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Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010

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Abstract

Background: The prevalence of asthma increased worldwide until the 1990s, but since then there has been no clear temporal pattern.

Objectives: To assess time trends in the prevalence of current asthma , asthma-like symptoms and allergic rhinitis in Italian adults from 1990 to 2010.

Methods: The same screening questionnaire was administered by mail or phone to random samples of the general population (age 20-44) in Italy, in the frame of three multi-center studies: ECRHS (1991-1993;n=6031); ISAYA (1998-2000;n=18873); GEIRD (2007-2010;n=10494). Time trends in prevalence were estimated using Poisson regression models in the centers which repeated the survey at different points in time.

Results: From 1991 to 2010, the median prevalence of current asthma, wheezing and allergic rhinitis increased from 4.1% to 6.6%, from 10.1% to 13.9% and from 16.8% to 25.8% respectively. The prevalence of current asthma was stable during the nineties and increased (RR=1.38 95%CI:1.19;1.59) from 1998-2000 to 2007-2010, mainly in subjects who did not report allergic rhinitis. The prevalence of allergic rhinitis has continuously increased since 1991.

Conclusions: The asthma epidemic is not over in Italy. During the last twenty years asthma prevalence has increased by 38%, paralleled by a similar increase in asthma-like symptoms and allergic rhinitis.

Key words

Asthma; allergic rhinitis; epidemiology; prevalence; temporal trends; wheezing.

Abbreviations used

ECRHS, European Community Respiratory Health Survey

ISAYA, Italian Study on Asthma in Young Adults

GEIRD, Gene Environment Interactions in Respiratory Diseases

sd, standard deviation

M:F, male and female ratio

GINA guidelines, The Global Initiative for Asthma guidelines

RR, relative risk

95%CI, Confidence interval at 95% level

NA, not available

INTRODUCTION

Asthma is the most common chronic respiratory disease in the world[1] and is a significant cause of morbidity worldwide. Approximately 300 million people in the world currently have asthma[2]. The prevalence of asthma increased worldwide in the second half of the last century until the 1990s, but since then there has been no clear temporal pattern[3].

In children, the prevalence of asthma is still increasing in the countries where the prevalence had been low and has decreased or levelled off in several westernized countries where the prevalence had been high[4]. However, in some of the industrialized countries, opposite trends were also found[5-6].

The evidence that there has been a change in prevalence in adults is conflicting, with some studies suggesting that asthma prevalence has stabilized or even decreased[7-10], while others suggest that it is still increasing[11-12].

While the recent trend in asthma prevalence is uncertain, all the studies agree that the prevalence of allergic rhinitis, a condition strongly associated with asthma[13], is still on the increase[4,7,8,14-16].

A reliable assessment of the trend of asthma prevalence requires repeated cross-sectional studies on different occasions on the same population, using the same methods over an adequate period of time. Unfortunately very few studies with these characteristics[17] are available.

Repeated cross-sectional surveys with identical study design and ascertainment methods were carried out among random samples of young adults (20-44 years) in several Italian areas between 1991 and 2010.

The present study is aimed at quantifying the temporal change in the prevalence of asthma and allergic rhinitis in the last twenty years in the adult population of Italy, a country that is characterized by a medium-low level of asthma prevalence [18].

METHODS

Study Samples and Design

Between 1991 and 2010, three repeated multi-center cross-sectional surveys on respiratory diseases were carried out by the same research team on random samples of young adults, using the same design.

The first study was the Italian arm of the European Community Respiratory Health Survey (ECRHS) and it was carried out between 1991 and 1993[19]. A random sample of the general population aged 20 to 44 years (M:F = 1:1) was randomly selected from the registry of the local health authority in each of three Italian centers (3000 in Turin and Verona, 1000 in Pavia). All the eligible subjects were administered a postal screening questionnaire up to three times in the case of non response. A final phone interview was carried out to reach the remaining non-responders.

Seven years later (1998-2000) the Italian Study on Asthma in Young Adults (ISAYA)[20] was carried out following the same design, targeting the same population, using the same sampling frame and the same protocol of questionnaire administration as the ECRHS. About 3000 subjects aged 20 to 44 years old were randomly selected from the general population in each of the nine Italian centers: Ferrara, Pavia, Pisa, Sassari, Sassuolo, Siracusa, Turin, Udine and Verona.

The third study, the Gene Environment Interactions in Respiratory Diseases (GEIRD) study[21], was conducted from 2007 to 2010, applying the same procedures as ECRHS and ISAYA. A random sample of about 3000 subjects from the general population aged 20 to 44 years old was randomly selected in each of seven centers: Ancona, Pavia, Terni, Salerno, Sassari, Turin and Verona.

Overall, 12 Italian centers were involved in at least one study and 4 in at least two studies. Six centers are located in Northern Italy and belong to the Sub-Continental climatic area (Udine, Verona, Pavia, Turin, Ferrara, Sassuolo) and the other six are located in central or southern Italy and belong to the Mediterranean climatic area (Pisa, Ancona, Terni, Sassari, Salerno, Siracusa) [Figure 1]. The Sub-Continental region is characterized by a lower average annual temperature and a higher annual temperature range than the Mediterranean one.

Ethical approval was obtained in each centre from the appropriate ethics committee.

Screening questionnaire, respiratory outcomes and potential confounders

The questionnaire used in the ISAYA[22] and GEIRD studies (available on www.geird.org web site) was the same as the one used in the ECRHS[23], with additional questions on the history of asthma, chronic bronchitis, eczema, dyspnea, smoking habits, self reported annoyance due to air pollution and direct and indirect costs of asthma or other breathing problems.

Based on the answers to the questionnaire, a subject was considered to have:

- *current asthma* if s/he answered affirmatively at least one of the following questions: "Have you had an attack of asthma in the last 12 months?" and/or "Are you currently taking any medicine (including inhalers, aerosol or tablets) for asthma?";
- *allergic rhinitis* if s/he gave a positive answer to the question: "Do you have any nasal allergies, including hay fever?" ;
- *asthma-like symptoms* if s/he gave a positive answer to the 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?" and "Have you woken up by an attack of shortness of breath at any time in the last 12 months?".

Gender, age, season at the time of the interview (spring, summer, autumn and winter) and type of contact (postal waves and telephone interview) were considered as potential confounders. Moreover, as the centers had different final response rates, each subject was attributed the center-specific cumulative response percentile rank to which s/he had answered. For this purpose, in each center and for each study, subjects were arranged according to the date the questionnaire had been filled in and their percentile rank was expressed as a percentage of the total number of eligible subjects. Summarizing, the percentile rank is a function of the promptness to respond, which is one of the main potential confounders associated with non response[19,24]. In fact, if the tendency to respond is associated to respiratory health, the crude estimate of prevalence is biased (i.e: early responders may report more symptoms than late or non responders). Similar methods were used in previous papers[20,25].

Statistical analysis

Categorical data were summarized as counts with percentages and continuous data as means with standard deviations (sd). Comparisons of variables across studies were performed by the Pearson Chi-squared test or by the Krusal-Wallis test as appropriate.

Adjusted prevalence rates of respiratory outcomes, stratified by study, climatic area and center, were obtained through a logistic regression model with respiratory outcomes as dependent variables (present vs absent) and gender, age, percentile rank of cumulative response, type of contact and season at the interview as covariates.

To study the change over time of the prevalence of respiratory outcomes, only the four centers participating in at least two of the three studies were considered (Pavia, Sassari, Turin and Verona). Two Poisson regression models[26] (with robust standard errors) were fitted to the data,

using the respiratory outcomes as the dependent variables, and center plus the other potential confounders as independent variables. The first model addressed the changes in prevalence occurring between ECRHS (1991-1993) and ISAYA (1998-2000), while the second model focused on the changes in prevalence occurring between ISAYA (1998-2000) and GEIRD (2007-2010). Data from three centers (Pavia, Turin and Verona) were available for the first model, while the second model could take into account an additional center (Sassari). The results were expressed as the relative risk (RR and 95% confidence interval, 95%CI) of reporting respiratory outcomes over the two sub-sequent calendar periods: 1998-2000 vs 1991-1993 and 2007-2010 vs 1998-2000.

Sensitivity analysis

Differences in the response rates could bias estimates of the change in prevalence over time. To assess the sensitivity of the results to this potential source of bias, the main analyses (Poisson regression models), were repeated after we had truncated the observations at different cumulative response rates (15%, 30%, 45%, 60%, 75% and 90%) in each center and each study. As an example, in the first set of sensitivity analyses, subjects with a cumulative response percentile rank greater than 15% were excluded. In general, this analysis makes it possible to estimate the time trends when the response rate is the same in different periods of time.

RESULTS

Response rates and subjects' characteristics

Between 1991-1993 and 2007-10, 35398 subjects in 12 Italian centers answered the screening questionnaire. The average response rate showed a statistically significant ($p<0.001$) decrease (see Table 1) from 86.2% in 1991-1993 (ECRHS) to 72.7% in 1998-2000 (ISAYA) and to 57.2% in 2007-2010 (GEIRD). The percentage of women (see Table 2) and the mean age of responders slightly increased during the study period ($p<0.001$). The percentage of responders who answered the phone interview decreased from 32.9% to 11.8% in the same period ($p<0.001$). This decrease was mainly due to the increase in the number of mobile phone users and the decrease in landline users. The percentage of current smokers in the total sample significantly decreased from 33.5% to 27.7% in the last ten years ($p<0.001$).

Prevalence of current asthma, allergic rhinitis and asthma-like symptoms in Italy

The median of the adjusted prevalence rates of current asthma, allergic rhinitis and asthma-like symptoms (see Table 3) was in general higher in the centers of the Mediterranean area than in those of the Sub-Continental area, and it increased from 1991-1993 to 2007-2010 in both regions. Overall, in the last decade the national median prevalence of asthma and allergic rhinitis increased from 4.6% to 6.6% and from 19.4% to 25.8% respectively. A similar consistent trend was also observed for the asthma-like symptoms.

The average percentage of women was 54.1% (95%CI 51.8%;56.4%) in subjects with asthma and 48.9% (95%CI 47.7%;50.0%) in subjects with allergic rhinitis. The sex composition did not

show any statistical significant variation during the period of the study (data not shown) both in asthmatic and allergic subjects.

Crude and adjusted center specific prevalence rates of respiratory outcomes, by study and climatic area, are reported in the Online depository (see Table S1a-e).

Temporal change in prevalence of current asthma, allergic rhinitis and asthma-like symptoms in Italy

In the four centers (Pavia, Sassari, Turin and Verona) that participated in at least 2 studies, the overall adjusted prevalence (see Figure 2) of allergic rhinitis and wheezing continuously increased between 1991-1993 to 2007-2010, while the prevalence of current asthma, shortness of breath and tightness in the chest was almost stable during the nineties, and then it steadily increased from 1998-2000 to 2007-2010.

The analysis of temporal trends (see Table 4), after adjusting for center and other confounders, showed no significant variation in the risk of reporting asthma or asthma-like symptoms from 1991-1993 to 1998-2000, except for shortness of breath, whose prevalence decreased (RR= 0.72, 95%CI 0.62;0.84, $p<0.001$). However, in the subsequent decade, the prevalence of current asthma increased by 38% (RR=1.38; 95%CI;1.19;1.59) and the prevalence of all asthma-like symptoms from 18% to 45%. The prevalence of allergic rhinitis showed a statistically significant 16% increase in the first period and a further 27% increase in the last decade.

No interaction was found between calendar period, sex or age and current asthma prevalence.

The temporal trends in prevalence of respiratory outcomes were similar in men and women and among different age groups (tables S2 and S3).

Temporal change in the prevalence of current asthma in subjects with and without allergic rhinitis

In the four centers with at least two repeated surveys, 3977 (19.9%) subjects reported hay fever or allergic rhinitis on at least one occasion in either survey and 16007 (80.1%) did not. The prevalence of current asthma was 17.8% in the former and 2.0% in the latter group ($p<0.001$). Overall, 31.5% (95%CI: 28.6%-34.3%) of all the current asthmatics did not report allergic rhinitis.

The trend in asthma prevalence was not influenced by the presence of allergic rhinitis in the period from 1991 to 2000; while in the last decade the prevalence of current asthma was particularly high in subjects who did not have allergic rhinitis (see Figure 3). In this group, there was a statistically significant increase of more than 36% (RR=1.36, 95%CI 1.04;1.78) in the prevalence of asthma 2007-2010 with respect to 1998-2000.

Temporal change in the use of asthma medicine among asthmatics

In the four centers with at least two repeated surveys, the percentage of subjects with current asthma who reported to be on treatment were 48.0% (122/254), 64.1% (266/415) and 58.1% (211/363) in 1991-1993 , 1998-2000 and 2007-2010 respectively.

After adjusting for potential confounders, the maximum increase in asthma treatment among asthmatics was registered at the end of the nineties (1998-2000 vs 1991-1993: RR=1.16, 95%CI 0.97;1.38) while this proportion slightly decreased afterwards (see Table 5).

Sensitivity analysis

When the analyses of time trends were limited to same fixed cumulative response rates in each center and in each study, the results were consistent with those previously presented (data not shown).

DISCUSSION

This analysis was aimed at assessing temporal changes in prevalence of current asthma, allergic rhinitis and asthma-like symptoms in Italy. The data of three multi-center studies, carried out between January 1991 and December 2010, that employed the same study design and the same methods, were used.

The main findings are:

- the asthma epidemic is not over in Italy. The prevalence of current asthma has increased by about 38% in the first decade of the third millennium, reaching an overall prevalence of 6.6%;
- the increase in asthma does not reflect only changes in diagnostic and treatment practices, as it is paralleled by a similar increase in asthma-like symptom prevalence;
- the increase in asthma prevalence mainly concerns subjects who did not report allergic rhinitis;
- the proportion of asthmatics in treatment increased in the nineties and then slightly decreased;
- the prevalence of allergic rhinitis has continuously increased since 1991-1993, affecting more than one out of four young adults in Italy at the end of 2010.

The asthma epidemic in Italy

At the end of the nineties' the few available data on the national[7] and international[8,27] prevalence of asthma in adults seemed to suggest that the epidemic of asthma, which started in the fifties, had reached a plateau and the trend in prevalence was fading away or even reversing.

Our analysis, which considers changes in prevalence from 1991 to 2010, documents that in Italy, the prevalence of asthma is on the increase again after an apparent period of stability at the end of the nineties. The increase in the prevalence of reported asthma attacks and/or use of asthma medications is paralleled by a similar or stronger increase in the prevalence of asthma-like symptoms and allergic rhinitis. Hence, our findings strongly suggest that the asthma epidemic is not over. It is rather unlikely that this conclusion could be due to an artefact, because our prevalence estimates were adjusted for the difference between studies in potential confounding factors and in response rates. Furthermore, the sensitivity analyses confirmed the stability of our results under a wide spectrum of conditions.

The increase in asthma prevalence in the last twenty years was substantial. In 1991-1993 the median prevalence recorded in the three Italian centers that participated in the ECRHS survey was 4.1%, ranging from 3.3% to 5.0%. According to this figure, Italy was classified as a country with a low-medium prevalence of asthma. Twenty years later, when exactly the same questions were administered in the frame of the GEIRD study, the median prevalence was 6.6% ranging from 4.5% to 8.0%. Interestingly, a cross-sectional survey performed by the Italian College of General Practitioners in December 2009, found similar prevalence values[28].

Time trends in asthma prevalence were similar in men and women and in different age groups, as suggested by the absence of a statistically significant interaction between time, age and sex.

The greatest increase in asthma prevalence was observed after 1998, while the trend showed an apparent plateau before that year[7,8].

The upward trend in prevalence of asthma, is consistent with other studies[3,11,12,27,28] and occurred while there was a concomitant substantial decrease in the percentage of current smokers. It may be the result of the increase in either the incidence and/or the persistence of the disease. The

cross-sectional design of our study does not permit to disentangle these two components of asthma. However, as asthma persistence is largely determined by the inability to achieve a good control and/or to have a proper management of the disease, there is no reason to speculate that this component had a primary role in explaining the increase in prevalence (in general, new asthma medications and tools have improved the management of asthma in the last decades). Furthermore, the fact that in our study the prevalence of "lifelong asthma" had the same temporal increase as the prevalence of "current asthma" (data not shown) suggests that the observed trend in prevalence is likely due to the rise of the asthma incidence over time". What the causes of the increase in asthma prevalence are, is still an open question. Proposed contributing factors have included exposure to air pollution, infections and microbial substances in the environment[3]. Obesity may be another[31] potential risk factor.

Our results confirm[25] that the prevalence of asthma and asthma-like symptoms in Italy is higher in the Mediterranean than in the Sub-Continental area. This difference could reflect the different exposures to outdoor and indoor allergens, or the difference in ozone concentration, which tends to reach higher levels at higher temperatures, or to the interaction between higher temperatures and pollution[20].

The prevalence of asthma has significantly increased in non-allergic subjects

Due to the strong association of asthma with atopic diseases reported in several studies[32] the role of non-atopic asthma has generally been underestimated[33], even if its prevalence in some countries is similar[34] or even greater than that of atopic asthma[35-37]. Only few studies have addressed the temporal variation of asthma prevalence in atopic and non-atopic subjects. In a study on Danish children[38] the prevalence of current asthma increased significantly from 1986 to

2001 and it was primarily due to non atopic asthma. A Scottish study on adults reported that the prevalence of asthma increased from 1972-6 to 1996 only in subjects without hay fever [39]. In a Swiss study, the decline in asthma consultations, that occurred between 1999 and 2005, was attributed to the decline in prevalence of the allergic component of asthma[40].

Our results document that also in Italy non-atopic asthma affects about one out of three current asthmatics and that the greatest increase in asthma prevalence observed in the last twenty years is due to non-allergic asthma.

As atopic and non-atopic asthma show distinct patterns of risk factors, the striking increase in the prevalence of non-atopic asthma in the last twenty years may reflect changes in population exposures, particularly in early life exposures to viruses and/or environmental pollutants, which are strong risk factors for non-atopic asthma[41].

Some caution is needed in interpreting this finding as objective indicators of atopy (such as skin prick tests) are lacking. We considered an associated symptom (hay fever), which is often used when skin test data are not available[39] and it has been shown to be a good marker of atopy[42-44].

Allergic rhinitis has continuously increased

The worldwide incidence and prevalence of allergic rhinitis has been on the rise since at least 1990[4,7,13,45] in almost all westernized countries. Whether the upward trend is due to increasing air pollution, indoor environmental factors, improved hygiene practices, geo-climatic factors or all of the above is open to the debate.

Our findings document that the prevalence of allergic rhinitis has also continuously increased in Italy in the last twenty years, affecting more than one out of four young adults at the end of 2010.

In 1991-1993, the percentage of sensitized subjects among those who reported allergic rhinitis in the frame of the Italian arm of ECRHS was 79%[42]. Provided that this proportion has not changed in the last decade, one can speculate that the increase in the prevalence of allergic rhinitis is the result of an increase in sensitization among Italian adults.

Temporal change in the use of asthma drugs

Since 1990, national studies showed that in Italy a considerable percentage of subjects with current asthma were not treated. Even when only patients with severe asthma were considered, the percentage of untreated patients was still high[46]. A recent analysis of the international ECRHS data-base documented that Italy is the country with the highest percentage of uncontrolled asthmatics[47], because of the high prevalence of untreated asthma. Our findings concerning temporal variations in the proportion of asthmatics in treatment, showed a slight increase at the end of the nineties, when particular attention to the dissemination of the Global Initiative for Asthma (GINA) guidelines probably reached a peak, followed by a minor decrease in the most recent years. Even though these variations were not statistically significant, they seem to underline that 20 years after the publication of the GINA guidelines, the management of asthma still needs to be improved.

Limits and merits of the study

The present study benefitted from applying the same study design, sampling frame, study protocol and administering the same questionnaire to three large, multi-center general population random samples of identical age, surveyed 10 years apart. The prevalence was computed according to self reported symptoms and asthma attacks collected from validated international

questionnaires[18]. Differently from diagnoses or medication use, self-reported symptoms are less influenced by diagnostic activity. Accordingly, it is extremely likely that temporal changes in symptoms reflect a trend in prevalence rather than changes in health care practice.

The Italian centers involved in the study were not chosen randomly but on the availability of research teams able to carry out the survey. However, the study areas are spread all over Italy and well represent the geographical (North vs.South, Sub-Continental vs.Mediterranean) features of the country. Furthermore, in order to avoid temporal changes in prevalence being biased by differences in geographic locations, the assessment of the time trend was limited only to those centers in which the survey was repeated at least twice.

In the past 30 years, participation rates in epidemiological studies have been declining in the whole industrialized world[48]. In Italy, like in other European countries, the average response rate decreased by about 15% every ten years between 1991 and 2010. The decreased response rates over time may have biased our estimates. In fact, overestimation of the symptom prevalence[19] in the latest surveys may have occurred, if the tendency to answering screening questionnaires is related to respiratory health. Fortunately, most empiric work in the last few years suggests that the decline in participation rates is not likely to have a substantial influence on exposure-disease associations or point estimates of the measure of interest[48]. Furthermore, our results were adjusted for an indicator of propensity to respond and the sensitivity analyses, which compared the data obtained with the same response rates in the three studies, confirmed the main results.

CONCLUSIONS

To sum up, we analysed the data of three large surveys carried out in Italy from 1990 to 2010, using the same protocol and methods, headed by the same research team. We found that asthma prevalence had increased by over 35%, and this increase was mainly due to non-atopic asthma. A similar or even greater increase was documented for asthma-like symptoms and allergic rhinitis. These findings demonstrate the increasing social burden and impact of asthma and allergic rhinitis and enable health-care providers and policy makers to plan effective clinical and public health strategies. Future research should focus on factors (allergen and pollutant outdoor concentrations, virus infections) that are potentially able to explain these temporal trends.

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The GEIRD study group

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Table 1. Number of participating subjects and response rates (%) to the screening questionnaire by centers, in the 3 surveys carried out in Italy between 1991 and 2010

	1991-1993 (ECRHS)	**1998-2000 (ISAYA)**	**2007-2010 (GEIRD)**
Udine	-	2082 (70.9%)	-
Verona	2713 (90.4%)	2166 (74.0%)	1746 (67.7%)
Pavia	816 (81.6%)	2444 (82.2%)	966 (37.1%)
Turin	2502 (83.4%)	2266 (78.4%)	1205 (54.6%)
Ferrara	-	2106 (70.2%)	-
Sassuolo	-	2143 (74.7%)	-
Sub-continental area	***6031 (86.2%)***	***13207 (75.0%)***	***3917 (53.0%)***
Pisa	-	2411 (81.0%)	-
Ancona	-	-	1866 (61.9%)
Terni	-	-	1660 (59.1%)
Sassari	-	2055 (70.3%)	1245(53.0%)
Salerno	-	-	1806 (64.7%)
Siracusa	-	1200 (48.7%)	-
Mediterranean area	***-***	***5666 (67.7%)***	***6577 (60.0%)***
Total	***6031 (86.2%)***	***18873 (72.7%)***	***10494 (57.2%)***

Table 2: Distribution of gender, age, smoking habits and type of contact for subjects who participated in the three respiratory surveys carried out in Italy between 1991 and 2010.

	1991-1993 (ECRHS)	**1998-2000 (ISAYA)**	**2007-2010 (GEIRD)**	**p-value**
	n=6031	n=18873	n=10494	
Gender (n.of female, (%))	2846 (50.4)	9555 (50.7)	5483 (52.3)	0.015
Age (mean, sd)	32.7 (7.0)	33.1 (6.9)	34.7 (7.1)	<0.001
Smoking habits (number (%))				
never smokers	NA*	9737 (51.8)	5773 (56.1)	<0.001
ex-smokers	NA*	2755 (14.7)	1662 (16.2)	
current smokers	NA*	6304 (33.5)	2854 (27.7)	
Type of contact (number (%))				
mail contact	4049 (67.1)	13599 (72.1)	9258 (88.2)	<0.001
phone call	1982 (32.9)	5274 (27.9)	1236 (11.8)	

*information not available (NA) in the ECRHS survey.

Table 3: Median of the adjusted* prevalence (%) [minimum; maximum] of current asthma, allergic rhinitis, wheezing, shortness of breath and tightness in the chest in the two main climatic regions (Sub-Continental and Mediterranean) and in the whole of Italy, estimated in the centers that participated in the three respiratory surveys between 1991 and 2010.

	1991-1993 (ECRHS)	1998-2000 (ISAYA)	2007-2010 (GEIRD)
	n=6031	n=18873	n=10494
Current asthma			
Sub-Continental	4.1 [3.3;5.0]	4.1 [3.9;4.6]	6.6 [4.5;6.6]
Mediterranean	NA†	5.4 [5.2;6.5]	7.3 [4.9;8.0]
Overall	4.1 [3.3;5.0]	4.6 [3.9;6.5]	6.6 [4.5;8.0]
Allergic Rhinitis			
Sub-Continental	16.8 [13. 8;17.0]	18.7 [14.7;20.8]	24.2 [23.1;25.6]
Mediterranean	NA†	19.4 [14.7;24.3]	26.6 [24.6;28.8]
Overall	16.8 [13.8;17.0]	19.4 [14.7;24.3]	25.8 [23.1;28.8]
Wheezing			
Sub-Continental	10.1 [9.0;12.2]	11.1 [9.2;12.4]	12.8 [12.0;14.0]
Mediterranean	NA†	14.3 [11.8;16.1]	14.2 [12.2;17.8]
Overall	10.1 [9.0;12.2]	12.0 [9.2;16.1]	13.9 [12.0;17.8]
Shortness of breath			
Sub-Continental	7.7 [5.7;9.3]	5.4 [4.3;6.4]	8.5 [7.6;10.4]
Mediterranean	NA†	6.9 [6.4;8.6]	8.8 [8.0;10.6]
Overall	7.7 [5.7;9.3]	5.7 [4.3;8.6]	8.5 [7.6;10.6]
Tightness in the chest			
Sub-Continental	7.6 [6.4;10.1]	7.6 [5.9;8.0]	10.2 [7.7;10.9]
Mediterranean	NA†	8.8 [7.9;11.1]	10.3 [8.3;13.2]
Overall	7.6 [6.4;10.1]	7.8 [5.9;11.1]	10.2 [7.7;13.2]

*adjusted for gender, age, season of response, type of contact (mail/phone) and percentile rank of cumulative response.

†information not available (NA) because no center of the Mediterranean area participated in the ECRHS survey.

Table 4: Temporal changes in the prevalence* of respiratory outcomes in the four centers (Pavia, Sassari, Turin, and Verona) that participated in at least two surveys.

	1998-2000 vs 1991-1993 (ISAYA vs ECRHS)	**2007-2010 vs 1998-2000 (GEIRD vs ISAYA)**
	RR [95%CI]	**RR [95%CI]**
Current asthma	0.94 [0.79-1.13]	1.38 [1.19-1.59]**
Allergic rhinitis	1.16 [1.07-1.26]**	1.27 [1.19-1.36]**
Wheezing	1.01 [0.90-1.13]	1.18 [1.07-1.28]**
Shortness of breath	0.72 [0.62-0.84]**	1.45 [1.28-1.63]**
Tightness in the chest	0.91 [0.79-1.04]	1.26 [1.13-1.40]**

*expressed as relative risks (RRs) with the 95%CI, obtained through Poisson regression models with robust estimates of the standard errors, adjusting for gender, age, season of response, type of contact (mail/phone) and percentile rank of cumulative response.

**$p \leq 0.001$

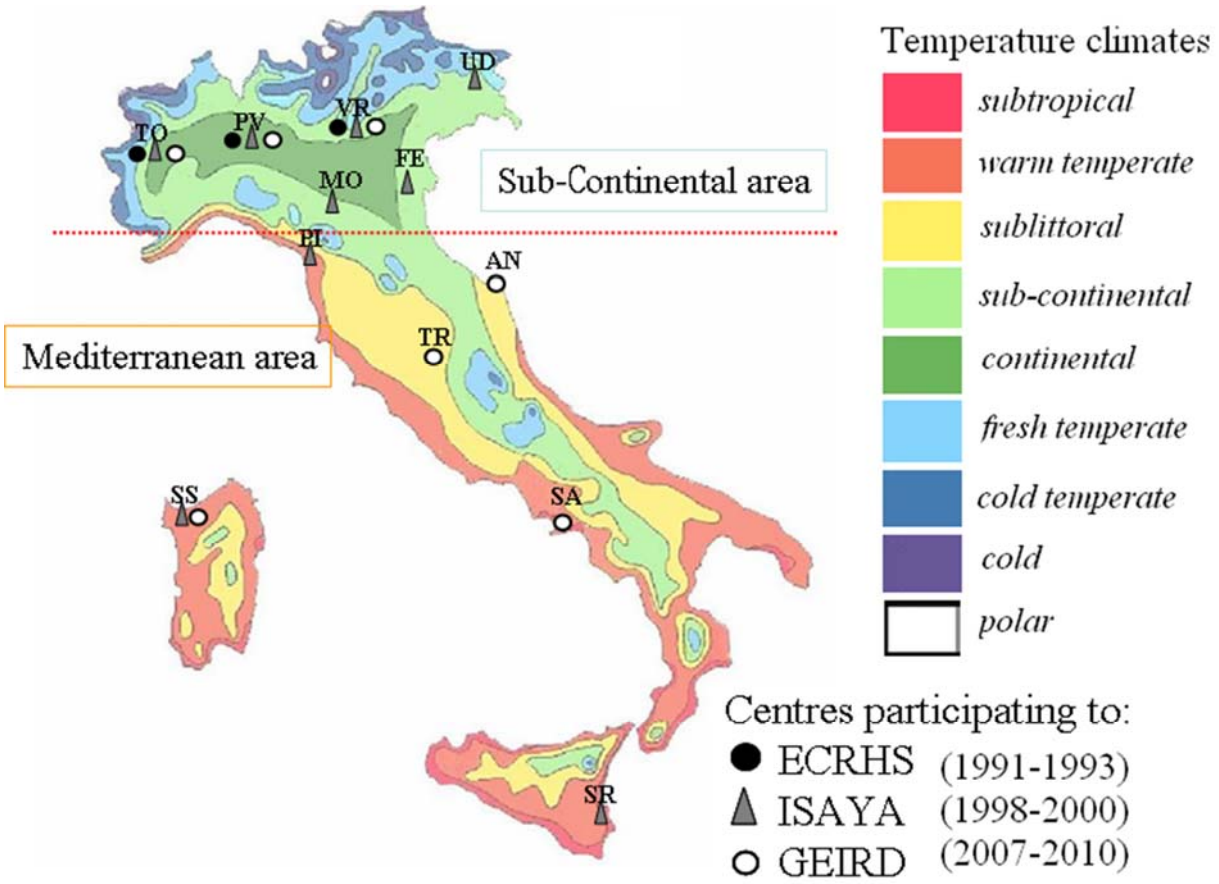
Table 5: Temporal changes in the use of asthma medications among subjects with current asthma, in the centers (Pavia, Sassari, Turin, and Verona) that participated in at least two surveys.

	1998-2000 vs 1991-1993 (ISAYA vs ECRHS)		**2007-2010 vs 1998-2000 (GEIRD vs ISAYA)**	
	RR [95% CI]	**p**	**RR [95%CI]**	**p**
Use of medicines for asthma	1.16 [0.97;1.38]	0.108	0.95 [0.85;1.07]	0.437

*expressed as relative risks (RRs) with the 95%CI, obtained through Poisson regression models with robust estimates of the standard errors, adjusting for gender, age, season of response, type of contact (mail/phone) and percentile rank of cumulative response.

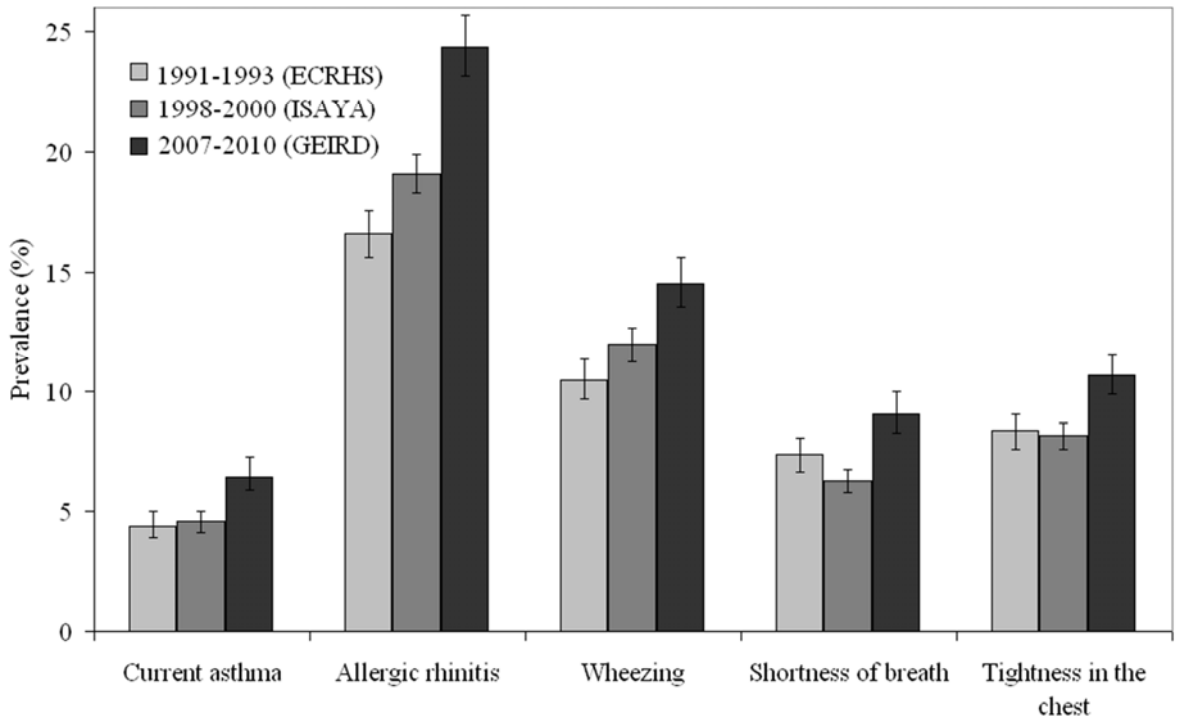
Figure legends

Figure 1: Italian centers* that participated in the ECRHS (1991-1993), ISAYA (1998-2000), and GEIRD (2007-2010) surveys, according to climatic regions.



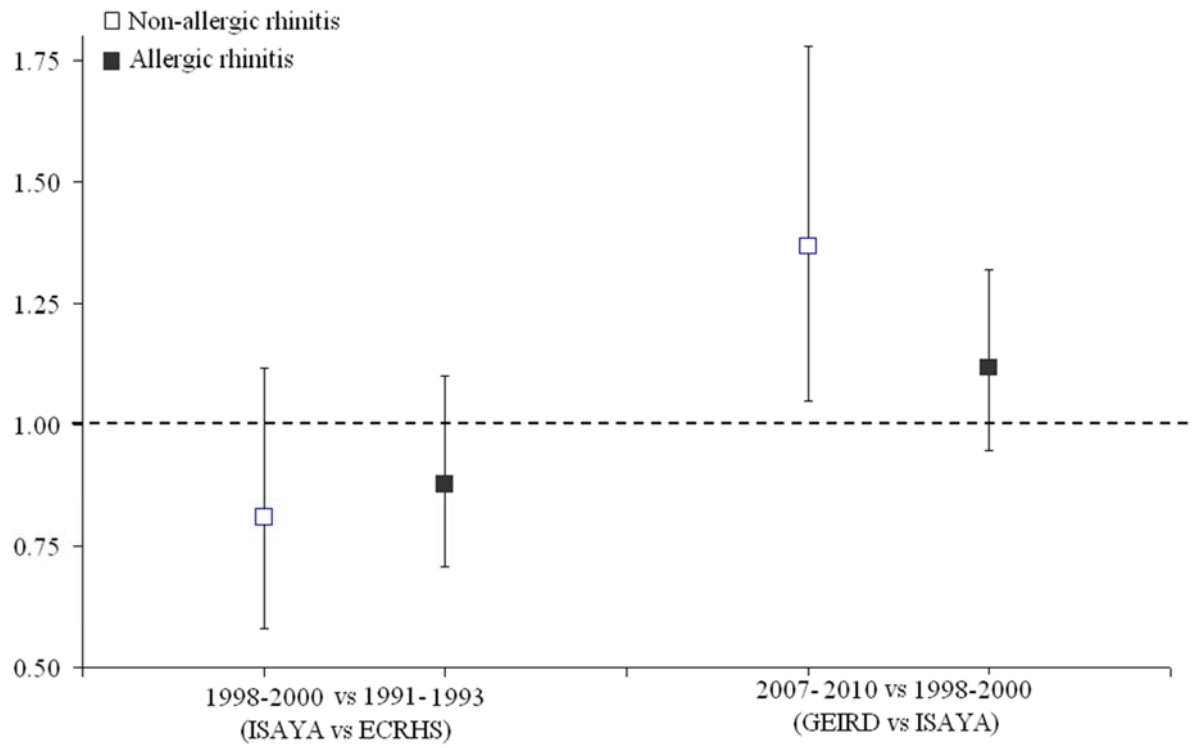
*Circles and triangles indicate: UD, Udine; VR, Verona; PV, Pavia; TO, Turin; FE, Ferrara; MO, Sassuolo; PI, Pisa; AN, Ancona; TR, Terni; SA, Salerno; SS, Sassari; SR, Siracusa.

Figure 2: Overall adjusted average prevalence* of current asthma, allergic rhinitis, wheezing, shortness of breath and tightness in the chest in the four centers (Pavia, Sassari, Turin and Verona) that participated in at least two surveys.



* adjusted for gender, age, season of response, type of contact (mail/phone) and percentile rank of cumulative response.

Figure 3: Temporal changes in the prevalence* of current asthma among subjects with and without allergic rhinitis in the four centers (Pavia, Sassari, Turin and Verona) that participated in at least two surveys.



* expressed as relative risks (RRs) with the 95%CI, obtained through Poisson regression models, adjusting for gender, age, season of response, type of contact (mail/phone) and percentile rank of cumulative response.