Rhinitis and conjunctivitis are common diseases worldwide that are frequently associated. Nevertheless, the risk factors for rhinoconjunctivitis are not well-described and the impact of conjunctivitis on rhinitis and asthma in children remains unknown. This study explored the different risk factors and evaluated the burden of rhinoconjunctivitis among adolescents. Methods: This was a cross-sectional study conducted on a random sample of schoolchildren, aged 10-17 years, using skin prick tests and a self-administered questionnaire on respiratory health investigating the impact of rhinitis and rhinoconjunctivitis on daily activities. Results: A complete evaluation was obtained for 2,150 children. The prevalence of rhinitis alone was 18.2% and rhinitis associated with conjunctivitis was 20.5%. Rhinoconjunctivitis was more frequently associated with females, a parental history of atopy, domestic exposure to mold/dampness, passive smoke exposure, and reported truck traffic in residential streets. Moreover, rhinoconjunctivitis was associated with a higher level of allergic sensitization. The prevalence of current asthma was 1.7% in subjects without rhinitis or rhinoconjunctivitis, 5.1% in rhinitis and 10.7% in rhinoconjunctivitis. In a logistic model, rhinoconjunctivitis yielded a 2-fold risk for current asthma with respect to rhinitis. Subjects with rhinoconjunctivitis had poorer quality of life (QoL); there was an impact on daily activities in 4.6% of rhinitis and 10.7% of rhinoconjunctivitis. Conclusions: Ocular symptoms increase the role of rhinitis as a risk factor for asthma and its impact on daily activities in children.
in the Mediterranean area of Southern Italy, between November 2005 and May 2006. Students completed a questionnaire based on SIDRIA and ISAAC surveys and underwent skin prick tests (SPTs) at school. A total of 2,150 children were evaluated. The study was approved by the Institutional Ethics Committee. All parents of invited adolescents signed a written informed consent. According to Italian law, individual privacy was respected.

Questionnaire

The self-administered questionnaire was completed by adolescents at school regarding respiratory allergic symptoms, diseases and personal information. The core questionnaire modules of ISAAC for 13-14 year olds for wheezing and rhinitis were used. According to ISAAC methods, a child’s history of asthma was defined as a positive answer to the question “Have you ever had asthma?”; Rhinitis was defined as a positive answer to the question “Have you ever had a problem with sneezing, or runny, or blocked nose apart from common cold or flu in the last 12 months?”; Conjunctivitis was defined by the question “In the past 12 months, has this nose problem been accompanied by itching and/or watering eyes?” Based on these criteria, we identified the following subgroups: subjects with asthma, subjects with rhinitis, subjects with rhinoconjunctivitis, and asymptomatic children without asthma or rhinoconjunctivitis. Current asthma was defined as asthma plus at least one wheezing episode in the last 12 months. Moreover, subjects with current asthma were asked if at least one visit to the hospital emergency department because of an asthma exacerbation had occurred.

Rhinitis-related impact on QoL was considered if the answer to the question “In the last 12 months, how much did nasal symptoms interfere with your daily activities?” was “moderately/highly”.

Information on possible confounders or effect modifiers was also collected. Domestic mold/dampness exposure was evaluated based on the question: “Have you ever seen mold/dampness/fungi on the walls or on the ceiling of your bedroom?” Environmental tobacco smoke (ETS) exposure was assessed based on the question “Are there smokers at home?” Self reported traffic exposure was recorded as the frequency of trucks passing on a residential street on weekdays (never/rare/frequent/constant) and subjects were considered exposed if they answered “frequent” or “constant.”

Parental history for atopy was defined as at least one parent with a personal history of allergic respiratory diseases (asthma and/or rhinitis). Householder crowding index (HCI) was defined as the total number of co-residents per household, excluding newborn infants, divided by the total number of rooms, excluding the kitchen and bathrooms. HCI was dichotomized at the level of its 50th percentile (< 1.0 and ≥ 1.0) and used as an index of socioeconomic status.

Height and weight were measured in all children in standing position without shoes using a stadiometer and an electronic digital scale: body mass index (BMI) was computed as weight/height$^2$ (kg/m$^2$). Overweight-obese children were defined following the gender- and age-specific BMI cut-offs by Cole.

SPTs were performed following EAACI recommendations with a panel including 8 common aeroallergens, as well as positive and negative controls (Stallergènes Italia S.r.l., Milan, Italy). Allergic sensitization was defined as the presence of at least one positive skin prick test. Atopic index (AI) was computed as the number of the individual positive SPT and classified as follows: 0, no allergic sensitization; 1, 1 positive SPT; 2, 2 positive SPTs; and 3, 3 or more positive SPTs. Allergens were grouped in perennial (Parietaria judaica, Dermatophagoides, dog and cat dander, Blattella germanica, and alternaria) and seasonal (grass mix and olive).

Data analyses

Frequency distribution of variables was evaluated using the $\chi^2$ test. To identify independent variables that influence the risk for a dependent variable, adjusting for confounders, logistic regression models were used and odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated for all predictors.

Computations were performed using the StatView statistical software package (SAS Institute, Cary, NC, USA). A probability
Table 2. Frequency distribution of subjects without rhinitis or rhinoconjunctivitis, subjects with rhinitis, and subjects with rhinoconjunctivitis with respect to the presence/absence of current asthma

| Current asthma | No rhinitis, no rhinoconjunctivitis (N, %) | Rhinitis (N, %) | Rhinoconjunctivitis (N, %) | Total sample (N, %) |
|----------------|-----------------------------------------------|----------------|----------------------------|-------------------|
|                | 1,296 (60.3)                                 | 371 (17.3)     | 393 (18.3)                 | 2,060 (95.8)     |
| No rhinitis, no rhinoconjunctivitis (N, %) | 23 (1.1)                                     | 20 (0.9)       | 47 (2.2)                   | 90 (4.2)         |
| Rhinitis (N, %) |                                              |                |                            |                   |
| Rhinoconjunctivitis (N, %) |                                              |                |                            |                   |
| Total sample (N, %) |                                              |                |                            | 2,150 (100)      |

Table 3. Effect of personal and environmental characteristics on the prevalence of rhinitis and rhinoconjunctivitis

| Atopic index | No rhinitis, no rhinoconjunctivitis | Rhinitis | Rhinoconjunctivitis |
|--------------|-------------------------------------|----------|---------------------|
| Class 0 (%)  | 66.3                                | 16.6     | 17.1                |
| Class 1 (%)  | 61.7                                | 20.4     | 17.9                |
| Class 2 (%)  | 57.8                                | 19.1     | 23.1                |
| Class 3 (%)  | 49.8                                | 22.0     | 28.2                |

Table 5. Multiple logistic regression analysis of determinants for having conjunctivitis associated with rhinitis. Data are expressed as odds ratios (OR) and 95% confidence intervals (95% CI)

| Allergen sensitization | OR (95% CI) | P value |
|------------------------|-------------|---------|
| Sensitization to seasonal allergens (ref. no sensitization) | 1.95 (1.4-2.90) | 0.0006 |
| Sensitization to perennial allergens (ref. no sensitization) | 1.44 (1.1-1.88) | 0.009 |
| Sensitization to seasonal-perennial allergens (ref. no sensitization) | 2.33 (1.7-3.2) | <0.0001 |

level < 0.05 was considered to indicate significance.

RESULTS

Sample characteristics (2,150 subjects: M 49.2 %) are shown in Table 1. Excluding asthma, no chronic pulmonary disease was reported; none of the children were active smokers. The prevalence of allergic sensitization was 39.2% (45.0% in males and 33.5% in females, $P = 0.0001$, $\chi^2$ test).

In the overall sample, we found a prevalence of 18.2% (391/2,150) for rhinitis (17.3% alone and 0.9% in association with CA) and of 20.5% (440/2,150) for rhinoconjunctivitis (18.3% alone and 2.2% in association with CA) (Table 2). The prevalence rate of CA was 4.2% (90/2,150). Because CA was strongly associated with rhinitis (74.4% of subjects with CA had rhinitis or rhinoconjunctivitis), to evaluate factors influencing the prevalence of rhinitis and rhinoconjunctivitis we excluded subjects with CA from the analyses. On the remaining 2,060 subjects, the proportion of rhinitis was 37.1%; 18.0% isolated and 19.1% in association with conjunctivitis.

There were fewer females than males among subjects without rhinitis or rhinoconjunctivitis (49.5%) and those with rhinitis (48.2%), while there were more females than males with rhinoconjunctivitis (59.3%, $P = 0.0014$, $\chi^2$ test). Similarly, parental history for atopy, domestic exposure to mold/dampness, ETS, and reported truck traffic in the residential streets were more frequent in rhinoconjunctivitis (Table 3). Rhinoconjunctivitis was significantly more frequent in those with higher AI than rhinitis (Table 4). In a multiple logistic regression model, high truck traffic, mold/dampness, and ETS were independent risk factors for the association of conjunctivitis with rhinitis (Table 5). In the same model, sensitization to perennial allergens and to perennial plus seasonal allergens increased the risk of having conjunctivitis, while isolated sensitization to seasonal allergens did not increase the risk for conjunctivitis.

In the overall samples (N=2,150), the prevalence of current asthma was 1.7% among subjects without rhinitis or rhinoconjunctivitis, 5.1% among those with rhinitis, and 10.7% among those with rhinoconjunctivitis ($P=0.0001$, $\chi^2$ test). Among sub-
Table 6. Multiple logistic regression analysis of determinants for current asthma. Data are expressed as odds ratios (OR) and 95% confidence intervals (95% CI).

| Determinants                  | OR   | 95% CI          | P-value |
|-------------------------------|------|-----------------|---------|
| Gender (reference: female)    | 1.36 | 0.86-2.16       | 0.19    |
| Heavy traffic (reference: “never/rare”) | 1.74 | 1.02-2.80       | 0.024   |
| Mold/dampness (reference no exposure) | 1.65 | 0.96-2.83       | 0.72    |
| Exposure to environmental tobacco smoke (ref. no exposure) | 1.40 | 0.87-2.24       | 0.17    |
| Parental history for atopy (reference: no history) | 4.92 | 2.97-8.16       | <0.0001 |
| Household crowding index (reference: <1) | 0.67 | 0.42-1.06       | 0.088   |
| Atopic index                  |      |                 |         |
| AI=1 (reference: AI=0)        | 3.29 | 1.79-6.05       | 0.0001  |
| AI=2 (reference: AI=0)        | 3.66 | 1.86-7.17       | 0.0002  |
| AI=3 (reference: AI=0)        | 4.45 | 2.42-8.16       | <0.0001 |
| Rhinitis (ref.: neither rhinitis nor rhinoconjunctivitis) | 2.28 | 1.21-4.30       | 0.010   |
| Rhinoconjunctivitis (ref.: neither rhinitis nor rhinoconjunctivitis) | 5.23 | 3.06-8.96       | <0.0001 |

*P for trend < 0.0001.

Table 7. Effects of different combinations of allergic sensitization and disease status (presence of rhinitis/rhinoconjunctivitis) on current asthma prevalence.

| Disease status                  | Allergic sensitization (%) | Frequency distribution of different combination between disease status and allergic sensitization (%) | Prevalence of current asthma (%) |
|---------------------------------|---------------------------|-------------------------------------------------------------------------------------------------|----------------------------------|
| No rhinitis, no rhinoconjunctivitis | No                        | 41.4                                                                                             | 0.7                              |
| Rhinitis                        | No                        | 10.3                                                                                             | 3.2                              |
| Rhinoconjunctivitis             | No                        | 10.7                                                                                             | 4.8                              |
| No rhinitis, No rhinoconjunctivitis | Yes                    | 21.5                                                                                             | 3.7                              |
| Rhinitis                        | Yes                       | 7.7                                                                                                | 7.6                              |
| Rhinoconjunctivitis             | Yes                       | 8.4                                                                                                | 17.3                             |

Table 8. Multiple logistic regression analysis for “moderate/high” rhinitis-related impact on quality of life. Data are expressed as odds ratios (OR) and 95% confidence intervals (95% CI).

| Determinants                  | OR   | 95% CI          | P-value |
|-------------------------------|------|-----------------|---------|
| Gender (reference: female)    | 1.59 | 0.95-2.65       | 0.080   |
| Household crowding index (reference: <1) | 1.32 | 0.76-2.29       | 0.33    |
| Overweight-obesity* (ref.: normal weight) | 1.75 | 0.92-3.33       | 0.087   |
| Allergic sensitization (reference: none) | 0.84 | 0.50-1.41       | 0.51    |
| Current asthma (ref.: no current asthma) | 2.64 | 1.31-5.32       | 0.007   |
| Rhinoconjunctivitis (ref.: rhinitis) | 2.08 | 1.19-3.62       | 0.010   |

*Overweight-obese children were defined following the gender- and age-specific cut-off points by Cole et al. 

DISCUSSION

In this cross-sectional evaluation, we identified an elevated prevalence of rhinitis and rhinoconjunctivitis among adolescents. The association of conjunctivitis with rhinitis (i.e., rhinoconjunctivitis) was more frequent in subjects with multiple allergic sensitizations and those exposed to environmental risk factors. The association of conjunctivitis with rhinitis strongly increased the risk for current asthma and had a significant impact on QoL.

Respiratory symptoms were investigated using the well-validated questionnaire-based definitions of the ISAAC Study. The core questions on rhinitis were highly specific, even though they showed a lower sensitivity for detecting atopy in a general population of children. To address this issue, individual allergic sensitization was objectively evaluated using SPT. In our population sample, the prevalence of rhinitis (not associated with conjunctivitis) was 18.2%, while rhinoconjunctivitis prevalence was 20.5%; i.e., 38.7% of subjects had rhinitis in the last 12 months with or without conjunctivitis, and conjunctivitis was present in 52.9% of children with rhinitis. These results are comparable to those found in 2002 in Italian metropolitan areas following the same rhinitis and rhinoconjunctivitis definitions; conjunctivitis was reported in 56.6% of children with rhinitis. A survey conducted on 396 Swedish schoolchildren showed a prevalence of 17.6% for rhinoconjunctivitis and observed a comorbidity between rhinitis and conjunctivitis of ~92%. According to the ISAAC-phase III study, the prevalence of nasal symptoms associated with itchy/watery eyes ranged from 2.2%-24.2% in children and 4.5%-45.1% in adolescents. Determination of the prevalence of conjunctivitis by alone was not possible in the present study; in fact, the adopted questionnaire evaluated conjunctivitis only as a comorbidity of rhinitis. This did not allow the assessment of individuals possibly hav-
ing conjunctivitis without symptoms of rhinitis. By analyzing risk factors for the association between rhinitis and rhinoconjunctivitis, we excluded subjects with current asthma, which was more frequent in rhinitis and rhinoconjunctivitis. Since current asthma was strongly associated with rhinitis, the exclusion of current asthma from the analysis allowed better evaluation of the factors influencing the prevalence of rhinitis and rhinoconjunctivitis, in so far as asthma is linked to somewhat different risk factors than rhinitis. As reported in previous studies, rhinoconjunctivitis was associated with an increased frequency of parental history of atopy with respect to rhinitis, suggesting that a family history of allergic disease represents a risk factor for rhinoconjunctivitis in children. Similarly, rhinoconjunctivitis was associated with a higher level of allergic sensitization (i.e., higher AI) than rhinitis. After allergen stratification, sensitization to perennial allergens yielded an increased risk for rhinoconjunctivitis; a further increase was observed in subjects sensitized to both perennial and seasonal allergens. Conversely, sensitization to seasonal allergens resulted in no increase in conjunctivitis with respect to non-sensitized individuals. These observations are in line with the study of Weinmayr et al., suggesting that atopy is an important risk factor for rhinoconjunctivitis but only marginally relevant for rhinitis without conjunctivitis. Similarly, in a recent survey conducted in Norway, children with rhinitis and sensitization to at least one inhalant allergen had more frequent conjunctivitis than children with rhinitis without sensitization. Conversely, in a recent report on 9-11-year-old Turkish schoolchildren, atopy was not shown as a risk factor for rhinoconjunctivitis in children, and Canonica et al. reported that ocular symptoms were more common in subjects with seasonal and seasonal plus perennial rhinitis than in those with perennial rhinitis.

The ISAAC questionnaire also provided information on possible confounding factors and effect modifiers. In particular, self-reported exposure to traffic could be affected by reporting bias altering the association between reported exposure to road traffic and disease. Nevertheless, Nuvolone et al. demonstrated that a strong relationship exists between self-reported exposure to vehicular traffic and residential proximity to main roads, as evaluated using the Geographical Information System technology. In our bivariate models, conjunctivitis was significantly associated with rhinitis among subjects exposed to mold/dampness, ETS, and truck traffic. In a multiple logistic model, these variables were independent risk factors for having conjunctivitis associated with rhinitis. As shown previously, these results emphasize the role of “preventablemodifiable” factors on rhinoconjunctivitis. Mold exposure or sensitization was associated with rhinitis in clinical observations and epidemiological surveys, in particular during the first year of life.

Studies examining the association between passive smoking and rhinoconjunctivitis are conflicting. Mitchell et al. found a weak association between ETS and symptoms of rhinoconjunctivitis, concluding that the relationship may not be causal. One study reported a reduced risk of rhinoconjunctivitis for children exposed to parental smoking. Conversely, Gonzalez-Diaz et al. showed that passive smoking is one of the risk factors for both rhinitis and rhinoconjunctivitis. More recently, we found that ETS is a significant risk factor for rhinoconjunctivitis. Similarly, a study by Montefort et al. reported that smoking by the mother alone was more common in children having current rhinitis, while smoking by the mother and/or father led to rhinoconjunctivitis.

We also found that an increased frequency of high reported truck traffic in the residential streets was an independent risk factor for the association between rhinitis and conjunctivitis (OR 1.57). Although evidence exists that allergic respiratory disorders are associated with traffic exposure in children, the findings are not consistent. Many studies have found an association between traffic exposure and atopic sensitization, and there is experimental evidence that diesel particles may enhance allergic sensitization to common inhalant allergens. In agreement with these findings, an association was found between increased exposure to self-reported truck traffic on the residential streets and childhood symptoms of rhinoconjunctivitis. Conversely, a recent study found little or no association between ambient particulate pollution and the global rhinoconjunctivitis prevalence.

Epidemiological and clinical data from many studies showed a significant association between rhinitis and asthma, supporting the hypothesis that rhinitis is a risk factor for asthma. Children with allergic rhinitis and asthma require a larger amount of medication than children with asthma alone, corroborating the hypothesis that the association between rhinitis and current asthma is characterized by increased disease severity. In the overall population sample, we found that rhinoconjunctivitis was more strongly associated with current asthma than rhinitis alone. In addition, using a logistics model, the presence of conjunctivitis significantly increased the risk for current asthma with respect to rhinitis independently of allergic sensitization. In sensitized children with rhinoconjunctivitis, the prevalence of current asthma increased to 17.3%; i.e., more than fourfold the current asthma prevalence in the overall sample (4.2%). Finally, rhinoconjunctivitis was associated with an increased number of visits to the hospital emergency department for asthma exacerbation, suggesting that the presence of conjunctivitis may be coupled with more severe disease. These results highlight the importance of conjunctivitis as an independent risk factor for asthma, supporting the link between upper and lower respiratory tracts (united airway disease). In this context, conjunctivitis should be considered part of this entity because the allergic inflammatory response involves the conjunctiva as well as the respiratory tract. In agreement with our results, recent studies have highlighted the significance of ocular symp-
toms, but few studies have explored the impact of allergic conjunctivitis as a comorbidity of asthma.3
Concerning the impact of rhinoconjunctivitis on QoL, we found that adolescents with rhinoconjunctivitis had significantly poorer QoL; in fact, 4.6% of subjects reported a high/moderate impact of rhinitis while 10.7% reported a high impact of rhinoconjunctivitis. Rhinoconjunctivitis is known to have an important impact on QoL, social interactions, and productivity both in children17 and adults.36 Ocular symptoms associated with allergic rhinitis, often under-diagnosed and under-treated, are increasingly recognized as a distinct disorder that imposes its own burden on medical costs and patient’s QoL, especially in those with persistent moderate/severe nose symptoms.4 Approximately 50% of patients with rhinitis stated that ocular symptoms were moderately to extremely bothersome in the recent “Allergies in America” survey, and 10% of those complained that red/itching eyes were the most annoying symptom.37
In conclusion, our study investigated the impact of conjunctivitis on rhinitis and current asthma, as well as the risk factors and burden of rhinoconjunctivitis in schoolchildren. We found that atopic parental history, allergic sensitization, and environmental factors such as exposure to mold/dampness, ETS and heavy traffic are important risk factors for rhinoconjunctivitis. We also found that rhinoconjunctivitis is more strongly associated with current asthma than rhinitis and that the presence of conjunctivitis increases the risk for current asthma with respect to rhinitis alone. Finally, the presence of conjunctivitis may significantly worsen the QoL in patients with rhinitis. Since allergic ocular symptoms are often underdiagnosed and under-treated, clinicians should investigate these disorders and the risk factors within routine clinical practice to reduce the burden of disease in allergic patients, improving their QoL.

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