



Geo-climatic heterogeneity in self-reported asthma, allergic rhinitis and chronic bronchitis in Italy



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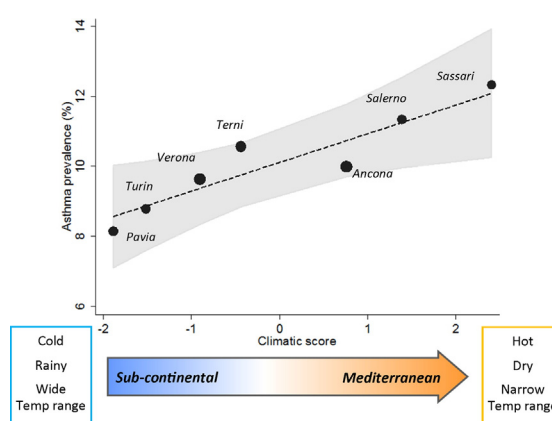
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HIGHLIGHTS

- Asthma and chronic bronchitis prevalence rates are heterogeneous across Italy
- A climatic and a topographic component explain most geo-climatic variability in Italy
- Greater asthma prevalence is found in cities with warmer and drier climate

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 21 July 2015

Received in revised form 29 October 2015

Accepted 4 December 2015

Available online xxxx

Editor: D. Barcelo

Keywords:

Epidemiology

Asthma

ABSTRACT

Background: Several studies highlighted a great variability, both between and within countries, in the prevalence of asthma and chronic airways diseases.

Aim: To evaluate if geo-climatic variations can explain the heterogeneity in the prevalence of asthma and respiratory diseases in Italy.

Methods: Between 2006 and 2010, a postal screening questionnaire on respiratory health was administered to 18,357 randomly selected subjects, aged 20–44, living in 7 centers in northern, central, and southern Italy. A random-effects meta-analysis was fitted to evaluate the between-centers heterogeneity in the prevalence of asthma, asthma-like symptoms, allergic rhinitis, and chronic bronchitis (CB). A principal component analysis (PCA) was performed to synthesize the geo-climatic information (annual mean temperature, range of temperature, annual rainfalls, global solar radiations, altitude, distance from the sea) of all the 110 Italian province capital

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Climate
Principal component analysis
Meta-regression
Chronic bronchitis
Allergic rhinitis
Asthma-like symptoms

towns. The associations between these geo-climatic components obtained with PCA and the prevalence of respiratory diseases were analyzed through meta-regression models.

Results: 10,464 (57%) subjects responded to the questionnaire. There was a significant between-centers heterogeneity in the prevalence of asthma ($I^2 = 59.5\%$, $p = 0.022$) and CB ($I^2 = 60.5\%$, $p = 0.019$), but not in that of asthma-like symptoms or allergic rhinitis. Two independent geo-climatic components explaining together about 80% of the overall geo-climatic variability were identified: the first principally summarized the climatic variables; the second the topographic ones. Variations in the prevalence of asthma across centers were significantly associated with differences in the climatic component ($p = 0.017$), but not with differences in the topographic one.

Conclusions: Our findings suggest that climate play a role in determining the between-center heterogeneity in the prevalence of asthma in Italy, with higher prevalence in dry-hot Mediterranean climates, and lower in rainy-cold northern climates.

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1. Introduction

Asthma, chronic bronchitis and allergic rhinitis are common health problems worldwide, with a high social and economic impact (Accordini et al., 2008). The European Community Respiratory Health Survey (ECRHS) and the International Study of Asthma and Allergies in Childhood (ISAAC) highlighted a great variability of asthma prevalence all over the world (Burney et al., 1996; Asher et al., 1998; Weiland et al., 2004). Although to a lesser extent, an important geographical variability has been observed even at national level in Italy both in children (Renzoni et al., 1997; de Sario et al., 2005) and adult population (de Marco et al., 2002; Zanolin et al., 2004; Bugiani et al., 2005).

A potential role of climatic conditions in the etiology of asthma and allergies has long been suspected. Several studies analyzed the short-term effects of meteorological factors in the exacerbations of respiratory symptoms, but there is still controversy about the potential long-term effects of climate on the regional variability in the prevalence of chronic respiratory diseases.

The aim of this study is to evaluate whether there is a variability in asthma, asthma-like symptoms, allergic rhinitis, and chronic bronchitis prevalence among different Italian cities, and whether this variability can be explained by geo-climatic differences. To achieve this, data from the population-based Gene–Environment Interaction in Respiratory Disease (GEIRD) survey were analyzed.

2. Methods

2.1. Study population and design

The GEIRD is an ongoing two-stage multicenter study, aiming at investigating allergic and respiratory conditions in the Italian adult population (de Marco et al., 2010).

Seven centers took part to the GEIRD study (Fig. 1): three of them – Turin, Pavia, and Verona – are sited in the Po River Valley in 3 different Regions of the northern part of Italy (Piedmont, Lombardy, and Veneto, respectively); the other four centers are located in 4 different Regions of central (Ancona and Terni), southern (Salerno), and insular part (Sassari) of Italy. Ancona, Salerno, and Sassari lie along the sea coast. The centers in northern Italy are characterized by a Sub-continental climate (Köppen climate classification: CFA), with relatively hot summers and cool winters and a temperature range between the coldest month and the hottest month that is of over 20 °C. Conversely, centers of central and southern Italy are characterized by a typical Mediterranean climate (Köppen climate classification: CSA), with hot summers, sea-mitigated winters and smaller temperature ranges between the cold and the hot season. The Mediterranean climate is accentuated in Salerno and Sassari, which lie in southern latitudes compared to Ancona and Terni.

As part of GEIRD stage-1, a cross-sectional screening questionnaire was administered between 2006 and 2010 to 18,357 subjects from the general population aged 20–44, living in one of the seven GEIRD centers.

The GEIRD screening questionnaire (www.geird.org) is a modified version of the European Community Respiratory Health Survey (ECRHS) questionnaire, and included items on the occurrence of allergic diseases, socio-demographic characteristics and environmental exposures (de Marco et al., 1999). The questionnaire was mailed up to 3 times in the case of non-response, and a final phone interview was carried out to reach the remaining non responders. Participants were informed about all the research aspects and consented to complete and return the questionnaire. Approval to conduct the study was granted from the local ethical committee in each participating center.

2.2. Respiratory outcomes

A subject was classified as having:

- ‘lifetime diagnosed asthma’ (asthma) in case of affirmative answer to the question ‘Have you ever had asthma?’ and ‘Was this confirmed by a doctor?’;
- ‘asthma-like symptoms’ in case of positive answers to at least one of the following questions: ‘Have you had wheezing or whistling in your chest



Fig. 1. Geographical distribution of GEIRD centers in Italy.

at any time in the last 12 months?', and/or 'Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?', and/or 'Have you been woken by an attack of shortness of breath at any time in the last 12 months?'.

- 'allergic rhinitis' (AR) in case of affirmative answers to the question 'do you have any nasal allergies, including hay fever?';
- 'chronic bronchitis' (CB) in the case of positive response to the question 'Have you had cough and phlegm on most days for a minimum of 3 months a year and for at least two successive years?'.

2.3. Covariates and potential confounders

The following covariates were collected from the questionnaire: sex, age (categorized in 20–29; 30–39; 40–44), smoking habits (non-smoker; smoker; ex-smoker), education level (university; high school; or lower education otherwise) and occupation (clerk; manager; unemployed; home maker; self-employed; workman; student) as proxy of socio-economic status, self-reported level of heavy traffic near home (low; medium; high). The season when the questionnaire was completed, and the type of contact (mail/phone) were regarded as potential confounders. As the GEIRD centers had different final response rates, the center-specific cumulative percentile rank of response was included to control for potential selection bias (de Marco et al., 1994).

2.4. Geo-climatic data

The meteorological and geographical data – annual average temperature, temperature range, mm of rainfalls; latitude North and longitude East, altitude above the sea, distance to the sea, global solar radiation – from all the 110 Italian Provincial Capitals (i.e. towns or cities where is the seat of administration and government of one of the 110 Provinces of Italy) were obtained from the *Italian National agency for new technologies, Energy, and Sustainable Economic Development* (ENEA – www.enea.it/en), and refer to a period of at least 10 years, with the exception of the data on global solar radiation that refers to the annual average of the period 1994–1999 (Table 1S in the Supporting information). These towns and cities are homogeneously distributed across the Italian territory, and reasonably represent the geo-climatic variability in Italy. The annual mean temperature is defined as the mean of the daily temperature mean values, and the temperature range is defined as the difference between the minimum and maximum temperature in a year.

2.5. Statistical analyses

The correlation between geo-climatic variables across 110 capitals was evaluated by Pearson's correlation coefficient. Given the high correlation between the variables, a *principal component analysis* (PCA) with orthogonal (varimax) rotation of the loading matrix was performed to synthesize the geo-climatic information in principal climatic components. The scores obtained with the PCA were used to characterize the climatic condition of the GEIRD centers.

A three-step approach was used to evaluate the heterogeneity in the prevalence of respiratory outcomes across the centers, and its association with geo-climatic variables.

In the first step, the adjusted prevalence (with 95% confidence interval, 95% CI) of the above-mentioned respiratory conditions in the GEIRD centers was calculated by logistic regression models, controlling for all the covariates and potential source of bias. In the second step, random-effects meta-analyses were used to estimate the between-center heterogeneity (I^2) in the prevalence of respiratory outcomes, weighting for its standard error (Harris et al., 2008).

Finally, in the third-step random-effects meta-analysis regressions (meta-regressions) were fitted to:

- evaluate the association of the identified geo-climatic components with asthma, allergic rhinitis and chronic bronchitis prevalence across centers;
- estimate the proportion of between-centers variance explained (r^2 , adjusted with Knapp–Hartung modification) by geo-climatic covariates;
- measure the percentage of the residual variation that is attributable to between-centers heterogeneity (I^2_{res}) (Harbord & Higgins, 2008).

The statistical analyses were performed with STATA 13.1, and a 0.05 significance level was adopted.

3. Results

3.1. Participants and response rates

In all, 10,464 subjects (57%) responded to the questionnaire in the seven GEIRD centers [Table 2S in the Supporting information]. The response rate was maximum in Verona (67%) and minimum in Pavia (37%). 88% of the sample responded to the postal questionnaire, compared to a 12% of the sample who was interviewed by telephone. Characteristics of participants across centers are summarized in Table 3S in the Supporting information.

3.2. Heterogeneity in the prevalence of asthma, asthma-like symptoms, allergic rhinitis, and chronic bronchitis across centers

The lower prevalence of asthma and asthma-like symptoms was recorded in Pavia (8.3% and 23.9%, respectively), while the higher prevalence was recorded in Sassari (12.5% and 29.1%, respectively). Salerno and Ancona had the maximum prevalence of AR and CB (28.9% and 17.6%, respectively), while the minimum prevalence was recorded in Verona (AR: 24.4%) and Pavia (CB: 11.5%), respectively (Table 4S in the Supporting information). The prevalence of respiratory symptoms, adjusted for all covariates and potential confounders, and the heterogeneity across centers are shown in Fig. 2. The weighted prevalence of asthma, obtained by random-effects meta-analyses, was 10.1%, while the weighted prevalence of asthma-like symptoms, AR, and CB was respectively 25.0%, 26.5%, and 12.7%. The adjusted prevalence of asthma and CB was significantly heterogeneous across centers (asthma: I^2 -squared 59.5%, p-value: 0.022; CB: I^2 -squared 60.5%, p-value: 0.019), while the prevalence of asthma-like symptoms and of AR were not (I^2 -squared 31.0% and 41.6%; p-value: 0.192 and 0.114, respectively).

3.3. Principal geo-climatic component analysis

The associations between geographical and meteorological variables of the 110 Italian Provincial Capitals are shown in Fig. 3. The geographical and meteorological variables considered in this study – average annual temperature, annual temperature range, rainfalls, altitude, distance to the sea, and annual global solar radiations, latitude – are all significantly correlated, with few exceptions. In particular, there is an almost perfect linear association between solar radiations and latitude ($r^2 > 0.95$), and, as a consequence, latitude was not included in the PCA.

The PCA identified 2 main geo-climatic components, which explained together about 80% of the overall geo-climatic variability across the Italian Provincial Capitals (proportion: 56% and 23%; Eigenvalue: 3.36 and 1.37, respectively). The weights of the geo-climatic variables in the two components are listed in Table 1: the annual mean temperature, the temperature range, the global solar radiations, and the rainfalls were the factors that weighted more in the *first component* – which was accordingly labeled as “climatic” component; the distance to the sea and the altitude were the factors that weighted more in the *2nd component* – which was labeled as “topographic” component. The *climatic* component was directly associated with annual mean temperature and global

annual solar radiations, and inversely associated with temperature range and rainfalls; consequently, its score was minimum in the Sub-continental centers of Northern Italy and maximum in the Mediterranean centers of Southern Italy. The *topographic* component was inversely associated with distance to the sea and positively associated with altitude, and it was higher in upcountry towns at higher elevation above sea level.

Seven of these Italian Province Capitals were also the centers that participated to the GEIRD survey. The distribution of geo-climatic variables and of the PCA scores of the GEIRD centers was similar to the one observed in the other Italian Provincial Capitals [Table 2].

3.4. Association of geo-climatic components with the prevalence of asthma and chronic bronchitis

In the meta-regression models, the variability in asthma prevalence across centers were significantly associated with the climatic component from the PCA, but not with the topographic one [Table 3]. In particular, the prevalence of asthma was significantly associated with the global solar radiations, average annual temperature, and rainfalls. The ecological relationship between asthma prevalence and the climatic component is displayed in Fig. 4, and an unitary increase in the climatic component was associated with an increase of about 0.8% in the prevalence of asthma. On the other hand, the heterogeneity in the prevalence of CB was not associated with any of the two components, but it had a significant, inverse association with temperature range. Meta-regression models were not fitted for testing the association between the geo-climatic components and the prevalence of asthma-like symptoms and AR, as this was not significantly heterogeneous between the GEIRD centers.

4. Discussion

Our study aimed at investigating whether geo-climatic differences could explain the heterogeneity in the prevalence of respiratory diseases in Italian cities. The geo-climatic variability among Italian towns

was synthesized in two principal components – arbitrarily labeled “climatic” and “topographic” component – using a principal component analysis (PCA). Our main results showed that the variability in the prevalence of asthma was significantly associated with climatic variables (annual average temperature, rainfalls, solar radiations, latitude), and with the overall score of the climatic component.

4.1. Long-term effects of geo-climatic variables in variability of asthma prevalence

Most studies on the effects of climate have investigated the association of short-term variations in climatic or meteorological conditions with the exacerbations of atopic diseases. Acute asthma attacks and hospitalizations are often reported in cold and very cold days, and the decline in outdoor temperature and air humidity has been linked to bronchial hyper-responsiveness, which may act as mediators for severe asthma episodes in sensitized individuals; (Epton et al., 1997; Piccolo et al., 1988; Hashimoto et al., 2004; Boner et al., 1995; Louie & Paré, 2004; Hervas et al., 2015) Another study reported that thunderstorms often precede acute asthma epidemics (Newson et al., 1998).

On the contrary, few studies have evaluated the long-term effects of geo-climatic characteristics on asthma and respiratory diseases.

In our study, higher asthma prevalence was associated with southern latitudes, greater exposure to solar radiations and annual temperature, and smaller annual rainfall; overall, a higher score in the climatic component score was associated with a greater prevalence in lifetime asthma.

These results indicate that long term exposure to more Mediterranean climates might be associated with the development of the lifetime asthma in Italy. This association might be at least in part mediated by solar radiations, which are higher in southern regions of Italy, as UV radiations are linked to vitamin D levels, which are thought to influence the polarization of the immune system toward the T_H2 phenotype and affect the atopic response, increasing the risk of asthma (Oktaria et al., 2013; Huges et al., 2011).

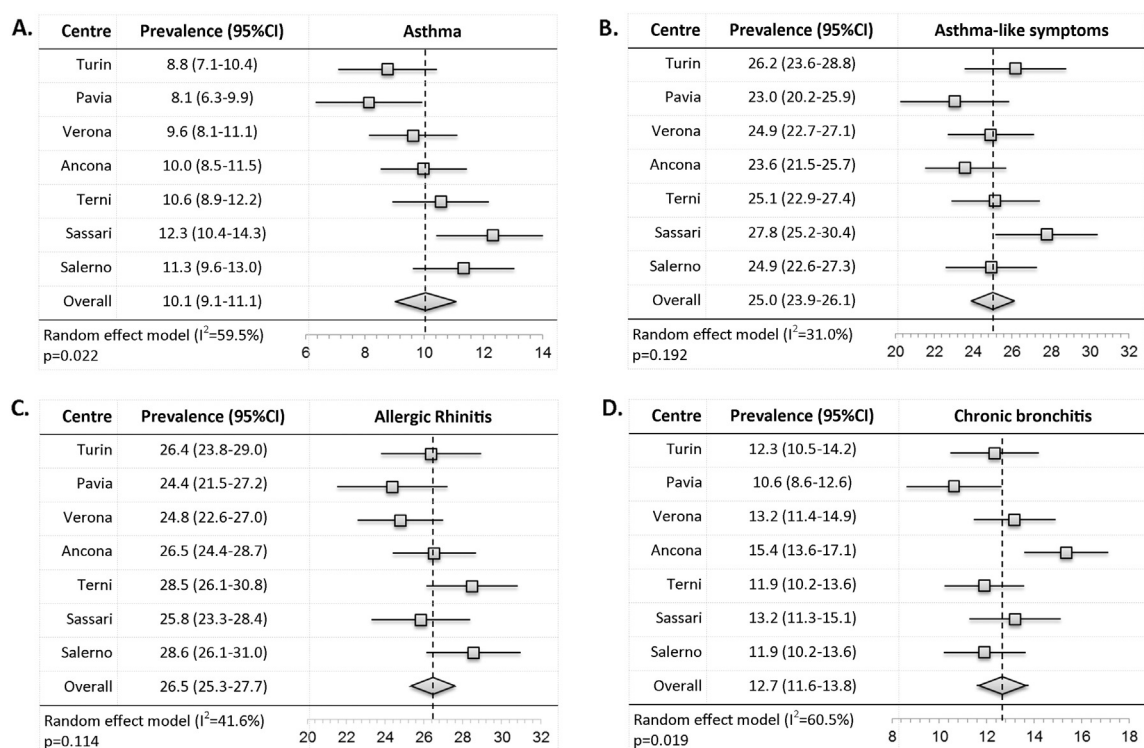


Fig. 2. Heterogeneity in the prevalence of (A) asthma, (B) asthma-like symptoms, (C) allergic rhinitis and (D) chronic bronchitis across GEIRD centers.

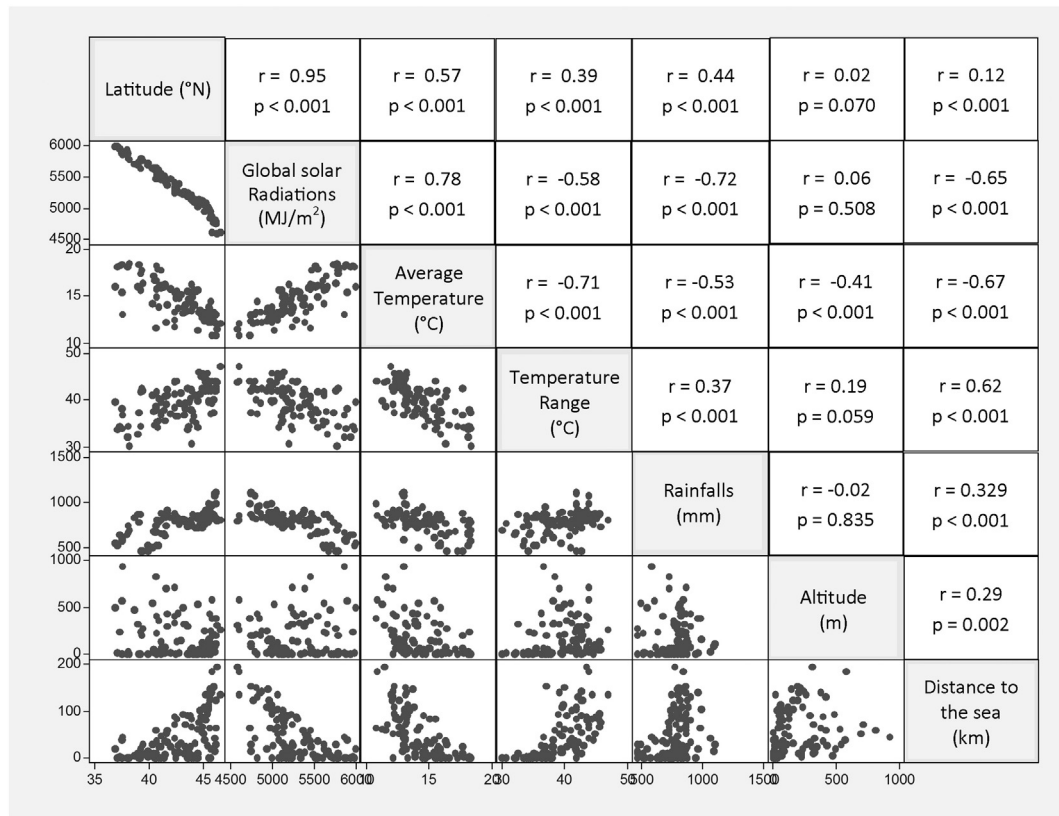


Fig. 3. Correlation between geo-climatic variables in the Italian Provincial capitals.

This also suggests that the meteorological factors that cause acute attacks may not be the same which affect the asthma prevalence. In fact, while our study suggests that warmer climates are associated with an increase in prevalence of lifetime asthma, low temperature can trigger asthma directly, inducing an obstruction of the lower airways in subjects with cold-sensitive asthma and resulting in acute exacerbations of symptoms (Millqvist et al., 2000).

The climate effect found in our study, i.e. warmer climate favors the development of asthma, is in agreement with the results other national studies in Australia, New Zealand, Spain, Turkey, and also with a previous study in Italy (de Marco et al., 2002; Oktaria et al., 2013; Huges et al., 2011; Hales et al., 1998; Metintas & Kurt, 2010; Garcia-Marcos et al., 2009), but in countertrend with respect of some international studies conducted in the EU and the US (Weiland et al., 2004; Verlato et al., 2002; Krstic, 2011), where the researchers reported that increases in the mean temperature were associated with lower prevalence of asthma.

It's worth noting that the greater asthma prevalence in the Mediterranean regions in Italy compared to the centers of the Po Valley mirrors what was recently found in a study on atopic dermatitis (Pesce et al., 2015).

Table 1
Coefficients of the geo-climatic variables in the identified principal components.

Variable	Climatic component	Topographic component	Unexplained
Global solar radiations	0.5878	0.1210	0.1021
Average temperature	0.4114	−0.2944	0.1441
Temperature range	−0.3531	0.2968	0.2974
Rainfalls	−0.5418	−0.2102	0.2696
1/Distance from sea	0.1758	−0.5245	0.2403
Altitude	0.1900	0.7009	0.2098

Table 2
Geo-climatic variability in the Italian Provincial Capitals and in the 7 GEIRD centers.

Variable	Provincial capitals (n = 110)	GEIRD centers (n = 7)	p-Value
Latitude (°N)			0.613 ^a
Mean +/−SD	42.8 ± 2.6	43.3 ± 2.6	
Median [min; max]	43.6 [36.9;46.5]	43.6 [40.7;45.4]	
Annual solar radiations (MJ/m²)			0.792 ^a
Mean +/−SD	5273 ± 350	5239 ± 345	
Median [min; max]	5214 [4589;5996]	5226 [4938;5648]	
Annual mean temperature (°C)			0.760 ^a
Mean +/−SD	14.4 ± 2.0	14.6 ± 2.1	
Median [min; max]	14.1 [10.8;18.4]	14.7 [12.3;18.2]	
Annual temperature range (°C)			0.998 ^a
Mean +/−SD	39.5 ± 3.9	39.5 ± 3.9	
Median [min; max]	39.8 [30.1;47.0]	39.8 [34.2;44.0]	
Rainfalls (mm/year)			0.728 ^a
Mean +/−SD	771 ± 129	767 ± 130	
Median [min; max]	797 [465;1103]	798 [517;905]	
Altitude (m)			0.762 ^b
Mean +/−SD	171 ± 202	107 ± 95	
Median [min; max]	76 [1;931]	77 [4;239]	
Distance to the sea (km)			0.744 ^b
Mean +/−SD	48 ± 49	57 ± 95	
Median [min; max]	31 [1;193]	81 [1;114]	
Climatic component			0.965 ^a
Mean +/−SD	0.0 ± 1.7	−0.0 ± 1.6	
Median [min; max]	−0.28 [−3.0;3.8]	0.22 [−2.5;3.5]	
Topographic component			0.560 ^a
Mean +/−SD	0.00 ± 1.36	−0.29 ± 1.36	
Median [min; max]	0.22 [−2.5;3.5]	−0.0 [−0.7;1.9]	

^a T-Student test.

^b Wilcoxon rank-sum test.

Table 3

Meta-regression analyses for the associations of geo-climatic factors with the prevalence of respiratory diseases. Estimates are obtained from entering one component into random-effect meta-regression. Coefficients are estimated per 1 standard deviation increase. Significant associations are in bold.

	Lifetime asthma	Chronic bronchitis
Variability (I^2)	59.5%	60.5%
Annual global solar radiations		
Residual I^2	0%	67%
Adjusted r^2	100%	0%
Coef [95% CI]	1.66 [0.45 to 2.86]	0.19 [−2.01 to 2.39]
p-Value	0.017	0.832
Latitude		
Residual I^2	0%	67%
Adjusted r^2	100%	0%
Coef [95% CI]	−1.60 [−2.79 to −0.42]	−0.09 [−2.27 to 2.09]
p-Value	0.017	0.918
Average annual temperature		
Residual I^2	0%	67%
Adjusted r^2	100%	0%
Coef [95% CI]	1.09 [0.23 to 1.95]	0.10 [−1.50 to 1.70]
p-Value	0.023	0.878
Temperature range		
Residual I^2	54%	13%
Adjusted r^2	23%	89%
Coef [95% CI]	−0.78 [−2.08 to 0.54]	−1.15 [−2.20 to −0.11]
p-Value	0.192	0.036
Rainfalls		
Residual I^2	17%	57%
Adjusted r^2	91%	17%
Coef [95% CI]	−1.13 [−2.19 to −0.72]	−0.74 [−2.22 to 0.73]
p-Value	0.041	0.252
Altitude		
Residual I^2	66%	66%
Adjusted r^2	0%	0%
Coef [95% CI]	0.14 [−3.31 to 3.60]	−0.52 [−4.11 to 3.05]
p-Value	0.918	0.720
Distance to the sea^(−1)		
Residual I^2	62%	58%
Adjusted r^2	0%	9%
Coef [95% CI]	0.38 [−0.90 to 1.65]	0.58 [−0.68 to 1.83]
p-Value	0.482	0.289
Climatic component		
Residual I^2	0%	60%
Adjusted r^2	100%	4%
Coef [95% CI]	0.82 [−0.22 to 1.41]	0.42 [−0.56 to 1.40]
p-Value	0.017	0.322
Topographic component		
Residual I^2	62%	61%
Adjusted r^2	0%	0%
Coef [95% CI]	−0.36 [−1.63 to 0.91]	−0.50 [−1.78 to 0.79]
p-Value	0.503	0.365

The prevalence of AR was quite homogeneous among the Italian centers, while the CB prevalence was significantly heterogeneous, with subjects from Ancona who were at significantly higher risk of reporting CB compared to the subjects from the other centers.

The prevalence of CB was associated with narrower annual temperature range but, interestingly, not with mean temperature itself, suggesting that the seasonal variability in weather conditions might influence the development of CB. Differently from asthma, there was no particular trend of association of CB with the considered geo-climatic components, confirming the results previously reported in the Italian Study of Asthma in Young Adults (de Marco et al., 2002). The lack of effect of other climatic variables on CB could be due to the greater importance of individual versus ecological factors, such as smoking habits and work related exposures.

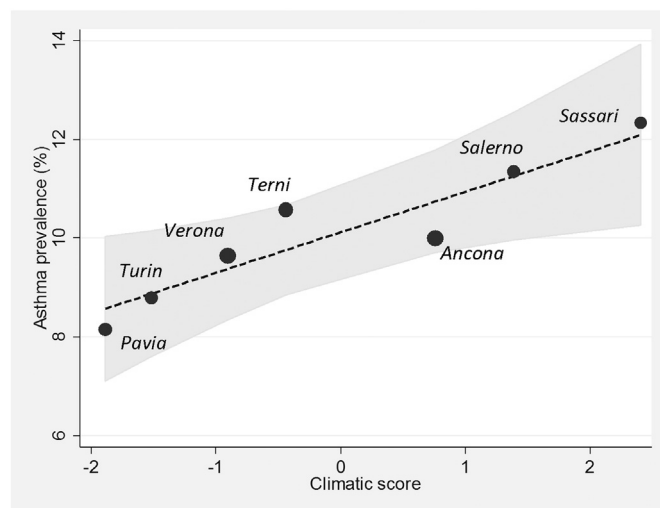


Fig. 4. Association between the climatic component from the PCA and asthma prevalence in the GEIRD centers, as estimated by meta-regression.

4.2. Climate is a complex combination of variables

What we call “climate” is the synthesis of different variables that are strongly inter-correlated: annual global solar radiations, for example, can predict 61% of the variability in annual average temperature, but is also significantly associated with rainfalls and temperature range, which are greater in northern regions of Italy compared to the southern ones.

For this reason, we looked at geo-climatic indices that could synthesize different inter-correlated variables in few components using a PCA. The variables analyzed – solar radiations, average temperature, temperature range, rainfalls, altitude, distance to the sea – define different aspects of the geo-climatic characteristics of the centers, and give a quite precise characterization of the climate of the area. Moreover, these variables are quite easy to find for any town, making our models easy to reproduce in other geographical areas for a comparison in Italy.

In addition to the variables that have been included in our models, there are other meteorological factors, such as humidity or atmospheric pressure, that are intrinsically associated with geo-climatic variations, but have not been considered in our analyses because of missing data (Huges et al., 2011; Norbäck et al., 2013). Moreover, climate directly influence the typology of native vegetation, and it determines the quality, concentration, and duration of the pollen season (Newson et al., 1998; Ariano et al., 2010; Norbäck et al., 2013). The inclusion of these variables in the statistical models might contribute to better describing the complexity of the climate and its interaction with respiratory diseases.

It is noteworthy that variations in climate can also influence people's behaviors and life-styles, such as the time spent outdoors, diet (e.g. seasonal fruit and vegetables, vitamin-D containing nutrients), and house characteristics (e.g. use of domestic heating, ventilation, use of air conditioning, etc.), all of which have been shown to impact the risk of developing asthma and respiratory diseases (Huges et al., 2011; Daly et al., 2012; Lips et al., 2014; Pfeffer et al., 2014; Dharmage et al., 1999). Therefore, climate may be linked to respiratory diseases through many paths, since it is directly and indirectly connected with several variables that may potentially influence the development of allergic and respiratory diseases.

4.3. Strengths and limits

This analysis gives information on the prevalence of asthma, allergic rhinitis and asthma-like symptoms in a large South European country, and evaluates the heterogeneity in the prevalence of respiratory

symptoms in relation to geo-climatic variations. The participants from each center were randomly selected from the general-population, aged 20–44 years, and do not represent extreme variations between small and highly selected groups. The use of a standardized methodology across the seven GEIRD centers made it possible a direct comparison of prevalence rates. Moreover, in our analysis we adjusted for the potential bias which could have occurred due to the differences among centers in the design variables (response prevalence, type and season of interview) (de Marco et al., 2010).

There is no widely applicable diagnostic test for asthma, and assessment of its frequency and determinants is based on responses to questionnaires with imperfect sensitivity and specificity. However, our definitions of asthma and of asthma-like based are based on the definitions of the ECRHS, which were widely used and validated in previous studies (de Marco et al., 1998; Anto et al., 2010).

The main limitation of the study is the small number of participating centers, which reduced the power of the study. Accordingly, we could only assess the association of one variable at the time in meta-regressions to avoid issues of overfitting (Babyak, 2004). Moreover, a common limitation of ecological studies is the difficulty in controlling for individual factors (Greenland & Morgenstern, 1989). In our two-step approach, however, we were able to adjust the analyses at the individual level for some common risk factors for respiratory diseases (e.g. smoking habits, social status, etc.), thus accounting for their different distribution among centers.

5. Conclusions

We synthesized the variability of the geo-climatic data in the Italian Province Capitals using a PCA approach. Our findings indicate that there is a great between-center heterogeneity in the prevalence of asthma in Italy, and suggest that climate may play a role in determining these variations; on the other hand, topographic variables seem to have a minor or null long-term impact on long-term respiratory health.

Funding sources

The GEIRD project was funded by the Cariverona Foundation (Bando 2006), the Italian Ministry of Health (RF-2009-1471235), Chiesi Farmaceutici, and the Italian Medicines Agency (AIFA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Conceived the study: GPe, MB, RdM; Ran the statistical analyses: GPe; wrote the first draft of the manuscript: GPe; Contributed to the survey design and data collection: RdM, MB, SA, LA, PP, GPo, SV, EC, FS; critically reviewed the manuscript for important intellectual content: GPe, MB, AM, SA, LA, AC, PM, PP, GPo, SV, RdM.

Appendix A. Supplementary data

Supplementary material.

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