Eur Respir J 1998; 11: 599–605
DOI: 10.1183/09031936.98.11030599

European Respiratory Journal
ISSN 0903 - 1936

An undetected burden of asthma in Italy: the relationship between clinical and epidemiological diagnosis of asthma

R. de Marco*, I. Cerveri+, M. Bugiani§, M. Ferrari‡, G. Verlato*

An undetected burden of asthma in Italy: the relationship between clinical and epidemiological diagnosis of asthma. R. de Marco, I. Cerveri, M. Bugiani, M. Ferrari, G. Verlato. ©ERS Journals Ltd 1998.

ABSTRACT: This study aimed to compare questions and tests used in asthma epidemiology with clinical diagnosis of current asthma and to assess the extent of undiagnosed asthma in Italy.

Thus, 811 attenders to the second stage of the European Community Respiratory Health Survey were classified by panels of respiratory physicians as current asthmatics or not.

Among those with a clinical diagnosis of asthma (n=105), 69% reported current wheezing and 68% asthma in their lifetime (ever asthma), while asthma attacks in the previous year and/or current treatment for asthma (self-reported current asthma) were mentioned by only 37%. Thirty two per cent did not mention asthma at any time, but nevertheless presented a rate of hospitalization close to that of people with self-reported current asthma.

On the other hand, almost no subjects labelled nonasthmatics by clinicians (n=706) presented self-reported current asthma (99.7%), while some reported ever asthma (5%) or current wheezing (9%).

A model simulation showed that, in its usual range (0–15%), asthma prevalence is markedly overestimated by the question on wheezing and underestimated by the questions on self-reported current asthma, with respect to clinical judgement. Prevalence estimates close to those obtained by clinical judgement were achieved by combining asthma-like symptoms in the previous year with the results of lung function and allergological tests, but especially by using the single question on ever asthma.

In conclusion, the present results suggest that the question on ever asthma gives prevalence estimates close to those obtained by clinical judgement and that asthma is greatly underdiagnosed in Italy.
Eur Respir J 1998; 11: 599–605.

Institute of *Medical Statistics and ‡Institute of Semiotics and Medical Nephrology, University of Verona, Verona, Italy. +Institute of Respiratory Diseases, University of Pavia, Pavia, Italy; §Public Health Service, USL 7, Torino, Italy.

Correspondence: R. de Marco
Cattedra di Statistica Medica
Istituto di Igiene
Universitá di Verona
Policlinico di Borgo Roma
Via delle Menegone
37134 Verona
Italy
Fax: 39 45 505357

Keywords: Asthma
epidemiology
Italy
physician diagnosis
treatment

Received: March 27 1997
Accepted after revision December 3 1997

Asthma represents a serious public health problem affecting over 100 million people worldwide [1]. In recent decades, the frequency and severity of asthma seems to have been increasing in several countries, both in children [2–4] and adults [5–7], even if the true extent of the problem cannot be fully assessed, given the extreme variability in epidemiological tools used for case identification [8–11] and the absence of a standard definition of asthma [12].

Even the most recent definition of asthma [1] cannot be fully applied to epidemiological research, due to the absence of an objective and noninvasive measurement of airflow limitation. Thus, in many epidemiological studies asthma has been assessed by short questionnaires based on symptoms alone, which may underestimate or overestimate the true prevalence of the disease. As an example, in the European Community Respiratory Health Survey (ECRHS) Stage I, aimed at estimating the worldwide prevalence of asthma, a mailed questionnaire with seven questions (screening questionnaire), was used. An indication of the prevalence of the disease was obtained through the prevalence of "self-reported current asthma", *i.e.* the self-reporting of asthma attacks in the last 12 months and/or current use of asthma drugs. The estimated prevalence ranged from 2% (Tartu, Estonia) to 12% (Melbourne, Australia) and 50% of the participating centres had a prevalence ranging 4–8% [13].

The relationship between what is measured with epidemiological instruments and what doctors call asthma is not well known. This is a crucial question for establishing the validity of epidemiological instruments and for assessing the true burden of the disease in the general population. As an attempt to deal with this problem, three experienced clinicians in each Italian ECRHS centre, were asked to independently classify subjects who attended ECRHS stage II as asthmatic or not on the basis of their "case histories", that is all the information collected in the frame of stage II. This information pertained to current and past history of asthma and respiratory symptoms, family history, exposure to potential risk factors, medical care utilization and physiopathological tests.

The aims of this paper were: 1) to compare the prevalence estimates obtained through standard questions and/or tests used in epidemiological research on asthma, with those that would have been obtained using the clinicians'

diagnosis, using a model simulation based on the sensitivity and specificity of the epidemiological items with respect to clinicians' diagnosis; and 2) to try to assess the extent of undiagnosed asthma in Italy.

Data presented in this report refer to subjects who participated in the ECRHS stage II in three Italian centres (Pavia, Turin and Verona) [14, 15].

Subjects and methods

The design of ECRHS [16, 17] involved two stages. In the first stage a screening questionnaire on respiratory symptoms was mailed to a probability sample of males and females aged 20–44 yrs resident in the three Italian centres. In the second stage a 20% random sample of responders to the mailed questionnaire was invited to the local chest clinic, in order to undergo a standardized clinical interview, allergological tests and a bronchial challenge test with methacholine. In addition, people who had reported asthma attacks, taking medicines for asthma or awakening from an attack of shortness of breath in the screening questionnaire were asked to attend stage II.

In this way, 1,850 subjects out of 6,031 who previously returned the questionnaire [14, 18] were invited to the clinical centres. Of these, 914 attended stage II (attendance rate 49%). An additional 190 subjects who declared asthma-like symptoms in the screening questionnaire underwent clinical examination.

Clinicians' diagnosis of current asthma

The full protocol that was followed to classify each subject is described elsewhere [19]. Briefly, in each centre all the data collected in stage II were independently examined by three experienced clinicians (pneumologists and/or allergologists), in order to establish whether a subject had asthma at the time of his/her visit to the clinic (clinicians' diagnosis of current asthma). Each clinician had to judge a subject on the basis of his/her response to:

1) A standardized clinical interview [17] lasting about 30 min. It comprised more than 200 questions about: current and past respiratory and allergic symptoms; family history of asthma and allergy; exposure to potential allergens and risk factors; and medication and health care utilization. Most of the questions on current symptoms and medical history were taken from the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire [20, 21].

2) Lung function and methacholine challenge test. This is described in detail in the ECRHS protocol [16–18]. Briefly, baseline forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured by means of the Biomedin spirometer (Biomedin srl, Padova, Italy) by choosing the best of five satisfactory manoeuvres. Airway reactivity was measured by administering methacholine until FEV_1 had fallen by 20% or more or until a maximum cumulative dose of 2 mg had been given. The provocative dose causing a 20% fall in FEV_1 (PD_{20}) was also computed.

3) Immunoglobulin E (IgE) and skin-prick tests [17]. Specific IgE levels were measured centrally (Pharmacia Diagnostics AB, Uppsala, Sweden) against *Dermatophagoides pteronyssinus*, timothy grass, cat, *Cladosporium herbarum* and *Parietaria judaica*. The limit of detection of the assay was 0.35 $kU \cdot L^{-1}$. Skin testing was carried out using Phazets (Pharmacia Diagnostics AB, Uppsala, Sweden). The allergens that were selected included: *D. pteronyssinus*, cat, *Alternaria alternate*, *C. herbarum*, timothy grass, birch, *P. judaica*, olive, ragweed, *D. pharinae* and *Artemisia vulgaris*. Fifteen minutes after application of allergens, wheal size was recorded as the mean of the long axis and its perpendicular.

The clinicians were instructed to make a diagnosis firstly by evaluating the clinical standardized interview (first step), secondly by adding the response to the lung function test (second step) and finally by considering the response to the allergological test (third step). At each step the introduction of a new piece of information confirmed or modified the previous diagnosis. Each clinician had to judge the response of a subject using his/her overall knowledge and experience. For each step the clinician had to adopt a four level diagnosis (asthma absent, probably absent, probably present, present). Decisions had to be made without consulting the colleagues. In the case of disagreement between clinicians on the final decision, a majority consensus was reached among the three, after discussing all the data.

For the present analysis: 1) only subjects with complete information were considered (n=811); 2) the final diagnosis was recoded as a dichotomous variable contrasting nonasthmatic (asthma absent or probably absent) with asthmatic subjects (asthma present or probably present).

The agreement among clinicians within each centre was good, with a mean Cohen Kappa coefficient of 0.71, while the agreement in the consensus diagnosis made by the panel of experts between centres was excellent, with a Cohen Kappa coefficient of 0.88 [19].

Model simulation to compare clinical and epidemiological estimates of asthma prevalence

The relationship between the estimates of asthma prevalence resulting from questions and/or tests and the estimates that would have been obtained using the clinicians' diagnosis of current asthma can be described by the following probabilistic equation:

$$P^* = P \cdot se + (1-P) \cdot (1-sp) \quad (1)$$

where: P^* = prevalence estimated through epidemiological questions and/or tests; P = prevalence estimated by clinicians (consensus diagnosis); se = sensitivity of a question and/or test against consensus diagnosis (percentage of positive answers/tests among subjects with a clinical diagnosis of current asthma); and sp = specificity of a question and/or test against consensus diagnosis (percentage of negative answers/tests among subjects without a clinical diagnosis of current asthma).

Assigning to P a range of plausible values, equation (1) returns the corresponding prevalence estimated by any epidemiological instrument, once its sensitivity and specificity with respect to the clinicians' diagnosis is known.

The percentage of false negatives and false positives on the whole population were then computed for the same range of prevalences according to the following equations:

$$\text{False negatives (\%)} = (1 - se)\cdot P\ (\%) \quad (2)$$
$$\text{False positives (\%)} = (1 - sp)\cdot(100 - P\ (\%)) \quad (3)$$

The epidemiological items considered in the present analysis were the following four questions, taken from the clinical standardized interview, alone or in combination with the results of physiological tests, according to criteria widely reported in the current literature [1, 9, 13, 15, 22]:
1) Wheeze. Have you had wheezing or whistling in your chest at any time in the last 12 months?
2) Shortness of breath. Have you been woken up by an attack of shortness of breath at any time in the last 12 months?
3) Asthma attack. Have you had an attack of asthma in the last 12 months?
4) Ever-asthma. Have you ever had asthma?
We also considered the following combinations of symptoms:
1) Self-reported current asthma. Asthma-attack and/or current use of any medicine, including inhalers, aerosols or tablets for asthma.
2) Past year symptoms. Wheeze and/or shortness of breath and/or self-reported current asthma were recorded.
We also considered the following combinations of symptoms and physiological tests:
1) Past year symptoms and bronchial hyperresponsiveness (BHR). Symptoms and BHR, defined as an initial FEV_1 less than 70% predicted or a PD_{20} less than 2 mg methacholine, occurring during the past year were recorded.
2) Past year symptoms and tests. The past year's symptoms and presence of either BHR or atopy or both were recorded. Atopy was defined as one or more wheals with a diameter Š4 mm [23] and/or a specific IgE assay Š0.7 $kU\cdot L^{-1}$.

Results

The sensitivity and specificity of the questions, or combinations of questions and tests, are reported in table 1. With

Table 1. – Sensitivity and specificity of questions, combinations of questions and combinations of questions and tests, used in epidemiological surveys on asthma

	Sensitivity %	Specificity %
Single questions		
1. Wheeze	68.6	91.2
2. Shortness of breath	32.4	93.9
3. Asthma attack	34.3	99.7
4. Ever-asthma	67.6	97.5
Combinations of questions		
5. Self-reported current asthma	37.1	99.7
6. Past year symptoms	82.9	86.7
Combinations of questions and tests		
7. Past year symptoms and BHR	48.6	98.6
8. Past year symptoms and either BHR or atopy	71.4	95.2

Self-reported current asthma: recent asthma attack or current use of asthma medicines. Past year symptoms: at least one symptom (wheeze or breath shortness or asthma attacks or medicines for asthma) in the last 12 months; Bronchial hyperresponsiveness (BHR) was defined as a provocative dose of methacholine <7.8 µmol or forced expiratory volume in one second <70% predicted; Atopy: positive skin prick test and/or positive specific immunoglobulin E assay.

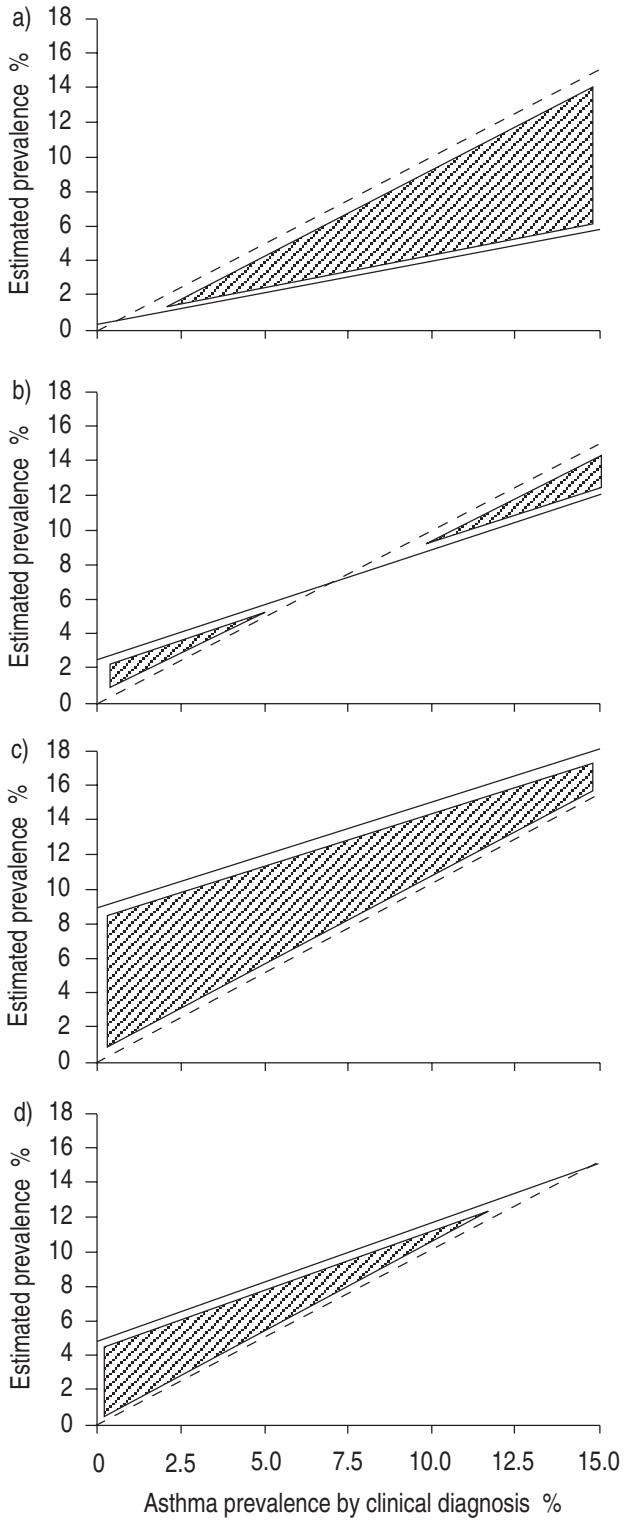

Fig. 1. – Estimates of asthma prevalence yielded by different methods when true prevalence ranges 0–15%. The estimates were computed through a model simulation, taking into account sensitivity and specificity with respect to clinical diagnosis. a) self-reported current asthma (self-reported asthma attack in the previous 12 months or current use of asthma drugs); b) ever asthma (asthma attacks in the lifetime); c) wheeze (self-reported wheezing in the previous 12 months); d) past year symptoms and tests (association of past year symptoms (wheeze or breath shortness or asthma attacks or medicines for asthma in the last 12 months) with bronchial hyperresponsiveness and/or atopy). ——: regression line; - – - : identity line; ▨ : degree of under- or overestimation.

Table 2. – False positives and false negatives (as a percentage of the whole population) with different methods of estimating asthma prevalence, obtained through a model simulation when prevalence itself is 1, 5, 10 and 15%.

	False negatives				False positives				False positives + False negatives			
	1%	5%	10%	15%	1%	5%	10%	15%	1%	5%	10%	15%
Self-reported current asthma	0.6	3.1	6.3	9.4	0.3	0.3	0.3	0.3	0.9	3.4	6.6	9.7
Ever asthma	0.3	1.6	3.2	4.9	2.5	2.4	2.2	2.1	2.8	4.0	5.4	7.0
Wheeze	0.3	1.6	3.1	4.7	8.7	8.4	7.9	7.5	9.0	10.0	11.0	12.2
Past year symptoms and tests	0.3	1.4	2.9	4.3	4.8	4.6	4.3	4.1	5.1	6.0	7.2	8.4

False negatives (%) = (1 - sensitivity) × prevalence (%); false positives (%) = (1 - specificity) × (100 - prevalence (%)).

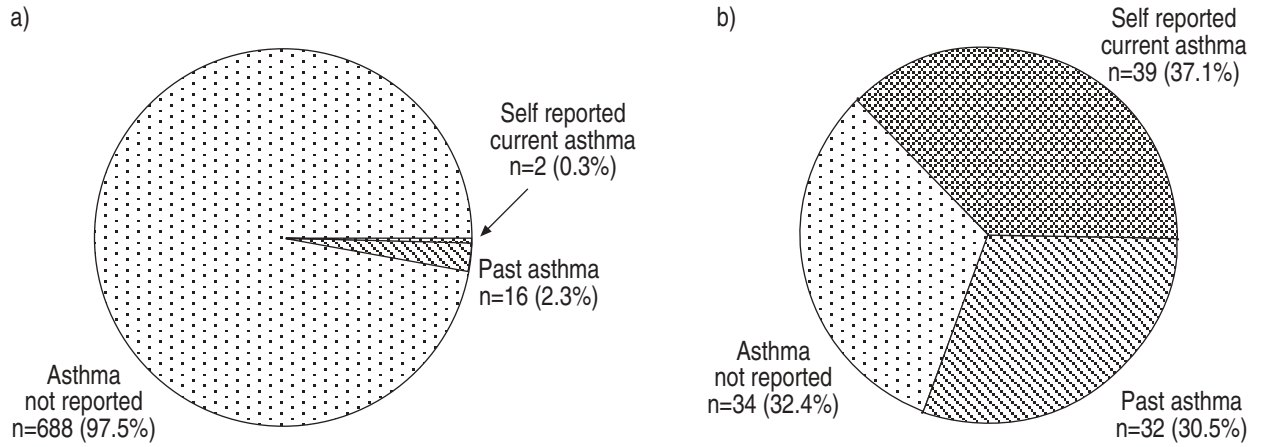

Fig. 2. – Distribution of self-reported asthma according to clinical diagnosis of current asthma: a) no diagnosis of current asthma (n=706); b) clinical diagnosis of current asthma (n=105). Self-reported current asthma: self-reported asthma attack(s) in the last 12 months or current use of asthma drugs; Past asthma: self-reported asthma attack(s) in the lifetime, but not in the last 12 months; Asthma not reported: asthma not reported by the subject.

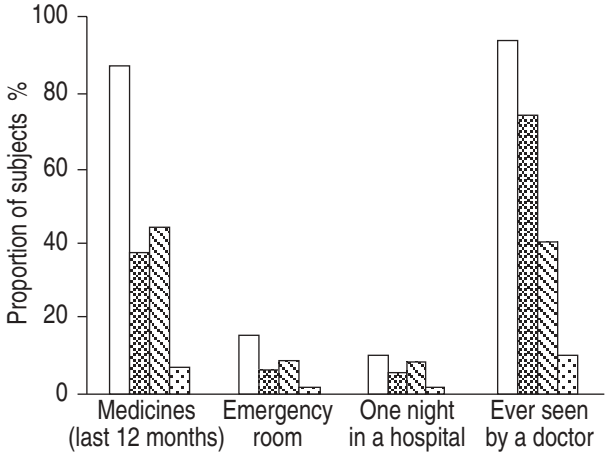

Fig. 3. – Utilization of health care resources for respiratory problems, according to clinical diagnosis of current asthma and the patient's awareness of the disease. ▭ : self-reported current asthma; ▩ : past asthma; ▨ : asthma not reported; ▦ : nonasthmatics (at consensus diagnosis). For definitions of groups see legend to figure 2. Questions on consumption of medicines for respiratory problems referred to the last 12 months, while other questions referred to the lifetime.

respect to the clinicians' diagnosis of current asthma, the specificity of the single questions pertaining to the last 12 months ranged from 91.2% to 99.7%, while the sensitivity was especially low, particularly for shortness of breath and asthma attack.

The single question maximizing the sum of sensitivity and specificity was that on asthma in the lifetime (ever-asthma), which had a sensitivity of 67.6% and a specificity of 97.5%.

The combination defined as self-reported current asthma did not improve the sensitivity, with respect to the single question on ever asthma, while the combination named past year symptoms achieved a good sensitivity (82.9%) at the expense of a substantial drop in specificity.

The use of past year symptoms associated with BHR only slightly increased the sensitivity. A noticeable improvement in sensitivity was obtained when adding the results of allergological tests (past year symptoms and tests): in this case the sensitivity was 71.4% and the specificity 95.2%.

Sensitivity and specificity of the different methods were then used in a model simulation, to compute the estimates of asthma prevalence yielded by wheeze, self reported current asthma, ever asthma and past year symptoms and tests, when prevalence ranges 0–15%, *i.e.* within the range reported in the current literature (fig. 1). With respect to the clinicians' diagnosis, asthma prevalence was dramatically underestimated by self-reported current asthma for the low sensitivity and dramatically overestimated by wheeze for the low specificity. With past year symptoms and tests, a moderate overestimation persisted, while ever-asthma gave prevalence estimates quite similar to those expected by the clinicians' diagnosis.

Thus, according to this model simulation, a high specificity is much more important than a high sensitivity in order to achieve estimates of prevalence consistent with the clinicians' diagnosis. Indeed, when specificity is lower than 95%, as it is in the case of wheeze, the number of false positives is so large that it dramatically inflates the prevalence estimates.

These mechanisms are further elucidated in table 2, showing the percentage of false positives, false negatives and

the overall misclassification rate, computed by model simulation. It can be appreciated that the underestimation of asthma prevalence with self-reported current asthma is due to an excess of false negatives with respect to false positives. On the other hand, the large overestimation observed with wheeze is due to a large excess of false positives as compared to false negatives. With ever asthma the number of false positives is approximately balanced by the number of false negatives, so that the estimation of prevalence is quite similar to that expected by clinicians' diagnosis and the overall misclassification rate is minimal, when the prevalence is greater than 4–5%.

Figure 2 illustrates the distribution of self-reported asthma according to the consensus diagnosis. Only 37.1% of the subjects with diagnosed current asthma reported an attack of asthma in the last 12 months, 30.5% reported asthma in the lifetime, but not in the previous year (past asthma) and 32.4% did not mention asthma at all during the clinical interview.

As shown in figure 3, among subjects with current asthma diagnosed by clinicians, subjects reporting only a past history of asthma or being completely unaware of having asthma, consumed less asthma drugs and consulted the physician for respiratory problems less frequently than those reporting current asthma in the clinical interview ($p<0.001$). However, all three groups of diagnosed asthmatics had very similar rates of hospitalization for respiratory problems.

It is also worth noting that more than 40% (44 out of 105) of subjects with a clinical diagnosis of current asthma did not use any medicine to help breathing in the last 12 months and about 30% (30 out of 105) reported never having been seen by a doctor for respiratory problems.

Discussion

As a universally accepted and "objective" definition of asthma does not exist, it seems reasonable to take the judgement of professional doctors [8] as a reference to evaluate the performance of questions and tests generally used in asthma epidemiology. As far as we know, this is one of the first attempts to compare questions and tests used in epidemiology with a clinical diagnosis of asthma [24], rather than against BHR [20, 25, 26] or different questionnaires [27, 28].

The main findings of the present paper are: 1) in Italy the questions that are usually employed in asthma surveys to estimate asthma prevalence present a high specificity but a very low sensitivity when confronted with clinical judgement; 2) as a consequence, in Italy asthma prevalence is probably greatly underestimated, with a true prevalence of about 10% according to a model simulation; 3) about one third of subjects diagnosed by clinicians as current asthmatic are unaware of the disease.

Indeed in the present study, when the clinical judgement was used as reference, the questions on shortness of breath, asthma attack, and asthma attack or asthma drugs in the last 12 months presented a good specificity (Š94%), but a very low sensitivity (ð37%). The question on wheezing showed the highest sensitivity (68.6%) but the lowest specificity (91.6%) while the single question minimizing the overall misclassification rate was ever asthma.

A definition of asthma, based on asthma-like symptoms within the past year associated with airway hyperresponsiveness, has been proposed as one of the most useful for epidemiological purposes [1, 9]. However, in the present analysis, this definition showed a high specificity (98.6%) but a very low sensitivity (48.6%), in agreement with other authors [24].

The model simulation pointed out (fig. 1) that for the question on ever asthma sensitivity and specificity are so well balanced as to result in prevalence estimates quite similar to those that would have been obtained by clinical judgement. On the contrary, when the prevalence of asthma is assessed through questions related to the presence of an asthma attack in the last 12 months or current use of asthma drugs (self-reported current asthma) the extent of the disease is dramatically underestimated with respect to the clinicians' diagnosis. For example, in the three Italian centres participating in ECRHS, the prevalence of "current asthma" assessed by a self-administered questionnaire was 3.3% in Pavia, 4.5% in Turin and 4.2% in Verona [13–15]. When these figures were corrected for the sensitivity and specificity of self-reported current asthma with respect to the consensus diagnosis, the resulting estimates of asthma prevalence were more than doubled: 8.2%, 11.4% and 10.6%, respectively.

Lastly, our data show that, when the expert clinicians' judgement is used to label asthmatics, 32.4% of them are not aware of having asthma (they did not mention asthma attack or ever asthma). As the individuals awareness of the disease depends, to a large extent, upon a previous diagnosis made by general practitioners or by some other health services, this result suggests that in Italy one third of subjects labelled as asthmatics by specialists do go undiagnosed by primary health care, in agreement with other international studies [29, 30].

It could be argued that the underestimation of asthma prevalence with epidemiological tools, with respect to clinical judgement, simply reflects the tendency of experienced clinicians to label as asthma minor and otherwise negligible respiratory symptoms [3, 31]. However the frequency of hospitalization for breathing problems is quite similar in subjects with diagnosed current asthma, whether reporting current asthma or not (fig. 3). These observations suggest that, when asthma is assessed with very strict definitions, a large part of the true burden of the disease could be missed.

An interesting finding of the present study was that more than 40% of subjects with diagnosed current asthma did not receive any treatment in the previous year. Similar or even higher percentages of undertreatment were recently reported in northern Europe [32, 33] and in Australia [34]. It should be stressed that undertreatment of asthma can have many deleterious consequences, such as an increase in the rate of hospitalization [35–38].

Some caveats should be considered in the interpretation of these results. In particular, the sensitivity and specificity of the questions considered in this analysis was computed against the clinical judgement based on a free evaluation of all the information collected in ECRHS stage II, including the five questions themselves. Thus, it is not possible to rule out a bias arising from lack of independence between the clinicians' diagnosis of current asthma and the five questions. However, since the clinical interview comprised more than 200 items, the five questions were only a very small part of the whole information considered, which also comprised physiopathological responses.

For this reason, the bias of lack of independence should have been of minor importance. Furthermore, to label a subject, we used the consensus diagnosis, that is the clinical judgement expressed independently by three experienced clinicians. This enhances the independence of the final decision upon the five questions studied.

An additional problem in the clinicians' diagnosis of current asthma was that there were no specific decision rules for combining the available information into a clinical diagnosis. This was done because: 1) any decision rule for asthma diagnosis would have been highly questionable, given the current state of the art; and 2) we wanted to compare the epidemiological questions and/or tests with a reference as similar as possible to the actual clinical practice of diagnosing asthma.

Furthermore, the agreement among experts within centres in labelling subjects was good, and the agreement in consensus diagnosis between centres was excellent, pointing out that its reliability and repeatability are very high. In other words, different expert teams label subjects in the same way.

In conclusion, our results suggest that: 1) when the clinical consensus diagnosis is used to evaluate the performance of epidemiological instruments, the question on ever asthma gives the most reliable prevalence estimates, while the use of questions related to asthma attacks in the last 12 months or current use of asthma drugs dramatically underestimates the true prevalence of the disease; and 2) when the clinical consensus diagnosis is used to identify true asthma cases, asthma is underdiagnosed and undertreated in Italy. About one third of true asthma patients are not diagnosed by primary health care services and more than 40% of cases are completely untreated.

The consensus diagnosis derived from only a sample of Italian clinicians was used for the present paper; as a consequence, the possibility of generalizing from our conclusions should be verified.

References

1. National Heart Lung and Blood Institute, National Institute of Health. Global initiative for asthma - Global strategy for asthma management and prevention - NHLBI/ WHO workshop report (March 1993), 1995. Publication No. 95–3659.
2. Aberg N, Hesselmar B, Aberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995; 25: 815–819.
3. Rona RJ, Chinn S, Burney PGJ. Trends in the prevalence of asthma in Scottish and English primary school children 1982–92. *Thorax* 1995; 50: 992–993.
4. Skjonsberg OH, Clenchaas J, Leegaard J, *et al.* Prevalence of bronchial asthma in schoolchildren in Oslo, Norway - Comparison of data obtained in 1993 and 1981. *Allergy* 1995; 50: 806–810.
5. Bruce IN, Harland RW, McBride NA, MacMahon J. Trends in the prevalence of asthma and dyspnoea in first year university students, 1972-89. *Q J Med* 1993; 86: 425–430.
6. Kivity S, Shochat Z, Bressler R, Wiener M, Lerman Y. The characteristics of bronchial asthma among a young adult population. *Chest* 1995; 108: 24–27.
7. Tirimanna PRS, Vanschayck CP, Denotter JJ, *et al.* Prevalence of asthma and COPD in general practice in 1992 - Has it changed since 1977? *Br J Gen Pract* 1996; 46: 277–281.
8. Burr ML. Diagnosing asthma by questionnaire in epidemiological surveys (editorial). *Clin Exp Allergy* 1992; 22: 509–510.
9. Toelle BG, Peat JK, Mellis CM, Salome CM, Woolcock AJ. Toward a definition of asthma for epidemiology. *Am Rev Respir Dis* 1992; 146: 633–637.
10. Toren K, Brisman J, Jarvohlm B. Asthma and asthma-like symptoms in adults assessed by questionnaires: a literature review. *Chest* 1993; 104: 600–608.
11. Shaw R, Woodman K, Ayson M, *et al.* Measuring the prevalence of bronchial hyperresponsiveness in children. *Int J Epidemiol* 1995; 24: 597–602.
12. Dodge RB, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980; 122: 57–75.
13. 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.
14. de Marco R, Verlato G, Zanolin E, Bugiani M, Drane JW. Nonresponse bias in EC Respiratory Health Survey in Italy. *Eur Respir J* 1994; 7: 2139–2145.
15. European Community Respiratory Health Survey - Italy. Prevalence of asthma and asthma symptoms in a general population sample from northern Italy. *Allergy* 1995; 50: 755–759.
16. Burney PGJ, Luczynska C, Chinn S, Jarvis D, for the European Community Respiratory Health Survey. The European Community Respiratory Health Survey. *Eur Respir J* 1994; 7: 954–960.
17. The European Community Respiratory Health Survey. "Medicine and Health", European Commission, Directorate-General XIII, Office for Official Publications, L-2920 Luxembourg, 1994.
18. Verlato G, Cerveri I, Villani A, *et al.* Evaluation of methacholine dose-response curves by linear and exponential mathematical models: goodness-of-fit and validity of extrapolation. *Eur Respir J* 1996; 9: 506–511.
19. Cerveri I, de Marco R, Bugiani M, *et al.* Can clinical judgement be a gold standard for identifying bronchial asthma in epidemiological studies? Interobserver agreement and contribution of specific diagnostic procedures. *Monaldi Arch Chest Dis* 1998; (in press).
20. Burney PGJ, Laitinen LA, Perdrizet S, *et al.* Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J* 1989; 2: 940–945.
21. Abramson MJ, Hensley MJ, Saunders MA, Wlodarczyk JH. Evaluation of a new questionnaire. *J Asthma* 1991; 28: 129–139.
22. Viegi G, Paoletti P, Prediletto R, *et al.* Prevalence of respiratory symptoms in an unpolluted area of Northern Italy. *Eur Respir J* 1988; 1: 311–318.
23. Pepys J. Atopy: a study in definition (editorial). *Allergy* 1994; 49: 397–399.
24. Jenkins MA, Clarke JR, Carlin JB, *et al.* Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996; 25: 609–616.
25. Shaw RA, Crane J, Pearce CD, *et al.* Comparison of a video questionnaire with IUATLD written questionnaire for measuring asthma prevalence. *Clin Exp Allergy* 1992; 22: 561–568.
26. Venables KM, Farrer N, Sharp L, Graneek BJ, Newman Taylor AJ. Respiratory symptoms questionnaires for asthma epidemiology. Validity and reproducibility. *Thorax* 1993; 48: 214–219.

27. Lebowitz MD, Burrows B. Comparison of questionnaires: the BMRC and NHLI respiratory questionnaires and a new self completion questionnaire. *Am Rev Respir Dis* 1976; 113: 627–635.
28. Samet JM, Speizer FE, Gaensler EA. Questionnaire reliability and validity in asbestos exposed workers. *Bull Eur Physiopathol Respir* 1978; 14: 177–188.
29. Frank P, Ferry S, Moorhead T, Hannaford P. Use of a postal questionnaire to estimate the likely under-diagnosis of asthma-like illness in adults. *Br J Gen Pract* 1996; 46: 295–297.
30. Nish WA, Schwietz LA. Underdiagnosis of asthma in young adults presenting for USAF basic training. *Ann Allergy* 1992; 69: 239–242.
31. Barsky AJ, Borus JF. Somatization and medicalization in the era of managed care. *JAMA* 1995; 274: 1931–1934.
32. Larsson L, Boethius G. Differences in utilization of asthma drugs between two neighbouring Swedish provinces - Relation to treatment in individuals with airway disease. *J Intern Med* 1995; 238: 307–316.
33. Renwick DS, Connolly MJ. Prevalence and treatment of chronic airways obstruction in adults over the age of 45. *Thorax* 1996; 51: 164–168.
34. Bauman A, Mitchell CA, Henry RL, *et al.* Asthma morbidity in Australia: an epidemiological study. *Med J Aust* 1992; 156: 827–831.
35. Hartert TV, Windom HH, Peebles RS, Freidhoff LR, Togias A. Inadequate outpatient medical therapy for patients with asthma admitted to two urban hospitals. *Am J Med* 1996; 100: 386–394.
36. Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. *N Engl J Med* 1991; 324: 285–288.
37. Stempel DA, Hedblom EC, Durcaninrobbins JF, Sturm LL. Use of a pharmacy and medical claims database to document cost centers for 1993 annual asthma expenditures. *Arch Family Med* 1996; 5: 36–40.
38. Wennergren G, Kristjansson S, Strannegard IL. Decrease in hospitalization for treatment of childhood asthma with increased use of anti-inflammatory treatment, despite an increase in the prevalence of asthma. *J Allergy Clin Immunol* 1996; 97: 742–748.