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Solar radiation, air pollution, and bronchiolitis hospitalizations in Chile: An ecological study

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Abstract

Objective: To evaluate trends and geographic distribution of infant bronchiolitis hospitalizations in Chile, a country with large variation in solar radiation (SR) and high rates of urban air pollution.

Methods: We performed a nationwide ecological study of bronchiolitis hospitalizations from 2001 to 2014. We investigated the associations of regional SR (a proxy of vitamin D status) and regional fine particulate matter (PM2.5) air pollution with bronchiolitis hospitalizations. We also evaluated the role of sociodemographic factors, including regional poverty, education, indigenous population, and rurality rates.

Results: During the study period, 119 479 infants were hospitalized for bronchiolitis in Chile; 59% were boys. The mean bronchiolitis hospitalization rate increased from 29 to 41 per 1000 infants per year ($P = .02$). There was an inverse correlation between regional SR and incidence of hospital admissions for bronchiolitis ($r = -0.52$, $P = .049$), accounting for 27% of these hospitalizations. There was also a significant direct correlation between regional ambient PM2.5 and bronchiolitis hospitalizations ($R = 0.68$, $P = .006$), accounting for 42% of the variation in admission rate. High firewood and/or coal residential use for heating, high regional poverty, lower years of education, and high rurality rates were also significantly correlated with bronchiolitis hospitalization rates. None of the environmental or sociodemographic factors evaluated were correlated with regional case fatality rates or length of stay at the hospital.

Conclusions: This ecological study revealed significant associations between regional SR, air pollution, and sociodemographic factors with infant bronchiolitis hospitalizations in Chile, suggesting that these factors play a major role in the incidence and severity of respiratory infections in early childhood.

KEYWORDS
air pollution, bronchiolitis, children, vitamin D, vitamin D deficiency

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; RSV, respiratory syncytial virus; RTI, respiratory tract infections; VD, vitamin D.

1 | INTRODUCTION

Bronchiolitis is the most common acute lower respiratory tract infection (RTI) among infants and the primary cause of hospitalization under 12 months of age.[1] Although it can be caused by several etiologic agents, the respiratory syncytial virus (RSV) is responsible for approximately 80% of cases.[2] Bronchiolitis is also linked to high mortality rates in both industrialized and developing countries, and it is the main cause of death by viral infection during the first year of life.[3,4] Thus, this childhood disease results in substantial expenses in public health care, with more than US$1730 million per year in the United States of America alone.[5]

Several environmental factors are involved in the pathogenesis of acute RTIs such as infant bronchiolitis. Multiple studies have shown that vitamin D (VD) deficiency is associated with increased incidence and severity of bronchiolitis.[6,7] VD is a pleiotropic hormone mostly synthesized in the skin upon solar ultraviolet B radiation exposure, that has multiple biological effects on most human organs and systems, including immune cells and respiratory epithelium. In particular, VD plays a prominent role in boosting innate immunity, regulating adaptive immunity, and strengthening airway mucosal responses. Previous epidemiological studies show consistent independent associations between lower circulating levels of 25-hydroxyvitamin D (25(OH)D) during childhood and an increased risk of upper and lower RTIs,[8] including tuberculosis,[9] pneumonia,[10] asthma exacerbations,[11] and bronchiolitis.[12,13] Moreover, data from a recent individual-patient-data meta-analysis of clinical studies show that VD supplementation protects against acute respiratory infections.[14] Variations in regional solar radiation (SR), a proxy of a population's VD status, have been associated with seasonal and latitudinal changes in the incidence and severity of respiratory infections such as influenza and tuberculosis,[15,16] but the associations of SR with infant bronchiolitis incidence and severity have not been evaluated.

Another strong environmental factor involved in the pathogenesis of acute RTIs in children is ambient air pollution.[17] Of the many air pollutants that have been associated with increased incidence and severity of respiratory infections, particulate matter smaller than 2.5 μm in diameter (PM2.5) appears to have a particularly harmful effect on bronchiolitis incidence.[18,19] A previous study performed on 504 infants from Santiago, Chile, found that an increase in 10 μg/m in PM2.5 was associated with a 5% increase in bronchiolitis incidence.[20] However, the association of ambient air pollution with bronchiolitis has not been evaluated on a nationwide basis. In addition, air pollution appears to influence the severity of respiratory infections in children. Ségala et al[21] observed that suspended particles smaller than 10 μm (PM10), black smoke, sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) were associated with emergency visits and hospitalizations due to bronchiolitis in Paris, France, revealing an association between ambient air pollution and both, bronchiolitis incidence and severity.[21] Another study showed a similar association between PM2.5 and bronchiolitis hospitalizations in Washington State, USA.[22]

Chile is a 4270-km long South American country characterized by a large latitudinal variation, spanning between 17°S at the extreme North and 56°S at the extreme South, without significant longitudinal variations (Figure 1). The country has a relatively homogenous ethnic background composed of a mixture of European, mainly Spanish, and indigenous ethnicities. Regional SR has a strong inverse correlation with latitude as we have previously demonstrated and is a good proxy of VD status in Chile.[23,24] On the contrary, air pollution is also unevenly distributed in Chile with several cities having among the highest air pollution rates in the continent.[25] Thus, Chile provides an excellent opportunity to evaluate the association of regional SR (as a proxy of VD status) and air pollution with the incidence of severe bronchiolitis requiring hospitalization.

The main objective of this study was to evaluate the association of regional SR and ambient PM2.5 with infant bronchiolitis and bronchitis hospitalizations. We hypothesized that both lower regional SR and higher regional ambient PM2.5 are independently associated with bronchiolitis hospitalization rates.

2 | MATERIALS AND METHODS

We conducted a nationwide ecological population study focused on children under 1 year of age who were hospitalized in Chile between the years 2001 and 2014 with a primary discharge diagnosis of bronchiolitis or bronchitis. The data were obtained through the national hospital discharge database of the Department of Health's Statistics and Information Department, which includes data of all hospitalizations throughout the country's public and private systems.[26] Data were extracted by one author (CT) in a standardized form and the collected data were reviewed by a second author (AB). In this database, the *International Classification of Diseases, 10th Revision* (*ICD-10*), is used for coding of diagnosis, and patient information is deidentified. Cases with age under 1 year and discharge diagnosis of acute bronchitis (*ICD-10* code J20) or bronchiolitis (*ICD-10* code J21) were included in the study (E-table 1). Given the fact that "acute

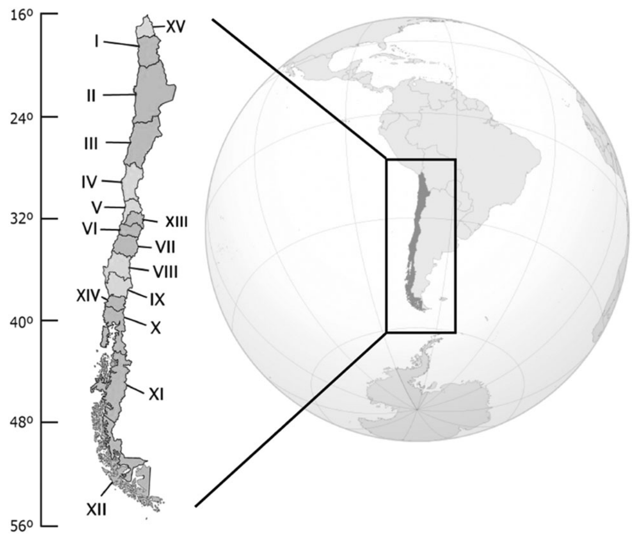

FIGURE 1 Geographical distribution of the 15 administrative regions of Chile

obstructive bronchitis" has been the most common diagnosis used for infants in Chilean clinical practice and guidelines,[27,28] infant hospitalizations in Chile coded as "acute bronchitis" represent *bona fide* bronchiolitis as defined by the American Academy of Pediatrics.[29] In addition, these terms have been used interchangeably in Chile over the years, with predominance of the bronchitis code during the first years of the study period and of bronchiolitis in later years and in academic centers. Thus, in the present study, bronchiolitis hospitalizations encompass all hospital admissions of infants with nonpneumonia lower respiratory infections (ie, discharge diagnosis coded as acute bronchitis or bronchiolitis).

SR data was taken from a public database of solar radiation for Chile.[30] The data are expressed as an annual average of global SR in a plane with an inclination equivalent to the latitude of the place in kWh/m^2/d. The regional mean annual temperature was obtained from the National Institute of Statistics 2017 environment annual report.[31] The regional environmental pollution data was extracted from the Pollutant Release and Transfer Registry between the years 2005 and 2014. This is a database with information about the potentially harmful chemical emissions and transfers with the environment. Regional fine particulate matter smaller than 2.5 microns (PM2.5) annual mean levels, measured in kilotons per year, were analyzed.

The population data were obtained from the age-specific population database from Chile's National Statistics Institute over the same period. We also evaluated the impact of sociodemographic factors on bronchiolitis hospitalizations. Regional demographic data on regional poverty, mean years of education, rate of the population living in rural areas (ie, rurality rate), and indigenous population rate, as well as the residential use of fuels and energy sources were obtained from the National Survey of Socioeconomic Characterization 2015 of the Ministry of Social Development of Chile that corresponds to the main survey of socioeconomic status in the country and the source of the official statistics on poverty and income distribution.

This study was approved by the Scientific Ethics Committee of the Faculty of Medicine, Pontificia Universidad Católica de Chile.

3 | STATISTICAL ANALYSES

Hospitalization rates were expressed as the number of new hospitalizations for bronchiolitis per 1000 infants, and the case fatality rate was expressed as the number of deaths from bronchiolitis in patients hospitalized for this disease. An additional dependent variable that was tested was the median number of days of hospitalization. Independent variables such as sex, a region of the country, and health insurance (public or private) were analyzed for association with bronchiolitis hospitalization rates. First, we performed descriptive statistical analyses, to better understand the data structure of each of the variables studied. Second, a deductive analysis was carried out using the Pearson correlation test and simple linear regressions to explore independent predictors (SR, PM2.5, poverty, education, rurality rate, firewood and/or coal residential use, and indigenous population) that may contribute to bronchiolitis hospitalization rates. Unstandardized b and 95% confidence intervals (CI) were calculated to determine the effect of independent variables on dependent outcomes in linear regression studies. Mean and the standard deviation was calculated for variables with a normal distribution, and median and interquartile range for variables with the nonparametric distribution. We used statistical software SPSS v22.0 (IBM Corp, Armonk, NY) for all analyses. A two-tailed $P < .05$ was considered statistically significant.

4 | RESULTS

Between the years 2001 and 2014, there were 119 479 hospitalizations for bronchiolitis in children under the age of 1 year, constituting 40% of all infant hospitalizations in Chile during this period. Fifty-nine percent were boys and 83% had public health insurance (Table 1). An etiological agent was identified in the discharge diagnosis of 36 349 hospitalizations (30%). In most of these, RSV was identified as the etiological agent (29 879 hospitalizations; 82% of the cases that disclosed etiology). The remaining 83 130 hospitalizations (70%) did not specify etiology in discharge diagnosis (E-Table 1). Bronchiolitis hospitalizations had a clear seasonality, with the highest percentage of cases occurring during winter and fall (51% and 26% of the cases, respectively) (Table 1 and E-Figure 1).

The global bronchiolitis hospitalization rate in Chile was 35.3 per 1000 infants per year. The region with the highest incidence was region XIV with a rate of 60.5, followed by Region IX with a rate of 57.1 (Table 2). A significant increase in annual bronchiolitis hospitalizations was observed during the study period, $b = 179$ (95% CI = 31 to 238), $R^2 = 0.37$, $P = .02$, from 29 in the 2001 to 2002 period to a maximum rate of 41.4 in the 2013 to 2014 period (Figure 2). The case fatality rate was 0.64% of all hospitalizations (Table 2). The median length of stay at the hospital was 4 days (interquartile range, 2-6 days; range, 1-1087 days).

Linear regression analyses of environmental and sociodemographic ecological variables and bronchiolitis hospitalizations are shown in Table 3. We found a significant inverse association between regional SR and incidence of severe bronchiolitis requiring hospitalization in Chile ($b = -5.9$ [95% CI = −11.8 to −0.03], $R = 0.52$, $P = .049$), explaining 27% of hospital admissions for bronchiolitis in infants ($R^2 = 0.27$) (Figure 3A). Regional SR has a strong correlation with other climatologic variables, most notably temperature ($R = 0.91$). However, regional mean annual temperature was not significantly associated with bronchiolitis hospitalizations ($b = -1.762$ [95% CI = −4.02-0.495], $R = 0.42$, $P = .12$). Regional SR strongly correlated with regional PM2.5 ambient air pollution ($r = -0.59$, $P = .02$). We found an important and significant direct correlation between PM2.5 ambient air pollution and hospitalizations for bronchiolitis ($b = 0.339$ [95% CI = 0.119-0.559], $R = 0.68$, $P = .006$), which would explain 46% of the hospitalizations throughout the country ($R^2 = 0.46$) (Figure 3B). A substantial part of PM2.5 ambient air pollution comes from fossil fuels used for residential heating.

TABLE 1 Demographic characteristics and seasonal distribution of incidence bronchiolitis admissions in Chile, 2001 to 2014

	n (%)
Sex	
Male	70 491 (59)
Female	48 988 (41)
Health system	
Public	99 428 (83)
Private	11 372 (10)
Armed forces/other	6688 (6)
Uninsured	1752 (2)
Unknown	239 (0.2)
Season	
Winter	61 059 (51)
Fall	31 007 (26)
Spring	19 221 (16)
Summer	8192 (7)

Thus, we analyzed the regional use of fuel and energy sources for residential heating. Most regions use liquefied or piped gas as the primary fuel, however, several southern regions (IX, X, XI, and XIV) have high rates of residential use of firewood and its by-products (pellets and briquettes) or coal (E-table 2). Regional rates of residential firewood and/or coal-based heating was also significantly associated with bronchiolitis hospitalizations ($b = 0.581$ [95% CI = 0.189-0.972], $R = 0.66$, $P = .007$.

Regarding sociodemographic variables, regional rates for poverty, education, rurality, and indigenous population are shown in E-Table 3. Significant direct correlations between regional poverty, education and rural population rates with incidence of bronchiolitis hospitalizations were found ($R = 0.69$, $P = .004$; $R = 0.66$, $P = .007$; and $R = 0.59$, $P = .02$, respectively); explaining 48%, 44%, and 34% of hospitalization for bronchiolitis, respectively (Table 3). No correlations between regional indigenous population rates with the incidence of hospitalizations for bronchiolitis were observed ($b = 0.126$ [95% CI = −0.782 to 1.972], $R = 0.08$, $P = .77$. Due to highly significant correlations among the different ecological variables across Chilean regions (SR, PM2.5, poverty, years of education, rurality rates, and firewood/coal residential use), multivariable analyses could not be performed.

None of the environmental or sociodemographic factors were significantly associated with case fatality rates or hospitalization length of stay (data not shown).

5 | DISCUSSION

The results of this ecological study show multiple environmental and sociodemographic factors to be associated with the incidence of bronchiolitis hospitalizations in Chilean infants. Significant associations were shown for regional SR, air pollution PM2.5, residential

TABLE 2 Hospitalization rate, case fatality rate and median length of hospitalization in infants hospitalized for bronchiolitis in Chilean regions between 2001 and 2014

Administrative regions[a]	Regional solar radiation	Regional PM2.5	N (cases)	Hospitalization rate	Case fatality rate	Median hospital stay, d
XV	7.08	79	327	7.0	0	4
I	7.28	135	1543	21.3	0.6	4
II	7.67	1443	2784	21.3	1.1	3
III	7.39	5292	1147	17.4	1.7	4
IV	6.69	766	3485	24.2	0.9	4
V	6.14	5059	13 473	41.8	0.8	4
XIII	5.50	5297	45 309	33.1	0.6	4
VI	5.67	17 474	5192	30.3	0.8	3
VII	5.44	32 135	7347	38.4	1	4
VIII	5.39	72 070	16 860	43.4	0.4	4
IX	4.85	91 622	10 661	57.1	0.3	3
XIV	4.44	33 297	4452	60.5	0.2	4
X	4.35	64 387	5462	32.4	0.5	3
XI	4.28	19 070	914	40.2	2.2	3
XII	3.40	1078	523	17.1	0	3

Note: Regional solar radiation and PM2.5 air pollution per region are also shown.
Abbreviation: PM2.5, particulate matter smaller than 2.5 μm in diameter.
[a]Listed in geographical order (from north to south).

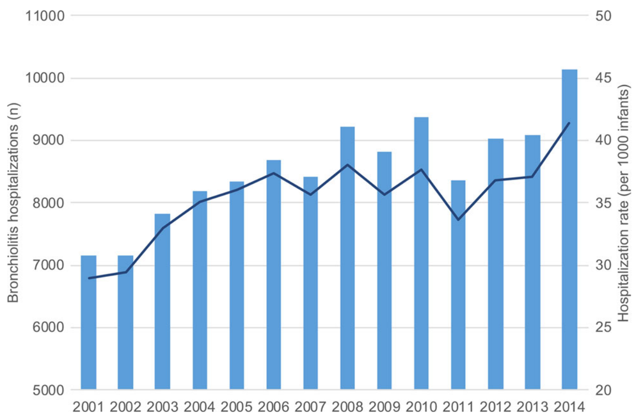

FIGURE 2 Yearly trends in infant bronchiolitis hospitalizations (columns) and hospitalization rates (line) in Chile between 2001 and 2014. Data are displayed as moving averages [Color figure can be viewed at wileyonlinelibrary.com]

use of firewood/coal fuel, poverty, education, and rurality with bronchiolitis hospitalizations. However, because most of these factors are inter-correlated, it was difficult to disentangle their exact contribution to bronchiolitis in this model.

Nevertheless, we observed an increased incidence of severe bronchiolitis requiring hospitalization in Chile, with a 1.5-fold increase from 2001 to 2014. These findings are similar to the increasing rates observed in Canada and England,[32,33] in contrast to decreasing rates of bronchiolitis hospitalizations in the United States of America.[34] Other demographic and clinical characteristics, such as seasonal distribution, male sex predominance, low case fatality rate, and high rates of RSV-associated bronchiolitis are similar to data reported in these and other developed nations.[35]

Regional SR, a good proxy of VD status in Chile, was inversely associated with severe bronchiolitis incidence in this study. We have previously shown that regional SR correlates with tuberculosis incidence and severity in Chile;[16] however, this is the first study to correlate regional SR with the incidence of infant bronchiolitis requiring hospitalization. The correlation between VD status and RTI during childhood has been broadly studied, showing a link between VD deficiency and a greater risk of developing RTI.[8] VD plays an essential role in the immune system by modulating the adaptive and innate immunity.[36] It regulates the natural inflammatory cascade by activating the antimicrobial function in monocytes, macrophage, and by stimulating the production of endogenous antimicrobial peptides, helping to prevent bacterial and viral infections. However, it is important to recognize that VD status in infants is influenced by several other factors besides SR, such as maternal VD status, breastfeeding, dietary sources and supplementation of VD, time spent outdoors, and use of sunscreen or other protective clothing. Therefore, the association of SR with bronchiolitis hospitalizations may also be related to additional factors other than VD status.

RSV is the most common cause of bronchiolitis and pneumonia in children younger than 1 year, accounting for over 80% of cases with identified etiology in our study. Belderbos et al[6] in a longitudinal study of 156 healthy term neonates demonstrated an association of plasma 25(OH)D concentrations at birth with the subsequent risk of

TABLE 3 Unadjusted linear regressions of environmental and sociodemographic factors with bronchiolitis hospitalizations in Chile during 2001 to 2014

	Bronchiolitis hospitalizations		
Regional ecological variables	***β***	**95% CI**	***P* value**
Solar radiation	−5.9	−11.8 to −0.03	**.049**
Mean annual temperature	−1.8	−4.0 to 0.5	.12
Ambient air pollution PM2.5[a]	0.34	0.12 to 0.56	**.006**
Firewood and/or coal residential use	0.58	0.19 to 0.97	**.007**
Poverty rate	1.8	0.67 to 2.9	**.004**
Years of education	−13.1	−22.0 to −4.3	**.007**
Rurality rate	0.69	0.12 to 1.26	**.02**
Indigenous population rate	0.13	−0.78 to 1.97	.77

Abbreviation: CI, confidence interval; PM2.5, particulate matter smaller than 2.5 μm in diameter.
In bold are shown $P < 0.05$.
[a]Regional PM2.5 data were obtained for years 2005 to 2014.

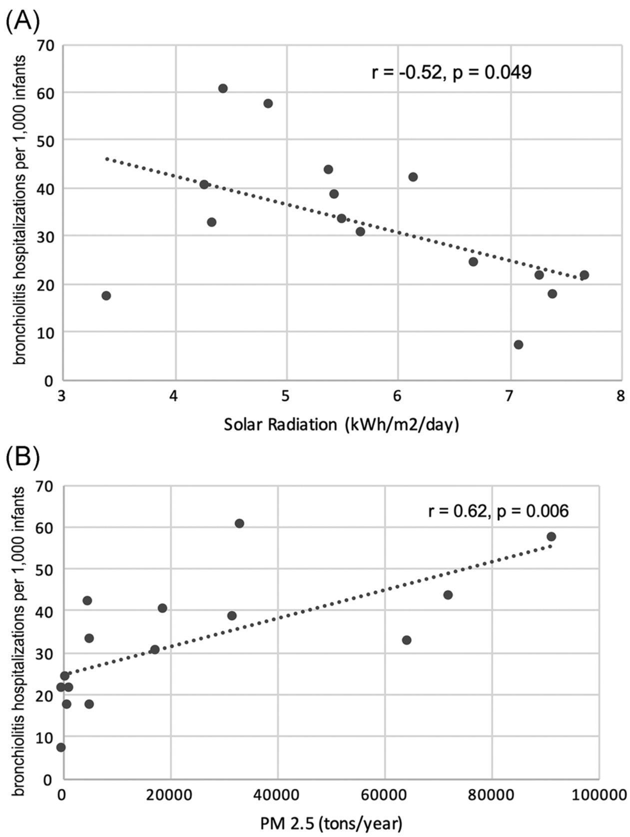

FIGURE 3 Association of mean solar radiation (A) and ambient fine particulate matter 2.5 air pollution (B) with infant bronchiolitis hospitalization rates by region (Chile, 2001–2014). Dots represent regions, dotted line shows a linear trend. *Regional PM2.5 data were obtained for years 2005 to 2014. PM2.5, particulate matter smaller than 2.5 μm in diameter

RSV lower RTI. Concentrations of 25(OH)D were lower in neonates who subsequently developed RSV lower RTI compared with those who did not (65 vs 84 nmol/L, $P = .009$, respectively). Also, neonates born with 25(OH)D concentrations less than 50 nmol/L had a six-fold increase in the risk of RSV lower RTI in the first year of life compared with those with 25(OH)D concentrations greater than or equal to 75 nmol/L. Camargo et al[13] reported that infants under 3 months of age, with a cord blood 25(OH)D concentration of less than 25 nmol/L had a two-fold increase in the risk of developing a respiratory infection compared to infants with a cord blood 25(OH)D concentration of greater than or equal to 75 nmol/L. Infants with cord blood 25(OH)D less than 25 nmol/L were also at increased risk for any infection.[13] A recent prospective multicenter study of infants (age <1 year) hospitalized with bronchiolitis, showed an association between low VD-related airway metabolites with risks of bronchiolitis severity. Among the set of 20 metabolites measured, nine metabolites were associated with a significantly higher risk of continuous positive airway pressure and/or intubation during hospitalization.[37] In this cohort, infants with total 25(OH)D less than 20 ng/mL at the time of hospitalization for bronchiolitis had increased risk of intensive care and longer length of stay at the hospital.[7]

Our study shows a significant trend for higher rates of bronchiolitis hospitalizations in areas further away from the Equator. Nevertheless, the association between SR and bronchiolitis hospitalizations is not linear. Chile's southernmost region has a comparatively lower rate, which could be explained by the extremely low ambient air pollution in that area, probably due to the widespread use of gas as residential fuel and energy source and strong environmental winds. In turn, region XIV, which has the greatest incidence of for bronchiolitis hospitalizations, has low regional SR but is also characterized by high levels of ambient air pollution, as well as high poverty and rurality rates. Furthermore, we observed that the association between high levels of PM2.5 with the incidence of bronchiolitis hospitalizations throughout Chile is stronger than that of SR. Previous studies from highly polluted Chilean cities like Santiago and Temuco have shown that an increase in PM2.5 is associated with an increase in acute respiratory infections and hospitalizations for respiratory diseases.[20,38] However, this is the first study to address the association of ambient air pollution and bronchiolitis hospitalizations on a nationwide basis, confirming that highly polluted cities have higher rates of bronchiolitis hospitalizations. A recent meta-analysis indicated that short-time exposure to fine particles could increase the risk of respiratory disease mortality.[39] Our study did not find any association of PM2.5 with case fatality rates, probably due to the low number of bronchiolitis-related deaths.

Air pollution has been reported as a significant factor in the etiology of VD deficiency in children,[40] which adds further complexity to the analysis of the differential impact of SR and PM2.5 on bronchiolitis incidence. PM2.5 pollutants can absorb or scatter solar radiation in the troposphere, and reports show that urban areas affected by air pollution have significantly reduced UV radiation reaching the surface.[41] Thus, the risk of VD deficiency associated with low SR is heightened in strongly polluted regions. The association between residential firewood and/or coal-based heating with bronchiolitis hospitalizations confirms the strong impact of ambient air pollution on bronchiolitis.

In addition to the environmental factors discussed above, we found that several sociodemographic variables correlate with bronchiolitis hospitalization rates, including higher regional rates of poverty and rurality, and fewer years of education. Once again, these variables are highly correlated in Chile so it's difficult to separate their direct effects. The socioeconomic disadvantage has been previously shown to be associated with bronchiolitis incidence and severity. In England, socioeconomic deprivation has been previously associated with bronchiolitis hospitalizations.[42] In another study performed in Ohio, USA, the population in the highest quintile of bronchiolitis hospitalization rates had significantly lower annual household income than that of lower hospitalization rate quintiles. In addition, significant hotspots of bronchiolitis hospitalizations in this county were noted in high-poverty areas of the inner city.[43]

The present study has some limitations. As it is an ecological study, the observed associations do not prove causality. It is possible that other demographic and environmental factors could influence the measured associations. In addition, we could not perform multivariable adjustment for covariates as the different exposures strongly correlated among them. Thus, it is difficult to separate the influence of the different environmental and socioeconomic factors on bronchiolitis incidence in this setting. Another potential limitation, inherent to the nature of the discharge database that is limited in terms of clinical information, is the risk of miscoding and misclassification of *ICD-10* diagnosis. In particular, due to varying definitions of infant bronchiolitis and bronchitis in Chile during the study period, we decided to merge diagnostic codes of acute bronchitis and bronchiolitis as we believe cases of infantile acute bronchitis really are bronchiolitis. It is possible, nonetheless, that some cases attributed as bronchiolitis might be of a different disease, as it is also possible that cases of bronchiolitis were miscoded as pneumonia or other unspecified respiratory infection and not included in this study. However, our study has multiple strengths, including its nationwide coverage, the high number of cases in the country, and the large SR and air pollution variations across the different regions of Chile.

In conclusion, this ecological study revealed significant associations between regional SR, air pollution, and sociodemographic factors with bronchiolitis hospitalizations in Chile, and highlights the complex interaction between VD status, air pollution, sociodemographic factors, and severe respiratory infections in infancy. Although individual-based studies are needed to clarify the direct effects of these different factors, the current study suggests that these factors play a major role in the incidence and severity of bronchiolitis during infancy.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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