing episode in the first year of life, risk/protective factors for pneumonia were different from those previously reported and also quite different between LA and EU (Table 4).

In fact, the only shared risk factor between LA and EU was infant eczema. Male gender, parental asthma, smoking in pregnancy, having a cold during the first 3 months, and additional siblings or persons at home were risk factors in LA but not in EU. Breast feeding 3 or more months, high maternal education, and higher body weight were protective factors in LA, but not in EU. In EU, only parental rhinitis and infant eczema were significant risk factors for pneumonia in non-wheezing infants. Although there was a trend for increased birth weight and breast feeding to be protective factors, they did not reach statistical significance, probably due to the smaller sample size in EU. A summary of risk and protective factors in both the continents in the whole population and after stratifying for recurrent wheeze within each continent is shown in Figure 2.

DISCUSSION

The present study shows that risk factors for pneumonia are quite similar to those reported previously¹⁴ for RW in the EISL population. Among recurrent wheezers, pneumonia shares a similar array of risk and protective factors with that of the whole population of children, which might be due, at least in part, to the considerable proportion (66.6%) of children with recurrent wheeze who also reported pneumonia. These factors were similar in LA and EU. Conversely, among European non-wheezing

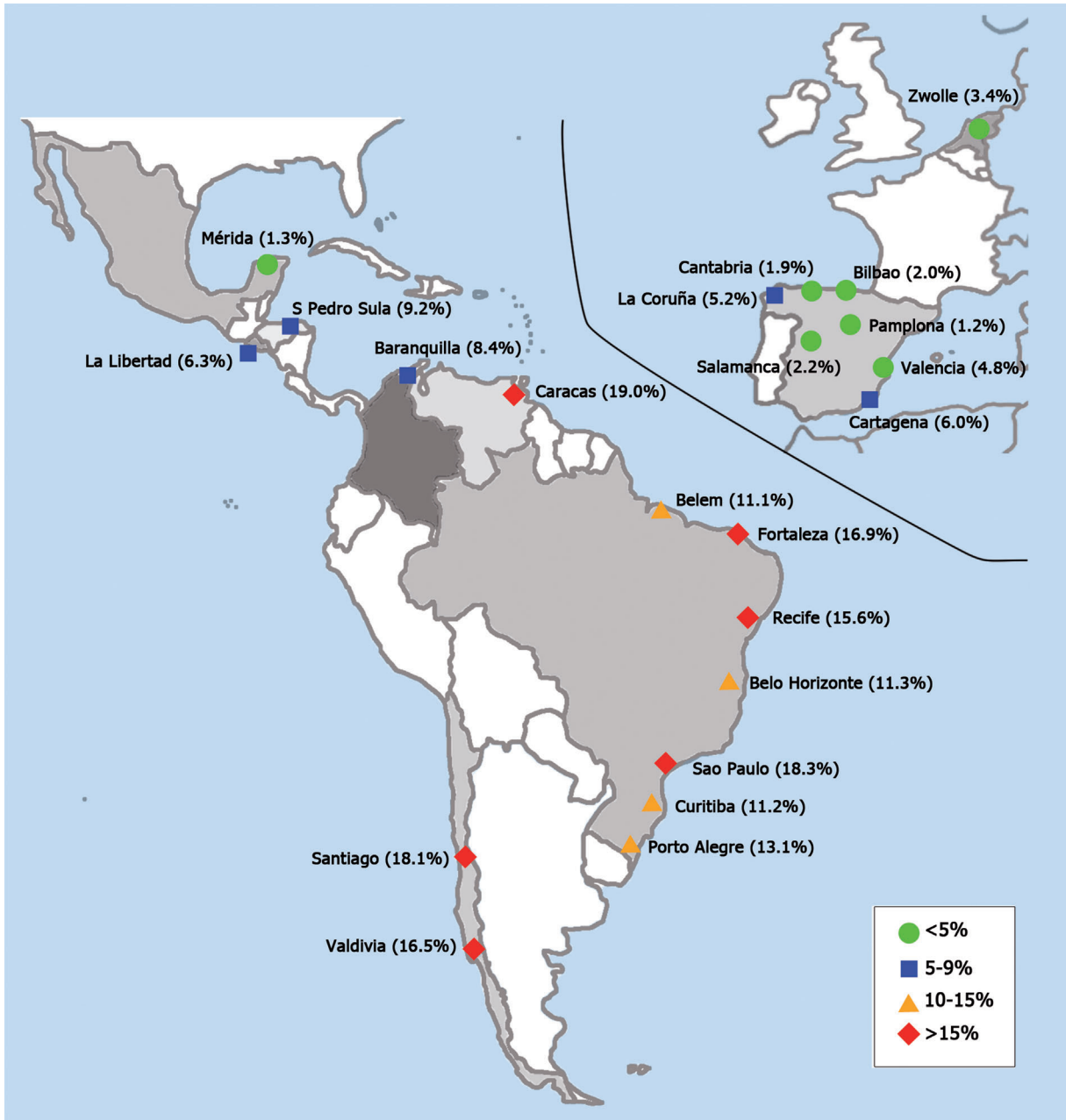


Fig. 1. Prevalence of pneumonia during the first year of life in the EISL study.

children, only two factors were associated to pneumonia (parental rhinitis and infant eczema), while in LA, the list was considerably longer.

It seems quite clear that children prone to RW are also prone to suffer from pneumonia. To what extent this is just reflecting a common infective cause for either condition; or the sharing of similar risk factors, either environmental or familial, is difficult to say. If, as some studies have shown,^{19,20} many pneumonia cases are due to viral infections, the idea of a common infective cause of the two conditions acting on predisposed lungs seems reasonable; also, the reduced airway caliber in wheezy

infants, hampering mucociliary clearance, may predispose to infections. Recently, a study performed in a high-risk cohort of children up to the age of 3 years in Denmark have shown that wheezing during the first months of life was associated to bacterial respiratory infections.¹⁸ In that study, wheezy episodes were associated (OR 2.9; 95%CI: 1.9–4.3) with *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*; and clinical pneumonia was associated to the same bacteria, although the association was stronger (OR 5.6; 95%CI: 2.4–13). Viruses (picornavirus, respiratory syncytial virus, coronavirus, parainfluenza virus, human metapneumovirus,

TABLE 1—Demographics and Factors Included in the Study According to the Four Possible Conditions (Number and Percentage of N in Each Column in Parenthesis Except When Indicated)¹

	With pneumonia N = 2768		Without pneumonia N = 22907	
	Recurrent wheezers N = 1844	Non-wheezers N = 924	Recurrent wheezers N = 4279	Non-wheezers N = 18628
Latin American	1708 (92.6)	843 (91.2)	3621 (84.6)	12182 (65.4)
Age ² (months)	13.4 ± 1.6	13.4 ± 1.5	13.4 ± 1.6	13.4 ± 1.7
Male gender	1151 (62.5)	492 (53.3)	2451 (57.3)	9161 (49.3)
Parental asthma	698 (38.7)	282 (30.7)	1466 (34.8)	3287 (17.8)
Parental rhinitis	876 (48.4)	372 (40.5)	1960 (46.3)	5966 (32.3)
Parental eczema	566 (31.3)	229 (24.9)	1209 (28.6)	3210 (17.4)
Infant eczema	1070 (58.3)	430 (46.8)	2322 (54.4)	5796 (31.3)
Mother smoked in pregnancy	305 (16.6)	135 (14.7)	592 (13.9)	1530 (8.2)
Cold(s) in the first 3 months	1106 (61.6)	363 (40.2)	2197 (52.9)	4997 (28.0)
Nursery school	443 (24.1)	162 (17.5)	920 (21.6)	3010 (16.2)
Breast feeding >3 months	1129 (62.9)	480 (53.3)	2635 (62.6)	11629 (63.4)
Number of siblings ³	1	1	1	1
Number of persons at home	5	5	4	4
Mold stains in household walls	695 (38.0)	259 (28.2)	1391 (32.7)	3648 (19.7)
University studies in mother	706 (38.7)	331 (36.2)	1820 (43.0)	10218 (55.4)
Pets at home	750 (41.2)	364 (39.8)	1858 (42.2)	7001 (38.1)
Birth weight ² (grams)	32225 ± 2339	3175 ± 573	3238 ± 1609	3338 ± 668
Up-to-date immunization status	1587 (86.3)	625 (67.8)	3716 (87.3)	16432 (88.9)

¹Due to missing values in some variables, which are not included in the calculations, percentages might not match exactly.

²Mean and standard deviation.

³Median.

adenovirus, or bocavirus) were also associated to wheezing episodes (aOR 2.8; 95%CI: 1.7–4.4) and to pneumonia (aOR 4.2; 95%CI: 2.4–7.4). In a birth cohort from a low-income area in Santiago (Chile),²¹ the association between wheezing episodes and X-ray

pneumonia during the first year of life was highly significant (aOR 7.69; 95%CI: 1.32–44.9) and similar to that found in the present study for LA centers (aOR 6.8; 95%CI: 6.22–7.47). An additional potential explanation of the association between RW and pneumonia is

TABLE 2—Factors¹ Associated to Suffering From Pneumonia During the First Year of Life.

	Latin America		Europe		Overall	
	aOR	95%CI	aOR	95%CI	aOR	95%CI
Male gender	1.37	(1.24–1.50)	1.23	(0.92–1.65)	1.35	(1.24–1.48)
Parental asthma	1.51	(1.36–1.67)	1.08	(0.72–1.62)	1.48	(1.34–1.64)
Parental rhinitis	1.25	(1.13–1.39)	1.62	(1.17–2.25)	1.29	(1.67–1.42)
Parental eczema	1.13	(1.01–1.26)	1.40	(0.96–2.05)	1.15	(1.04–1.28)
Infant eczema	1.34	(1.21–1.47)	2.08	(1.47–2.95)	1.39	(1.27–1.53)
Mother smoked in pregnancy	1.65	(1.43–1.90)	1.68	(1.16–2.43)	1.63	(1.43–1.86)
Cold(s) in the first 3 months	1.79	(1.63–1.97)	2.50	(1.84–3.39)	1.85	(1.69–2.02)
Nursery school	1.90	(1.68–2.16)	2.19	(1.58–3.04)	1.93	(1.72–2.17)
Breast feeding >3 months	0.76	(0.69–0.84)	0.68	(0.50–0.93)	0.76	(0.69–0.84)
Per additional sibling	1.04	(1.01–1.08)	1.04	(0.89–1.23)	1.04	(1.01–1.08)
Per additional person at home	1.04	(1.02–1.07)	1.00	(0.91–1.11)	1.04	(1.02–1.06)
Mold stains in household walls	1.29	(1.17–1.42)	1.39	(0.91–2.11)	1.30	(1.18–1.44)
University studies in mother	0.74	(0.66–0.82)	0.82	(0.56–1.21)	0.73	(0.66–0.81)
Pets at home	0.85	(0.77–0.93)	0.81	(0.58–1.13)	0.85	(0.77–0.93)
Birth weight (per additional gram)	0.95	(0.88–1.03)	0.80	(0.63–1.01)	0.93	(0.86–1.00)
Up-to-date immunization status	0.80	(0.64–1.00)	0.43	(0.21–0.89)	0.75	(0.60–0.93)

Base: children without pneumonia.

¹Adjusted for all factors in the table.

TABLE 3— Factors¹ Associated to Suffering From Pneumonia During the First Year of Life Among Those Who Also Had Recurrent Wheezing.

	Latin America		Europe		Overall	
	aOR	95%CI	aOR	95%CI	aOR	95%CI
Male gender	1.74	(1.54–1.97)	1.92	(1.28–2.87)	1.75	(1.56–1.97)
Parental asthma	2.12	(1.86–2.43)	1.87	(1.11–3.15)	2.11	(1.85–2.40)
Parental rhinitis	1.57	(1.37–1.79)	1.48	(0.94–2.32)	1.57	(1.38–1.78)
Parental eczema	1.16	(1.01–1.34)	1.75	(1.08–2.83)	1.20	(1.05–1.37)
Infant eczema	1.74	(1.54–1.97)	2.65	(1.68–4.18)	1.81	(1.60–2.04)
Mother smoked in pregnancy	1.78	(1.48–2.14)	2.59	(1.65–4.09)	1.86	(1.57–2.20)
Cold(s) in the first 3 months	3.14	(2.78–3.54)	5.41	(3.60–8.12)	3.29	(2.93–3.70)
Nursery school	3.23	(2.74–3.80)	3.74	(2.45–5.70)	3.25	(2.79–3.78)
Breast feeding >3 months	0.72	(0.63–0.82)	0.61	(0.40–0.92)	0.71	(0.63–0.81)
Per additional sibling	1.05	(1.01–1.10)	1.13	(0.95–1.34)	1.06	(1.01–1.10)
Per additional person at home	1.07	(1.04–1.10)	1.00	(0.90–1.12)	1.07	(1.04–1.09)
Mold stains in household walls	1.60	(1.41–1.81)	1.70	(0.94–3.05)	1.60	(1.41–1.81)
University studies in mother	0.71	(0.62–0.81)	0.80	(0.48–1.34)	0.71	(0.62–0.81)
Pets at home	0.79	(0.70–0.90)	0.71	(0.45–1.12)	0.79	(0.70–0.89)
Birth weight (per additional gram)	0.96	(0.91–1.02)	0.78	(0.55–1.11)	0.96	(0.89–1.02)
Up-to-date immunization status	0.64	(0.48–0.85)	0.43	(0.15–1.26)	0.61	(0.46–0.80)

Base: non-wheezers without pneumonia.

¹Adjusted for all factors in the table.

diagnostic confusion between the two conditions: many physicians call a virus-induced wheezing episode in an infant “pneumonia” or prescribe a course of antibiotics. A recent retrospective study from the Netherlands suggests that this diagnostic confusion may be, at least in part, an explanation for the identification of asthma as a risk factor for recurrent pneumonia in older children.²⁵ To end, being

born with a lower lung function for reasons, such as prematurity, bronchopulmonary dysplasia, or low birth weight, could explain the association of both diseases in certain cases.

Many environmental factors associated to RW have been found to be associated to pneumonia. Previous studies have shown that male gender, low socioeconomic

TABLE 4— Factors¹ Associated to Suffering From Pneumonia During the First Year of Life Among Those Who Did Not Wheeze.

	Latin America		Europe		Overall	
	aOR	95%CI	aOR	95%CI	aOR	95%CI
Male gender	1.20	(1.03–1.40)	0.83	(0.52–1.32)	1.17	(1.01–1.35)
Parental asthma	1.29	(1.08–1.54)	0.75	(0.36–1.58)	1.25	(1.05–1.48)
Parental rhinitis	1.12	(0.95–1.33)	1.71	(1.03–2.83)	1.17	(1.00–1.37)
Parental eczema	1.14	(0.95–1.38)	1.44	(0.75–2.76)	1.17	(0.98–1.40)
Infant eczema	1.30	(1.11–1.52)	2.33	(1.30–4.18)	1.39	(1.19–1.62)
Mother smoked in pregnancy	2.03	(1.61–2.56)	0.77	(0.33–1.81)	1.81	(1.45–2.26)
Cold(s) in the first 3 months	1.37	(1.17–1.60)	1.01	(0.56–1.81)	1.35	(1.16–1.57)
Nursery school	1.50	(1.19–1.88)	1.42	(0.83–2.45)	1.46	(1.19–1.80)
Breast feeding 3+ months	0.60	(0.51–0.71)	0.67	(0.41–1.08)	0.63	(0.54–0.74)
Per additional sibling	1.07	(1.01–1.13)	1.03	(0.73–1.47)	1.07	(1.02–1.13)
Per additional person at home	1.04	(1.01–1.06)	0.94	(0.72–1.21)	1.04	(1.01–1.06)
Mold stains in household walls	1.08	(0.91–1.28)	1.26	(0.65–2.47)	1.12	(0.94–1.32)
University studies in mother	0.64	(0.54–0.76)	1.04	(0.57–1.92)	0.64	(0.54–0.76)
Pets at home	0.93	(0.80–1.09)	1.02	(0.61–1.69)	0.95	(0.82–1.11)
Birth weight (per additional gram)	0.84	(0.73–0.97)	0.76	(0.55–1.07)	0.81	(0.71–0.92)
Up-to-date immunization status	0.77	(0.52–1.14)	0.44	(0.16–1.21)	0.77	(0.53–1.14)

Base: non-wheezers without pneumonia

¹Adjusted for all factors in the table.

	LATIN AMERICA			EUROPE		
	All Children	Recurrent wheezers	Non wheezers	All Children	Recurrent wheezers	Non wheezers
Infant eczema	Red	Red	Red	Red	Red	Red
Parental rhinitis	Red	Red	Grey	Red	Red	Red
Mother smoked in pregnancy	Red	Red	Red	Red	Red	Red
Cold(s) in the first 3 months	Red	Red	Red	Red	Red	Red
Nursery school	Red	Red	Red	Red	Red	Red
Male gender	Red	Red	Red	White	Red	Red
Parental asthma	Red	Red	Red	Red	Red	Red
Parental eczema	Red	Red	Grey	Red	Red	Red
Per additional sibling	Red	Red	Red	Red	Red	Red
Per additional person at home	Red	Red	Red	Red	Red	Red
Mould stains in household walls	Red	Red	Grey	Red	Red	Red
Breast feeding >3 months	Blue	Blue	Blue	Blue	Blue	Blue
Up-to-date immunization status	Blue	Blue	Grey	Blue	Blue	Blue
University studies in mother	Blue	Blue	Blue	Blue	Blue	Blue
Pets at home	Blue	Blue	Grey	Blue	Blue	Blue
Birth weight (per additional gram)	Grey	Grey	Blue	Grey	Grey	Grey

Fig. 2. Summary of significant risk (red) and protective (blue) factors of suffering from pneumonia during the first year of life in Latin America and Europe, in the whole population and after stratifying for recurrent wheeze within each continent.

status and education, day care attendance, and crowding at home are the risk factors for both conditions.^{4,14,15,17,20}

The present study found that many factors associated to recurrent wheeze in a previous analysis¹⁴ were also associated to pneumonia both in LA and in EU. If diagnostic confusion can be excluded, the latter suggests that RW is a potent and transversally acting risk for pneumonia very early in life, and suggests that preventive treatment in infants with RW may help avoid this complication.

Risk factors of pneumonia included: parental rhinitis and eczema, infant eczema, smoking in pregnancy, day care attendance, and having had a cold during the first 3 months of age. Conversely, breast feeding during 3 or more months and a complete and up-to-date immunization status were associated to lower prevalence of pneumonia in both continents. Interestingly, several factors were not shared by both the continents: male gender, parental asthma, and factors related to crowding were associated to higher prevalence of pneumonia in LA, but not in EU; while high (university) maternal education was a protective factor in LA but not in EU (although this may be more related to university education accessibility due to socioeconomic status than to continent). The scenario was quite similar when the analysis was restricted to those infants who had recurrent wheeze. This may indicate that certain familial and environmental

factors predispose to both conditions. Alternatively, it suggests that diagnostic criteria for pneumonia differ between continents, in particular, when it relates to wheezing episodes associated with an upper respiratory tract infection with fever and respiratory distress.

As for the population of infants without RW, only parental rhinitis and eczema were associated to pneumonia in EU. There was also some trend that higher birth weight and breast feeding were associated to a lower prevalence of pneumonia. To those factors, centers in LA also added crowding and colds as risk factors; and high maternal education as protective. Thus, our results indicate that several markers of poverty and lower education are the main environmental factors related to pneumonia in the first year of life among non-wheezing children; and that breast feeding and higher birth weight appear to be protective factors.

The main limitation of the present study relates to classification bias both in the diagnosis of RW and of pneumonia. Although there is some feeling among pediatricians that the relationship between what parents and doctors call wheezing is low, due to certain studies carried out in the English language in the past,^{26,27} this might not apply to other languages for several reasons. Firstly, one of those past studies actually found a very good agreement between parents (direct auscultation after training) and doctors (stethoscope auscultation) when

parents heard the sound easily (94%) or did not hear it at all (99%). It was just when physicians barely heard it when disagreement was relatively high (32%), as parents tended not to hear the sound.²⁶ This would indicate that certain non-wheezing children in our study might in fact have suffered from mild wheezing in the first year without parents knowing, and thus be classified as non-wheezers. If this was the case, our findings are even more robust as the differences between wheezers and non-wheezers would have been lower. In other words, misclassification bias, if random (as it could be assumed in this case), would have tended to reducing differences between groups. Secondly, some of those validation studies are actually focused on what doctors and parents understand by the word “wheezing”, and not necessarily on the agreement on a specific question,²⁷ such as the one in the present study, which specifies “in the chest”. Thirdly, infants included as cases had at least three wheezing episodes, which make agreement between parents and pediatricians quite probable after the first episode. Finally, and which has even greater importance, the results of studies performed in the English language cannot be extended to the languages used in the present study, as none of them has the term “wheezing” in their dictionary. Accordingly, the local term for “whistling” was used, specifying “in the chest” to avoid sounds coming from the upper airways. The three validation studies^{22–24} carried out by EISL groups using the same question, either in the emergency or in the primary care settings, allow us to be quite reassured that the potential classification bias is not affecting the results significantly. Contrary to wheezing, pneumonia was classified according to the diagnosis made by doctors (independently of the prescription of a specific medication, such as antibiotics) from very different backgrounds and cultures; thus, criteria might have been different. We could not check whether the diagnosis was made after an X ray was performed in every instance, but have relied on the diagnosis made by a doctor, which probably included an X ray. On the other hand, it is unlikely that parents have been confused or have invented such a diagnosis. Moreover, a previous cohort study in Chile, conducted in a pediatric pulmonology unit, found a fairly similar association between wheeze and X-ray pneumonia²¹; thus, misclassification of both conditions does not appear to have played a major role in the present study. Furthermore, the prevalence of pneumonia in LA in the EISL study (15.5%) is consistent with that found in the aforementioned birth cohort (13.3%). Moreover, if misclassification of pneumonia had been random among centers, which is a reasonable scenario, the shift would have been, as said, toward the null hypothesis, thus reinforcing all significant associations found. A second important limitation is derived from the cross-sectional nature of the study, which precludes causal inference. Finally, although a statistical analysis

using the center as a panel variable and stratification by continent was performed, variability between centers might be important enough to avoid the general results from being applied everywhere.

In summary, the present study, performed on a very large sample of infants from different centers in LA and EU, shows that RW and pneumonia are associated conditions, which share many risk/protective factors. Breast feeding for at least 3 months was the most consistent protective factor in both continents and in all populations, while infant eczema was the most consistent risk factor. Other risk or protective factors varied in LA and EU, the difference between continents being more pronounced in the population of non-wheezing children. The association between pneumonia and RW provides some evidence for preventive interventions in infants with RW or asthma-like symptoms.

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