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Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents

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Large variations in prevalence of atopy and allergic diseases are reported worldwide in children, but in epidemiological studies the use of skin prick tests (SPT) and spirometry along with questionnaires is not common in the Mediterranean Area. The present work was aimed at evaluating the prevalence of current asthma (CA), rhinoconjunctivitis (RC), and eczema (E), with atopy and respiratory function, and the role of risk factors for allergic respiratory diseases. A total of 2150 Italian schoolchildren were cross-sectionally investigated through respiratory questionnaire, SPT, and spirometry. A proportional Venn diagram quantified the distribution of CA, RC, and E, stratifying for allergic sensitization to show differences in prevalence of allergic diseases among subjects with and without positive SPT. CA prevalence was 4.2%, RC 17.9%, and E 5.3%. CA and RC increased, while E decreased, with respect to previous local studies. Allergic sensitization prevalence (evaluated as positive response to at least one SPT) was 39.2%. A double Venn diagram identified 15 categories. Atopic CA was threefold more frequent than non-atopic CA. Atopic vs non-atopic RC and E were 9.6% vs 10.3% and 2.0% vs 3.3%, respectively. Atopic vs non-atopic RC associated with CA were 1.6% vs 0.5%; the same figures for RC associated with E were 0.8% vs 1.3%. Asymptomatic atopic subjects were 27.0%. Atopy, RC, parental asthma, and environmental risk factors were associated with CA. Atopy and environmental factors were risk factors also for RC. Asthma and traffic exposure were linked to reduced lung function. Respiratory allergic diseases are still increasing and largely concomitant in Italian adolescents. Atopy is more important for CA than RC. Avoiding exposures to measured environmental risk factors would prevent 41% of current asthma and 34% of rhinoconjunctivitis.

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Large variations in the prevalence of allergic sensitization and symptoms of asthma (2.8–32.6%) (1) and rhinoconjunctivitis (3.9–45.1%) (2) have been reported in children and adolescents worldwide. In Italy, a trend toward a stabilization of asthma prevalence (as *lifetime asthma*) has been recently observed in adolescents in the period 1994–2002 (3, 4), while a 40–49% prevalence of subjects positive to skin prick testing has been found (5, 6). Both host susceptibility and environmental factors seem to contribute to these changes (1–6).

Indeed, it is difficult to compare the prevalence rates among surveys because of differences in study populations, diagnostic criteria, environmental and host risk factors, and methodological approach. As regards the latter, only the questionnaire without pulmonary function testing is

commonly applied. Also skin prick tests are uncommonly used, even though skin prick testing improves the classification of allergic diseases based on a structured allergy history alone (7). In the last 5 years, few studies were performed in the Mediterranean Area including questionnaire, pulmonary function testing, and skin prick tests (8).

The use of a Venn diagram, seldom used after the ISAAC 1998 report (12), may offer a more realistic information on the prevalence of allergic diseases by simultaneously quantifying the frequencies of different coexistent allergic diseases.

Thus, aims of this study were (i) to carry out an epidemiological survey investigating a large sample of adolescents of the Mediterranean area through questionnaire, spirometry, and skin prick test to quantify the proportion of prevalence of asthma, RC, and eczema (E), in association with allergic sensitization and respiratory function, and (ii) to evaluate the role of environmental and host risk factors for allergic respiratory diseases and to estimate the reduction in their burden obtainable through the abatement of avoidable environmental exposures.

Materials and methods

Study design

This cross-sectional study was conducted in a random sample of adolescents, aged 10–17 yr, living in the city of Palermo, Mediterranean area of Southern Italy (November 2005–May 2006). In the whole city, there were 59 junior high schools with 27,813 students. After subdividing the municipality in three geographical zones (coastal, downtown, and hilly), 16 schools with 9922 children were selected. From them, 2481 children were randomly selected (one every four). Three hundred and three adolescents did not obtain parental consent or were not present at school on the day of the study. The response rate was 87.8%: 2178 students completed a questionnaire based on SIDRIA Study, the Italian section of ISAAC (3, 8) and underwent lung function tests and skin prick tests (SPT) at school. Twenty-eight children refused SPT and/or were not able to perform a valid spirometry, leaving 2150 children (86.7% of the 2481 subjects of the random sample), mean age 12.6 yr ($\pm$1.0 s.d.), with a complete evaluation. The study was approved by the Institutional Ethical Committee. All parents of the invited adolescents signed a written informed consent. According to the Italian law, the respect of individual privacy concerning clinical data was granted.

Questionnaire

The SIDRIA self-administered questionnaire was completed by adolescents at school, regarding past and current respiratory allergic symptoms and personal information (smoke and other environmental exposures) (3). The three core questionnaire modules of ISAAC for 13- to 14-yr-olds (wheezing, rhinitis, and eczema) (9) were used: questionnaires were included in the analyses only if all the three core sections were completed.

Child's history of 'asthma ever' was defined as a positive answer to the question 'Have you ever had asthma?'. Rhinoconjunctivitis was defined as a positive answer to both the questions 'Have you ever had a problem with sneezing, or runny, or blocked nose apart from common cold or flu in the last 12 months?' and 'In the past 12 months, has this nose problem been accompanied by itching and/or watering eyes?' (9). Based on these criteria, we identified three subgroups: subjects with asthma ever (A), regardless of the presence of rhinoconjunctivitis; subjects with rhinoconjunctivitis (RC); and children without asthma or rhinoconjunctivitis (nAnRC). Moreover, current asthma (CA) was defined as asthma ever plus at least a wheeze episode in the last 12 months. Eczema (E) was defined as positive answers to both the following questions: 'In the last 12 months, have you had an itchy rush which was coming and going for at least 6 months?' and 'Has this itchy rush at any time affected any of the following places: folds of elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?'. Information on possible confounders or effect modifiers were also collected. Mold/dampness exposure was evaluated using the question: 'Have you ever seen mold/dampness/fungi on the walls or on the ceiling of your bedroom?'. In children, current passive smoking exposure (ETS) was assessed through the question 'Are there smokers at home?'. Self-reported traffic exposure was recorded as the frequency of trucks passing on the street of residence on weekdays (*never*/*rare*/*frequent*/*constant*), and subjects were considered exposed if they answered 'frequent' or 'constant'.

Family history in parents for asthma was defined as at least one parent with personal history of asthma.

Skin prick tests

Skin prick tests were performed according to EAACI recommendations (10) with a standard

panel including *dermatophagoides* mix, grass mix, *parietaria judaica*, olive, dog and cat dander, alternaria, and *blattella germanica*, plus a positive (histamine 1%) and a negative (saline) control (Stallergènes Italia S.r.l., Milan, Italy). The reading was performed after 15 min: reactions were considered positive if the mean wheal diameter (computed as the maximum diameter plus its orthogonal divided by two) was 3 mm or greater, after having subtracted the wheal diameter of the reaction to the negative control. Allergic sensitization was defined as the presence of at least one positive skin prick test. Atopic index (AI) was computed as the number of individual positive skin prick tests and classified as follows: 0-non-atopic, 1-one positive skin test, 2-two positive skin tests, 3-three or more positive skin tests. Allergens were grouped in outdoor (grass mix, *parietaria judaica*, olive), indoor (*dermatophagoides*, dog and cat dander, and *blattella germanica*) allergens, and mold (alternaria).

Spirometry

Height (in cm) and weight (in kg) were measured in all the children in standing position without shoes, using a stadiometer and an electronic digital scale. Pulmonary function tests were performed through a portable spirometer (MicroLoop, Micro Medical, Chatham Maritime, Kent, UK). Forced expiratory volume in one-second (FEV_1), forced vital capacity (FVC), and maximum midexpiratory flow ($FEF_{25–75\%}$) were measured according to ATS/ERS guidelines (11): the best FVC and FEV_1 were retained, and $FEF_{25–75\%}$ was selected from the manoeuvre with the largest sum of FEV_1 and FVC. Spirometric predicted values were those from Pistelli et al. (12). An impaired pulmonary function was defined when FEV_1/FVC% was below the 5th percentile of its normal distribution (below 87% of predicted for boys and below 90% for girls) (12).

Data analyses

A double proportional Venn diagram, following Viegi et al. (13), was used to describe the distribution of CA, RC, and E among subjects, and their association, according to the presence of atopy. Parametric (chi-square test and one-way analysis of variance – ANOVA) and non-parametric statistical tests (Kruskal–Wallis) were performed. To study the independent variables able to influence the risk for a dependent variable, logistic regression models were used, and odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated for all predictors. The population attributable risk (PAR%) was computed to estimate the amount of asthma (as both A and CA) and rhinoconjunctivitis because of atopy and other variables, which might be prevented by eliminating the exposure to the specific risk factor, following the equation: $PAR = [N_1(R_1 - R_0)]/(N_1R_1 + N_0R_0) = [p(RR-1)]/[p(RR-1)+1]$ where p is the proportion of population exposed and RR is the adjusted estimate of relative risk of the exposed vs the unexposed (14).

All computations were performed by StatView statistical software package (SAS Institute, Cary, NC, USA). A probability level of $p < 0.05$ was selected as statistically significant.

Results

Prevalence rates

Sample characteristics (2150 subjects: M = 1057, 49.2%) are shown in Table 1. Except for asthma, no chronic pulmonary diseases were reported; none of the children declared to be an active smoker. Prevalence of allergic sensitization was 39.2% (45.0% in boys and 33.5% in girls, $p < 0.0001$, χ^2). About one of two students was exposed to ETS and over one of five reported a relevant exposure to traffic in the zone of residence.

In the overall sample, prevalence rates of CA, RC, and E were 4.2%, 17.9%, and 5.3%, respectively: they are described as double proportional Venn diagram (8), separately for

Table 1. General characteristics of the sample

	Males	Females
Gender (No., %)	1057 (49.2)	1093 (50.8)
Age (mean ± s.d.)	12.60 (±1.05)	12.59 (±1.03)
Height, cm (mean ± s.d.)	154.9 (±9.4)	153.5 (±7.2)
Weight, kg (mean ± s.d.)	51.9 (±13.7)	50.1 (±12.3)
BMI, kg/m^2 (mean ± s.d.)	21.4 (±4.4)	21.1 (±4.3)
Subjects with at least one positive SPT (No., %)	476 (45.0)	366 (33.5)*
Exposure to environmental tobacco smoke (No., %)	589 (55.7)	627 (57.4)
Exposure to traffic in the zone of residence		
Rare (No., %)	586 (55.4)	619 (56.6)
Frequent (No., %)	150 (14.2)	175 (16.0)
Constant (No., %)	61 (5.8)	67 (6.1)
Mold/dampness exposure† (No., %)	147 (13.9)	175 (16.0)

Unless specified, no significant difference was found between male and female subgroup.
*$p < 0.0001$ (χ^2).
†Positive answer to the question: 'Have you ever seen mold/dampness/fungi on the walls or on the ceiling of your bedroom?'.

subjects with and without allergic sensitization (Fig. 1). Fifteen categories were identified through the Venn diagram: allergic CA (3.1%) was almost threefold more frequent than non-allergic CA (1.1%). Conversely, allergic vs non-allergic RC and E were 9.6% vs 10.3% and 2.0% vs 3.3%, respectively. Allergic vs non-allergic RC associated with CA were 1.6% vs 0.5%; the same figures for RC associated with E were 0.8% vs 1.3%. Asymptomatic subjects with allergic sensitization were 27.0%.

Overall RC prevalence was 20.0% (17.9% alone and 2.1% in association with CA). Indeed, when considering only individuals with CA (4.2% of the total), one half of them had also RC. Prevalence rates of wheeze ever, wheeze in the last 12 months, and A were 21.7%, 10.5%, and 12.0%, respectively. Subjects without symptoms were 77.9%. No significant difference in gender distribution was found for asthma and wheeze. RC was 21.0% among girls and 14.7% among boys ($p = 0.0001$, χ^2); similarly, E was 6.3% among girls and 4.2% among boys ($p = 0.026$, χ^2).

Allergic sensitization and respiratory function data

Gender, prevalence of allergic sensitization, and respiratory function data for CA, RC, and nAnRC in the total sample are described in Table 2. Allergic sensitization was more frequent among CA (73.3%) than RC (44.6%) and nAnRC (36.0%, $p < 0.0001$, χ^2).

There were 17.3% subjects with one, 10.1% with two, and 11.8% with three or more positive SPT, while subjects without allergic sensitization were 60.8%. With increasing AI (Fig. 2 panel a), the proportion of CA increased from 1.8% to 10.3% ($p < 0.0001$, χ^2); also, the proportion of RC significantly changed (from 16.3% to 24.9%, $p = 0.005$, χ^2). Among 581 asymptomatic subjects with allergic sensitization, an AI = 1 (i.e., monosensitization) was significantly more frequent than among allergic symptomatics (46.5% vs 38.6%), while AI = 3 was less frequent (27.6% vs 35.9%, $p = 0.035$, χ^2). Significant increases in the proportion of CA were also found as an effect of sensitization to indoor ($p < 0.0001$, χ^2) and outdoor allergens ($p < 0.0001$, χ^2, Fig. 2, panel b and c, respectively). No significant increase of CA was found for sensitization to mold ($p = 0.057$, χ^2, Fig. 2, panel d).

Sensitization to dermatophagoides was the most represented, followed by parietaria pollen: among 842 subjects with positive SPT, 59.6% were sensitized to dermatophagoides (18.6% monosensitized) and 37.1% to parietaria (7.6% monosensitized). Prevalence of CA was higher among subjects monosensitized to dermatophagoides (9.0%) with respect to the remaining subjects (3.8%, $p = 0.002$, χ^2), while no significant difference was found for subjects monosensitized to parietaria. Prevalence of RC among subjects monosensitized to dermatophagoides or parietaria was not significantly different from those in the whole sample.

Lung function indices, as percent of predicted, were (mean ± s.d.): FVC 92.9 ± 12.6%, FEV_1 92.2 ± 11.8%, FEV_1/FVC 99.8 ± 6.6%, and $FEF_{25–75\%}$ 85.8 ± 19.2% among boys; FVC 91.5 ± 10.9%, FEV_1 88.6 ± 10.8%, FEV_1/

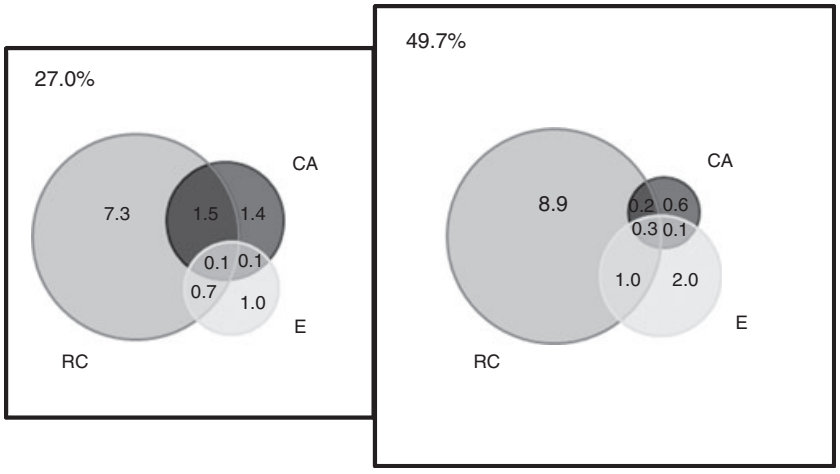

Fig. 1. Proportional double Venn diagram. A proportional double Venn diagram has been used to quantify the distribution in the whole population sample of current asthma (CA), rhinoconjunctivitis (RC), and eczema (E) separately for the 842 subjects with (on the left) and the 1308 subjects without (on the right) positive skin prick test. Each prevalence value is referred to the whole investigated population sample. The prevalence of asymptomatic subjects with positive skin prick test (27%) and that of asymptomatic subjects with negative skin prick test (49.7%) is indicated.

Table 2. Distribution of gender, allergic sensitization, and respiratory function data for each subgroup of current asthma, rhinoconjunctivitis, and non-asthmatic non-rhinitic subjects

	Total sample (N = 2150)	CA (N = 90)	RC (N = 385)	nAnRC (N = 1675)
Gender (M/F)	1057/1093	50/40	155/230	852/823
Subjects with pos. SPT (No, %)	839 (39.2)	66 (73.3)*	171 (44.6)	602 (36.0)
No. of sensitizations (median and IQ range)	0 (0–1)	1 (0–3)**	0 (0–2)	0 (0–1)
Sensitized to dermatoph. (No, %)	500 (23.3)	44 (48.9)*	113 (29.5)	343 (20.5)
Sensitized to parietaria (No, %)	311 (14.5)	30 (33.3)*	70 (18.3)	211 (12.6)
FEV_1 (% pred, mean ± s.d.)	90.3 (11.4)	87.5 (±11.6)[#]	89.9 (±11.4)	90.6 (±11.4)
FVC (% pred, mean ± s.d.)	92.2 (11.8)	91.4 (±12.3)	92.1 (±11.5)	92.3 (±11.8)
FEV_1/FVC% (% pred, mean ± s.d.)	100.5 (6.5)	97.6 (±7.5)[##]	100.6 (±6.7)	100.6 (±6.4)
$FEF_{25–75\%}$ (% pred, mean ± s.d.)	84.8 (19.1)	76.0 (±18.3)[§]	84.7 (±19.5)	85.2 (±19.0)
Impaired lung function (No, %)	90 (4.3)	10 (11.2)[§§]	18 (4.7)	62 (3.8)

CA: current asthma; RC: Rhinoconjunctivitis; nAnRC: non-asthmatic non-rhinitic; SPT: skin prick tests; IQ range: interquartile range.
*$p < 0.0001$ (χ^2).
**$p < 0.0001$ (Kruskal–Wallis).
[#]$p = 0.012$ with nAnRC (one-way anova).
[##]$p < 0.0001$ with both RC and nAnRC (one-way anova).
[§]$p = 0.0004$ with RC, $p < 0.0001$ with nAnRC (one-way anova).
[§§]$p = 0.003$ (χ^2).

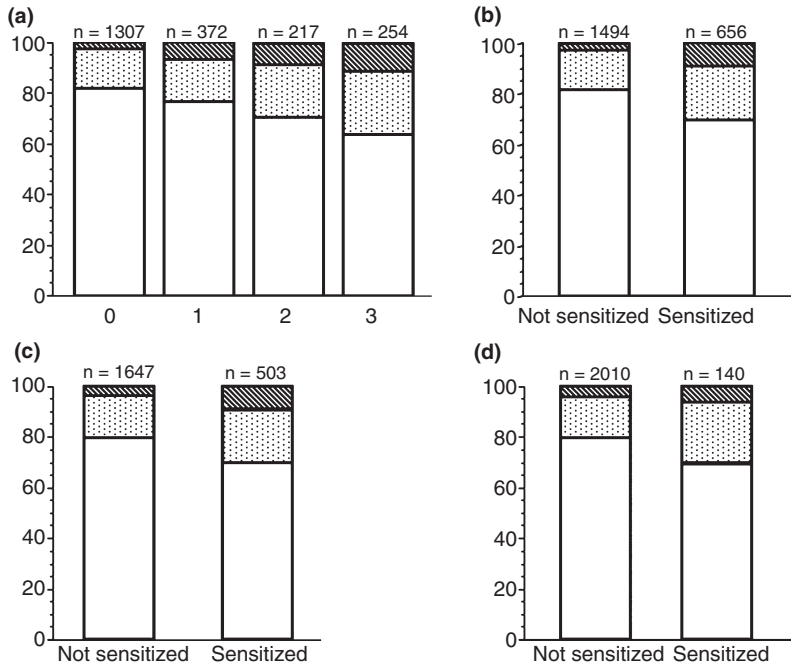

Fig. 2. Asthma and rhinoconjunctivitis distribution in different classes of atopic sensitization. Panel a: Distribution of children with current asthma, with rhinoconjunctivitis, and without current asthma/rhinoconjunctivitis, as percentages within each class of atopic index. Class 0: non-atopic; class 1: one positive skin reaction; class 2: two positive skin reactions; and class 3: three or more positive skin reactions. The absolute number of subjects in each subclass is shown. p for trend <0.0001 current asthma and $p = 0.005$ for rhinoconjunctivitis (χ^2). Panels b–d: Differences in distribution of children with current asthma, with rhinoconjunctivitis, and without current asthma/rhinoconjunctivitis because of sensitization to indoor allergens ($p < 0.0001$, χ^2, panel B), outdoor allergens ($p < 0.0001$, χ^2, panel C), and molds ($p = 0.057$, χ^2, panel D).

FVC 100.1 ± 6.3%, and $FEF_{25–75\%}$ 83.8 ± 19.0% among girls.

Asthmatics had significantly lower FEV_1/FVC% and $FEF_{25–75\%}$ (% predicted) with respect to nAnRC and RC subjects, while FEV_1 was significantly lower in CA with respect to nAnRC. An impaired lung function was found in 4.3% of the whole sample *vs* 11.2% of subjects with CA ($p = 0.0009$, χ^2). Among subjects without CA (i.e., RC + nAnRC), 6.1% of those reporting exposure to traffic had impaired lung function with respect to 3.4% of those not exposed.

Table 3. Multiple logistic regression analysis for current asthma, rhinoconjunctivitis not associated with asthma, and impaired lung function

	Current asthma		Rhinoconjunctivitis		Impaired lung function		Eczema	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Gender (female vs male)	0.74	0.47–1.17	1.51	1.21–1.89	1.62	1.04–2.52	1.43	0.96–2.12
ETS	1.41	0.88–2.25	1.43	1.14–1.79	0.68	0.44–1.04	1.05	0.70–1.55
Mold/dampness	1.57	0.91–2.70	1.51	1.14–2.01	0.95	0.52–1.71	1.19	0.73–1.94
Exposure to traffic	1.84	1.14–2.95	1.39	1.08–1.79	1.78	1.12–2.83	1.19	0.76–1.85
Current asthma	–	–	3.14	1.98–4.99	3.13	1.46–6.73	2.80	1.42–5.53
Rhinoconjunctivitis	3.28	2.08–5.18	–	–	1.00	0.59–1.70	2.56	1.69–3.86
Eczema	3.20	1.62–6.32	2.57	1.71–3.88	1.02	0.42–2.47	–	–
Parental asthma	5.54	3.34–9.17	1.15	0.80–1.66	0.81	0.39–1.69	0.93	0.49–1.77
Atopic index 1	3.33*	1.81–6.10	1.13*	0.84–1.54	0.75	0.39–1.43	1.06	0.64–1.74
Atopic index 2	4.16*	2.12–8.18	1.73*	1.22–2.46	0.92	0.44–1.93	0.41	0.17–0.98
Atopic index 3	5.05*	2.75–9.28	2.07*	1.50–2.85	1.32	0.71–2.44	0.72	0.38–1.37

Data are expressed as odds ratio (OR) and 95% confidence interval (95%CI). ETS: current passive smoking exposure.
Atopic index: 0-non-atopic, 1-one positive skin test, 2-two positive skin tests, and 3-three or more positive skin tests.
*p for trend for Atopic index: <0.0001.

Risk factors associated with allergic sensitization and respiratory diseases

Self-reported traffic exposure was a significant risk factor for allergic sensitization (OR 1.29, CI 1.04–1.60) when corrected for gender, mold/dampness, ETS, and parental history for allergic diseases in a logistic model. In particular, the association was found for individual sensitized to indoor allergens (OR 1.30, CI 1.04–1.63).

Self-reported traffic exposure, RC, E, parental asthma, and AI were significant risk factors for CA (Table 3). In a different logistic model, significant risk factors for RC were female gender, ETS, mold/dampness exposure, traffic exposure, CA, E, and the highest AI classes, while female gender, CA, and exposure to traffic were significant predictors of impaired lung function (Table 3).

In Table 4, PAR% for CA, RC, impaired lung function, and E are reported. Allergic sensitization, RC, and parental asthma accounted for the largest attributable fractions for CA. Avoidable environmental factors (exposures to mold/dampness, ETS, and traffic) were responsible of 40.8% CA cases. For RC, allergic sensitization and CA had lower influence (17.2% and 8.6%, respectively), while the cumulative attributable risk because of avoidable environmental factors was 33.6%. Sensitization to *dermatophagoides* was responsible of 6.7% of PAR for RC. At last, CA and traffic accounted for 8.5% and 14.1% of impaired lung function, respectively.

In Table 5, PAR% for CA and RC attributable to each individual allergen are reported. The most important contribution to PAR% from an individual allergen came from sensitization to *dermatophagoides* for both CA and RC (19.8% and 8.9%, respectively).

Table 4. Population attributable risk, expressed as percent (PAR%), for different variables and relevant to current asthma, rhinoconjunctivitis not associated with asthma, and impaired lung function (FEV_1/FVC% below the 5th percentile of its normal distribution)

	Current asthma	Rhinoconjunctivitis	Impaired lung function	Eczema
Atopy	54.5	17.2	–	–
Parental asthma	29.8	–	–	–
Current asthma	NA	8.6	8.5	6.7
Rhinoconjunctivitis	32.2	NA	–	23.1
Eczema	10.1	7.4	–	NA
Environmental tobacco smoke	18.1	18.8	–	–
Mold/dampness exposure	7.6	7.0	–	–
Exposure to traffic	15.1	7.8	14.1	–

Missing PAR values were not computed because of very low ORs in the relevant logistic models.
NA, value not available.

Table 5. Population attributable risk, expressed as percent (PAR%), for sensitization to different allergens and relevant to current asthma and rhinoconjunctivitis not associated with asthma

	Current asthma	Rhinoconjunctivitis
Dermatophagoides mix	19.8	8.9
Parietaria judaica	5.4	3.0
Olive	6.1	5.0
Dog dander	5.3	1.4
Cat dander	7.2	1.0
Alternaria	–	1.3

No PAR calculation was possible for Grass mix and *Blattella germanica* because of their low and not significant ORs in the logistic regression model.

Determinants of eczema

Distribution of E was significantly different among male and female subjects (4.2% and 6.3%, respectively, p = 0.026, χ^2). In a logistic model, when corrected for gender, environmental factors, and family history for atopic diseases, only CA (OR 2.80, CI 1.42–5.53) and RC (OR 2.56, CI 1.69–3.86) were significant risk factors for E, while female gender was close to the level of significance (OR 1.43, CI 0.96–2.12, Table 3). RC and CA accounted for 23.1% and 6.7% of E, respectively (Table 4).

Discussion

We found an elevated prevalence of allergic sensitization among adolescents, with an increased risk for CA associated with the increasing number of individual positive SPT. Sensitization to dermatophagoides was associated with increased prevalence of CA also in monosensitized individuals. Environmental factors appeared to be relevant for allergic sensitization, CA, and RC. The latter was only in part linked to atopy in our sample. Conversely, only CA and RC, and not environmental factors, were associated with E.

Respiratory symptoms

Our prevalence rates of respiratory symptoms rank intermediate with respect to worldwide prevalence values (1, 2). Because our classification of A, CA, RC, and E followed the definition of previous Italian epidemiological studies (3, 4), we could perform a meaningful comparison with earlier evaluations. A and CA prevalence rates are higher than in the Southern Italian part of the SIDRIA2 Study (12.0% vs 9.7% and 4.2% vs 3.7%, respectively) (4). Our data are close to those found in 2002 in Italian metropolitan areas (lifetime asthma 12.6%, current asthma 5.4%) (3). RC prevalence was 20.0% (17.9% as single condition and 2.1% in association with CA), slightly lower than in Italian metropolitan areas (21.1%) (3), but higher than in the Southern Italian part of the SIDRIA2 Study (17.9%) (4).

Wheezing in the last 12 months (6.2%) and lifetime asthma (9.3%) found in Palermo in 2002 (data on file, SIDRIA2 Study) (4) were lower than the current data obtained about 4 yr later. The cumulative and the yearly changes have been +4.3% and +1.2% per yr for wheezing in the last 12 months and +2.7% and +0.7% per yr for lifetime asthma, respectively. Rhinoconjunctivitis prevalence in Palermo in 2002 was 11.9%, i.e., much lower than the current result (20.0%), yielding a + 8.1% cumulative and a + 2.2% yearly change. Thus, asthma and rhinoconjunctivitis epidemics are still going on in our population sample.

Conversely, eczema prevalence (5.3%) was lower than previously reported for adolescents of Southern Italy (7.4%) (4). With regard to 2002 Palermo data (8.6%), total and yearly changes were −3.3% and −0.9% per yr: such decrease might be related to climatic changes, as suggested by Suárez-Varela et al. who reported eczema as dependent on meteorological conditions being positively associated with precipitation and humidity and negatively associated with hot climate (15).

No significant gender difference was found in both A and CA prevalence rates, differently from previous observations (16). Indeed, SIDRIA male adolescents (13–14 yr) did not have higher prevalence of A than girls (4).

Evaluation of allergic sensitization

The use of skin prick testing allowed the objective evaluation of allergic sensitization. Prevalence of positive SPT among adolescents appeared high (39.2%), but comparable to the values of 40% (5) and 49% (6) previously found in industrialized areas of North Italy. We detected a risk increase for CA depending on the increasing number of sensitizations: when compared to unsensitized adolescents (i.e., AI = 0), the adjusted OR of having three or more sensitizations (AI = 3) was almost fivefold for CA. Interestingly, in asymptomatic subjects with positive SPT, the sensitization to only one allergen was more frequent than in symptomatic allergic subjects, among which polysensitizations significantly increased. This is in agreement with previous reports indicating that sensitization to inhalant allergens remains a major risk factor for asthma in allergic individuals (17).

The objective evaluation of allergic sensitization also allowed the construction of a double proportional Venn diagram of allergic respiratory diseases showing differences in the prevalence of allergic diseases among subjects with and without positive SPT: in Fig. 1, the large role of allergic sensitization for CA is evident. It is also to point out that the PAR% value because of allergy was 53.3% for CA (19.8% due a single allergen, *dermatophagoides*) and that subjects with allergic rhinoconjunctivitis reporting also CA were threefold with respect to non-allergic RC. Thus, as previously demonstrated by Sears et al. in New Zealand boys and girls (18), asthma

is strongly associated with atopy in adolescents. In another Italian population study, atopy was also associated with asthma and asthma-like symptoms in both sexes (19). Similarly, in the present study, we found that sensitization to indoor perennial allergens was associated with a significantly increased prevalence of CA also in dermatophagoides monosensitized individuals. This could be explained by the increase in markers of airway inflammation found in allergic subjects, in particular those sensitized to indoor perennial allergens (20).

Determinants of allergic respiratory diseases

Interestingly, environmental factors (ETS, mold/dampness, and traffic exposures) appear to play a significant role in CA, in agreement with a previous study on Italian children demonstrating an increased risk of asthma and rhinoconjunctivitis for exposure to home dampness (21) and with a recent report from Xepapadaki et al., remarking the effect of ETS on wheeze and on doctor diagnosed asthma in Greek pre-school children (22). Moreover, we found a significantly increased risk of allergic sensitizations to indoor allergens among subjects reporting traffic exposure: we are aware of the risk that, without a validation by Geographical Information System, self-reported vehicular traffic exposure around the house of residence could be affect by recall bias. Nevertheless, our findings are in total agreement with those recently obtained by Annesi-Maesano et al. (23) in French children and also by Han et al. in children of Southern Taiwan (24), suggesting an interaction between perceived traffic-related pollution and allergens possibly producing an enhanced allergic response in children. Moreover, Cesaroni et al. found that self-reported traffic density in area of residence was clearly correlated to particulate matter emission and estimated nitrogen dioxide, strongly suggesting that individual perception of traffic intensity in the area of residence correlates to more objective indices of exposure (25).

In our study, the presence of RC determined a significant increase of the risk for CA (OR = 3.48) and the relevant PAR% (i.e., the reduction in CA prevalence that would be observed if the population were entirely unaffected by RC) accounted for 32.2%. This finding is in agreement with previous reports demonstrating that rhinitis is an independent risk factor for asthma as stated in ARIA Guidelines (26) and underscores the need for the physician to always perform a comprehensive assessment of the airways and to consider of evaluating lower airways in patients with rhinitis. The concurrent association of RC with CA confirms that allergic sensitization is the prominent risk factor for asthma onset.

We found a higher prevalence of RC among girls, according to the SIDRIA2 Study (4) and to a more recent epidemiological survey performed on Italian schoolchildren (27). RC alone was not strongly linked to allergic sensitization in our sample: (i) only 44.6% of RC had a positive skin test (close to the prevalence in the total population sample) compared to 77.8% of subjects with both CA and RC; (ii) the distribution of Dermatophagoides and Parietaria sensitizations was not far from that in the whole sample; (iii) atopic index was lower with respect to children with CA; and (iv) the increase in RC prevalence with increasing AI (from 16.3% to 24.9%) was lower than for CA (from 1.8% to 10.3%); the PAR value of allergic sensitization for RC was 16.5%, less than one-third with respect to the PAR for CA. Thus, other determinants than allergic sensitization appear relevant for RC. In fact, while exposure to traffic is a risk factor also for CA, all the investigated environmental factors (mold/dampness, ETS, and exposure to traffic) play a larger role in RC, in agreement with the results of Corbo et al. (28) and with previous studies demonstrating that RC may be linked to ETS (29).

Pulmonary function

Asthmatic subjects showed lower values of FEV_1, FEV_1/FVC, and $FEF_{25–75\%}$, and among subjects with CA, the risk of impaired lung function (i.e., a low FEV_1/FVC) was threefold with respect to asymptomatic children. Performing spirometric measures made possible to identify subjects with impaired lung function also among subjects not reporting CA, strongly suggesting the effect of environmental factors in the absence of any history of respiratory disease. In particular, we found that self-reported residential traffic-related air pollution exposure was associated with impaired lung function, as recently shown by Oftedal et al. (30) and by Rosenlund et al. (31) through objective estimates of outdoor air pollution exposure. Indeed, our results are in agreement with the very recently published results of SIDRIA2 Study, which have linked reported traffic exposure to questionnaire-variables such as asthma and productive cough (32). Conversely, according to Jaén et al. (33), atopy *per se* was never associated with poorer pulmonary function, as defined on $FEV_1/FVC\%$ below

the 5th percentile of its normal distribution. We also made a sensitive analysis by using a milder definition for impaired lung function based on $FEF_{25–75\%}$ (cut-off of 60% of predicted for boys and 62% for girls). Also in this case, no significant independent effect of atopy was found on lung function.

Our study indicates that (i) prevalence rates of allergic sensitization, asthma, and rhinoconjunctivitis are still increasing and Venn diagram provides additional information about the prevalence of the coexistent allergic diseases in adolescents; (ii) the role of allergen sensitization (and perennial indoor allergens in particular) is more important for CA than RC; and (iii) avoiding exposures to measured environmental risk factors would prevent 39% of current asthma and 34% of rhinoconjunctivitis. Both presence of current asthma and self-reported traffic exposure in the zone of residence are associated with a poorer lung function in our population sample.

Eczema

As previously reported, female gender was associated to E (27), while both RC and CA were significant risk factors for E. Moreover, CA and RC accounted for about 30% of PAR for E. Thus, the concurrent association of CA, RC, and E may be viewed in the context of the *atopic March* theory, confirming that allergic sensitization is the prominent risk factor for asthma onset (34).

Conclusion

Public health policies aimed at the abatement of these avoidable environmental risk factors (exposures to mold/dampness, ETS, and traffic) could obtain a significant reduction of the worldwide increasing burden that CA and RC cases determine to governments, health care systems, families, and patients.

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