

The Impact of Diagnosed and Undiagnosed Current Asthma in the General Adult Population

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Key Words

Asthma · Burden of illness · Epidemiology · Undiagnosed asthmatics

Abstract

Background: Restrictive definitions of current asthma are used in epidemiological studies to achieve a highly specific classification of subjects. However, undiagnosed asthmatics should be taken into account to correctly evaluate the impact of the disease in the general population. **Methods:** In an Italian multi-centre cross-sectional survey carried out in 1998–2000, 18,647 responders (20–44 years old) to a screening questionnaire were classified as having physician-diagnosed current asthma or current respiratory symptoms. Similarities in the risk factor profile and in the socioeconomic burden were considered suggestive of undiagnosed current asthma. **Results:** In Italy, the prevalence of physician-diagnosed current asthma was 4.9% (95% CI 4.4–5.4), while that of ‘asthma attacks and/or use of anti-asthmatic drugs in the past 12 months without a diagnosis of asthma’ (ADWD) was 1.5% (95% CI 1.3–1.7). Allergic rhinitis was highly associated

with diagnosed current asthma [relative risk ratio (RRR) 12.48; 95% CI 9.12–17.07; reference category: neither asthma during lifetime nor current respiratory symptoms] and with ADWD (RRR 8.42; 95% CI 6.33–11.19). Chronic cough/phlegm was homogeneously associated with all the respiratory conditions, and the strongest relationship was with ADWD (RRR 7.79; 95% CI 4.95–12.25). Subjects with ADWD and diagnosed current asthmatics were characterised by high and homogeneous percentages of individuals who reported productivity losses (19.0 and 15.1%) and hospitalisations (9.2 and 6.2%) because of respiratory problems in the past year. **Conclusions:** The impact of current asthma seems to be largely underestimated among Italian adults, since the individuals with ADWD may be undiagnosed current asthmatics.

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Introduction

Bronchial asthma is a common chronic disease in industrialised countries, both among children [1] and young adults [2]. Moreover, the socioeconomic burden

generated by current asthma is substantial [3–5] and is largely due to poor control of symptoms in the general adult population [6].

Restrictive definitions of asthma, which take into account a physician diagnosis reported by subjects, are commonly used in epidemiological studies in order to achieve a highly specific classification of asthmatics and a non-biased evaluation of risk factors. However, the prevalence of undiagnosed asthma is presumably high in the general adult population [7]. Therefore, undiagnosed asthmatic subjects should be taken into account to correctly evaluate the impact of the disease in the general population, both in terms of prevalence and socioeconomic costs, and to clarify the differences in clinical and demographic characteristics between diagnosed and undiagnosed patients [8, 9].

The aim of this study was to evaluate the impact of diagnosed and undiagnosed current asthma in the general adult population (20–44 years old) using the data from the Italian Study on Asthma in Young Adults (ISAYA). To reach this goal, similarities in the risk factor profile and in the socioeconomic burden due to respiratory problems were considered to identify subgroups of subjects with a high likelihood of having undiagnosed current asthma.

Subjects and Methods

Study Design

ISAYA is a cross-sectional survey on respiratory health in the general Italian population, carried out between 1998 and 2000 in 9 centres located in the sub-continental (Ferrara, Pavia, Sassuolo, Turin, Udine, Verona) and Mediterranean (Pisa, Sassari, Siracusa) climatic regions [10]. Each centre selected an up-to-date sampling frame of the residents in the target area, from which a random sample of about 3,000 subjects aged 20–44 years (men/women ratio = 1) was chosen, using the same design as the European Community Respiratory Health Survey (ECRHS) – stage I [11, 12]. The protocol of the study was approved by the locally appointed ethics committees and the individual information was collected in compliance with the Italian law concerning the protection of privacy regarding individual health data.

A 2-page screening questionnaire, previously tested in a pilot study [13], was mailed up to 3 times in case of non-response and finally administered by telephone to the remaining non-responders (overall response rate 72.7%; response rate in the sub-continental and Mediterranean climatic regions 75.0 and 67.7%, respectively) [10]. The first page contains validated questions (mainly taken from the ECRHS questionnaires) on the presence of asthma (self-report of the disease during lifetime with or without a physician diagnosis, frequency of asthma attacks in the past 12 months and current use of anti-asthmatic drugs), asthma-like symptoms (wheezing, nocturnal tightness in the chest and attacks of shortness of breath at night time in the past 12 months), allergic rhinitis and chronic cough/phlegm (on most days for a minimum

of 3 months a year and for at least 2 successive years), as well as questions on smoking habits and outdoor air pollution (measured by a visual analogue scale regarding the subjective impact of air pollution) [14]. The second page of the screening questionnaire collects information on the socioeconomic burden [including (1) leisure time forgone, i.e. average number of days per month with limited – not work-related – activities, such as looking after children, housework, studying, (2) productivity losses, i.e. number of lost working days, and (3) use of hospital services, i.e. number of emergency department (ED) visits and hospital admissions] due to respiratory problems in the past 12 months. The second page is only completed by the subjects who report asthma during their lifetime or current use of anti-asthmatic drugs or respiratory symptoms (wheezing, attacks of shortness of breath at night time, attacks of asthma) in the past 12 months.

Subjects and Definitions

Out of the 18,873 responders to the ISAYA screening questionnaire, 18,647 subjects provided complete information on the presence of asthma during their lifetime (with or without a physician diagnosis), respiratory symptoms and use of anti-asthmatic drugs in the past 12 months. These individuals were classified as having:

- physician-diagnosed current asthma (i.e. self-reported asthma confirmed by a doctor during their lifetime and at least 1 respiratory symptom – wheezing, nocturnal tightness in the chest, attacks of shortness of breath at night time – or at least 1 asthma attack or use of anti-asthmatic drugs in the past 12 months);
- asthma attacks and/or use of anti-asthmatic drugs in the past 12 months without a diagnosis of asthma (ADWD);
- both nocturnal tightness in the chest and attacks of shortness of breath at night time in the past 12 months, without either a diagnosis of asthma during their lifetime or asthma attacks/use of anti-asthmatic drugs in the past year;
- nocturnal tightness in the chest or attacks of shortness of breath at night time in the past 12 months, without either a diagnosis of asthma during their lifetime or asthma attacks/use of anti-asthmatic drugs in the past year;
- only wheezing in the past 12 months;
- asthma during their lifetime (having had or not had a physician diagnosis), without either respiratory symptoms, asthma attacks or use of anti-asthmatic drugs in the past 12 months;
- neither asthma during their lifetime nor respiratory symptoms/use of anti-asthmatic drugs in the past 12 months (considered as the reference category).

Statistical Analysis

The prevalence of physician-diagnosed current asthma and the prevalence of respiratory symptoms in the past 12 months were estimated by logistic regression models with adjusted standard errors for intra-centre correlation.

The physician-diagnosed current asthmatics and the subjects who reported current respiratory conditions were compared on the basis of the pattern of risk factors using a multinomial logistic regression model and on the basis of the socioeconomic burden due to respiratory problems in the past 12 months using logistic regression models. Standard errors were adjusted for intra-centre correlation and the Bonferroni correction was used for multiple testing pertaining each risk factor and each component of the burden. In the analysis of the disease burden, the days with limit-

ed – not work-related – activities reported by full-time housepersons were considered as lost working days. Moreover, the group of subjects who reported 1 nocturnal respiratory symptom in the past 12 months (without either a diagnosis of asthma during their lifetime or asthma attacks/use of anti-asthmatic drugs in the past year) was excluded from the analysis of the burden since the 502 individuals with only nocturnal tightness in the chest did not have to complete the second page of the screening questionnaire (on leisure time forgone, productivity losses and use of hospital services) [13].

The 529 subjects who reported asthma during their lifetime without current respiratory symptoms (i.e. probable ever asthmatics) were considered in the calculation of the prevalence and association estimates, but the data pertaining to this group of individuals are not shown.

The statistical analysis was performed using STATA software, release 10 (StataCorp, College Station, Tex., USA).

Results

In Italy, the overall prevalence of current asthma and respiratory symptoms was 19.1% (95% CI 17.3–21.1) among young adults (20–44 years old). In particular, the prevalence of physician-diagnosed current asthma was 4.9% (95% CI 4.4–5.4), whereas the prevalence of current respiratory symptoms was 14.2% (95% CI 12.7–15.9) (fig. 1).

The distribution of the main characteristics of the individuals considered in the present analysis was significantly different among the study groups (table 1). Specifically, the percentage of current smokers was the highest among the subjects who reported only wheezing in the past 12 months (66.1%), and the percentage significantly decreased according to the presence of respiratory symptoms and current asthma ($p < 0.001$). The opposite was observed for the percentage of subjects with allergic rhinitis, ranging from 23.0% among the individuals with wheezing alone to 66.3% among the physician-diagnosed current asthmatics ($p < 0.001$). The percentage of subjects with coexisting chronic cough/phlegm (43.3%) was the highest among the individuals with ADWD.

In the multivariable analysis, allergic rhinitis was highly associated with physician-diagnosed current asthma [relative risk ratio (RRR) 12.48; 95% CI 9.12–17.07] and with ADWD (RRR 8.42; 95% CI 6.33–11.19) (table 2), and its relationship with these conditions was significantly stronger than that observed with wheezing alone and with nocturnal respiratory symptoms (RRRs ranging from 2.10 to 2.57) (fig. 2). Chronic cough/phlegm was significantly and homogeneously associated with all the study groups, in particular with ADWD (RRR 7.79; 95%

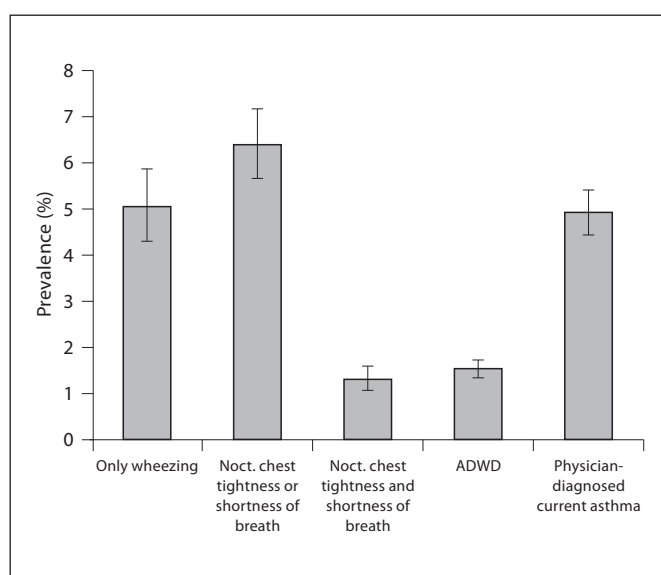


Fig. 1. Prevalence of physician-diagnosed current asthma and respiratory symptoms in the past 12 months with the 95% CI. Noct. = Nocturnal.

CI 4.95–12.25). Current smoking was highly associated with wheezing alone (RRR 4.82; 95% CI 3.99–5.82), and its relationship with this symptom was significantly stronger than that observed with each of the other respiratory conditions (RRRs ranging from 1.25 to 1.97).

The subjects who reported both nocturnal tightness in the chest and attacks of shortness of breath at night time, those with ADWD and the physician-diagnosed current asthmatics showed a heavy and homogeneous socioeconomic burden due to respiratory problems in the past 12 months (fig. 3). In particular, the percentage of subjects who reported leisure time forgone (at least 1 day per month with limited – not work-related – activities; 16.0%), productivity losses (at least 1 working day lost; 19.0%) and use of hospital services (at least 1 ED visit and/or 1 hospital admission; 9.2%) because of respiratory problems in the past 12 months was the highest among the individuals with ADWD.

When the subjects with ADWD are considered asthmatics, the prevalence of current asthma among the young Italian adults from the general population increases from 4.9 to 6.4% (95% CI 5.8–7.1), and therefore, 23.6% of the asthmatic patients are likely to be undiagnosed (fig. 4).

Table 1. Main characteristics of the subjects considered in the analysis, according to the presence of physician-diagnosed current asthma or respiratory symptoms in the past 12 months

	Neither asthma during lifetime nor respiratory symptoms/use of anti-asthmatic drugs in the past 12 months (n = 14,554)	Physician-diagnosed current asthma or respiratory symptoms in the past 12 months					p value ¹
		only wheezing (n = 937)	nocturnal chest tightness or shortness of breath (n = 1,187)	nocturnal chest tightness and shortness of breath (n = 243)	ADWD (n = 283)	physician-diagnosed current asthma (n = 914)	
Mediterranean climatic region, %	29.2	30.9	30.9	37.9	36.0	33.4	0.112
Females, %	51.2	45.4	51.6	59.3	53.4	49.9	0.001
Mean age $\pm$ SD, years	33.2 $\pm$ 6.9	33.4 $\pm$ 6.6	33.2 $\pm$ 6.9	33.8 $\pm$ 6.9	33.1 $\pm$ 6.9	32.2 $\pm$ 7.1	<0.001
Socioeconomic status, %							0.001
Managers, businessmen, entrepreneurs, clerks	56.3	56.0	56.6	50.8	53.7	54.0	
Blue-collar workers	17.4	20.2	15.3	16.1	16.6	15.8	
Unemployed persons	6.2	7.7	6.1	9.5	7.4	5.9	
Retired persons, students, housewives	20.1	16.1	22.0	23.6	22.3	24.3	
Smoking habits, %							<0.001
Non-smokers	55.1	21.3	37.3	39.2	47.9	49.5	
Past smokers	14.3	12.6	18.5	17.5	18.9	16.2	
Current smokers	30.6	66.1	44.2	43.3	33.2	34.3	
Median pollution annoyance score ²	4.5 (2.0–7.0)	4.5 (2.0–7.0)	5.0 (2.0–8.0)	6.0 (2.0–8.0)	5.0 (2.5–8.0)	5.0 (2.0–7.5)	0.004
Allergic rhinitis, %	13.1	23.0	25.4	29.3	58.7	66.3	<0.001
Chronic cough/phlegm, %	7.3	35.5	28.7	35.4	43.3	32.1	<0.001

¹ p value for comparison among the subjects with physician-diagnosed current asthma or respiratory symptoms in the past 12 months.

² Ranging from 0 = 'not disturb at all' to 10 = 'insupportable annoyance'. Figures in parentheses are interquartile ranges.

Table 2. Association between the main characteristics of the studied subjects and the presence of physician-diagnosed current asthma or respiratory symptoms in the past 12 months

	Only wheezing (n = 937)	Nocturnal chest tightness or shortness of breath (n = 1,187)	Nocturnal chest tightness and shortness of breath (n = 243)	ADWD (n = 283)	Physician-diagnosed current asthma (n = 914)
Mediterranean climatic region (vs. sub-continental)	1.13 (0.79–1.63)	1.10 (0.79–1.54)	1.49 (0.94–2.36)	1.30 (1.00–1.70)	1.19 (1.02–1.39)*
Female	0.88 (0.70–1.11)	0.99 (0.89–1.11)	1.39 (1.05–1.84)*	1.11 (0.84–1.46)	0.95 (0.85–1.06)
Age (1-year increase)	1.00 (0.99–1.01)	0.99 (0.99–1.00)	1.01 (0.98–1.04)	1.00 (0.99–1.01)	0.98 (0.97–0.99)**
Socioeconomic status					
Manager, businessman, entrepreneur, clerk	1.00	1.00	1.00	1.00	1.00
Blue-collar worker	0.90 (0.80–1.02)	0.77 (0.63–0.94)*	1.05 (0.69–1.59)	1.04 (0.70–1.54)	0.90 (0.73–1.11)
Unemployed person	1.15 (0.89–1.49)	0.93 (0.62–1.40)	1.55 (0.90–2.70)	1.06 (0.70–1.61)	0.95 (0.74–1.23)
Retired person, student, housewife	0.91 (0.80–1.04)	1.11 (0.94–1.30)	1.28 (0.90–1.82)	1.19 (0.72–1.97)	1.21 (1.02–1.45)*
Smoking habits					
Non-smoker	1.00	1.00	1.00	1.00	1.00
Past smoker	2.19 (1.49–3.22)**	1.89 (1.55–2.30)**	1.69 (1.24–2.29)**	1.48 (1.10–1.99)*	1.43 (1.15–1.77)*
Current smoker	4.82 (3.99–5.82)**	1.97 (1.52–2.55)**	1.89 (1.21–2.96)*	1.25 (1.03–1.52)*	1.43 (1.22–1.67)**
Pollution annoyance score (1-unit increase)	1.02 (1.00–1.05)	1.04 (1.02–1.06)**	1.09 (1.03–1.17)*	1.04 (0.99–1.08)	1.02 (1.00–1.04)*
Allergic rhinitis	2.10 (1.81–2.43)**	2.18 (1.85–2.56)**	2.57 (1.65–3.99)**	8.42 (6.33–11.19)**	12.48 (9.12–17.07)**
Chronic cough/phlegm	5.02 (4.18–6.02)**	4.35 (3.48–5.45)**	5.58 (4.66–6.69)**	7.79 (4.95–12.25)**	4.77 (3.84–5.91)**

Mutually adjusted RRRs are reported with the 95% CI in parentheses (reference category: neither asthma during lifetime nor respiratory symptoms/use of anti-asthmatic drugs in the past 12 months). * p < 0.05; ** p < 0.001.

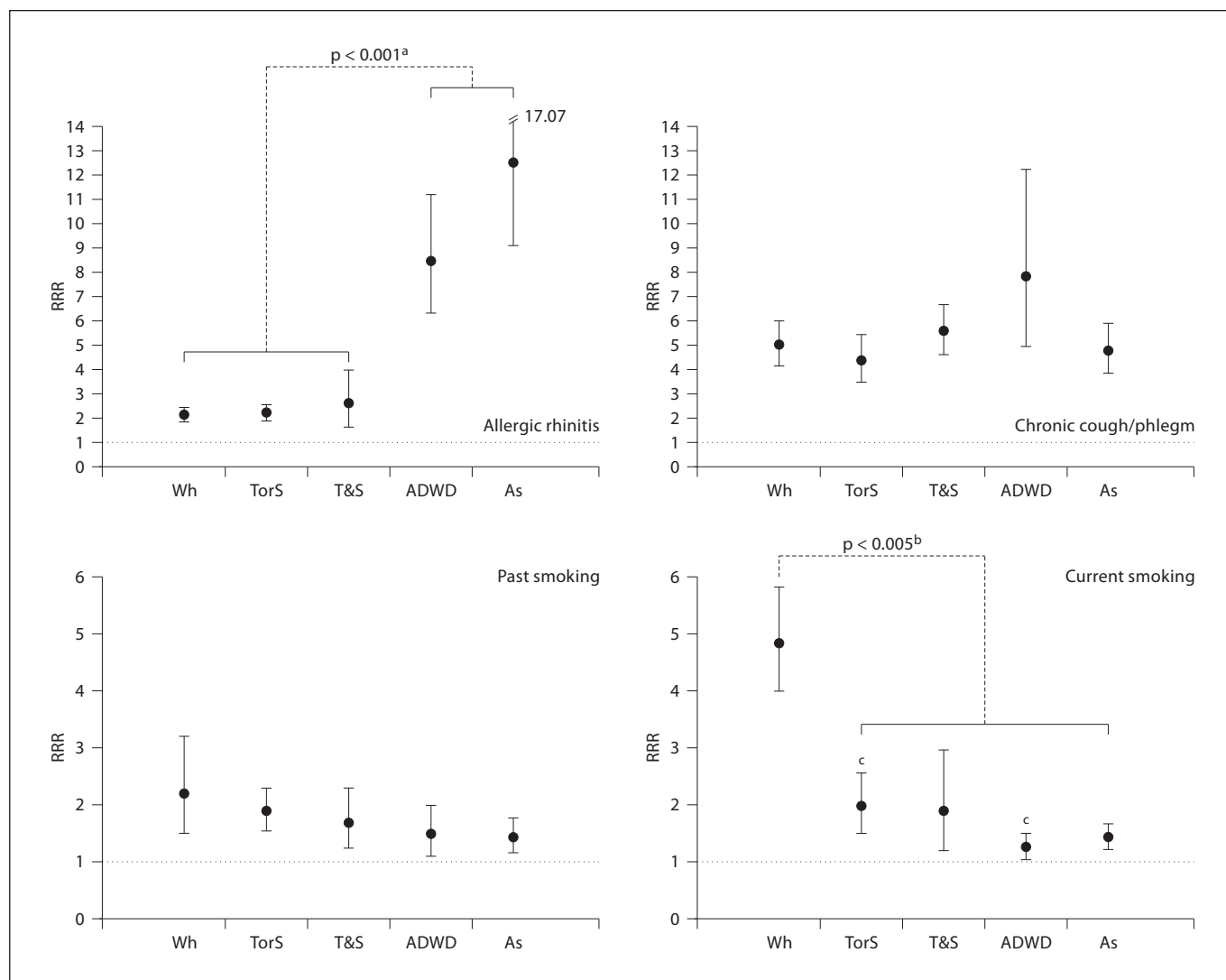


Fig. 2. Association between allergic rhinitis, chronic cough/phlegm, smoking habits and physician-diagnosed current asthma or respiratory symptoms in the past 12 months. Mutually adjusted RRRs are reported with the 95% CI. The dotted lines connect heterogeneous estimates. Wh = Only wheezing; TorS = nocturnal chest tightness or shortness of breath; T&S = nocturnal chest tightness and shortness of breath; As = physician-diagnosed current asthma. RRRs also adjusted for climatic region, gender, age, socioeconomic status and pollution annoyance score. ^a The RRRs for the association of allergic rhinitis with physician-diagnosed

current asthma and with ADWD were both significantly higher than each of the other RRRs (the Bonferroni-adjusted p value for each comparison is reported). ^b The RRR for the association of current smoking with wheezing alone was significantly higher than each of the other RRRs (the Bonferroni-adjusted p value for each comparison is reported). ^c RRR for the association of current smoking with nocturnal chest tightness or shortness of breath versus RRR for the association of current smoking with ADWD: Bonferroni-adjusted p value <0.05.

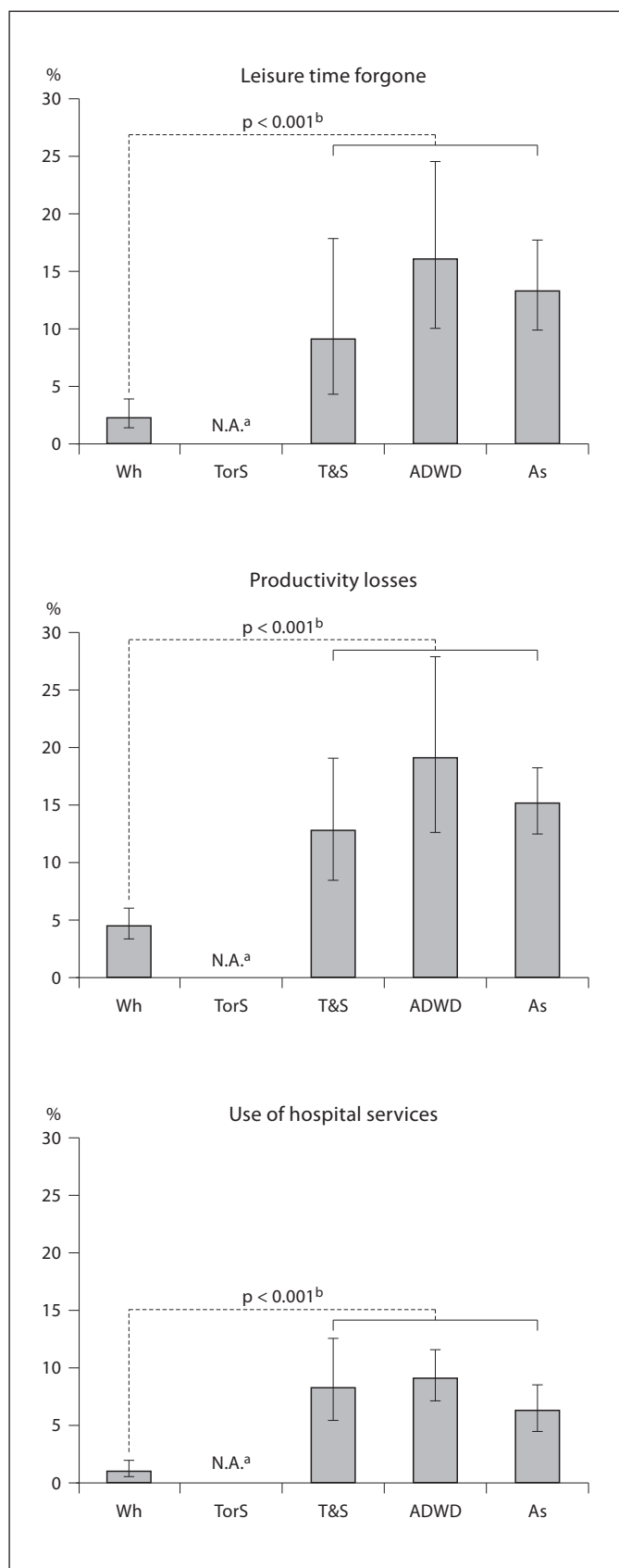
Discussion

The aim of this study was to evaluate the impact of diagnosed and undiagnosed current asthma in the general population, both in terms of prevalence and socioeconomic burden. For this purpose, a large sample of young Italian

adults (20–44 years old), randomly selected from the general population in different areas in Italy, has been used.

The main findings can be summarised as follows:

- similarities in the risk factor profile and in the socioeconomic burden suggest that the subjects who report ADWD may be undiagnosed current asthmatics;



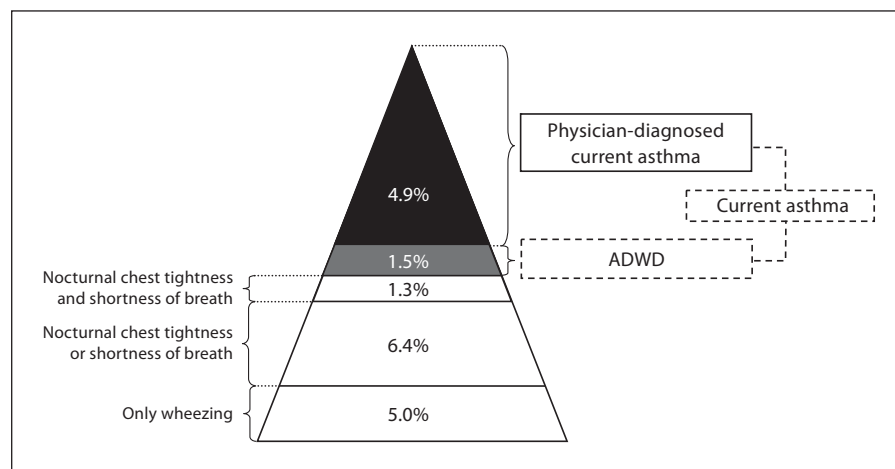
- a considerable percentage (1.5%) of young Italian adults report ADWD; accordingly, about 1 asthmatic patient out of 4 is likely to be undiagnosed;
- subjects who report both nocturnal tightness in the chest and attacks of shortness of breath at night time in the past 12 months (without either a diagnosis of asthma during their lifetime or asthma attacks/use of anti-asthmatic drugs in the past year) show a disease burden that is similar to subjects with diagnosed current asthma.

We found that the physician-diagnosed current asthmatics and the subjects with ADWD showed a stronger association with allergic rhinitis than the association observed for those who reported wheezing alone or nocturnal respiratory symptoms. Several studies have identified rhinitis as a risk factor for asthma, with the prevalence of this condition ranging from 80 to 90% in asthmatic patients [15]. These studies and others [16] have demonstrated that the coexistence of asthma and allergic rhinitis is frequent, and that allergic rhinitis usually precedes the onset of asthma. An analysis of the ECRHS data [17] has shown that in the early 1990s the prevalence of asthma was more than 6 times higher in subjects with rhinitis than in those without this disease. Moreover, the prevalence of asthma increased as subjects experienced more frequent symptoms of rhinitis. The presence of allergic rhinitis, regardless of other respiratory symptoms, has also been found to be a strong predictor of the incidence of asthma in young Italian adults [18], as reported in other longitudinal studies [19].

In our sample, current smoking was highly associated with the presence of wheezing alone, while its relationship with each of the other respiratory conditions was less strong. In most developed countries, about 1 adult asthmatic patient out of 4 is a current smoker, and asthma and active cigarette smoking interact to cause more severe

Fig. 3. Percentage of subjects who reported leisure time forgone, productivity losses or use of hospital services because of respiratory problems in the past 12 months, according to the presence of physician-diagnosed current asthma or respiratory symptoms in the past year. The dotted lines connect heterogeneous estimates. Wh = Only wheezing; TorS = nocturnal chest tightness or shortness of breath; T&S = nocturnal chest tightness and shortness of breath; As = physician-diagnosed current asthma. ^a Estimate not available for the subjects who reported only nocturnal tightness in the chest in the past 12 months. ^b The estimate for the subjects who reported wheezing alone was significantly lower than each of the other estimates (the Bonferroni-adjusted p value for each comparison is reported).

Fig. 4. Prevalence (%) of diagnosed and undiagnosed current asthma among young adults from the general population in Italy.



symptoms, accelerated lung function decline and impaired short-term therapeutic response to corticosteroids [20]. Moreover, tobacco smoking reduces the likelihood of asthma being controlled [21]. The strong association between current smoking and the presence of wheezing (without having any other respiratory condition) suggests that the individuals in our sample who reported only this symptom may have an early manifestation of chronic obstructive pulmonary disease (COPD) or belong to a group at risk of developing the disease, since cigarette smoking is still the major cause of COPD [22].

We found a strong association between chronic cough/phlegm and ADWD. In addition to chronic bronchitis and COPD, the presence of chronic cough/phlegm may both be a marker of asthma severity [23] and poor control of symptoms [24], which in turn are associated with a heavy socioeconomic burden (in particular, high costs of hospitalisations and high indirect costs due to productivity losses and leisure time forgone) [4, 6]. In fact, good control achieved by adequate therapy could prevent hospitalisation [25], and indirect costs will only be incurred when the disease has become sufficiently intrusive to interfere with a patient's lifestyle [26]. Accordingly, the present study has shown that the percentage of subjects who reported indirect costs and the percentage of subjects with hospital services utilisation because of respiratory problems in the past 12 months were highest among the individuals with ADWD, and these percentages were similar to the figures observed among diagnosed current asthmatics, which reflects both the level of disease severity and the appropriateness of patient management in Italy.

These results suggest that young adults with asthma, who are not diagnosed and, consequently, do not receive a

proper treatment, are prone to have a worsening form of respiratory inflammation due to asthma, to develop chronic cough/phlegm, and to have a heavier disease burden.

Since we found that 4.9% of the subjects in our sample aged 20–44 years were physician-diagnosed current asthmatics and 1.5% reported ADWD, the consequence is that the prevalence of current asthma seems to be largely underestimated in the general young adult population in Italy, and a considerable percentage of asthmatic patients (23.6%) is likely to be undiagnosed. In the early 1990s, asthma among young adults had already been found to be greatly under-diagnosed in Italy [7]. The proportion of undiagnosed asthmatic patients estimated in our sample, which was obtained from the data collected through a screening questionnaire, is comparable with the figure (19.2%) obtained in a population of adults (>18 years) in South Australia, using spirometric criteria to define undiagnosed asthma [9]. Furthermore, Nolte and colleagues [27] had found that the proportion of both undiagnosed and untreated asthmatic patients in an adolescent and adult population (14–44 years old) in Copenhagen was 50%. Our results suggest that the definitions of asthma commonly adopted in epidemiological studies (which take into account a physician diagnosis reported by subjects) are too restrictive when used to evaluate the impact of the disease in terms of prevalence and costs, and that greater efforts are needed to increase the likelihood of establishing an early diagnosis in order to implement the appropriate therapy and to reach the control of symptoms, as indicated by the Global Initiative for Asthma guidelines [28]. However, the clinical and socioeconomic outcomes would be improved by a comprehensive and more effective management of asthma, which not only

includes an increased diagnostic sensitivity and the use of adequate treatment but also the development of a partnership with patients, the implementation of a regular follow-up and the avoidance of risk factors [28].

Finally, 1.3% of the subjects in our sample reported both nocturnal tightness in the chest and attacks of shortness of breath at night time in the past 12 months (without either a diagnosis of asthma during their lifetime or asthma attacks/use of anti-asthmatic drugs in the past year). These individuals showed a heavy socioeconomic burden, which was not significantly different from the one observed among current asthmatics, but they did not share the pattern of risk factors with the current asthmatics (in particular, the association with allergic rhinitis was weaker than the one observed among asthmatic patients). Unfortunately, since all the information was collected through a screening questionnaire, from the clinical point of view, we could not ascertain if the subjects who reported both the nocturnal asthma-like symptoms (without either a diagnosis of asthma during their lifetime or asthma attacks/use of anti-asthmatic drugs in the past year) are really asthmatic patients or not. However, these subjects should be accurately examined in clinical practice due to the high impairment generated by symptoms.

This is one of the few population-based studies showing the extent to which asthma is undiagnosed in the general adult population. Despite the fact that the centres participating in the ISAYA were selected on a voluntary basis, their different geographical locations and the relatively high response rate obtained guarantee that the sample studied is representative of young adults in Italy.

A few caveats should be taken into account when interpreting our results. It was not possible to confirm the diagnosis of asthma through objective measures, such as lung function tests as recommended by the Global Initiative for Asthma guidelines [28], or matching the diagnosis of asthma with general practitioners' or hospital records. Furthermore, self-reporting could have influenced the accuracy of our estimates, in particular those pertaining to the socioeconomic burden [29], since all the information was collected through a self-administered postal questionnaire. However, the potential measurement error could have mainly been related to indirect costs (productivity losses and leisure time forgone), and it could have influenced our results only to a minor extent because our study did not involve elderly subjects and the recall period considered in the questionnaire was relatively short (12 months) for respiratory symptoms and for crucial events, such as ED visits and hospital admissions, which tend to be recalled with greater accuracy. More-

over, the self-report of physician-diagnosed asthma has been shown to have a great specificity [30]. Finally, the socioeconomic burden was solely attributed to asthma or asthma-like symptoms, even if we cannot exclude that the burden could have been generated by other coexisting respiratory conditions, and it was not assessed for the subjects who reported only nocturnal tightness in the chest in the past 12 months.

In conclusion, less restrictive definitions of current asthma should be adopted in epidemiological studies to correctly evaluate the prevalence and the socioeconomic burden of the disease in the general population. In Italy, the impact of current asthma among young adults seems to be largely underestimated when a physician diagnosis reported by subjects is taken into account in the definition of the disease, since about 1 asthmatic patient out of 4 is likely to be undiagnosed.

Appendix

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Acknowledgements

This work was partially supported by grants from the Italian Ministry of University and Scientific and Technological Research; GlaxoSmithKline Italia; National Health Service, AUSL Ferrara; National Health Service, AUSL Pavia; National Health Service, ASL 4 Turin; IRCCS Policlinico San Matteo; Municipality of Udine; Councillorship for Health, Modena Province; Pavia Province; Siracusa Province; Veneto Region.

References

- Pearce N, Weiland S, Keil U, Langridge P, Anderson HR, Strachan D, Bauman A, Young L, Gluyas P, Ruffin D, et al: Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: an international comparison using the ISAAC protocol. *Eur Respir J* 1993;6:1455–1461.
- European Community Respiratory Health Survey: Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9:687–695.
- Weiss KB, Sullivan SD: The health economics of asthma and rhinitis. 1. Assessing the economic impact. *J Allergy Clin Immunol* 2001;107:3–8.
- Accordini S, Bugiani M, Arossa W, Gerzeli S, Marinoni A, Olivieri M, Pirina P, Carrozzi L, Dallari R, De Togni A, de Marco R: Poor control increases the economic cost of asthma. A multicentre population-based study. *Int Arch Allergy Immunol* 2006;141:189–198.
- Braman SS: The global burden of asthma. *Chest* 2006;130(suppl 1):4S–12S.
- Accordini S, Corsico A, Cerveri I, Gislason D, Gulsvik A, Janson C, Jarvis D, Marcon A, Pin I, Vermeire P, Almar E, Bugiani M, Cazzoletti L, Duran-Tauleria E, Jögi R, Marinoni A, Martínez-Moratalla J, Leynaert B, de Marco R: The socio-economic burden of asthma is substantial in Europe. *Allergy* 2008;63:116–124.
- de Marco R, Cerveri I, Bugiani M, Ferrari M, Verlato G: An undetected burden of asthma in Italy: the relationship between clinical and epidemiological diagnosis of asthma. *Eur Respir J* 1998;11:599–605.
- Nathell L, Larsson K, Jensen I: Determinants of undiagnosed asthma. *Allergy* 2002;57:687–693.
- Adams RJ, Wilson DH, Appleton S, Taylor A, Dal Grande E, Chittleborough CR, Ruffin RE: Underdiagnosed asthma in South Australia. *Thorax* 2003;58:846–850.
- de Marco R, Poli A, Ferrari M, Accordini S, Giammanco G, Bugiani M, Villani S, Ponzio M, Bono R, Carrozzi L, Cavallini R, Cazzoletti L, Dallari R, Ginesu F, Lauriola P, Mandrioli P, Perfetti L, Pignato S, Pirina P, Struzzo P: The impact of climate and traffic-related NO₂ on the prevalence of asthma and allergic rhinitis in Italy. *Clin Exp Allergy* 2002;32:1405–1412.
- Burney PG, Luczynska C, Chinn S, Jarvis D: The European Community Respiratory Health Survey. *Eur Respir J* 1994;7:954–960.
- European Community Respiratory Health Survey – Italy: Prevalence of asthma and asthma symptoms in a general population sample from northern Italy. *European Community Respiratory Health Survey – Italy. Allergy* 1995;50:755–759.
- de Marco R, Zanolin ME, Accordini S, Signorelli D, Marinoni A, Bugiani M, Lo Cascio V, Woods R, Burney P: A new questionnaire for the repeat of the first stage of the European Community Respiratory Health Survey: a pilot study. *Eur Respir J* 1999;14:1044–1048.
- Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G, Bongard JP, Brändli O, Domenighetti G, Elsasser S, Grize L, Karrer W, Keller R, Keller-Wossidlo H, Künzli N, Martin BW, Medici TC, Perruchoud AP, Schöni MH, Tschopp JM, Villiger B, Wüthrich B, Zellweger JP, Zemp E: Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *Am J Respir Crit Care Med* 1997;155:122–129.
- Leynaert B, Neukirch F, Demoly P, Bousquet J: Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000;106(suppl 5):S201–S205.
- Bugiani M, Carosso A, Migliore E, Piccioni P, Corsico A, Olivieri M, Ferrari M, Pirina P, de Marco R: Allergic rhinitis and asthma comorbidity in a survey of young adults in Italy. *Allergy* 2005;60:165–170.
- Leynaert B, Neukirch C, Kony S, Guénégou A, Bousquet J, Aubier M, Neukirch F: Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol* 2004;113:86–93.
- de Marco R, Locatelli F, Cazzoletti L, Bugiani M, Carosso A, Marinoni A: Incidence of asthma and mortality in a cohort of young adults: a 7-year prospective study. *Respir Res* 2005;6:95.
- Guerra S, Sherrill DL, Martinez FD, Barbee RA: Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;109:419–425.
- Thomson NC, Chaudhuri R, Livingston E: Asthma and cigarette smoking. *Eur Respir J* 2004;24:822–833.
- Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC: Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003;168:1308–1311.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management and prevention of COPD. Updated 2008. www.goldcopd.com (accessed September 24, 2009).
- de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M, Carolei A, Cazzoletti L, Corsico A, Gislason D, Gulsvik A, Jögi R, Marinoni A, Martínez-Moratalla J, Pin I, Janson C: Prognostic factors of asthma severity: a 9-year international prospective cohort study. *J Allergy Clin Immunol* 2006;117:1249–1256.
- de Marco R, Bugiani M, Cazzoletti L, Carosso A, Accordini S, Buriani O, Carrozzi L, Dallari R, Giammanco G, Ginesu F, Marinoni A, Lo Cascio V, Poli A, Struzzo P, Janson C: The control of asthma in Italy. A multicentre descriptive study on young adults with doctor diagnosed current asthma. *Allergy* 2003;58:221–228.
- Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R: Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;277:887–891.
- Barnes PJ, Jonsson B, Klim JB: The costs of asthma. *Eur Respir J* 1996;9:636–642.
- Nolte H, Nepper-Christensen S, Backer V: Unawareness and undertreatment of asthma and allergic rhinitis in a general population. *Respir Med* 2006;100:354–362.
- Global Initiative for Asthma (GINA) Report: Global Strategy for Asthma Management and Prevention. Updated 2008. www.gin-asthma.com (accessed September 24, 2009).
- Evans C, Crawford B: Patient self-reports in pharmaco-economic studies. Their use and impact on study validity. *Pharmacoeconomics* 1999;15:241–256.
- Torén J, Brisman J, Järholm B: Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993;104:600–608.