

Prevalence of asthma symptoms in schoolchildren, and climate in west European countries: an ecologic study

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Abstract The aim of the present study was to estimate the associations between the prevalence of asthma symptoms in schoolchildren and meteorological variables in west European countries that participated in the International Study of Asthma and Allergies in Children (ISAAC), Phase III 1997–2003. An ecologic study was carried out. The prevalence of asthma was obtained from this study from 48 centers in 14 countries, and meteorological variables from those stations closest to ISAAC centers, together with

other socioeconomic and health care variables. Multilevel mixed-effects linear regression models were used. For schoolchildren aged 6–7 years, the prevalence rate of asthma decreased with an increase in mean annual sunshine hours, showed a positive association with rainy weather, and warm temperature, and a negative one with relative humidity and physician density (PD). Current wheeze prevalence was stronger in autumn/winter seasons and decreased with increasing PD. Severe current wheeze decreased with

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PD. For schoolchildren aged 13–14 years, the prevalence rates of asthma and current wheeze increased with rainy weather, and these rates decreased with increased PD. Current wheeze, as measured by a video questionnaire, was inversely associated with sunny weather, and nurse density. Severe current wheeze prevalence was stronger during autumn/winter seasons, decreased with PD, and indoor chlorinated public swimming pool density, and increased with rainy weather. Meteorological factors, including sunny and rainy weather, and PD may have some effect on the prevalence rates of asthma symptoms in children from west European countries.

Keywords Asthma · Schoolchildren · Climate · Sunshine · Rainfall · Vitamin D

Introduction

The processes involved in asthma genesis are still not well understood. Numerous hypotheses have been proposed to explain it. One hypothesis suggests a causal relationship between vitamin D deficiency and asthma (Litonjua and Weiss 2007); however, the effects of vitamin D on asthma remain controversial (Wjst and Dold 1999; Searing and Leung 2010) and, for some authors, e.g., Paul and co-authors (2012) “there is insufficient evidence of a causal association between vitamin D status and asthma per se”. In this hypothesis, meteorological variables such as sunshine and rainfall can be determinants of vitamin D status, as exposure to sunlight is the main source of vitamin D in humans.

Epidemiological studies that assess geographic variations in asthma prevalence in relation to meteorological variables could be useful in order to generate hypotheses on the origin and prevention of asthma (Mitman and Numbers 2003). The few such studies that have been performed, which include only one or two countries (Kaur et al. 1998; Hales et al. 1998; Staples et al. 2003; Zanolin et al. 2004; García-Marcos et al. 2009; Arnedo-Pena et al. 2011; Krstic 2011; Hughes et al. 2011), arrive at contradictory conclusions with regard to sunshine and asthma prevalence association. In western European (WE) countries, two international ecologic studies have been carried out on the relationship between the prevalence of asthma and climate (Weiland et al. 2004; Verlato et al. 2002), and another one on the association between indoor chlorinated swimming pools and asthma prevalence (Nickmilder and Bernard 2007). However, sunshine was not included in the analysis. The aim of the present study was to estimate the associations between the prevalence of asthma and meteorological variables in WE countries that participated in the International Study of Asthma and Allergies in Children (ISAAC), Phase III.

Material and methods

An ecologic study with the WE countries that had data on asthma prevalence from ISAAC Phase III study (Lai et al. 2009) was carried out. The dependent variable was the prevalence of asthma as measured by several definitions according to ISAAC Phase III. Independent variables included climatic and socio-economic factors from national and international sources.

The definition of symptoms of asthma were those of the ISAAC questionnaire (Lai et al. 2009) as follows: *current wheeze* as a positive response to: “Have you (has your child) had wheezing or whistling in the chest in the last 12 months?”; *asthma ever* as a positive response to: “Have you (has your child) ever had asthma?”; *severe current wheeze* as those with current wheeze who, according to the written questionnaire, in the last 12 months, have had ≥ 4 attacks of wheeze, or ≥ 1 night per week sleep disturbance from wheeze, or wheeze affecting speech. The definition of wheeze by video questionnaire was after a positive response to symptoms similar to those shown in a scene displaying a young person wheezing at rest (first scene), which had occurred in the last 12 months.

ISAAC Phase III in WE included 32 centers from 10 countries in the 6–7 years old group, and 46 centers from 13 countries in the 13–14 years old group. Studies were carried out mainly in 2001 and 2002, with a range of 1997 to 2003. The countries and centers (n) were: Austria ($n=2$), Belgium ($n=1$), Channel Islands ($n=2$), Finland ($n=1$), Germany ($n=1$), Greece ($n=1$), Ireland ($n=1$), Isle of Man ($n=1$), Italy ($n=13$), Netherlands ($n=1$), Portugal ($n=5$), Spain ($n=12$), Sweden ($n=1$), and United Kingdom ($n=6$). Studies were performed predominantly in autumn–winter.

The independent variables were obtained from different sources. For meteorological factors several sources of data were used: <http://www.aemet.es> (Spain), <http://www.metoffice.gov.uk> <http://www.ukclimate> (United Kingdom), <http://www.meteam.it> (Italy), <http://www.meteo.pt> (Portugal), <http://www.theweathernetwork.com>, <http://www.worldweather.org>, <http://www.climatedate.eu> <http://www.weatherbase.com>, <http://www.climateemp.info>. Meteorological data were usually means of years 1991–2000, or 1971–1999. Gross domestic product (GDP) based on purchasing-power-parity (PPP) per capita in 2001 (US dollars) for each country was retrieved from <http://www.indexmundi.com>. Indoor chlorinated public swimming pools per 100,000 inhabitants for each center was found at <http://www.swimmersguide.com>. Populations of each center in 2001 came from: <http://www.citypopulation.de>. Information from the World Health Organization (WHO) (<http://www.who.int>) was used to obtain the number of physicians and nurses per 10,000 inhabitants per country in 2002. These two variables were included after considering that asthma

diagnosis and its severity could be associated with certain characteristics of the health care organization of countries (Yeatts et al. 2003; Cazzoletti et al. 2007).

Statistical analysis

According to Lai and coauthors (2009), the prevalence rates of current wheeze, asthma ever, and severe current wheeze were estimated as the number of cases divided by the number of participants and multiplied by 100, except for severe current wheeze, in which the denominator was the number of participants with current wheeze. The Pearson correlation coefficient was estimated for independent variables. Multilevel mixed-effects linear regression models were used in the statistical analysis with the country as random effect variable, considering the hypothesis of normality (Weiland et al. 2004; Albright and Marinova 2010). Initially, a bivariate analysis was carried out with every dependent variable and one by one of the independent variables in the multilevel model. After that, multiple multilevel models were built. Independent variables associated with the prevalence of asthma symptoms with a P of <0.20 , were included in the models, to finally obtain those associated with a $P < 0.05$. Regression coefficients and their 95 % confidence intervals (CI) were calculated. Interclass correlation coefficient was calculated as the proportion of variance attributable to each country. In order to measure the goodness-of-fit of the models, deviance was calculated. All models presented a good fit. The statistical analyses were performed with Stata 9 software (StataCorp 2005).

Results

The characteristic of the study population are shown in Table 1. Overall, the study includes 14 countries with 32 centers in the young age group and 46 centers in the older age group. Important variations in the prevalence of current wheeze, asthma ever and severe current wheeze were observed. In addition and as expected, some climatologic variables such as sunshine, rainfall, and temperature showed considerable variations. Physician and nurse density together with GDP also showed important differences within WE countries. Pearson correlation coefficients of independent variables are shown in Table 2. Positive high correlations were observed between temperature and sunshine. Negative high correlations were found between latitude and temperature; and latitude and sunshine. Rainfall and sunshine showed a negative correlation.

The results of regression coefficients between dependent and independent variables following a bivariate analysis with multilevel models are depicted in Tables 3, 4 and 5. For the younger age group, regression coefficients of the

prevalence rates of current wheeze, asthma ever and severe current wheeze are shown in Table 3. All these dependent variables had an inverse association with physician density. In addition, the prevalence rate of current wheeze decreased when the study was carried out during spring–summer versus autumn–winter. The prevalence of asthma ever was associated inversely with sunny weather, and positively with rainy weather. For the older age group, regression coefficients of the prevalence rates of current wheeze, asthma ever and severe current wheeze are shown in Table 4. Current wheeze presented an inverse association with sunny weather and physician density, and a positive association with rainy weather. The prevalence rate of asthma ever was associated positively with latitude, rainfall, relative humidity; and it decreased with increased sunny weather, temperature and physician density. The prevalence rate of severe current wheeze decreased when the study was carried out during spring–summer versus autumn–winter, and also decreased with increased sunny weather and physician density, but increased with rainy weather. Regression coefficients of the prevalence rate of current wheeze by video-questionnaire are shown in Table 5; it increased with more rainfall and decreased with more sunshine, and greater physician and nurse densities.

The results of multilevel models are summarized in Table 6. For schoolchildren 6–7 years old, the prevalence of current wheeze was associated with the autumn/winter seasons when the study was carried out, and decreased with increased physician density. The prevalence rate of asthma ever decreased by 0.97 % (95 % CI: 1.40 %–0.53 %) with a 100 h increase in sunshine, and increased by 0.58 % (95 % CI: 0.09 %–1.07 %) with an increase of 100 mm rainfall. This prevalence rate increased with warm temperature and decreased with relative humidity and physician density. Severe current wheeze decreased with the increase in physician density. For schoolchildren 13–14 years old, the prevalence rates of asthma ever and current wheeze increased respectively by 0.62 % (95 % CI 0.36 %–0.88 %) and by 0.49 % (95 % CI 0.21 %–0.77 %) with an increase of 100 mm rainfall. Those prevalence rates decreased by 0.40 % (95 % CI 0.67 %–0.13 %) and by 0.48 % (95 % CI 0.73 %–0.22 %), respectively, with an increase in the physician density. The prevalence rate of severe current wheeze was associated with the autumn/winter seasons of study, increased by 0.21 % (95 % CI 0.09 %–0.34 %) with an increase of 100 mm rainfall. Physician density and indoor chlorinated public swimming pool density were associated inversely with this prevalence rate. Finally, the prevalence rate of current wheeze by video questionnaire was associated inversely with sunny weather, and nurse density.

Table 1 Characteristic of study population: schoolchildren 6–7 years old and 13–14 years old. Western Europe (WE) countries International Study of Asthma and Allergies in Children (ISAAC) Phase III: 1997–2003

Variable	6–7 years Median (range)	13–14 years Median (range)
Number of centers	32	46
Current wheeze	9.1 % (5.4 %–0.9 %)	10.8 % (4.1 %–31.2 %)
Asthma ever	9.5 % (4.1 %–6.7 %)	12.7 % (5.0 %–28.6 %)
Severe current wheeze	3.1 % (1.6 %–10.7 %)	4.8 % (0.9 %–12.4 %)
Current wheeze (video questionnaire)	-	7.7 % (3.3 %–11.5 %)
Seasons when the study was carried out:		
Autumn-winter: centers (<i>n</i>)	21	31
Spring-summer: centers (<i>n</i>)	11	15
Latitude (degrees)	43.3 (32.7–58.4)	43.6 (32.7–62.9)
Average annual sunshine 100 h	21.6 (14.6–30.1)	19.6 (11.9–30.1)
Average annual rainfall 100 mm	7.4 (2.0–12.7)	7.7 (2.0–17.4)
Relative humidity (%)	71.0 (57.0–83.5)	73.5 (57–84.3)
Altitude 100 m	0.6 (0.03–6.67)	0.6 (0.0–7.4)
Average annual temperature °C	14.6 (5.7–19.7)	13.9 (2.7–19.7)
Gross domestic product (2001) US \$1,000	24.5 (19.0–29.4)	25.5 (19.0–31.4)
Physicians per 10,000 inhabitants	32.5 (21.3–61.9)	31.5 (21.3–61.9)
Nurses per 10,000 inhabitants	44.6 (36.7–113.9)	44.6 (36.7–221.9)
Swimming pools per 100,000 inhabitants	1.1 (0.0–4.8)	1.6 (0.0–4.8)

Discussion

The present study found significant associations between the prevalence rates of current wheeze, asthma ever and

severe current wheeze, and several meteorological variables and physician density in both groups of schoolchildren. Overall, rainy weather was associated positively with higher prevalence rates of current wheeze (13–14 years old),

Table 2 Pearson correlation coefficients for meteorological, socio-economic and health care variables. WE counties. *GDP* Gross domestic product

Variable	Latitude	Sunshine (100 h)	Relative humidity (%)	Altitude (100 m)	Rainfall (100 mm)	Temperature (°C)	GDP (US \$1,000)	Physicians per 10,000	Nurses per 10,000	Swimming pools per 100,000
Latitude	1.00									
Sunshine (100 h)	−0.84	1.00								
Relative humidity (%)	0.62	−0.67	1.00							
Altitude (100 m)	−0.10	0.17	−0.44	1.00						
Rainfall (100 mm)	0.30	−0.53	0.37	−0.16	1.00					
Temperature (°C)	−0.92	0.84	−0.49	−0.08	−0.30	1.00				
GDP ^a (US \$ 1,000)	0.58	−0.57	0.24	0.07	0.10	−0.52	1.00			
Physicians per 10,000	−0.33	0.34	−0.33	0.01	−0.08	0.39	0.11	1.00		
Nurses per 10,000	0.67	−0.52	0.28	−0.11	−0.03	−0.66	0.50	−0.16	1.00	
Swimming pools per 100,000	0.40	−0.29	0.25	0.17	0.21	−0.30	0.25	−0.07	0.18	1.00

^a GDP per capita (US \$)

Table 3 Regression coefficients (RC), 95 % confidence intervals (CI) and level of significance following a multilevel mixed-effects linear regression model of prevalence rate of current wheeze, asthma ever,

and severe current wheeze in children 6–7 years old. WE countries ISAAC Phase III. 1997–2003

Variables	Wheeze last 12 months			Asthma ever			Severe current wheeze		
	RC	95 % CI	P-value	RC	95 % CI	P-value	RC	95 % CI	P-value
Season ^a	−1.14	(−0.26 – 0.17)	0.03	−1.27	(−3.87 1.33)	0.34	−0.32	(−0.86 0.22)	0.25
Latitude	0.08	(−0.15 0.31)	0.70	0.25	(−0.16 0.65)	0.23	−0.00	(−0.11 0.11)	1.00
Sunshine 100 h	−0.06	(−0.24 0.12)	0.51	−0.52	(−0.80 −0.24)	0.00	−0.21	(−0.10 0.05)	0.57
Rainfall 100 mm	0.07	(−0.20 0.34)	0.59	0.68	(0.24 1.12)	0.002	−0.01	(−0.12 0.11)	0.93
Relative humidity	0.07	(−0.06 0.19)	0.28	0.19	(−0.05 0.42)	0.12	−0.02	(−0.03 0.07)	0.45
Altitude 100 m	−0.36	(−0.74 0.03)	0.07	−0.23	(−1.02 0.56)	0.57	−0.09	(−0.25 0.07)	0.29
Temperature	0.14	(−0.19 0.47)	0.41	−0.49	(−1.10 0.12)	0.13	0.08	(−0.07 0.22)	0.28
GDP ^b US \$ 1,000	−0.13	(−0.84 0.57)	0.57	0.38	(−1.15 0.74)	0.50	−0.06	(−0.51 0.38)	0.78
Physicians per 10,000	−0.23	(−0.37 −0.08)	0.002	−0.28	(−0.56 −0.004)	0.05	−0.15	(−0.24 0.06)	0.001
Nurses per 10,000	−0.02	(−0.10 0.07)	0.72	−0.08	(−0.21 0.05)	0.24	−0.01	(−0.06: 0.05)	0.76
Swimming pools per 100,000	−0.05	(−0.64 0.53)	0.86	0.62	(−0.47 1.82)	0.25	0.01	(−0.22: 0.26)	0.88

^a Season: autumn–winter=0, spring–summer=1^b GDP per capita (US \$)

asthma ever, and severe current wheeze (13–14 years old), while sunny weather was associated inversely with lower prevalence rates of asthma ever (6–7 years old) and current wheeze by video-questionnaire (13–14 years old). Physician density was linked to lower prevalence of all three conditions. Other variables, such as nurse density, relative humidity, temperature, and indoor chlorinated public swimming pool density, had small effects on asthma prevalence.

Few ecologic studies have explored wheeze and asthma prevalence in relation to climate worldwide (Weiland et al. 2004; Patel et al. 2008; Sembajwe et al. 2010). It has been

suggested that environmental factors could explain, in part, the large variations in asthma prevalence. However, the effect of climate factors seems to be limited (Asher et al. 2010). In Europe, our results are partly along the lines of those from Weiland and co-authors (2004) in ISAAC Phase I. In the study, indoor mean relative humidity was associated with a higher prevalence of current wheeze in both age groups; if indoor humidity is related to an increase of rainy weather, then the results are similar to those of the older group in the present study. However, the prevalence of current wheeze was not associated with meteorological

Table 4 Regression coefficients, 95 % CI and level of significance following a multilevel mixed-effects linear regression model of prevalence rates of current wheeze, asthma ever, and severe current wheeze in the 13–14 years old children. WE countries ISAAC Phase III. 1997–2003

Variable	Wheeze last 12 months			Asthma ever			Severe current wheeze		
	RC	95 % CI	P-value	RC	95 % CI	P-value	RC	95 % CI	P-value
Season ^a	−1.03	(−3.15 1.08)	0.34	−0.35	(−2.53 1.83)	0.75	−0.99	(−1.96 −0.01)	0.05
Latitude	0.32	(−0.02 0.66)	0.06	0.35	(0.01 0.69)	0.05	0.06	(−0.10 0.22)	0.48
Sunshine 100 h	−0.31	(−0.59 −0.02)	0.03	−0.54	(−0.78 −0.29)	0.000	−0.14	(−0.28 −0.01)	0.04
Rainfall (mm)	0.48	(0.20 0.77)	0.001	0.62	(0.36 0.88)	0.000	0.19	(0.05 0.34)	0.01
Relative humidity	0.12	(−0.10 0.35)	0.28	0.24	(0.02 0.46)	0.03	0.03	(−0.07 0.14)	0.54
Altitude 100 m	−0.20	(−0.83 0.43)	0.54	−0.31	(−0.96 0.33)	0.34	−0.09	(−0.39 0.21)	0.56
Mean temperature	−0.33	(−0.84 0.18)	0.20	−0.53	(−1.03 −0.03)	0.04	−0.07	(−0.31 0.17)	0.56
GDP ^b US \$ 1,000	−0.22	(−1.38 0.93)	0.71	−0.57	(−1.64 0.50)	0.30	−0.14	(−0.64 0.36)	0.59
Physicians per 10,000	−0.48	(−0.73 −0.22)	0.000	−0.40	(−0.67 −0.13)	0.004	−0.20	(−0.32 −0.09)	0.000
Nurses per 10,000	0.01	(−0.06 0.09)	0.70	−0.04	(−0.10 0.03)	0.29	−0.01	(−0.04 0.03)	0.69
Swimming pools per 100,000	0.56	(−0.35 1.47)	0.23	0.48	(−0.45 1.41)	0.32	−0.30	(−0.71 0.12)	0.16

^a Season: autumn–winter=0; spring–summer=1^b GDP per capita (US \$)

Table 5 Regression coefficients, 95 % CI and level of significance following a multilevel mixed-effects linear regression model of prevalence rate of current wheeze according to the video questionnaire, in the 13–14 years old children. WE countries ISAAC Phase III. 1997–2003

Variable	Wheeze last 12 months		
	RC	95 % CI	P-value
Season ^a	−0.57	(−2.34 1.20)	0.53
Latitude	−0.02	(−0.20 0.16)	0.84 ^b
Sunshine 100 h	−0.26	(−0.40 −0.13)	0.00
Rainfall (mm)	0.25	(0.07 0.43)	0.01
Relative humidity	0.09	(−0.05 0.23)	0.20
Altitude 100 m	0.11	(−0.27 0.49)	0.58
Temperature	−0.28	(−0.57 0.01)	0.06
GDP ^c US \$ 1,000	−0.15	(−0.70 0.41)	0.60
Physicians per 10,000	−0.37	(−0.64 0.11)	0.01 ^b
Nurses per 10,000	−0.03	(−0.05 −0.01)	0.01
Swimming pools per 100,000	0.72	(−0.42 1.85)	0.22

^a Season = autumn–winter=0; spring–summer=1

^b No converge

^c GDP per capita (US \$)

variables in the group of younger children. In the European Study on Respiratory Health, Verlato and coauthors (2002) found a higher prevalence of asthma in adults 20–44 years of age in countries with an Atlantic coast and English language. In Spain, and following ISAAC Phase III, Arnedo-Pena and coauthors (2011) found that more sunny hours had a protective effect on the prevalence of asthma in schoolchildren 6–7 years and 13–14 years old, while relative humidity was associated negatively with the prevalence of asthma in the older age group. Furthermore, gross province product per capita was associated positively with asthma in the younger age group. In the present study, outdoor relative humidity was associated negatively with asthma ever in the younger group. In a recent ecologic study, Krstic (2011) demonstrated that annual and winter insolation were associated inversely with asthma prevalence in adults in the United States and Australia; and a 10° increase in latitude signified a 2 % increased in asthma prevalence. In eight ISAAC centers in Brazil, Franco and coauthors (2009) estimated positive correlations between latitude and active and severe asthma prevalence.

However, other studies have different results. In a case–control study of individuals aged 18–61 years in Australia, Hughes and coauthors (2011) found a significant inverse latitude gradient for asthma, but it disappeared after adjusting for mean daily temperature. Moreover, those authors did not find an association between ultraviolet radiation exposure or serum vitamin D and childhood asthma. In addition, the intake of supplemental cod liver oil in childhood increased

the risk of asthma and hay fever. Also in Australia, a survey in the general population (Staples et al. 2003) found a positive association between the prevalence of asthma and ultraviolet radiation in the winter period. In New Zealand, an ecologic study on adults found no association between sunshine and asthma prevalence (Hales et al. 1998). In Latin America, the prevalence of asthma symptoms in schoolchildren included in ISAAC Phase III found no association with latitude (Mallol et al. 2010). In Italy, two studies (Zanolin et al. 2004; SIDRIA 1997) found a higher prevalence of asthma (adults) and wheeze (children) in central and southern Italy than in the northern zones. In those latter three studies, sunshine or rainfall variables were not included in the analysis.

Overall, vitamin D status depends greatly on solar radiation. It is hypothesized that, in zones with more sunshine, the level of vitamin D in the population could be higher than in populations who live in zones with lower insolation. The roles of vitamin D in the innate and adaptive immune system are very complex and are just beginning to be understood (Lange et al. 2009). Considering that many immune cell types have vitamin D receptors, the regulatory role of vitamin D might be considerable (Hewison 2010). That role against infections may have a protective effect on asthma (Walker and Modlin 2009), as well as on autoimmune diseases and cancer (Grant 2008).

Some epidemiological studies have found that vitamin D is associated with asthma and atopy. In Iran, a cross-sectional study with 50 asthmatic children and 50 healthy controls aged 6–18 years found that vitamin D level was a protective factor for asthma (Alyasin et al. 2011). Another cross-sectional study in the United States found that vitamin D deficiency was higher in asthmatic versus control children (Freishtat et al. 2010). In Qatar (Bener et al. 2012), a case–control study with 483 asthmatic and 483 healthy control children showed that vitamin D deficiency (<30 ng/ml 25-hydroxyvitamin D) was associated significantly with asthma. In addition, some studies of birth cohort studies found that when the mother consumed more foods rich in vitamin D during pregnancy the risk of wheezing in newborns was lower (Nurmatov et al. 2011). In Perth (Australia), a cohort study with 689 children aged 6–14 years reported increasing risk of asthma, atopy, and bronchial hyperresponsiveness in males if vitamin D status was inadequate (Hollams et al. 2011). In addition, hospitalizations for asthma after osteoporosis suggest that vitamin D could be important in asthma development (Ji et al. 2010). In New Zealand, in a cohort of 922 newborns (Camargo et al. 2011) it was found that vitamin D levels in cord-blood had an inverse association with the risk of respiratory infections by 3 months, and with the risk of wheezing by ages 15 months, 3 years, and 5 years. However, no association between asthma diagnosis and vitamin D levels was found. Other epidemiological studies did not find these associations. In Spain, in a population-

Table 6 Multilevel mixed-effects linear regression models for current wheeze, current wheeze (video-questionnaire) and asthma ever children 6–7 and 13–14 years old. WE countries ISAAC Phase III. 1997–2003; ICC interclass correlation coefficient

Symptoms	Variable	RC	95 % CI	P-value	ICC Model
6–7 year old age group					
Current wheeze	Season ^a	−1.41	(−2.63 −0.18)	0.024	0.68
	Physicians per 10,000	−0.22	(−0.35 −0.08)	0.002	
Asthma ever	Sunshine (100 h)	−0.97	(−1.40 −0.53)	0.000	0.92
	Rainfall (100 mm)	0.58	(0.09 1.07)	0.019	
	Relative humidity (%)	−0.33	(−0.54 −0.13)	0.001	
	Temperature (°C)	1.13	(0.44 1.82)	0.001	
	Physicians (per 10,000)	−0.40	(−0.77 −0.04)	0.030	
Severe current wheeze					0.84
	Physicians (per 10,000)	−0.15	(−0.24 −0.06)	0.001	
13–14 year old age group					
Current wheeze	Rainfall (100 mm)	0.49	(0.21 0.77)	0.001	0.75
	Physicians (per 10,000)	−0.48	(−0.73 −0.22)	0.000	
Asthma ever	Rainfall (100 mm)	0.62	(0.36 0.88)	0.000	0.80
	Physicians (per 10,000)	−0.40	(−0.67 −0.13)	0.003	
Current wheeze (video questionnaire)	Sunshine (100 h)	−0.28	(−0.41 −0.15)	0.000	0.59
	Nurses (per 10,000)	−0.04	(−0.06 −0.02)	0.000	
Severe current wheeze	Season ^a	−0.87	(−1.67 −0.08)	0.032	0.78
	Rainfall (100 mm)	0.21	(0.09 0.33)	0.001	
	Physicians (per 10,000)	−0.21	(−0.33 −0.09)	0.000	
	Swimming pools (per 100,000)	−0.47	(−0.81 −0.12)	0.008	

^a Season = autumn-winter=0; spring-summer=1

based birth cohort of 1,724 children, maternal vitamin D levels during pregnancy were associated with lower risk of respiratory infection in the 1st year of life; but not with wheezing or asthma (Morales et al. 2012). In a recent population-based birth cohort in 219 newborn in Tucson (Arizona), no association between vitamin D status and asthma was found, but both low and high levels of vitamin D in cord blood were associated with increased aeroallergen sensitization (Rothers et al. 2011). In another birth cohort, Gale and coauthors (2008) reported increased risk of asthma associated with higher vitamin D levels in mothers during pregnancy.

Sunshine and rainfall are inversely correlated could be considered to have complementary effects. Geographic zones with a dry and sunny climate are associated with a lower prevalence of asthma than humid and hot zones (Peat et al. 1993). Rainy weather implies less sunshine, increased humidity, and more time spent indoors. This circumstance increases the exposure time to indoor risk

factors of asthma, including dust mites, chemicals, molds and pets (Chavarría 2001). Depending on the insulation, rainy weather may be associated with dampness, together with mold and fungal concentrations in households, thus increasing the risk of asthma and wheeze (Mendell et al. 2011; Karvonen et al. 2009). In addition, some evidence exists that acute asthma epidemic is associated with more rainfall and warmer temperature (Newson et al. 1998). In a birth cohort study in California, early wheezing was associated with higher exposure to fungi spores and pollen during the rainy season (Harley et al. 2009). In addition, *Poaceae* pollen is a frequent and well characterized allergen, and the development of this *Gramineae* is associated positively with weather variables such as rainy days and warmer temperatures (Jato et al. 2009; Altintas et al. 2004). However, in regions with continental climate such as Ankara (Turkey), sunshine hours and wind were associated with high levels of pollen (Kizilpinar et al. 2011). In addition, in a prospective

study in New Zealand (Epton et al. 1997), it was found that the effects of weather, mainly of temperature, on asthma symptoms were limited.

The present study found that the higher the physician density, the lower the prevalence rate of wheeze and asthma. Furthermore, nurse density was inversely associated with current wheeze according to the video-questionnaire. These results should be interpreted with caution. Firstly, the number of physicians included general practitioners and specialists per country. Secondly, national differences in asthma diagnosis and treatment cannot be excluded. Thirdly, the different languages of countries could produce some variations in the meaning of asthma and, especially, wheeze (Netuveli et al. 2007; Fernandes et al. 2011). Finally, the knowledge of childhood asthma differs in European countries (García-Marcos et al. 2004). For instance, a US study found higher asthma mortality in areas that had more medical specialists (Sly and O'Donnell 1992). In relation to nurse health care, a decrease in asthma severity associated with the improvement of nurse training on asthma has been observed (Yang et al. 2005). On the other hand, geographical differences in asthma control, management and health care access have been shown in many countries (Janson et al. 1997; Plaza et al. 2008; Holgate et al. 2008; Sembajwe et al. 2010), which underlines the important roles of physicians and nurses in the management of asthma patients (Omenaas et al. 2008).

A noteworthy issue raised by the present study is that the season when the study was carried out in each center is related to some of the outcomes. The prevalence of current wheeze in the 6–7 age-group and severe current wheeze in the 13–14 age-group were associated with the field work being carried out in autumn–winter. In New Zealand (ISAAC Phase One), some questions about asthma presented an effect of season in the older group (Stewart et al. 1997). In children, asthma exacerbations have seasonal characteristics that are associated with the viral infections that begin in September in European countries (Fleming et al. 2000; Sears 2008), which probably has some influence on the results. The prevalence of wheeze and asthma were not associated with indoor chlorinated swimming pool density, contrary to a report by Nickmilder and Bernard (2007), based on data of the 13–14 year old group of children of ISAAC Phase One, and using multiple linear regression analysis. In our study, positive and significant associations between indoor chlorinated swimming pools and wheeze in the last 12 months and asthma ever were found using multiple linear regression. However, when multilevel mixed-effect analysis was performed, these associations, although remaining positive, were no longer significant. In addition, a birth cohort study in England with 5,738 children from birth to 7 years found that the use of swimming pools was protective against current asthma (Font-Ribera et al. 2011). However, the debate continues about the use of swimming pools as risk factor of asthma (Bernard et al. 2011).

The study has some strengths, including the data provided from the same ISAAC methodology in a comparable period, the multilevel mixed-effects models analysis, which has been recommended to study asthma disparities (Wright and Subramanian 2007), and the important climatic variations among countries. Nevertheless, the study has some limitations. First, there are high correlations between some variables, which may produce collinearity and thus make regression analysis difficult to interpret. Second, several sources were used to obtain all data. Third, the ecological approach is prone to some bias such as ecological bias: i.e., aggregate data could differ from individual data. Fourth, sunshine exposure depends not only upon sunny hours but also of cultural and lifestyle habits, which may vary between and within countries. Fifth, other measures of sunshine exposure could be used, including ultraviolet (UV) B irradiance index, UV-index and vitamin D UV dose (Webb and Engelsens 2006; Chen et al. 2010; Fioletov et al. 2010, <http://www.temis.nl>). Sixth, asthma is a multifactorial disease, thus other factors not included in the present study such as genetic background, diet and nutrition, allergic sensitization, smoking exposition, airborne allergens exposition, air pollution, respiratory infections, stress, and others (Polosa 2001; Raukas-Kivioja et al. 2007; Subbarao et al. 2009; Bryant-Stephens 2009; Gupta et al. 2010; D'Amato et al. 2010; Huynh et al. 2010) could be important in explaining geographic variations of asthma prevalence. Finally, gender is not considered in the analysis, for several countries only one center was available, and two countries—Ireland and the Netherlands—presented the results as a mean.

In summary, the present study adds some evidence to a protective effect of sunny weather and a risk effect of rainy weather on the prevalence of wheeze and asthma among children and adolescents from WE countries. The study cannot differentiate between direct effects on the individuals and on the environment, but it supports the hypothesis of vitamin D as a protective factor against asthma (Litonjua 2012).

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