

The impact of climate and traffic-related NO₂ on the prevalence of asthma and allergic rhinitis in Italy

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Summary

Background Environmental factors are likely to be involved in explaining the wide geographical variation in asthma and atopic diseases that has been documented in many recent epidemiological studies.

Aim To evaluate to what extent climate and outdoor NO₂ pollution can explain the geographical variation in the prevalence of asthma and allergic rhinitis, and to estimate the relative risk for exposure to different levels of these two factors.

Methods The impact of climate and long-term exposure to nitrogen dioxide (NO₂) pollution on asthma and allergic rhinitis was assessed in a cross-sectional study, carried out during 1998 to 2000 on young adults aged 20 to 44 years ($n = 18\,873$), living in 13 areas from two different Italian climatic regions (subcontinental and Mediterranean).

Results Mediterranean areas had a significantly higher prevalence of asthma-like symptoms ($P < 0.001$), higher annual mean temperature (16.2°C vs. 12.9°C), lower temperature range (16.0°C vs. 22.1°C) and lower NO₂ levels ($31.46\,\mu\text{g}/\text{m}^3$ vs. $57.99\,\mu\text{g}/\text{m}^3$) than subcontinental ones. Mediterranean climate was associated with an increased risk of wheeze (OR = 1.23; 95% CI 1.13 to 1.35), tightness in the chest (OR = 1.21; 95% CI 1.11 to 1.33), shortness of breath (OR = 1.21; 95% CI 1.08 to 1.36) and asthma attacks (OR = 1.19; 95% CI 1.07 to 1.31). After adjusting for climate, an increase of $18.3\,\mu\text{g}/\text{m}^3$ in NO₂ levels moderately increased the risk of asthma attacks (OR = 1.13; 95% CI 0.98 to 1.32), tightness in the chest (OR = 1.11; 95% CI 0.98 to 1.26) and wheeze (OR = 1.11; 95% CI 0.96 to 1.28). When the levels of outdoor NO₂ exposure rose, the prevalence of allergic rhinitis increased significantly in the Mediterranean region (OR = 1.38; 95% CI 1.12 to 1.69), but not in the subcontinental one (OR = 1.03; 95% CI 0.83 to 1.28).

Conclusion Our results show that the prevalence of asthma increases when annual mean temperature increases and temperature range decreases. Furthermore, climate interacts with NO₂ outdoor exposure, increasing the risk for allergic rhinitis in people exposed to high stable temperatures. A long-term role for the effect of traffic pollution on asthma is also suggested.

Keywords allergic rhinitis, asthma, climate, outdoor NO₂ pollution, traffic-related pollution

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Introduction

Asthma and allergy affect a substantial proportion of the population and have shown an increasing trend in the last few decades in western countries. The two international studies on asthma in adults [1] and in children [2] have documented up to 10-fold regional differences in the prevalence of asthma and atopic diseases. Britain, Australia, New Zealand and the USA showed the highest prevalence rates, whereas Eastern and Continental Europe, China and Indonesia showed the lowest. This variation is not an artefact due to a cultural bias or difference in diagnostic habits, as it was confirmed when objective markers of asthma [3] and atopy [4] were used.

The reasons for such a wide variation are so far unexplained. Genetics could be involved to a minor extent, because a substantial heterogeneity is present among countries with genetically similar populations or even within the same country. Environmental factors are likely to be involved in explaining this geographical pattern. Among these, climate could be a candidate. The influence of climate on asthma has been addressed in several studies, with contrasting results according to whether acute or long-term effects were considered. Although on a short-term scale low temperatures may have a direct effect, resulting in exacerbations of asthma symptoms [5–7], warmer average temperatures seem to be associated with increased asthma prevalence [8,9]. In a recent analysis of the international data from the European Community Respiratory Health Survey (ECRHS), a positive association was found between asthma and asthma-like symptoms prevalence and the average non-summer temperature [10].

Air pollution is another possible culprit. Researchers have paid special attention to the steadily rising traffic-related pollution, of which nitrogen dioxide (NO₂) is one of the best indicators [11]. However, epidemiological and clinical studies have mainly addressed the acute effects of NO₂, whereas few population-based studies have evaluated the effects of long-term exposure to NO₂, with inconsistent results [12–14].

The aim of this study was to evaluate to what extent climate and outdoor NO₂ pollution can explain the geographical variation in the prevalence rates of asthma and allergic rhinitis, and to estimate the relative risk for the exposure to different levels of these two factors. For this purpose, the data collected in the frame of the Italian Study on Asthma in Young Adults (ISAYA) were used.

Methods

Study design

ISAYA is a multicentre cross-sectional survey of the young adult general population, specifically aimed to assess: (i) the variations of asthma, asthma-like symptoms and chronic bronchitis prevalence in Italy; and (ii) the current management of asthmatics, and the individual and social costs of asthma in Italy. The survey was carried out between 1998 and 2000 in nine Italian centres: six in northern Italy (Ferrara, Pavia, Sassuolo, Turin, Udine and Verona); one in central Italy (Pisa, which comprised the areas of Livorno, Lucca and Pisa); and two in southern Italy (Sassari, on the Island of Sardinia, and Siracusa, on the Island of Sicily, which comprised three small

areas corresponding to three different air pollution monitoring stations: Augusta, Priolo and Siracusa). All the northern centres belonged to the subcontinental climatic region, while the central/southern centres belonged to the Mediterranean climatic region. The two climatic regions differ with respect to the annual mean temperature and to the annual temperature range. Figure 1 shows the climatic map of Italy [15] with the centres participating in the study.

Each centre selected an up-to-date sampling frame of the residents of the target area, from which a random sample of about 3000 people aged 20 to 44 years (men : women ratio = 1) was chosen, using the same design utilized in the ECRHS stage 1 [16, 17]. A two-page screening questionnaire was sent by post to each subject up to three times in the case of non-response; finally, the questionnaire was administered by phone to the remaining non-responders.

Questionnaire

The questionnaire used has been published elsewhere and tested in a pilot study in 1998 [18]. The first page contains validated questions, most of them taken from the ECRHS questionnaire [17], on the presence of asthma and asthma-like symptoms, the frequency of asthma attacks, time of onset and remission of asthma, doctor diagnosis of asthma, the presence of chronic cough and phlegm, and smoking. The second page collects information related to direct and indirect costs due to asthma.

Air pollution and climatic data

In all the centres, NO₂ levels were monitored by the local authorities according to the Italian Government law on air

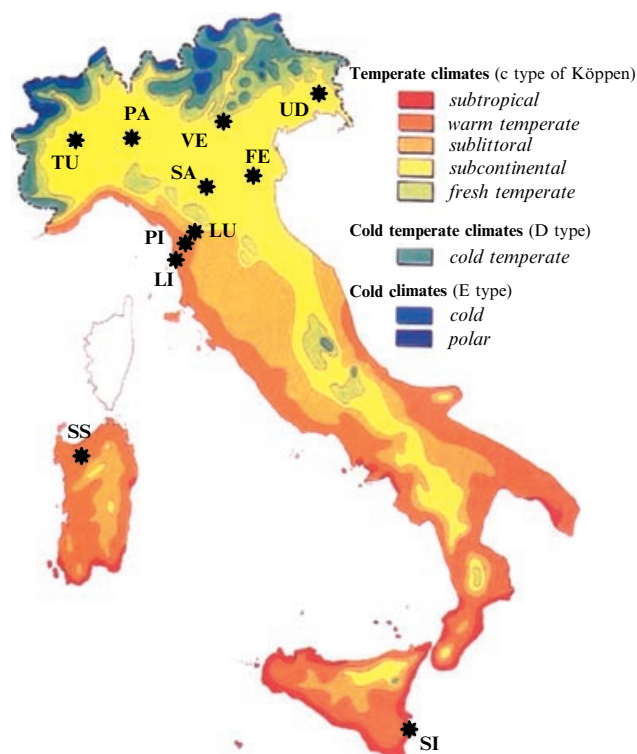


Fig. 1. Climatic map of Italy. Stars indicate centres participating in ISAYA: FE, Ferrara; LI, Livorno; LU, Lucca; PA, Pavia; PI, Pisa; SS, Sassari; SA, Sassuolo; SI, Siracusa; TU, Turin; UD, Udine; VE, Verona. Modified from <http://www.meteo89.it/climbi34.jpg>.

quality control. The sampling was made at fixed sites, chosen in accordance with the local environmental authorities: in each area, one or more monitoring sites were chosen close to the living area of the participant subjects, and were not strongly influenced by specific local pollution sources, such as an intense concentration of traffic and industries (background exposure). NO₂ levels were measured continuously with chemiluminescence. A quality control surveillance was carried out in each area twice a month by the local authorities. The reported annual mean data were calculated on the hourly mean concentration of NO₂ for the period 1996 to 1999. Overall, data on annual mean NO₂ concentration from the 13 areas were obtained.

The monthly average temperature for each area was obtained from official meteorological statistics for the year 1997 [19]. The annual temperature range was defined as the difference between the average temperature of the hottest and coldest month. As the average annual temperature and the annual temperature range were strongly correlated in Italy, each area was characterized by a climate indicator (CLI) computed as a linear function of the two variables. For this purpose, a principal component analysis [20] of the mean annual temperature and annual temperature range was performed and each area was assigned the respective score on the first factor. CLI was strongly and negatively associated with the annual temperature range ($r = -0.98$) and positively associated with the mean temperature ($r = 0.98$).

Data management and statistical analysis

Subjects were classified as having wheeze, tightness in the chest and shortness of breath, if they answered affirmatively to the following questions: Have you had wheezing or whistling in your chest at any time in the last 12 months? Have you woken up with a feeling of tightness in your chest at any time in the last 12 months? Have you been woken by an attack of shortness of breath at any time in the last 12 months? Subjects were classified as having asthma attacks in the case of a positive response to the question: Have you had an attack of asthma in the last 12 months? Subjects were classified as having allergic rhinitis in the case of a positive response to the question: Do you have any nasal allergies, including hayfever?

Subjects were classified according to smoking habits as current smokers, past smokers and non-smokers. Subjects were considered smokers if they stated in the questionnaire that they were current smokers and had smoked at least one cigarette per day or one cigar a week for 1 year. Subjects were considered past smokers if they had been smokers (as defined above) and had stopped smoking at least 1 month previously. All the other subjects were considered to be non-smokers. Subjects were also classified according to their socio-economic status in six groups: managers, entrepreneurs and businessmen; clerks; workers; retired and unemployed persons; housewives and students; other conditions.

As the centres had different final cumulative response rates, obtained with different percentages of telephone interviews, for the sake of comparison the prevalence rates were adjusted for cumulative response rate and type of contact (telephone vs. postal), and for age and sex as well. For this purpose, each subject was attributed the median of the cumulative response rate of the contact to which he/she had answered (first, second, third postal contact and telephone interview) and a dummy

indicator of the type of interview (telephone vs. postal). Adjusted prevalence rates were then obtained through a logistic regression model, considering symptoms as the dependent variable (present vs. absent) and sex, age (categorized in 5-year age classes), cumulative response rate and type of interview as the covariates. The prevalence in each centre was estimated setting the distribution of age, sex and type of contact equal to the average distribution, and the cumulative response rate to the overall mean [21]. Adjusted prevalence rates with their 95% confidence intervals were obtained using STATA software, release 7.0 (Stata Corp, College Station, TX, USA).

The heterogeneity of prevalence rates between the two climatic regions was assessed by decomposition of the total chi-square according to Fleiss [22].

Multilevel binary response models [23] were used to assess the association of climate and outdoor NO₂ exposure with the prevalence of each respiratory symptom (see Appendix). Associations were expressed by odds ratios (OR) and 95% confidence intervals (95% CI), adjusted for sex, age, smoking habits, social class, season of response, cumulative response rate and type of interview. The climate indicator (CLI) and the mean annual NO₂ concentration were divided by their standard deviation (1.385 units and 18.3 µg/m³, respectively), in order to express the variation of ORs for a change by one standard deviation.

Before fitting the multilevel models with both CLI and NO₂ as covariates, the homogeneity of the association between NO₂ and each symptom prevalence in the two climatic regions was tested using a dummy indicator for the region (Mediterranean vs. subcontinental) and its product with NO₂ (i.e. the interaction term). When a significant interaction was present, the association between NO₂ and symptoms was estimated within each climatic region. MLwiN software [24] was used to fit all the multilevel regression models.

Results

Out of 25 969 eligible subjects in the nine centres, 18 873 filled in the questionnaire, with an overall response rate of 72.7% (Table 1). The percentage of women among responders was 50.7% (95% CI 49.9%-51.4%), not significantly different from what was expected (50%) according to the design of the study, and the average age of participants was 33.1 years (standard deviation = 6.9).

A substantial and statistically significant variation in the prevalence rates of asthma-like symptoms, asthma and allergic rhinitis was present among Italian centres, with the Mediterranean region showing higher rates than the subcontinental region (wheeze, $P < 0.001$; shortness of breath, $P < 0.001$; tightness in the chest, $P < 0.001$; asthma attacks, $P < 0.001$; allergic rhinitis, $P = 0.002$) (Table 2). The variability between climatic regions was significantly higher than the variability within each climatic region for all the symptoms except allergic rhinitis.

The subcontinental region was characterized by a wider temperature range (22.1 °C vs. 16.0 °C) and a lower annual mean temperature (12.9 °C vs. 16.2 °C) than the Mediterranean region (Table 3). The climate indicator (CLI) always had negative values for the subcontinental areas and positive values for the Mediterranean ones. The annual mean concentration of

Table 1. Number of areas, number of eligible subjects*, number (%) of responders, percentage of women and mean age (standard deviation) by centre and climatic region (subcontinental and Mediterranean)

Centre	Areas	Eligible subjects*	Responders (%)	Women (%)	Age (SD)
Ferrara (FE)	1	3000	2106 (70.2)	52.1%	32.9 (6.9)
Pavia (PA)	1	2981	2444 (82.0)	50.9%	35.7 (6.3)
Sassuolo (SA)	1	2869	2143 (74.7)	51.3%	33.2 (7.0)
Turin (TU)	1	2892	2266 (78.4)	50.5%	33.0 (6.7)
Udine (UD)	1	2936	2082 (70.9)	51.7%	33.4 (6.7)
Verona (VE)	1	2927	2166 (74.0)	51.5%	32.9 (7.0)
<i>Subcontinental</i>	6	17605	13207 (75.0)	51.3%	33.5 (6.8)
Pisa (PI)	3	2976	2411 (81.0)	51.3%	32.7 (7.0)
Sassari (SS)	1	2925	2055 (70.3)	48.0%	31.8 (6.5)
Siracusa (SI)	3	2463	1200 (48.7)	46.5%	31.7 (7.0)
<i>Mediterranean</i>	7	8364	5666 (67.7)	49.1%	32.1 (6.8)
Total	13	25969	18873 (72.7)	50.7%	33.1 (6.9)

*Eligible = initial sample – (dead or moved away from the target area).

Table 2. Prevalence* and 95% confidence interval of wheeze, tightness in the chest, shortness of breath, asthma attacks and allergic rhinitis by centre and climatic region (subcontinental and Mediterranean)

Centre	Wheeze	Tightness in the chest	Shortness of breath	Asthma attacks	Allergic rhinitis
Ferrara (FE)	11.0 (9.7–12.3)	6.1 (5.2–7.1)	3.6 (2.9–4.4)	3.1 (2.4–3.9)	14.8 (13.3–16.3)
Pavia (PA)	8.8 (7.7–10.0)	5.5 (4.7–6.5)	5.5 (4.7–6.5)	2.6 (2.0–3.4)	17.6 (16.1–19.2)
Sassuolo (SA)	11.1 (9.9–12.5)	7.0 (6.0–8.2)	5.8 (4.9–6.8)	3.6 (2.9–4.5)	15.6 (14.1–17.2)
Turin (TU)	9.4 (8.3–10.6)	6.8 (5.9–7.9)	5.3 (4.4–6.2)	3.4 (2.8–4.2)	19.5 (17.9–21.2)
Udine (UD)	9.3 (8.2–10.6)	7.2 (6.2–8.3)	4.7 (3.9–5.6)	3.4 (2.7–4.2)	20.0 (18.3–21.7)
Verona (VE)	11.1 (9.9–12.5)	7.4 (6.4–8.5)	4.7 (3.9–5.6)	3.7 (3.0–4.6)	21.1 (19.4–22.9)
<i>Subcontinental</i>	10.0 (9.5–10.6)	6.6 (6.2–7.1)	4.9 (4.5–5.3)	3.3 (3.0–3.6)	18.0 (17.3–18.7)
Pisa (PI)	14.1 (12.6–15.6)	7.7 (6.6–8.9)	6.5 (5.5–7.6)	4.2 (3.4–5.1)	23.8 (22.1–25.6)
Sassari (SS)	14.9 (13.4–16.5)	9.9 (8.7–11.3)	7.7 (6.6–8.9)	3.9 (3.2–4.8)	19.2 (17.5–20.9)
Siracusa (SI)	11.7 (9.7–14.0)	9.3 (7.6–11.5)	7.5 (5.9–9.5)	5.2 (3.9–6.8)	13.8 (11.8–16.0)
<i>Mediterranean</i>	14.0 (13.1–15.0)	8.9 (8.2–9.7)	7.2 (6.5–7.9)	4.2 (3.7–4.8)	20.2 (19.2–21.4)
Total	11.2 (10.7–11.7)	7.3 (6.9–7.7)	5.6 (5.2–5.9)	3.6 (3.3–3.9)	18.7 (18.1–19.2)

*Adjusted for sex, age, cumulative response rate and type of contact (telephone vs. mail).

NO₂ showed a wide variation ($P < 0.001$) among the monitoring stations corresponding to the 13 areas, with the subcontinental region having approximately a twofold average outdoor NO₂ concentration with respect to the Mediterranean region in each season (Fig. 2).

Figures 3 and 4 show the ecological relationship between wheeze prevalence, the climate indicator and the outdoor NO₂ concentration. A strong positive correlation between wheeze prevalence and CLI was present, indicating that areas characterized by a higher average annual temperature and a lower temperature range had the highest prevalence (Fig. 3); an overall negative association between wheeze and NO₂ emerged, due to the fact that areas in the Mediterranean climatic region had lower NO₂ outdoor exposure levels. However, when the association between prevalence and NO₂ was considered within each climatic region, a positive relationship emerged (Fig. 4). This result exemplifies the pattern of most symptoms, as can be seen in Table 4, where the associations of respiratory symptoms with climate on the one hand and with NO₂ on the other hand are presented. Climate was significantly and positively associated with all the asthma-like symptoms but not with allergic rhinitis, while the NO₂ outdoor concentration was negatively associated

Table 3. Average annual temperature (Year temp.), annual temperature range (Temp. range), climate indicator (CLI) and annual mean concentration of NO₂ in each area and climatic region (subcontinental and Mediterranean)

Area	Year temp. (°C)	Temp. range (°C)	CLI	NO ₂ (µg/m ³)
Ferrara (FE)	13.0	22.5	– 1.401	60.34
Pavia (PA)	12.6	23.0	– 1.653	41.49
Sassuolo (SA)	13.3	22.9	– 1.375	57.13
Turin (TU)	12.4	22.9	– 1.705	78.96
Udine (UD)	12.7	19.8	– 0.945	51.68
Verona (VE)	13.7	21.4	– 0.914	58.33
<i>Subcontinental</i>	12.9	22.1	– 1.332	57.99
Livorno (LI)	15.7	16.9	0.764	36.33
Lucca (LU)	14.8	17.7	0.266	42.13
Pisa (PI)	15.1	16.8	0.565	51.83
Sassari (SS)	15.3	15.4	0.932	30.33
Augusta (SI)	17.5	15.0	1.822	18.34
Priolo (SI)	17.5	15.0	1.822	23.44
Siracusa (SI)	17.5	15.0	1.822	17.85
<i>Mediterranean</i>	16.2	16.0	1.142	31.46

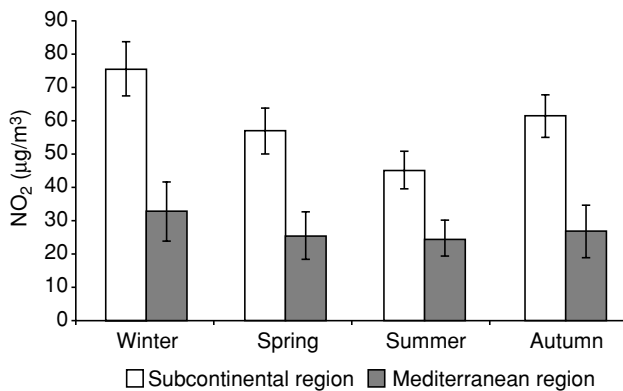


Fig. 2. Annual mean concentration of NO₂ by season and climatic region (1996 to 1999).

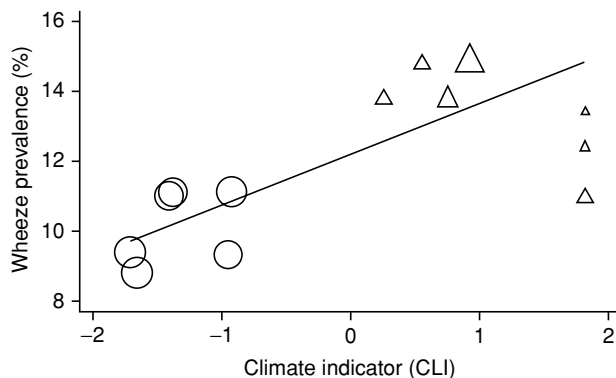


Fig. 3. Relationship between wheeze prevalence and the climate indicator (CLI). The continuous line represents the linear regression of the prevalence on CLI, weighted by the number of subjects in each area. The size of the symbols is proportional to the number of subjects in each area (○, subcontinental areas; △, Mediterranean areas).

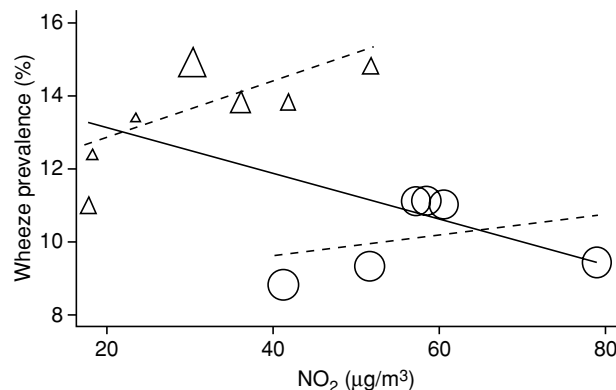


Fig. 4. Relationship between wheeze prevalence and outdoor NO₂ concentration. The continuous line represents the linear regression of the prevalence on NO₂ mean concentration considering all the areas, weighted by the number of subjects in each area. Dotted lines are the regression lines estimated within each climatic region. The size of the symbols is proportional to the number of subjects in each area (○, subcontinental areas; △, Mediterranean areas).

with the asthma-like symptoms and positively associated with allergic rhinitis.

When climate and outdoor NO₂ levels were mutually adjusted (Table 5), climate remained the main determinant of wheeze (OR = 1.34; 95% CI 1.15 to 1.56), tightness in the chest

Table 4. Odds ratios* and 95% confidence intervals for the association between the climate indicator (CLI) and the outdoor NO₂ concentration, and each respiratory symptom

	Wheeze	Tightness in the chest	Shortness of breath	Asthma attacks	Allergic rhinitis
CLI†	1.23 (1.13–1.35)	1.21 (1.11–1.33)	1.21 (1.08–1.36)	1.19 (1.07–1.31)	0.96 (0.82–1.12)
NO ₂ (µg/m ³)†	0.89 (0.78–1.01)	0.89 (0.79–1.01)	0.85 (0.75–0.95)	0.91 (0.81–1.02)	1.10 (0.95–1.27)

*Estimated separately for CLI and the outdoor NO₂ concentration, and adjusted for sex, age, smoking habits, social class, season of response, cumulative response rate and type of contact (telephone vs. mail) through a multilevel binary response model. †Odds ratios are expressed for a change in CLI and NO₂ by one standard deviation (1.385 units and 18.3 µg/m³, respectively).

Table 5. Mutually adjusted odds ratios* and 95% confidence intervals for the association between the climate indicator (CLI) and the outdoor NO₂ concentration, and each respiratory symptom

	Wheeze	Tightness in the chest	Shortness of breath	Asthma attacks
CLI†	1.34 (1.15–1.56)	1.33 (1.17–1.52)	1.16 (0.96–1.42)	1.32 (1.12–1.56)
NO ₂ (µg/m ³)†	1.11 (0.96–1.28)	1.11 (0.98–1.26)	0.95 (0.79–1.15)	1.13 (0.98–1.32)

*Adjusted for sex, age, smoking habits, social class, season of response, cumulative response rate and type of contact (telephone vs. mail) through a multilevel binary response model. †Odds ratios are expressed for a change in CLI and NO₂ by one standard deviation (1.385 units and 18.3 µg/m³, respectively).

Table 6. Odds ratios* and 95% confidence intervals for the association between the outdoor NO₂ concentration and allergic rhinitis

	Subcontinental region	Mediterranean region
NO ₂ (µg/m ³)†	1.03 (0.83–1.28)	1.38 (1.12–1.69)

*Estimated separately in each climatic region, and adjusted for sex, age, smoking habits, social class, season of response, cumulative response rate and type of contact (telephone vs. mail) through a multilevel binary response model. †Odds ratios are expressed for a change in NO₂ by one standard deviation (18.3 µg/m³).

(OR = 1.33; 95% CI 1.17 to 1.52) and asthma attacks (OR = 1.32; 95% CI 1.12 to 1.56). After adjusting for climate, the NO₂ outdoor exposure becomes positively related with asthma attacks, tightness in the chest and wheeze: an increase of 18.3 µg/m³ in NO₂ exposure increased the risk of having these symptoms by 11%, even if the association did not reach a statistical significance when using two-tailed tests.

Only in the case of allergic rhinitis, was a statistically significant interaction found between climatic region and NO₂ ($P = 0.006$), pointing out that climate modifies the association of NO₂ with allergic rhinitis (Fig. 5). In fact, an increase in the NO₂ outdoor level was significantly associated with the risk of having allergic rhinitis in the Mediterranean region (OR = 1.38; 95% CI 1.12 to 1.69, for an increase in NO₂ by one standard

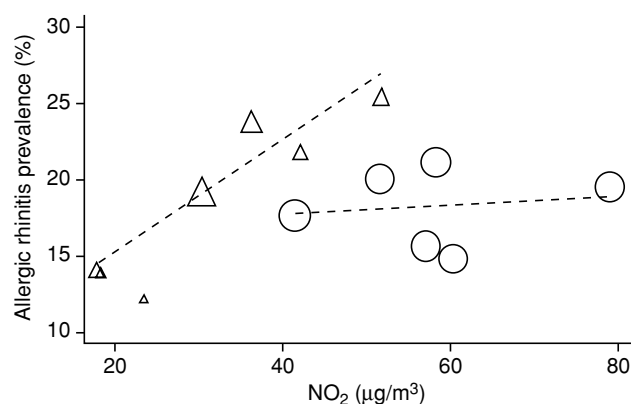


Fig. 5. Relationship between allergic rhinitis prevalence and outdoor NO₂ concentration. Dotted lines represent the linear regression of the prevalence on NO₂ mean concentration within each climatic region, weighted by the number of subjects in each area. The size of the symbols is proportional to the number of subjects in each area (○, subcontinental areas; △, Mediterranean areas).

deviation), but not in the subcontinental one (OR = 1.03; 95% CI 0.83 to 1.28) (Table 6).

Discussion

The main results of our analysis are:

- Climate is associated with the prevalence of asthma attacks and asthma-like symptoms: a low annual temperature range and a high annual temperature (Mediterranean climate) seem to increase the risk of having asthma. In multicentre studies on air pollution, climate could be a strong confounder if not controlled when centres belong to different climatic regions.
- A positive association between the prevalence of allergic rhinitis and NO₂ was detected only in the Mediterranean region, which may indicate that climate interacts with outdoor air pollution.
- The positive relationship between NO₂ and most asthma-like symptoms suggests that long-term exposure to traffic pollution increases the risk of having asthma.

Several studies have assessed the short-term effect of climate on asthma in different geographical areas, reporting an increase in daily incidence of acute attacks of asthma on cold days [5–7], probably due to induced lower airway obstruction in patients with cold-sensitive asthma [25]. On the contrary, few studies have addressed the long-term effect of climate on asthma; they have shown a positive association between asthma and average annual temperature [8] or non-summer temperatures [9, 10].

Our analysis of Italian data, which guarantees a substantial variation in climatic conditions, shows that asthma and asthma-like symptom prevalence increased in those centres characterized by a higher annual average temperature and a lower temperature range. Mediterranean centres, situated on or near the coast, showed higher prevalences of asthma and asthma-like symptoms, in agreement with previous geographical studies reporting a coastal effect [26, 27].

The reason for the effect of climate on the prevalence of asthma symptoms is unclear. Higher temperatures and a humid coastal climate are associated with higher levels of allergen exposure [28], like house dust mites and moulds, that could increase the risk of developing asthma [29–32].

People living at higher temperatures could be more exposed to ozone [33], which may have a long-term effect on the development of new cases of asthma and on the decrement of baseline lung function [34–37]. Unfortunately, the data on ozone exposure were not available for all centres at the time of this analysis.

One could argue that climate could mask a socio-economic effect, as Mediterranean areas in Italy had a lower economic development than northern ones in the last century. However, in our analysis we adjusted for both individual socio-economic status and smoking habits.

Part of the observed association between climate and asthma could be due to genetic differences between people living in the two Italian climatic regions. However, studies on the genetic similarity of the Italians [38] showed that major genetic differences only exist between the inhabitants of the Island of Sardinia and the rest of the Italian population. When the analysis was repeated, excluding the Sardinian centre (Sassari), the results were completely consistent.

Furthermore, differences in climate could also entail differences in life-style that could partially explain the observed differences in symptoms prevalence.

While climate is associated with asthma, on the whole it does not show a statistically significant association with the prevalence of allergic rhinitis. This may reflect the fact that allergic rhinitis is to a large extent a pollen-related disease and that the type and concentration levels of pollen vary widely, even within Italian climatic regions [39].

It is worthwhile to note the confounding effect of climate on the association between asthma and pollution: the Mediterranean climate is associated with increased asthma prevalence and reduced NO₂ pollution, and the opposite holds for the subcontinental climate. As a consequence, the crude estimate of the association between outdoor NO₂ pollution (or other compounds) and asthma prevalence is biased and could lead to misleading interpretations (see Table 4).

Furthermore, according to our results, climate might be a modifier of the association between traffic pollution (as indicated by NO₂) and the prevalence of allergic rhinitis: in fact, when levels of outdoor exposure rose, the prevalence increased in the Mediterranean region (OR = 1.38; 95% CI 1.12 to 1.69), but not in the subcontinental one (OR = 1.03; 95% CI 0.83 to 1.28), despite the fact that the former had a lower level of NO₂ than the latter. These findings are in agreement with previous studies indicating an association between traffic-related pollution and rhinitis [40–42] and suggest that the effect of the exposure depends on the climatic scenario. This could be either because the effect of NO₂ at stable, higher temperatures (Mediterranean climate) may aggravate the inflammation of the respiratory epithelium in susceptible subjects, making them more prone to react to airborne allergens [43], or because higher temperatures could favour the adjuvant effect of NO₂ (or other pollution components), potentiating the pollen effect [44], or both. Finally, air pollution and climatic variations could also have an indirect effect on allergic response by influencing the pollen production of allergenic plants both quantitatively and qualitatively [45].

Whereas numerous studies have shown that asthma symptoms may be triggered or exacerbated by a short-term increase in air pollution [46–48], there is no consistent evidence that asthma prevalence is positively associated with increasing levels of air pollution [11, 13, 14, 49].

When climate and outdoor NO₂ levels were mutually adjusted, we found a positive association between pollution exposure and asthma. In fact, the association of NO₂ was consistent for most asthma symptoms, and the strength of the association would have been statistically significant at the 5% level for tightness in the chest and asthma attacks, if one-tailed rather than two-tailed tests had been performed.

In interpreting our results, some points should be considered. Up to now, ISAYA is the largest epidemiological study on adult asthma carried out in Italy and the first to allow a direct comparison of prevalence rates in the two Italian climatic regions. The response rate was relatively high, guaranteeing the representativeness of the target population. In our analysis, we adjusted for the potential bias that could have occurred due to differences among centres, either in the way the study was performed (response rate, type of interview and season of response) or in individual characteristics (age, sex, smoking habits and social class). However, the centres involved in the study, particularly the Mediterranean ones, had not been randomly chosen and therefore may not be fully representative of the respective climatic regions in Italy. Moreover, factors not controlled for in our study (such as life-style) could partially be responsible for the observed association.

Therefore, cultural differences in symptom reporting are likely to be a negligible source of bias in our context. In fact, the questions used to collect information on symptoms were the same as used in the ECRHS [1] and the results of this survey have clearly demonstrated, at an international level, that the variation in prevalence of reported symptoms reflects the variation of objective markers of asthma and atopy, like bronchial hyper-responsiveness [3], specific IgE and skin prick tests [4]. Accordingly, cultural differences in symptoms reporting are to a large extent a negligible source of bias when interpreting the geographical pattern of prevalence in Italy.

In conclusion, our analysis shows that in Italy the prevalence of asthma is higher in the centres characterized by a Mediterranean climate and it suggests that the association of NO₂ outdoor pollution with the risk of having allergic rhinitis is modified by climatic conditions. Furthermore, our data suggest that the risk of having asthma increases with the level of long-term exposure to traffic pollution (NO₂).

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Appendix

A full account of multilevel regression is given elsewhere [23]. In brief, the models used explicitly take the hierarchical structure of the data into account, that is individual subjects (level 1 units) are nested within the 13 areas (level 2 units). Consequently, the models assume two sources of variation: the variation among subjects (level 1), part of which could be explained by the individual characteristics, and the variation among areas (level 2), part of which could be explained by the variables measured at area level.

The two-level models considered in the analysis assume that: (i) the response variable (y_{ij}) follows a Bernoulli distribution with $P(y_{ij}=1)=\pi_{ij}$ and $P(y_{ij}=0)=1-\pi_{ij}$, where $y_{ij}=1$ and $y_{ij}=0$ denote the presence and absence, respectively, of the symptom for the i th subject ($i=1,\dots,n_j$) in the j th area ($j=1,\dots,13$); (ii) the intercept term is random at the area level; (iii) all the explanatory variables are fixed effects. The general form of the models is:

$$\text{logit}(\pi_{ij}) = (\beta_0 + u_{0j}) + X_{ij}\beta_1 + Z_j\beta_2$$

where u_{0j} is the level 2 residual (random departure of the j th area from the general prevalence β_0 on the logit scale); X_{ij} are known covariates measured on each subject (sex, age, smoking habits, social class, season of response, cumulative response rate and type of contact), whose association with the prevalence is estimated by β_1 ; Z_j are known covariates measured at area level (climate indicator and mean annual NO₂ concentration), whose association with the prevalence is estimated by β_2 .