

**Epidemiology of asthma exacerbations and their relation with
environmental factors in the Basque Country
(Epidemiology of asthma)**

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ABSTRACT

Background: Asthma is a highly prevalent chronic inflammatory disease characterized by reversible airflow obstruction and hyperreactivity and inflammation of the airways. Factors that cause and/or trigger asthma attacks include host-related factors (genetic predisposition, obesity and sex) and environmental factors (allergens, infections, occupational sensitisation, smoking status, pollution and diet).

Objective: To describe the epidemiology of asthma exacerbations in the Basque Country and explore its relationship with potentially associated environmental variables.

Material and Methods: We studied a total of 31,579 Emergency Department visits and 28,189 hospitalisations due to asthma. We describe the trends, incidence, seasonality and the influence of age and sex, as well as of exposure to NO₂, CO, PM, O₃, and pollen, temperature, relative humidity and flu status. We calculated the Pearson's R correlation coefficient for the study variables.

Results: The incidence was 486 and 88.9 cases per 100,000 people for Emergency Department visits and hospitalisations, respectively. Slightly over half (53.5%) of the Emergency Department cases were male, while females represented 62.6% of the hospital admissions. Hospitalisations are tending to decrease in children and increase in over 64-year-olds. Peaks in cases occur at the beginning of autumn in children and in winter in adults. Asthma exacerbations were correlated positively with exposure to NO₂, CO and to the influenza virus and negatively with temperature and exposure to O₃. These relationships vary, however, with age and season.

Conclusions: Rates of hospitalisation for asthma exacerbations and trends in these rates over time are different in adults and children with the patterns varying by sex, season and environmental conditions.

Key words: Asthma exacerbation, emergency department, hospitalisation, air pollutants, pollen, weather, influenza

Introduction

Asthma is a highly prevalent chronic inflammatory disease that affects 300 million people across the world. The disease is characterized by reversible airflow obstruction and hyperreactivity and inflammation of the airways causing wheezing, breathlessness, coughing and chest tightness. However, there is not a universally accepted definition and this affects the reliability of comparisons between data sets. Factors that cause or trigger asthma attacks include host-related factors (genetic predisposition, obesity and sex) and environmental factors (allergens, infections, occupational sensitization, smoking status, air pollution and diet) [1].

With a prevalence ranging from 1 to 18% in the general population across countries [1], it is believed that asthma affects 5% of adults and 10% of children in Spain [2], and it is the most commonly reported chronic disease among children and adolescents in the Basque Country [3]. The Spanish group of the European Asthma Study found a prevalence in adults of between 4.9 and 14.3% in men and between 5 and 14.9% in women in five Spanish regions [4]. More recently, in 2001 and 2002, the International Study of Asthma and Allergies in Childhood (ISAAC) analysed the prevalence in children of 6 to 7 years of age and 13 to 14 years of age in 10 Spanish regions. For the entire area studied, the mean prevalence was 9.9% in the 6- to 7-year-olds and 10.6% in the 13- to 14-year-olds, while in the participating Basque regions, the prevalence ranged from 7.1 to 12.2% in the younger age group and from 8 to 13.9% in the adolescents [5]. Around 20% of asthma patients have asthma exacerbations (AEs) which require a visit to the Emergency Department (ED) or even hospitalisation, accounting for more than 80% of the total direct costs associated with asthma. These AEs may be determined by

the nature of asthma itself, but above all are triggered by external factors, such as respiratory infections and air pollutants, as well as inadequate treatment or poor adherence [6].

Sex and age have an influence on prevalence, incidence, seasonality and need for medical attention in asthma, the pattern changing through life. Epidemiological and clinical studies have suggested that children experience a worsening of their condition after the summer holidays [7].

Numerous authors have described an association between air pollutants (mainly those associated with road traffic) and the use of medication, ED visits and hospital admissions for asthma [8:11]. Further, it has been observed that high 1-hour maximum NO₂ concentrations can increase asthma admissions, even with relatively low mean daily concentrations [12].

There are numerous studies on the influence of aeroallergens on the development and exacerbation of asthma. Both ED visits [13] and hospitalisations [14:16] due to AEs have been found to be positively correlated with the levels of pollen in the air.

Meteorological variables such as temperature and relative humidity have also been found to be associated with asthma in adults, temperature being correlated negatively [17,18] and relative humidity positively with AEs [17]. However, other authors did not find these correlations [19]. Various studies have also explored the interaction between air pollutants, meteorological variables and air pollen levels in the development of asthma attacks but results have been mixed results [13,19,20:22],

Viral infections of the airways have traditionally been associated with AEs, especially in children but also in adults [23,24]. The viruses most commonly implicated are the human respiratory syncytial virus and the influenza virus, despite parents reporting a higher rate of flu vaccination in children with history of asthma than in healthy children [27]. Synergies have also been described between viral infection and allergen exposure [28].

Given all this, the objective of this study was to describe the epidemiology of asthma exacerbations in our region and the behaviour of environmental factors considered potential asthma triggers.

Material and Methods

The Basque Country is a Spanish region at the eastern end of the Cantabrian coast. It has an area of 7,234 km² and three distinct climatic zones: an Atlantic climate in the northern coastal areas, and sub-Atlantic and sub-Mediterranean climates inland to the south. It consists of three provinces: Gipuzkoa, Bizkaia and Araba, their capitals having populations of 186,000 (Donostia), 352,000 (Bilbo) and 239,000 (Gasteiz), respectively. The total population in the Basque Country remained stable, at around 2,100,000 people, throughout the study period [29].

The descriptive study of sex and age distribution, trends, seasonality and the relationship to influenza epidemics was performed based on all the population of the Basque Country. For the remaining analysis (pollutants, pollen and meteorological variables), we used the populations of the three major cities (777,000 people) because pollen counters were only operating in these locations.

Using the International Classification of Diseases, 9th revision (ICD-9) codes, we included all the episodes for which the primary diagnosis was coded as ICD-9-CM: 493. We based our study on AEs requiring ED visits or hospitalisations. Data regarding the EDs (2009-2011) were obtained from the Hospital Emergency Department dataset of the Basque Health Service (Osakidetza). This database collects information on all emergency care activity in all public hospitals in the Basque Country, which provide more than 80% of all the emergency medical activity in our region [30].

Information on hospitalisations was obtained from the Hospital Discharge Minimum Data Set. These data span from 1996 to 2010 and cover 100% of hospital admissions (public and private) across the whole population of the Basque Country (2,100,000 inhabitants).

We made daily counts of AEs for both ED visits and hospitalisations. Then we obtained total numbers, mean values, incidence rates and AE percentages. Analysis was then conducted by year, month, epidemiological week and time of year (warm or cold).

The distribution of AEs is described by age, sex and seasonality for both ED visits and hospitalisations. Annual hospitalisations were calculated by age and sex to describe trends. The goodness of fit of the prediction method was expressed as the R^2 coefficient.

Crude and specific rates were calculated to describe the mean incidence of exacerbations over the study period. The specific rates for asthma exacerbations per 100,000 people were calculated for three age groups: <15 years old, 15-64 years old and

>64 years old. The average population during the study period was used for both of the types of event considered (ED visits and hospitalisations).

For seasonal comparisons, we defined spring-summer spanning from week 13 to 39 as the warm period and autumn-winter from week 40 to week 12 of the following year as the cold period.

Pearson's correlation coefficient (r) was used as a measure of the strength of linear relationship between the episodes of asthma seen in the ED and hospital admissions for asthma. The relationship was also explored between hospital admissions and each of the study variables using weekly mean values (52) for each of the years studied: 6 years in the case of pollutants, 8 years for pollen and 13 years for weather variables.

Analysis of the correlation with influenza was based on weekly rates for each of the 33 weeks of the Influenza Sentinel Surveillance System over 14 years of study.

Statistical analysis was performed using R 2.15 statistical software (<http://www.r-project.org/>).

Regarding *air pollutant exposure*, data were obtained from the air quality surveillance network of the Department of Environment of the Government of the Basque Country between 2004-2009 [31]. We selected a total of 12 urban and 3 urban background monitoring stations in Bilbo, Donostia and Gasteiz. We used the maximum and minimum concentrations as well as the weekly averages for NO₂ ($\mu\text{g}/\text{m}^3$), CO (mg/m^3) and suspended particles PM_{2.5} and PM₁₀ ($\mu\text{g}/\text{m}^3$). In the case of tropospheric ozone, O₃

($\mu\text{g}/\text{m}^3$), weekly mean and maximum 8-hour average ozone concentrations were calculated. We only included the data from stations with at least 75% of valid data for each week. Due to the seasonal variation in levels of NO_x gases and tropospheric ozone, we analysed the data for the aforementioned two periods: warm, namely, spring-summer (week 13 to 39) and cold, namely, autumn-winter (week 40 to 12 of the following year) corresponding to the times of year with the lowest and highest levels for NO_x gases and vice versa for O_3 . Correlation analysis was performed with data from urban stations.

The *data on temperature and relative humidity* of the Spanish Meteorology Agency (AEMET) were taken from the weather stations located in Igeldo (Donostia), Bilbao Airport (Bilbo) and Foronda-Txokiza (Gasteiz). We obtained the minimum, maximum and daily mean temperatures and the relative humidity (%) measured at 00, 07, 13 and 18 hours (Current local time in UTC). From these, we calculated the mean weekly measurements of temperature and relative humidity for the period 1999 to 2011.

Pollen counts were taken from the pollen monitoring network of the Department of Health and Consumers Affairs of the Basque Country, measured in number of pollen grains per cubic meter of air (grains/m^3) during the sampling period. Pollen was collected with a Hirst-type trap, 45 different pollen types being analysed in daily samples taken from the three capitals. For each station and for each type of pollen, daily and weekly averages were calculated, as well as the total pollen count. For the period 2004-2011, we obtained the averages of the total counts per week.

The effect of the *influenza virus* was assessed using the weekly incidence rate (per 100,000 people) of influenza, from the Basque Influenza Surveillance Network for the period 1998-99 to 2010-2011. This network manages weekly epidemiological and virological surveillance for the entire Basque Country, with data covering 3% of the population.

Results

Incidence per age and sex

During the study period, there were 31,579 ED visits for asthma in public hospitals in the Basque Country. The annual mean incidence rate per 100,000 people during the study period was 486.5 visits, 533.2 for males and 442.0 for females. As for age groups, there were 2583.7 visits by <15-year-olds, 172.4 by 15- to 64-year-olds, and 213.2 by >64-year-olds (Table 1). Within the under 15-year-olds, the rates were 4046.4 and 1640.2 in the < 5-year-olds and 5- to 14-year-olds respectively.

Patients <15 years old accounted for 67.5% of the total number of ED visits for asthma, 61.4% of these being <5 years of age. The highest rate of visits was in 2-year-olds. Overall, only 6.9% of <15-year-olds were hospitalized. People 15 to 64 years of age accounted for 24% of the emergency attendances and, of these, 18.3% were admitted to hospital. The >64-year-old group had a mean age of 77.5 ± 7.4 years and accounted for just 8.4% of the ED visits but, of these cases, 45.4% were admitted. A total of 53.5% of the ED visits were by males.

Overall, there were 4,096,863 all-cause hospitalisations between 1996 and 2010 and, among these, ICD-9-CM: 493 was the primary diagnosis in 28,189 cases. That is, asthma represented 0.68% of all hospitalisations, and further, asthma accounted for 7.6% of hospitalisations related to the respiratory system (ICD-9: 460-519).

The pattern of hospitalisation varies through the period with age and sex. There were slight decreases in rates for <15-year-olds (coefficient of determination, $R^2=0.1533$) and the 15- to 64-year-olds ($R^2= 0.6563$). In contrast, there was a clear increase in the >64-year-olds with an R^2 of 0.6759. By sex, there was a downward trend in men ($R^2=0.3734$) and an upward trend in women ($R^2=0.4542$).

The mean incidence rate during the study period was 88.9 hospitalisations per 100,000 overall, 68 for males and 108.8 for females. By age group, the incidence was 82.2 per 100,000 in <15-year-olds, 47.4 in 15- to 64-year-olds and 186.4 in the >64-year-olds (Table 1). In the youngest group, the incidence rates were 316.8 and 110.5 in the <5-year-olds and 5- to 14-year-olds, respectively. There was an upward trend in hospitalisation from 6 months to 2 years of age, and then a progressive decrease to 15 years of age. Until puberty, there were more hospitalisations in males, while thereafter, the balance reversed, such that in the >64-year-olds, there were 4.2-fold more hospitalisations in women than men. In this age group, the female-to-male incidence ratio was 2.95:1, with a peak at 77 years of age. Overall, women accounted for 62.6% of asthma-related hospitalisations.

In the oldest age group, the peak of admissions occurred at 77 years of age. The correlation between the episodes of asthma seen in the ED and hospital discharges related to asthma during the study period was 0.70.

Seasonality

The likelihood of having an ED visit for an asthma exacerbation varied through the year. The largest numbers of episodes were recorded in September (14%), followed by December (12%) and November (11.4%), and the fewest in August. The mean number of cases/day rose from just 15.2 in August to a maximum of 51.8 in September. This autumn peak in ED visits occurred in early in the season, week 38 in 2010 and week 39 in 2009 and 2011.

In the case of hospitalisations, the peak occurred in January with 7.1 cases/day (11.8%), followed by December (11.3%) and September (10.5%), while again there were the fewest in August with 2.7 cases/day (4.7%). The yearly mean was 5.2 hospital admissions per day. For children, the peak in asthma hospitalisations occurred in early autumn (weeks 38 and 39), together with the peak in ED visits, whereas there were more episodes in adults in winter (Figure 1).

Air pollutants

The urban background monitoring stations generally detected lower levels of all pollutants than urban stations, but with a great variability, some stations detecting higher levels than the urban stations. At the urban and urban background monitoring stations respectively, the average concentrations were 29.2-45.2 and 24.3-38.1 $\mu\text{g}/\text{m}^3$ for NO_2 , 303.1-439.7 and 251.1-442.7 $\mu\text{g}/\text{m}^3$ for CO, 61.6-82.2 and 56.4-91.9 $\mu\text{g}/\text{m}^3$ for

O₃, 11.2-15.4 and 10.1-14.7 µg/m³ for PM_{2.5}; and 21.9-28.7 and 18.4-26.8 µg/m³ for PM₁₀.

The mean annual concentrations of NO₂ were on average 2.9 µg/m³ higher at urban than urban background sites. Similarly, the mean annual concentrations were 44.3, 1.1 and 0.5 µg/m³ higher at urban sites for CO, PM_{2.5} and O₃, respectively, while the concentration of PM₁₀ was 1.52 µg/m³ lower. For the spring-summer and autumn-winter periods, the mean concentrations at the urban monitoring stations were respectively 293.01 and 382.95 µg/m³ (p<0.0001) for CO, 28.87 and 39.04 µg/m³ (p<0.0001) for NO₂, 124.26 and 85.53 (p<0.0001) for O₃, 19.14 and 14.78 (p<0.0001) for PM_{2.5} and 24.66 and 26.17 (p<0.0913) for PM₁₀.

Weekly and daily mean values of pollutants met the regulations on air quality, established by Royal Decree 102/2011 of 28 January, based on limit values for the protection of human health of Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe.

Assessing correlations with hospitalisation, in the warm period of the year, we found a statistically significant positive correlation for NO₂ in children and adults (p<0.0001; cor=0.424 [0.281; 0.549] and p<0.0001; cor=0.536 [0.416; 0.637] respectively). There were also significant positive correlations for CO in both children and adults (p=0.003; cor=0.242 [0.083; 0.389] and p=0.022; cor=0.179 [0.026; 0.325] respectively). In the case of O₃, we found a significantly negative correlation in children (p=0.008; cor=-0.217 [-0.366;-0.056]), but not in adults (p=0.405; cor=-0.066 [-0.218; 0.089]).

In the cold period, the correlations were in general less strong and the clearest were found for PM_{2.5} in children (p=0.012; cor=-0.204 [-0.353; -0.045]), O₃ in adults (p=0.013; cor=-0.201 [-0.35; -0.043]), CO in adults (p=0.015; cor=0.197 [0.038; 0.347]) and PM₁₀ in children (p=0.02; cor=-0.189 [-0.339; -0.03]) (Table 2).

Temperature and relative humidity

The mean monthly temperatures vary greatly with maximum temperatures in July and August and minimum temperatures in December. A temperature of 41.9°C, the highest of the series, was recorded in week 33 of 2003, while the lowest of -12°C was recorded in week 3 of 2010. The mean relative humidity was 76.36%, with peaks of 100% in all the years and the lowest mean of 11.75% (in February 2007).

Hospital admissions for asthma exacerbations were found to be associated with temperature. Specifically, there was a significant negative correlation with temperature, admissions increasing at the lowest temperatures p<0.0001; cor=-0.485 [-0.543;-0.423]) in the case of adults. On the other hand, in children the correlation was very weak (p=0.36; cor=-0.073 [-0.151; 0.005]) (Figure 2). No correlations were found in the case of relative humidity.

Pollen counts

Total pollen counts were made throughout the period 2004-2010 and reveal a seasonal pattern: an increase in counts towards week 5, continually higher levels with some fluctuations up to week 14, a peak around week 23 (depending on the dominant pollen species) and a decrease to the lowest levels around week 31. The highest pollen counts were observed between February and March in Bilbo and Donostia and between April

and May in Gasteiz. Interestingly, we did not detect any associations between total pollen counts and AEs during the study period ($p=0.36$; $\text{cor}=-0.048$ [-0.150; 0.055]).

Incidence of influenza

Seasonal influenza epidemics tend to occur in our setting between November and February. During the study period, the incidence rates ranged from <100 cases/100,000 people (2000-2001) up to 832 cases /100,000 (2001-2002), but there was no trend over time. The most prevalent strains were AH₃N₂ and AH₁N₁, depending on the influenza season, and type B virus was almost always present though responsible for fewer cases. In 2009, the new influenza A H₁N₁ (pdm)09 appeared, causing a pandemic with an epidemiological peak in week 43 in 2009 and incidence rates of 546/100,000 people. Our data showed a direct association between hospitalisations for AEs and the incidence of influenza in adults ($p<0.0001$; $\text{cor}=0.617$ [0.564; 0.665]), while the weak negative trend observed in children was not significant ($p=0.57$; $\text{cor}=-0.002$ [-0.105; 0.058]) (Figure 3).

Discussion

Our results show a decreasing trend in hospitalisation for asthma in children (< 15 years of age) and young to middle-age adults. These data are consistent with other reports describing a decrease in cases of acute asthma over the last two decades in our setting, as well as in ED visits and hospital admissions for asthma in <15-year-olds [32-34]. In contrast, however, we observed an upward trend in hospitalisation in >64-year-olds especially in women. A similar trend in older adults was also observed in a study carried out in a region with a similar climate to ours, although those authors reported an upward trend in all age groups [35].

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Data from one of the hospitals in our region show a decrease in the hospitalisation of paediatric patients who attend the emergency department over the period 1993-2003 [36,37]. Some authors have suggested that this may be due to an increase in the prescription of inhalers and better monitoring of their use [32]. In a case-control study [28], the regular use of inhaled corticosteroids was significantly less frequent in patients admitted for AEs than in controls with stable asthma. According with the Clinical Practice Guideline for Asthma for our health service, there was a progressive increase in the use of inhaled corticosteroids over the period 2000-2004 in our setting, together with stabilisation or even a decrease in the use of short-acting beta-adrenergic agents. Other reasons that have been suggested are the changes in the criteria for assessing the severity of exacerbations and in the severity threshold for admission [38], more intensive treatments in emergency units and the better management of the disease in primary care [36].

More than half of the patients seen at the ED were male (53.5%) and under 15 years of age (67.5%), while among this child group, 61% were under 5 years of age, a lower percentage than that found in a previous study at one of our hospitals (75%) [37]. Our findings in adults, however, are consistent with those of other authors [39] in relation to the high rate of ED visits for asthma by older women, in particular among >64-year-olds.

Considering just hospitalisations, there were clearly more admissions of women (62.6%), consistent with the 2010 Hospital Morbidity Survey of National Statistics Institute that found that 65.5% of those admitted to hospital for asthma were women [40]. Other authors have reported similar results in patients of all ages (55.7%) [41], in

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18- to 50-year-olds (68.6%) [42], and in >15-year-olds (70.9%) [35,43]. The composition by age and sex of the population analysed is a key factor in evaluating the proportion of cases in females. In our study, <15-year-olds admitted were mostly male, 1.5 boys being admitted for every 1 girl, while among the >64-year-olds, 4.2 women were admitted for every man. Similarly, a review of the sex differences in asthma found that among <15-year-olds the risk of admission for asthma is two-fold higher in males than females, while in patients >15 years old, females are three-fold more likely to be admitted than males [44]. This difference in the predisposition to asthma between adults and children has been related to an effect of sex hormones in the pathogenesis of asthma, among other factors [6, 44]

The seasonality observed both in ED visits and in hospitalisations is similar to that described by other authors and the age-related annual cycle may suggest different responses to various causal factors.

Specifically, the peak among school-age children that we observed between weeks 38 and 39 corresponds to reported increases asthma-related care activity for the pediatric population of Biscay (one of our provinces) [45] from September 15, and is consistent with peaks observed by other authors 2 or 3 weeks after the start of the school year [46]. These peaks have frequently been associated with adherence to inhaled corticosteroid treatment, exposure to viral infections, exposure to allergens and falling temperatures [7,16,28]. In our series, among the environmental variables analysed, only particulate matter (PM_{2.5} and PM₁₀) in the colder part of the year showed a statistically significant correlation with asthma hospitalisations in children. It would be very interesting to

analyse the effect of respiratory viruses other than influenza as well as summer interruptions of maintenance treatments.

With regards to the air pollutants analysed, the clearest correlations were observed with NO₂, CO and O₃. However, as noted by other authors, increases in EAs occurred with low mean concentrations [12] and the patterns were not consistent across age groups or periods of the year [20, 47].

The associations were strongest in the warmer part of the year, and were stronger in adults than in children in the case of NO₂, while the weak positive correlation in the case of CO was slightly stronger in children than adults. In the case of O₃, our results for the warmer part of the year are in agreement with what has been reported by other authors, that is, a protective effect against wheezing in children [48]. The weak correlation with PM concentration in our study has been found by other authors [48, 49], contrasting with reports that high concentrations of PM contribute to an increase in asthma exacerbations [11, 50, 51].

The relationship observed between minimum temperatures and AEs is consistent with suggestions by other authors that exposure to cold temperatures may trigger asthma exacerbation episodes in adult asthma patients [17]. In the case of children, however, we did not observe this relationship, in line with those who consider that cold weather does not contribute significantly to triggering asthma exacerbations in children [18]. Further, our data do not enable us to confirm the relationship with relative humidity found by other authors [17].

Pollen has been studied as a triggering factor for AEs, independently and in combination with other factors, with mixed results. Some authors have reported a statistically significant association between certain types of pollen and ED visits [13], while others, including studies in our area and other regions with similar climatic conditions [14,52,53], have not found such an association. One study reported an association between pollen counts and ED visits in spring, but not for AEs in autumn and winter [17], while other authors have found an association between pollen count and AEs under specific meteorological and/or pollution conditions [19,21]. In our study, we did not find any correlation between AEs and total pollen counts in the Basque Country. However, differences in the patterns of presentation of the pollen types across areas within the region [54,55], variations in the prevalence of patients with pollinosis as a function of the climatic zone [56], and sensitisation patterns towards various different plant species reported for our setting [57] suggest that it is important to undertake more extensive analysis considering different types of pollen.

Several authors have found a relationship between the influenza virus and AEs in children [27] and adults [39]. In our study, the positive correlation found in adults was not observed in the <15-year-olds and this may be due to the different seasonality of influenza epidemics and AEs in children.

Strengths of this study include the large number of observations and size of the series analysed both with regards to the health events and the other variables, and the stability of the databases used, all being well-established systems in the Basque Country. We believe that the main limitation is related to the identification of asthma episodes. Problems related to the quality of coding of patients' medical conditions on discharge

may bias the results. In particular, variability in the selection of the primary diagnosis, the thoroughness in the recording of the diagnoses and the coding criteria between hospitals represent the greatest weaknesses of these databases.

Conclusions

In our setting, asthma exacerbations have a different epidemiological profile in children and adults. In children, the highest peak occurs at the beginning of autumn while in adults it occurs in the winter months. The incidence rate of hospitalisations for asthma in children has decreased over the last decade. However, we have detected an increase in hospital admissions among >64-year-olds.

We found relationships between asthma exacerbations and potential environmental triggers including air pollution, cold weather and influenza. These are not, however, consistent across the age groups or the seasons and we did not find any relationship between total pollen counts and asthma exacerbations.

The results of this study could be useful for establishing strategies for the prevention of asthma and for identifying new avenues for research. These new avenues could include the geographical distribution of asthma exacerbations and associated factors including the potential link to pollution from traffic and other factors with a strong spatial dimension.

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Conflict of interest

We confirm that this paper has not been published, has not be accepted for publication, and is not under review elsewhere. There are no conflicts of interest for any of the authors.

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Figure Legends

Figure 1. Seasonality of emergency department (ED) visits (2009-2011) and hospitalisations (1996-2010) for asthma

Figure 2. Correlation between asthma and temperature. Child [$p = 0.36$; $\text{cor} = -0.073$ (-0.151; 0.005)]; Adult [$p < 0.0001$; $\text{cor} = -0.485$ (-0.543; -0.423)]

Figure 3. Correlation between asthma and influenza. Child [$p = 0.57$; $\text{cor} = -0.002$ (-0.105; 0.058)]; Adult [$p < 0.0001$; $\text{cor} = 0.617$ (0.564; 0.665)]

Tables

Table 1. Episodes of asthma by age and sex in the Basque Country

	Emergency Department Visits 2009-2011		Hospital Admissions 1996- 2010	
	Cases (%)	Incidence rate*	Cases (%)	Incidence rate*
Total	31,579	486.5	28,189	88.9
Sex				
Male	16,893 (53.5)	533.2	10,543 (37.4)	68.0
Female	14,686 (46.5)	442.0	17,646 (62.6)	108.8
Age				
< 15 years old	21,307 (67.5)	2,583.7	7,160 (25.4)	182.2
< 5 years old	13,084 (61.4)	4,046.4	4,330 (15.4)	316.8
5-14 years old	8,223 (38.6)	1,640.2	2,839 (60.4)	110.5
15-64 years old	7,632 (24.2)	172.4	10,486 (37.2)	47.4
> 64 years old	2,640 (8.3)	213.2	10,543 (37.4)	186.4

* Mean crude and specific rates for the period analysed by age group (100,000 people).

Table 2. Correlation of air pollutants as a function of age group and period of the year

Pollutant	Spring-Summer				Autumn- Winter			
	p-value	cor	CI min	CI max	p-value	cor	CI min	CI max
CO								
Children	0.003 **	0.242	0.083	0.389	0.088	-0.139	-0.293	0.021
Adults	0.022 *	0.179	0.026	0.325	0.015 *	0.197	0.038	0.347
NO₂								
Children	< 0,0001***	0.424	0.281	0.549	0.15	-0.118	-0.273	0.043
Adults	< 0,0001***	0.536	0.416	0.637	0.28	0.088	-0.073	0.245
O₃								
Children	0.008 **	-0.217	-0.366	-0.056	0.317	-0.082	-0.239	0.079
Adults	0.405	-0.066	-0.218	0.089	0.013 *	-0.201	-0.35	-0.043
PM_{2.5}								
Children	0.037 *	0.173	0.011	0.326	0.012 *	-0.204	-0.353	-0.045
Adults	0.13	0.119	-0.035	0.268	0.809	0.019	-0.141	0.179
PM₁₀								
Children	0.045 *	0.166	0.004	0.32	0.02 *	-0.189	-0.339	-0.03
Adults	0.162	0.11	-0.044	0.26	0.739	0.027	-0.133	0.187

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$



