

Incidence and remission of asthma: A retrospective study on the natural history of asthma in Italy

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Background: The knowledge of the natural history of asthma from birth to adulthood could provide important clues for its cause and for the understanding of epidemiologic findings.

Objective: This study is aimed at assessing the incidence and remission of asthma from birth to the age of 44 years by using data from 18,873 subjects involved in a large, nationally representative, cross-sectional study carried out in Italy from 1998 through 2000.

Methods: The onset of asthma was defined as the age at the first attack, and remission was considered present when a subject was neither under treatment nor had experienced an asthma attack in the last 24 months. Person-years and survival techniques were used for the analysis.

Results: The average annual incidence rate for the 1953 to 2000 period was 2.56/1000 persons per year. Incidence peaked in boys less than 10 years of age (4.38/1000 persons per year) and in women 30 years of age or older (3.1/1000 persons per year) and showed a generational increase (incident rate ratio = 2.63 and 95% CI = 2.20-3.12 for 1974-1979 vs 1953-1958 birth cohort). The overall remission rate was 45.8% (41.6% in women and 49.5% in men, $P < .001$). Asthmatic patients in remission had an earlier age at onset (7.8 vs 15.9 years, $P < .001$) and a shorter duration of the disease (5.6 vs 16.1 years, $P < .001$) than patients with current asthma. The probability of remission was strongly ($P < .001$) and inversely related to the age at onset (62.8% and 15.0% in the <10- and ≥ 20 -years age-at-onset groups, respectively).

Conclusion: With respect to its natural history, asthma pre-

sents 2 different forms: early-onset asthma, which occurs early in childhood, affects mainly boys, and has a good prognosis, and late-onset asthma, which generally occurs during or after puberty, mainly affects women, and has a poor prognosis. The minority of patients with early-onset asthma who do not remit represents more than 35% of patients with current asthma in the general young adult population. (*J Allergy Clin Immunol* 2002;110:228-35.)

Key words: Asthma incidence, asthma remission, persistence of asthma

Despite substantial and successful efforts to standardize the methods used in asthma epidemiology, the results of the epidemiologic research are, in many aspects, conflicting, particularly concerning the major risk factors for asthma, such as exposure to microbial infections in childhood (hygiene hypothesis),¹ exposure to active smoking, or exposure to gas cooking.²

One of the main reasons is that almost all epidemiologic studies on asthma rely on prevalence,^{3,4} which depends on the incidence of the disease, the persistence of the disease, or both.

In general, the factors associated with incidence are different from those associated with persistence. As a consequence, the standardization of methods of case identification, which do not distinguish between relatively recent and long-term persistent cases of asthma, does not guarantee that the resulting prevalent cases are a homogeneous group, sharing the same risk factors. There is a need to have a deeper insight into the natural history of asthma to fully understand the existing epidemiologic findings.

The few available studies⁴⁻⁶ that used different case definitions and ascertainment methods estimated the incidence to be between 0.5 and 5/1000 persons per year. The occurrence of asthma, which peaks in childhood,⁷ seems to have increased in the last generations^{6,8} and seems to show a different age pattern according to sex.⁹ There are even fewer studies on remission; in childhood the rate of remission seems to be about 50%,¹⁰⁻¹² and the rate is very low in adults.¹³

In this article we describe the pattern of the incidence, persistence, and remission of asthma, from birth to the age of 44 years during the period between 1953 and 2000, in a large, nationally representative sample of young Italian adults who took part in the multicenter Italian Study on Asthma in Young Adults.

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METHODS

Study design

The Italian Study on Asthma in Young Adults is a multicenter, cross-sectional survey on the young general adult population specifically aimed at assessing the prevalence and current management of asthma in Italy.

The survey was carried out between 1998 and 2000 in 9 Italian centers belonging to 2 different climatic regions: subcontinental (Northern Italy) and Mediterranean (Central/Southern Italy). Each center identified an up-to-date sampling frame of the residents of the target area, from which a random sample of about 3000 persons aged 20 to 44 years (male/female ratio = 1:1) was selected with the same design used in the European Community Respiratory Health Survey stage 1.¹⁴ A 2-page screening questionnaire¹⁵ enquiring about respiratory symptoms, past and present history of asthma, and use of asthma drugs was sent by post to each subject up to 3 times in the case of nonresponse. A telephone interview was administered to the remaining nonresponders.

Data management and statistical analysis

The presence of lifetime asthma and age at onset of asthma were identified on the basis of the answers the subjects gave to the following questions:

1. Have you ever had asthma?
2. How old were you when you had your first attack of asthma?

The 10-year reproducibility of the previous questions assessed in a preliminary analysis of the data obtained in the ongoing European Community Respiratory Health Survey (ECRHS II) in Italy proved very good, with the Cohen κ coefficient being 0.83 and 0.75, respectively (Locatelli F et al, personal communication).

A subject was considered in remission if he or she had not had an asthma attack during the 2 years before the interview and had not used asthma drugs in the last 12 months. The duration of the disease (time since onset) was computed as the time (in years) between the first and the last asthma attack for subjects in remission and as the time between the first asthma attack and the age at the interview for patients with current asthma. Centers were categorized in 2 climatic regions according to the area of residence.

Analysis of lifetime asthma incidence

Incidence rates were computed by dividing the number of events (asthma onset) by the total number of person-years at risk.⁹ Person-years is defined as the time a subject is at risk for development of asthma (ie, the time from birth to the age of the first attack of asthma if the subject had asthma or the time from birth until the date of interview if he or she did not have asthma). Events and person-years were computed by 5-year age groups.

Because incidence rates were computed with retrospective data, recall bias could have differentially influenced our estimate; the reporting of an event in the past could depend on the time elapsed since the event (recall lag), which is a function of the age at interview or the year of birth. For this reason, each subject was classified in one of 5 birth cohorts (1953-1958, 1959-1963, 1964-1968, 1969-1973, and 1974-1979), for each of which it was reasonable to assume a homogeneous effect of the recall.¹⁶ All analyses and estimates were then adjusted for the cohort effect, which is a variable summarizing both the effect of the generation and that of the recall bias.

A further potential source of bias is the selection bias¹⁷ caused by the fact that centers had different final response rates obtained through different percentages of telephone interviews.¹⁸ Each subject was attributed the median of the cumulative response rate of the contact to which he or she had answered (first, second, and third postal contact and telephone interview) and a dummy indicator of the type of interview (postal vs telephone) to control for this potential bias.

Finally, to obtain the estimates of the incidence of asthma and of the effects of the main determinants, controlling for potential confounding factors, we fitted a set of hierarchical Poisson models of the following form:

$$\lambda = \alpha + \sum_i \beta_i X_i + \sum_j \beta_j Y_j + \sum_{ij} \gamma_{ij} X_i Y_j,$$

where λ is the log of incidence of asthma; X_i is the set of potential confounding factors (birth cohort, cumulative response rate, and type of interview), the effects of which are estimated by β_i ; Y_j is the set of potential determinants (sex, age at onset, and climatic region), the effects of which are estimated by β_j ; and γ_{ij} is the effect of the interaction between the potential confounding factors and the determinants. When an interaction term is statistically significant for some relevant combination of X_i and Y_j , it points out that the potential confounding factor exerts a differential effect across the various strata of the determinant, so that the overall adjusted estimates are biased. For example, if the interaction between birth cohort and age at onset is statistically significant, it means that the pattern of incidence by age at onset varies according to the cohort of birth. Only the factors that significantly contributed to explain the data, tested by using the likelihood ratio test,¹⁹ were introduced in the final model.

Analysis of remission of asthma

The analysis of asthma remission was limited to subjects who had asthma during their lives. Survival analysis was applied to the data by using the presence or absence of remission as "failure" and the time since onset as time at risk. The cumulative probability of remission of asthma attacks was estimated with the Kaplan-Meier method. Parametric survival regression models were used to analyze the variation of the hazard of remission in time and to assess relevant prognostic factors (sex, age at onset, and climatic region). Among the family of parametric models²⁰ allowing the hazard to vary in time (gamma, Weibull, log-logistic, and log-normal), we chose the gamma model, which had the best result according to the Akaike Information Criterion.²¹ The goodness of fit of the final model was tested by means of Cox-Snell residual analysis²⁰ and proved to be very good.

The gamma regression model was fitted to the data, adjusting for potential confounding factors in a similar way to that used in the analysis of the incidence of asthma. The statistical analysis was performed with STATA software, release 7.0.²²

RESULTS

Asthma incidence

Of 25,969 eligible subjects in 9 centers, 18,873 filled in the questionnaire, with an overall response rate of 72.7%. All the centers but one had a response rate greater than 70%. The age and sex distribution of responders was similar to that of nonresponders. One thousand five hundred twenty-six subjects (8.1%) reported ever having had asthma during their life, of which 91.3% were given a diagnosis by a doctor, and the total person-years amounted to 589,716.

The overall crude incidence (Table I) was 2.59/1000 persons per year (2.76/1000 persons per year in men and 2.42/1000 persons per year in women), which peaked in the less than 10 years age group and increased in successive generations, ranging from 1.59/1000 persons per year in the 1953 to 1958 birth cohort to 4.73/1000 persons per year in the 1974 to 1979 birth cohort. The Mediterranean region showed a slightly greater incidence rate than the subcontinental region (2.86/1000 persons per year vs 2.48/1000 persons per year).

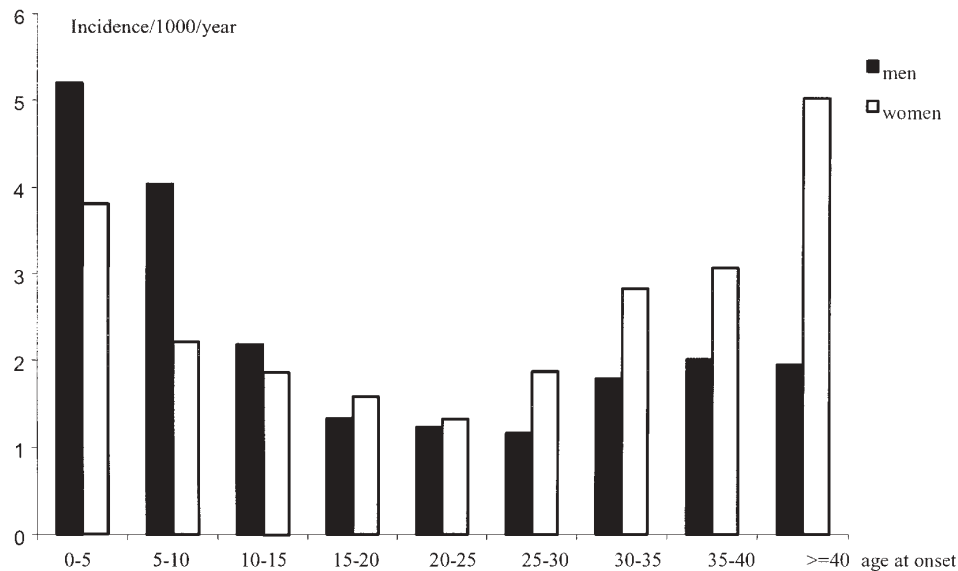


FIG 1. Adjusted age-specific incidence rates of asthma in men and women. Rates were adjusted by birth cohort, response rate, type of contact, and climatic region by using the Poisson regression model.

TABLE I. Person-years, number of subjects reporting ever having asthma, and crude incidence (95% CI) of asthma by sex, age at onset, birth cohort, and climatic region (period 1953-2000)

	Person-years	No. of cases	Incidence/1000 persons per year	95% CI
Whole sample	589,716	1526	2.59	2.46-2.72
Sex				
Men	288,405	797	2.76	2.57-2.96
Women	300,951	729	2.42	2.25-2.61
Age at onset (y)				
0-5	92,170	477	5.17	4.72-5.66
5-10	90,101	321	3.56	3.18-3.97
10-15	88,882	206	2.32	2.01-2.66
15-20	88,123	147	1.67	1.41-1.96
20-25	82,157	115	1.40	1.15-1.68
25-30	65,511	97	1.48	1.20-1.81
30-35	46,341	91	1.96	1.58-2.41
35-40	26,740	50	1.87	1.39-2.46
40-45	9,692	22	2.27	1.42-3.43
Birth cohort				
1953-1958	158,209	252	1.59	1.40-1.80
1959-1963	137,577	288	2.09	1.86-2.35
1964-1968	131,898	338	2.56	2.30-2.85
1969-1973	102,015	364	3.57	3.21-3.95
1974-1979	60,018	284	4.73	4.20-5.31
Climatic region				
Subcontinental	419,220	1038	2.48	2.33-2.63
Mediterranean	170,495	488	2.86	2.61-3.13

The results of fitting several Poisson models to the incidence data are depicted in Table II. The associations of age at onset, sex, climatic region, birth cohort, response rate, and type of interview with the incidence of asthma were statistically significant (models 1-4). Furthermore, there was a statistically significant interaction between sex and age at onset, suggesting a different pattern in the incidence of asthma between men and women. There was not a statistically significant interaction between potential confounding factors and the relevant covariates, meaning

that the pattern of incidence is constant across the strata of potential confounding factors (birth cohort, type of interview, and response rate). Adjusted estimates were obtained by using Poisson model number 4.

Adjusted incidence rates (Fig 1) show the interplay of age and sex in the occurrence of asthma. The incidence of asthma peaked in boys less than 10 years of age (4.38/1000 persons per year) and in women 30 years of age or older (3.1/1000 persons per year). The age-sex pattern of incidence rates was consistent in all the centers

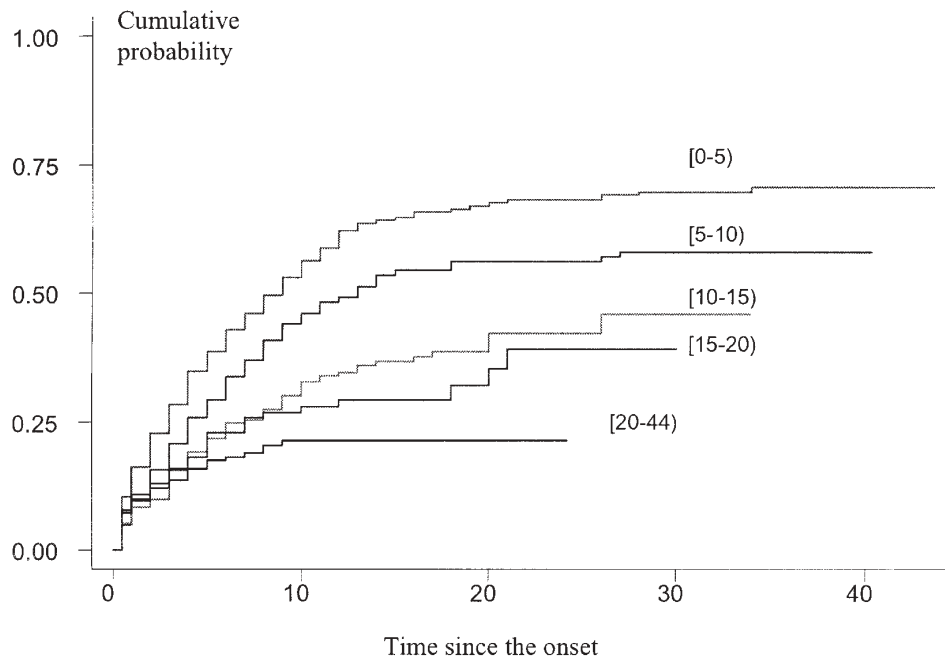


FIG 2. Kaplan-Meier cumulative probability curves of remission in different age-at-onset groups of asthmatic subjects (ie, 0-5, 5-10, 10-15, 15-20, and 20-44 years of age).

TABLE II. Results of fitting several hierarchical Poisson models

Models*	Likelihood ratio test (df)	P value
(1) Sex + onset + area†	367.5 (10)	<.001
(2) Sex + onset + area + sex × onset	51.8 (8)	<.001
(3) Sex + onset + area + sex × onset + birth	150.7 (4)	<.001
(4) Sex + onset + area + sex × onset + birth + contact + CUMRES	71.6 (2)	<.001
(5) Sex + onset + area + sex × onset + birth + contact + CUMRES + birth × sex‡	2.19 (4)	.70
(6) Sex + onset + area + sex × onset + birth + contact + CUMRES + birth × onset‡	18.1 (22)	.70

Results of fitting several hierarchical Poisson Models aimed at evaluating the effects of (1) sex, age at onset (*onset*), and climatic region (*area*); (2) interaction between sex and age at onset; (3) birth cohort (*cohort*); (4) type of interview (*contact*) and cumulative response rate (*CUMRES*); (5) interaction of sex and birth cohort (differential recall/cohort bias); and (6) interaction of age at onset and birth cohort (differential recall/cohort bias).

*No statistical significance was found in other first-order interactions not presented in the Table.

†Likelihood ratio test performed with respect to the null model.

‡Likelihood ratio test performed with respect to model 4.

when assessed with the Mantel-Haentzel test for heterogeneity (data not reported).

The asthma incidence showed a significant generational increase (Table III); persons born from 1974 to 1979 had about a 3-fold higher risk of asthma development (incidence rate ratio, 2.64 [95% CI, 2.20-3.17]) than persons born from 1953 to 1958. Furthermore, the occurrence of asthma was significantly higher in persons living in the Mediterranean region (incidence rate ratio, 1.13 [95% CI, 1.01-1.26]).

Asthma remission

Seventy-seven asthmatic subjects were excluded from the analysis because of missing data for the questions on drugs, age at the last asthma attack, or both. Six hundred sixty-three (45.8%) of 1449 asthmatic subjects remitted, and the percentage of remission was significantly higher ($P < .001$) in men (49.5%) than in women (41.6%). Sub-

jects in remission were characterized by an earlier mean age at onset (7.4 vs 15.9 years, $P < .001$) and a shorter duration (5.6 vs 16.1 years, $P < .001$) of the disease than subjects with current asthma; the last attack of asthma was on average 19 years before the interview (ranging from 25 years in the 1953-1958 birth cohort to 13 years in the 1974-1979 birth cohort).

On average, subjects with current asthma had the disease develop during or after puberty, whereas asthmatic subjects in remission had asthma in early childhood and recovered before or during puberty. This pattern was similar in both sexes (data not reported) and in all the different birth cohorts.

The probability of remission was strongly influenced by the age at onset, being particularly high in children (<10 years of age, Fig 2). The remission cumulative rates were 62.8% (95% CI, 59%-67%), 40.3% (95% CI, 32%-49%), and 15.0% (95% CI, 11%-21%), respectively, in

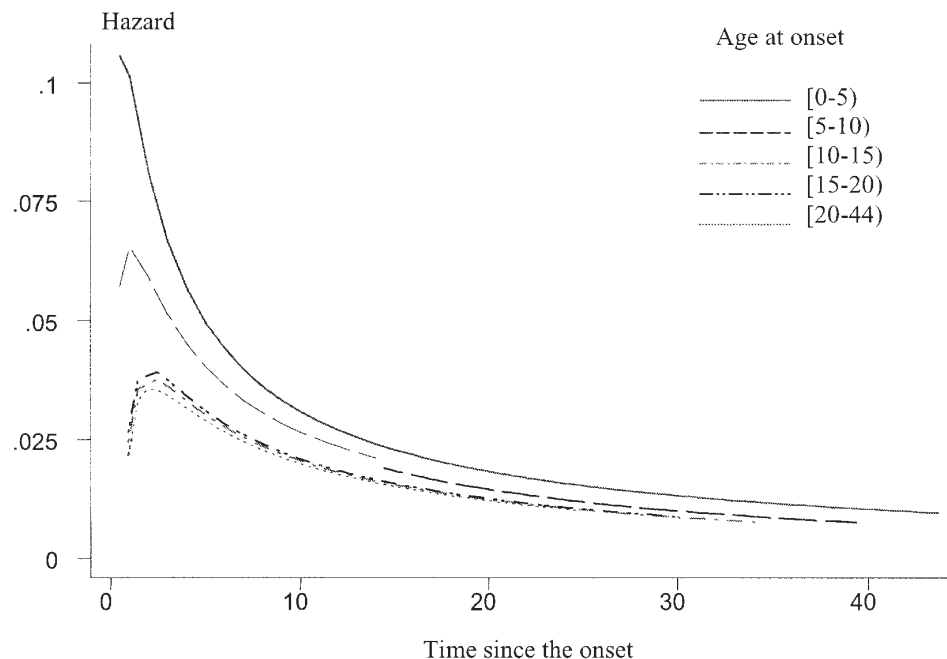


FIG 3. Hazard of remission (instantaneous probability of remission) as a function of time since onset in groups of asthmatic subjects with different ages at onset. Curves were obtained through gamma survival regression, adjusting for sex, birth cohort, climatic region, type of contact, and cumulative response rate.

TABLE III. Incidence rate ratio (95% CI) estimates for the association among birth cohort, climatic region, and risk of incidence of asthma obtained through the Poisson regression model

	IRR*	95% CI	P value
Birth cohort			
1953-1958	1		
1959-1963	1.33	1.12-1.59	.001
1964-1968	1.62	1.37-1.93	<.001
1969-1973	2.19	1.84-2.61	<.001
1974-1979	2.64	2.20-3.17	<.001
Climatic region			
Subcontinental region	1		
Mediterranean region	1.13	1.01-1.26	.04

IRR, Incidence rate ratio.

*Adjusted by age at onset, sex, onset-sex interaction, cumulative response rate, and type of interview.

the groups with ages at onset of less than 10 years, 10 to 20 years, and 20 years and older.

Furthermore, after controlling for the age at onset, the rate of remission varied dramatically with the time elapsed since the onset, as shown in Fig 3. The hazard of remission (instantaneous risk of remission) was quite high in the short term after the onset (4-7 years), and then it decreased quickly. If the remission of asthma does not occur in the first years after the onset, the disease tends to become chronic.

When adjusting for all the potential confounders (Table IV), the age at onset was the main determinant of remission, whereas the birth cohort did not influence the

probability of remission. Sex was no longer significantly associated with the probability of remission, suggesting that the lower remission rate of women with respect to men is entirely due to the fact that women are mainly affected by a late-onset asthma. Subjects living in the Mediterranean region had a lower probability of remission than subjects living in the subcontinental region.

The balance among incidence, remission, and persistence determines the distribution of the age at onset in prevalent cases. Of 786 subjects with current asthma, 35.4% (95% CI, 30%-41%) reported that asthma occurred early in childhood (<10 years of age), whereas 37% (95% CI, 31%-43%) reported late onset of the disease (≥ 20 years of age).

DISCUSSION

The main findings of the analysis of the incidence and remission of asthma in Italy are as follows:

- The average incidence rate of asthma in the 0- to 44-year age group during the period from 1953 to 2000 was 2.6/1000 persons per year, with strong variation by age, sex, and generation.
- In the presence of a generational increase, the incidence of asthma shows a constant age-specific U-shaped pattern, implying 2 different forms of the disease: early-onset asthma, mainly affecting boys (3.8/1000 persons per year in boys <15 years of age), and late-onset asthma, mainly affecting women (3.1/1000 persons per year in women ≥ 30 years of age).
- The age at onset of the disease is the main determinant of the prognosis of asthma: persons with early-onset

TABLE IV. Regression coefficient estimates, 95% CIs, and associated *P* values for sex, age at onset, birth cohort, and climatic region adjusted also for type of contact and cumulative response rate by using the gamma regression model

	Coefficient (β)*	95% CI	<i>P</i> value
Sex (women vs men)	-0.08	-0.34 to 0.14	.43
Age at onset, y (vs 0- to 5-y age class)			
5-10	0.49	0.18-0.80	<.01
10-15	0.98	0.59-1.36	<.001
15-20	0.93	0.48-1.39	<.001
20-44	1.04	0.66-1.42	<.001
Birth cohort (vs 1953-1958)			
1959-1963	-0.03	-0.44 to 0.38	.88
1964-1968	-0.11	-0.50 to 0.28	.59
1969-1973	-0.01	-0.40 to 0.38	.95
1974-1979	0.24	-0.18 to 0.66	.26
Climatic region (Mediterranean vs subcontinental)	0.34	0.08-0.60	.01

* $\beta > 0$ when a covariate decreases the risk of remission with respect to reference; $\beta < 0$ when a covariate increases the risk of remission with respect to reference.

asthma have, on average, a shorter duration of the disease and a much higher remission rate than persons with late-onset asthma (68% vs 25%). If asthma does not remit in the first years after the onset (4-7 years), it tends to become chronic.

- The minority of persons with early-onset asthma who do not recover represents approximately 35% of prevalent cases of the young adult population (20-44 year of age).

To our knowledge, this is one of the largest population-based studies on asthma, allowing the natural history of the disease to be studied retrospectively. It relies on the recall of past events of persons interviewed at one point in time. Its strength is that it gives information on incidence and remission in a wide age range from birth to adult life that would hardly have been possible to obtain by means of a longitudinal study. Its weakness is that recall bias could have influenced the recall of events experienced in the past.

In our study incidence and remission were defined with respect to the occurrence or absence of a relevant clinical event, the attack of asthma, which is a crucial experience for a patient and is less likely to be influenced by recall bias. The 10-year reproducibility of the questions used proved very good, suggesting that persons in this age group are highly reliable in recalling their history of asthma. In the analysis we adjusted for potential confounding factors, particularly those related to the time lag between the time of the interview and the time of the recalled event. Our analysis showed that the age-sex patterns of incidence were constant across groups of persons having different recall lags (age at interview/birth cohort); consequently, the incidence and remission patterns presented are not influenced by potential differences in recall among various groups of persons. Should the recall bias have exerted an effect on our results, only the absolute value of our estimates could have been influenced. Our incidence figures, mainly in the first age groups, could be slightly underestimated because of underreporting of events or because of the tendency to attribute the onset of the disease to an age closer to the

time of interview than the true age at onset (telescoping bias) by older persons.

Overall, recall bias seems to have affected our estimates only to a minor extent. In fact, the incidence of asthma in Italy has been estimated to be 2.6/1000 persons per year, which is in the middle of the range (0.5-5/1000 persons per year) reported in longitudinal studies in other countries.^{4,6} In comparison with other countries, Italy ranks about the same when using our estimated incidence or when using previously reported prevalence data.²³

Another factor potentially influencing our results is related to the validity of the diagnosis of asthma before the age of 3 years. Some authors^{24,25} reported that only about 40% of children with a diagnosis of asthma between the ages of 0 and 3 years continue to have the disease, concluding that the diagnosis of asthma in these young children is unreliable because of the very short duration of the disease. Even if we assume that the previous interpretation is true, it does not modify our main conclusion, as can be seen by the similarity of the history of incidence and remission in the 0- to 4-year and 5- to 9-year age groups. Thanks to the retrospective nature of our study, we could observe the history of incidence, persistence, and remission of asthma in a long period of life, including puberty, which seems to be a crucial time for both incidence and remission. In fact, asthmatic subjects in remission were likely to have the disease in early childhood and to recover quickly before or during puberty, whereas asthmatic subjects still having the disease in adulthood were likely to have a chronic form of the disease starting during or after puberty.

Previous studies described the history of childhood asthma,^{26,27} whereas others described that of asthma in adults,^{13,28,29} separately reporting that remission of asthma is high in children and low in adults. However, to our knowledge, such a clean division between the natural history of early- and late-onset asthma has not been observed before because of the limited age range considered in previous studies.

Another prospective study¹² reported the pattern of incidence and prognosis of wheezing illness in a younger

adult population up to 33 years of age, who had been contacted at intervals since birth. The results of this study are somewhat different because wheezing illness refers to a broader range of diseases than asthma, according to our definition. In particular, wheezing illness seems to be an intermittent disease characterized by disease-free intervals of 7 or more years between childhood and youth. In contrast, even if our results do not exclude the existence of disease-free periods, they seem to suggest that there are mainly 2 different courses of asthma that occur at different ages, have a completely different prognosis, and affect male and female subjects differently.

The interplay among incidence, remission, and persistence determines the number and the type of prevalent cases present at a certain point of time in the population. We have shown that approximately 35% of subjects with current asthma in the young adult population (20-44 years of age) are made up of the minority of subjects with early asthma who do not recover. This particular group of persons is likely to share a common set of factors (mostly unknown at present) that are responsible for the long-term persistence of the disease. This implies that every cross-sectional study on adults that does not distinguish between early and late asthma will confuse the role of the determinants involved in the 2 completely different steps of the natural history of the disease: incidence and persistence.

Our results confirm previous findings concerning the difference between men and women in the age-related pattern of incidence⁹ and the generational increase in asthma.^{8,30}

Finally, our analysis points out that subjects living in the Mediterranean region have higher incidences and lower remission rates than persons living in the subcontinental region. This result agrees with a recent finding of our group, according to which the prevalence of current asthma and asthma-like symptoms in Italy increased in the Mediterranean region,³¹ and further suggests that the observed difference in prevalence is due both to differences in exposure to risk factors and to factors related to the prognosis of asthma.

In conclusion, the main result of our retrospective analysis is the evidence that, with respect to its natural history, asthma presents 2 different forms, which we called early- and late-onset asthma. The former occurs early in childhood, affects mainly boys, and has a good prognosis; the latter generally occurs during or after puberty, affects mainly women, and has a poor prognosis. A minority of subjects with early-onset asthma, representing approximately 35% of subjects with current asthma in the young adult population, have long-term persistent asthma. When using prevalent cases in risk-factor assessment, it is necessary to distinguish between subjects with early- and late-onset asthma to avoid confusion between determinants of persistence and determinants of occurrence of asthma.

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APPENDIX

List of principal participants in the Italian Study on Asthma in Young Adults

Project leader: R. de Marco.

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Asthma, rhinitis,
other respiratory
diseases

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