Effects of childhood and adolescence-adulthood respiratory infections in a general population


ABSTRACT: The role of childhood respiratory infections before 12 yrs of age (CRI) and during adolescence-adulthood (ARI) was studied in a general population sample (n=3,289), living in an unpolluted area of Northern Italy. The presence of respiratory symptoms and diseases, as well as risk factors for obstructive airways disease (OAD), was assessed by a standardized questionnaire. Forced vital capacity and derived expiratory flows, and single-breath diffusing capacity were measured using computerized instrumentation. There were 1,185 (36.2%) subjects who reported pertussis (PT), 374 (11.4%) recurrent chest colds, pneumonia and cough, singly or in combination, with or without pertussis (CRI), and 1,718 (52.4%) reported no respiratory infections in childhood (NOCR). Prevalence rates of respiratory symptoms and diseases were significantly higher in subjects of the CRI group in all ages, and in older smokers. Wheeze and attacks of shortness of breath with wheeze were significantly higher in younger nonsmoking subjects with a history of CRI. Respiratory symptoms and diseases were not more prevalent in subjects of the PT group. Prevalence rates of respiratory symptoms and diseases were significantly higher in subjects with a history of ARI, both in smokers and nonsmokers. Lung function parameters adjusted for sex, age and smoking were significantly lower in CRI subjects; PT subjects showed lower values than NOCRI subjects. A significantly higher prevalence rate of ARI was present in subjects who reported CRI, both in smokers and nonsmokers. Subjects with both CRI and ARI showed the highest prevalence of respiratory symptoms and diseases. In addition, they had the lowest lung function values regardless of smoking habit.


Respiratory infections in childhood (CRI) and during adolescence-adulthood (ARI) have been considered among the different risk factors for obstructive airways diseases (OAD). Their role, however, is not yet completely established. It is hypothesized that CRI may cause alterations in anatomical structures (bronchiolar walls, smooth muscles, interstitium, etc) and affect the lung during growth [1-6]. Recent data support the possibility that CRI may cause an increased susceptibility to the development of airways hyperreactivity and atopy [7-11].

ARI may cause transient pathological changes (mucus hypersecretion, direct damage to bronchiolar walls, muscles and obliteration of small airways, etc), with consequent impairment of lung function [6, 12, 13]. Recurrent infections in adolescence-adulthood have been related to mucus hypersecretion and both these factors were the basis of the so called "British hypothesis" on the pathogenesis of OAD [6, 14, 15]. Respiratory infections may lead to the recruitment of neutrophils in the bronchial mucosa, submucosa and interstitial space, and recently, the role of neutrophils in the pathogenesis of emphysema [16, 17] and of bronchial hyperreactivity [18] has been pointed out.

The hypothesis that CRI may affect the development of OAD is based mainly on cross-sectional observations in large population studies [19-21] or on follow-up studies of children [22-27]. Further cross-sectional confirmation from large population studies may be useful. We have investigated the relationships between CRI, ARI, respiratory symptoms and lung function in a general population sample enrolled in a longitudinal study on the natural history of obstructive airways lung disease. Furthermore, we have evaluated the importance of pertussis, as immunization is infrequent in Italy and some other industrial countries.

Materials and methods

This longitudinal study is being carried out in the area of the Po river delta (near Venice) in Northern Italy [28-30]. The population residing in the area (of about
1,040 square kilometres) is about 115,000. Agricultural, trading and fishing activities are predominant. The objectives of the study are the evaluation of the aetiology and natural history of OAD and the long-term effects of sulphur dioxide (SO₂) exposure emanating from a new, large thermoelectric power plant. In this paper, we describe the results deriving from the first cross-sectional survey before the start of the operation of the plant. The level of air pollution was negligible during the data collection of the first survey (SO₂ 0.005–0.013 ppm and total suspended particulate matter 40–90 μg·m⁻³). A multi-stage stratified geographic cluster methodology was used to select a sample of 3,289 subjects aged 8–64 yrs, representative of the general population [28–30].

**Questionnaire and assessment of childhood respiratory diseases and adolescence-adulthood respiratory illnesses**

Using a modified NHLI questionnaire [30, 31], developed by the Special Project on Chronic Obstructive Lung Disease (COLD) of the Italian Research Council (CNR), the following information was obtained:

1. general health information;
2. presence of respiratory symptoms (cough, phlegm, wheeze during and apart from cold, etc);
3. presence of cardiac or pulmonary diseases (chronic bronchitis, asthma, emphysema, coronary disease, etc);
4. presence of allergic rhinitis and other allergic diseases;
5. familial history of chronic bronchitis, emphysema, asthma, lung cancer, atopy, tuberculosis and heart diseases;
6. smoking history;
7. occupational exposure;
8. socio-economic conditions.

The following symptoms and diseases were considered for the analysis:

1. chronic cough (presence of usual cough most days for at least three months in a year for two years);
2. chronic phlegm (presence of usual phlegm most days for at least three months in a year for two years);
3. wheeze (any wheeze);
4. SOBWHZ (any attacks of shortness of breath with wheeze);
5. COLD (presence of physician’s diagnosis of chronic bronchitis and/or emphysema);
6. asthma (presence of physician’s diagnosis of asthma).

The history of respiratory diseases in childhood was investigated by the following question: “Before 12 yrs did you have one of the following diseases and how many times?”

- A. chest cold none rarely frequently
- B. pneumonia none n =
- C. pertussis yes no
- D. croup yes no

Positive answers were considered for all these conditions singly or in combination with the exception of chest cold for which only “frequently” (≥3 episodes each year) was taken into account. There were 318 subjects under 12 yrs (146 males and 172 females); however, only for those ≤10 yrs old, the mothers answered this question as well as the others from the remaining sections of the questionnaire.

The occurrence of respiratory diseases after 12 yrs, during adolescence-adulthood, was investigated by the following question: “From 12 yrs up to three years ago how many events did you have such as:

- A. chest cold none rarely frequently
- B. pneumonia none n =

Frequent colds or at least one pneumonia episode singly or in combination were considered positive answers for ARI.

The following groups were considered for the analyses: 1) subjects who only had pertussis (PT) (n=1,185); 2) those who reported recurrent chest colds, pneumonia, croup singly or in combination, with or without pertussis (CRI) (n=374); 3) those without CRI and PT (NOCRI) (n=1,718). For subjects over 12 yrs:

- 4) subjects who complained of recurrent chest colds, pneumonia or both these conditions (ARI) (n=373); 5) those who did not report ARI (NOARI) (n=2,585).

The number of subjects who succeeded in the performance of lung function tests was no different among these groups: CRI, n=365 (95%); PT, n=1,115 (94%); NOCRI, n=1,599 (93%) and ARI, n=342 (92%); NOARI, n=2,426 (94%).

With regard to smoking habits, smokers were considered to be those who smoked at least one cigarette per day currently; ex-smokers were those who quit smoking at least 6 months before the study and nonsmokers were those who had never smoked any kind of cigarette.

**Lung function**

Lung function tests were performed, as previously described [26, 27, 30], using automated equipment (Hewlett-Packard pulmonary system 47804S). A pneumotachograph (Fleisch No. 3) connected to a computer (Hewlett-Packard 9825A) was used for flow and volume measurements; calibration was performed daily using a standard syringe (3 l). Subjects performed single-breath diffusing capacity for carbon monoxide (DLco) and forced vital capacity manoeuvres (FVC) from which were derived forced mid-expiratory flows between 25–75% and 75–85% as well as reference values derived from “normal” subjects selected within the sample (FEF₂₅–₇₅, FEF₁₂₅–₇₅, Vmax₂₅, Vmax₅₀ and Vmax₇₅). Criteria of performing, acceptability and analysis of the tests as well as reference values have been reported [28, 29, 32, 33].

Statistical analyses were performed at the Computer Center of the University of Pisa (CNUCE), using the routines of the statistical package for the social sciences (SPSS). Chi-squared test, analysis of variance and covariance and multiple logistic models were used.
Results

Prevalence rates of CRI and ARI are reported in table 1: pertussis showed the highest prevalence both in males (32.5%) and females (39.6%), while rates of CRI were consistently lower in both sexes (11.2% and 11.5% in males and females, respectively). Within CRI, pneumonia and recurrent chest colds showed the highest prevalence rates in both sexes (27% and 19% for pneumonia and 20% and 17% for recurrent chest colds, in males and females, respectively). Croup and the combination of all the conditions investigated by the questionnaire showed consistently lower prevalence rates. Within ARI, recurrent chest colds showed the highest prevalence rate, both in males (72%) and females (70%); the total number of subjects considered for the analyses is lower, because only those older than 12 yrs answered the question on the presence of ARI.

Table 1. – Prevalence of PT, CRI and ARI by sex

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>%</th>
<th>Females</th>
<th>%</th>
<th>n</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>512</td>
<td>32.5</td>
<td>673</td>
<td>39.6</td>
<td>1,185</td>
<td>36.2</td>
<td></td>
</tr>
<tr>
<td>CRI</td>
<td>178</td>
<td>11.2</td>
<td>196</td>
<td>11.5</td>
<td>374</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>NOCRI</td>
<td>886</td>
<td>56.3</td>
<td>832</td>
<td>48.9</td>
<td>1,718</td>
<td>52.4</td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>187</td>
<td>15.0</td>
<td>186</td>
<td>14.2</td>
<td>373</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>NOARI</td>
<td>1,241</td>
<td>85.0</td>
<td>1,344</td>
<td>85.8</td>
<td>2,585</td>
<td>85.9</td>
<td></td>
</tr>
</tbody>
</table>

PT: pertussis infection only; CRI: recurrent chest colds, pneumonia or croup, singly or in combination, with or without pertussis; NOCRI: subjects without PT and CRI. ARI: recurrent chest colds, pneumonia or both; NOARI: subjects without ARI.

The distributions of sex, age, socio-economic status (SES) and smoking habits (number of smokers, exsmokers and nonsmokers and pack-years in smokers) are shown in table 2. Proportions by gender, SES and smoking habit did not differ among CRI groups. Likewise, CRI and PT were no more prevalent in any one smoking group or sex. Subjects with CRI were significantly younger.

Sex and SES distributions did not differ between ARI groups, but subjects with ARI were significantly older. In addition, there were significantly more smokers and less exsmokers with ARI, and those with ARI had a greater number of pack-years.

The prevalence rates of respiratory symptoms and physicians’ diagnoses of pulmonary diseases were analysed by smoking categories and age groups. In table 3, age-specific prevalence rates are reported for smokers and nonsmokers in the CRI, PT and NOCRI groups. In nonsmokers aged 8–20 yrs, all symptoms were more prevalent in subjects with CRI; significant associations were observed for wheeze, SOBWHZ and asthma. In smokers and nonsmokers aged 21–44 yrs, chronic cough, chronic phlegm, and either asthma (smokers) or SOBWHZ (nonsmokers) were significantly more prevalent in subjects with CRI.

In the oldest age group (45–64 yrs), all symptoms and reported diagnoses of asthma and COLD were significantly associated with CRI in smokers; only chronic phlegm was significantly more prevalent in nonsmokers with CRI. The analyses in exsmokers for the same age groups showed similar trends to those observed in smokers and nonsmokers but statistical testing was limited by the small number of CRI in all age groups (42 subjects). The effect of smoking cessation was evident since prevalence rates were consistently lower in exsmokers than in smokers.

Table 2. – Distribution of sex, age, socio-economic status and smoking habit according to the presence of respiratory infections in childhood and in adolescence-adulthood

<table>
<thead>
<tr>
<th></th>
<th>CRI (n=374)</th>
<th>PT (n=1,185)</th>
<th>NOCRI (n=1,718)</th>
<th>p</th>
<th>ARI (n=373)</th>
<th>NOARI (n=2,585)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>% 47.5</td>
<td>43.2</td>
<td>50.7</td>
<td>NS*</td>
<td>50.1</td>
<td>48.0</td>
<td>NS*</td>
</tr>
<tr>
<td>Females</td>
<td>% 52.5</td>
<td>56.8</td>
<td>48.4</td>
<td></td>
<td>49.9</td>
<td>52.0</td>
<td></td>
</tr>
<tr>
<td>Age (mean±sd)</td>
<td>30.4±17.0</td>
<td>32.4±15.7</td>
<td>36.0±15.9</td>
<td>&lt;0.001*</td>
<td>39.9±15.6</td>
<td>36.2±14.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Low SES</td>
<td>% 17.6</td>
<td>14.3</td>
<td>16.7</td>
<td>NS*</td>
<td>15.1</td>
<td>15.8</td>
<td>NS*</td>
</tr>
<tr>
<td>Current smokers</td>
<td>% 33.4</td>
<td>38.1</td>
<td>38.2</td>
<td></td>
<td>48.0</td>
<td>40.9</td>
<td></td>
</tr>
<tr>
<td>Exsmokers</td>
<td>% 11.9</td>
<td>13.2</td>
<td>12.4</td>
<td>NS*</td>
<td>35.4</td>
<td>45.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>% 54.7</td>
<td>48.6</td>
<td>49.4</td>
<td>NS*</td>
<td>16.6</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>Pack-years (mean±sd)</td>
<td>12.9±13.7</td>
<td>13.8±13.7</td>
<td>14.7±13.7</td>
<td>NS*</td>
<td>18.1±16.4</td>
<td>13.5±13.0</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

See legend to table 1 for main abbreviations. SES: socio-economic status; #: age in years; °: low SES is defined according to census classification [28–30]; #: cigarettes per day/20 x years smoked; #: by chi-squared test; #: by analysis of variance; ns: p>0.05.
Table 3. Prevalence rates of respiratory symptoms and diseases in relation to CRI, PT and NOCRI in smokers and nonsmokers of different age groups

<table>
<thead>
<tr>
<th></th>
<th>8-20 yrs</th>
<th></th>
<th>21-44 yrs</th>
<th></th>
<th>45-64 yrs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRI %</td>
<td>PT %</td>
<td>NOCRI %</td>
<td>CRI %</td>
<td>PT %</td>
<td>NOCRI %</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cough</td>
<td>5.3</td>
<td>3.9</td>
<td>8.0</td>
<td>25.6</td>
<td>9.4</td>
<td>14.0***</td>
</tr>
<tr>
<td>Chronic phlegm</td>
<td>0</td>
<td>3.9</td>
<td>10.3</td>
<td>19.2</td>
<td>9.0</td>
<td>12.0*</td>
</tr>
<tr>
<td>Wheeze</td>
<td>10.5</td>
<td>3.9</td>
<td>9.2</td>
<td>3.8</td>
<td>4.5</td>
<td>3.8</td>
</tr>
<tr>
<td>SOBWHZ</td>
<td>5.3</td>
<td>2.6</td>
<td>0</td>
<td>3.8</td>
<td>1.6</td>
<td>1.8</td>
</tr>
<tr>
<td>COLD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asthma</td>
<td>5.3</td>
<td>2.6</td>
<td>0</td>
<td>2</td>
<td>1.6</td>
<td>0.3***</td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>76</td>
<td>87</td>
<td>78</td>
<td>244</td>
<td>343</td>
</tr>
</tbody>
</table>

|        |        |          |          |          |          |          |          |          |          |
| Nonsmokers|        |        |          |          |          |          |          |          |          |
| Chronic cough | 3.4 | 0.7 | 0.07 | 10.3 | 2.8 | 2.1* | 4.3 | 4.6 | 5.2 |
| Chronic phlegm | 3.4 | 1.5 | 1.0 | 10.3 | 1.1 | 4.5* | 11.4 | 3.8 | 2.6** |
| Wheeze | 8.5 | 3.0 | 1.7 | 7.7 | 2.1 | 2.8 | 4.3 | 2.3 | 4.1 |
| SOBWHZ | 11.9 | 3.3 | 4.8* | 5.1 | 1.7 | 0.7** | 2.2 | 3.8 | 3.7 |
| COLD | - | - | - | 0 | 0 | 0.03 | 2.2 | 3.8 | 3.7 |
| Asthma | 15.3 | 4.8 | 4.5*** | 2.6 | 2.8 | 2.8 | 2.2 | 0.8 | 0 |
| n | 118 | 269 | 291 | 39 | 176 | 287 | 46 | 131 | 270 |

See legend to table 1 for main abbreviations; SOBWHZ: shortness of breath associated with wheeze; COLD: chronic obstructive lung disease; §: prevalence rates within CRI, PT and NOCRI groups; *: p<0.05; **: p<0.01; ***: p<0.001; comparison among groups by chi-squared test.

Table 4. Prevalence rates of respiratory symptoms and diseases in relation to ARI and NOARI in smokers and nonsmokers of different age groups

<table>
<thead>
<tr>
<th></th>
<th>12-20 yrs</th>
<th></th>
<th>21-44 yrs</th>
<th></th>
<th>45-64 yrs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARI %</td>
<td>NOARI %</td>
<td>ARI %</td>
<td>NOARI %</td>
<td>ARI %</td>
<td>NOARI %</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic cough</td>
<td>22.2</td>
<td>4.3**</td>
<td>25.8</td>
<td>11.7***</td>
<td>61.8</td>
<td>23.2***</td>
</tr>
<tr>
<td>Chronic phlegm</td>
<td>16.7</td>
<td>5.5</td>
<td>18.3</td>
<td>10.7</td>
<td>60.3</td>
<td>22.6***</td>
</tr>
<tr>
<td>Wheeze</td>
<td>16.7</td>
<td>6.1</td>
<td>7.5</td>
<td>3.0***</td>
<td>23.5</td>
<td>6.5***</td>
</tr>
<tr>
<td>SOBWHZ</td>
<td>5.6</td>
<td>1.2</td>
<td>6.5</td>
<td>1.2***</td>
<td>16.2</td>
<td>1.2***</td>
</tr>
<tr>
<td>COLD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.4</td>
<td>0.3**</td>
</tr>
<tr>
<td>Asthma</td>
<td>5.6</td>
<td>1.2</td>
<td>3.2</td>
<td>0.5***</td>
<td>19.1</td>
<td>0.9***</td>
</tr>
<tr>
<td>n</td>
<td>18</td>
<td>163</td>
<td>93</td>
<td>572</td>
<td>68</td>
<td>323</td>
</tr>
</tbody>
</table>

|        |        |          |          |          |          |          |
| Nonsmokers|        |        |          |          |          |          |
| Chronic cough | 2.7 | 0.6 | 14.3 | 2.1** | 13.3 | 2.9** |
| Chronic phlegm | 5.4 | 1.2 | 8.6 | 3.4 | 11.7 | 2.6** |
| Wheeze | 13.5 | 1.8*** | 14.3 | 1.9*** | 11.7 | 2.5** |
| SOBWHZ | 10.8 | 3.6 | 8.6 | 0.9*** | 13.3 | 2.1*** |
| COLD | - | - | 0 | 0.2 | 3.3 | 0.0*** |
| Asthma | 16.2 | 4.9** | 17.1 | 1.3*** | 13.3 | 2.1*** |
| n | 37 | 329 | 35 | 467 | 60 | 285 |

See legends to tables 1 and 3 for abbreviations. §: prevalence rates within ARI and NOARI groups.

Prevalence rates of respiratory symptoms and physicians' diagnoses of asthma and COLD by smoking categories and age groups is reported in table 4 for ARI. The number of subjects reported in this table is lower than that of table 3, because only those aged >12 yrs answered the question on the presence of ARI. All symptoms were more prevalent in smokers aged 12-20 yrs who complained of ARI; a significant association was observed for chronic cough. In nonsmokers of the same age, all symptoms were more prevalent in ARI; significant associations were present for wheeze and asthma. All symptoms, with the exception of chronic phlegm and COLD, were significantly more prevalent in subjects aged 21-44 yrs with ARI, for both smoking groups. All symptoms and diseases were significantly related to ARI in smokers and nonsmokers of the oldest age group. In exsmokers, the prevalence rate of symptoms and diseases was higher in subjects with ARI in all
age groups, but significant associations were observed in a few instances. The effect of smoking cessation was evident in the analyses as well.

In figure 1, the percentage predicted forced expiratory volume in one second (FEV$_1$), Vmax$_{50}$ and Dlcorb, adjusted for sex, smoking and age, are reported for subjects with CRI, PT and NOCRI. Analysis of variance showed that lung function parameters were significantly lower in CRI subjects (p<0.05), especially FEV$_1$ (p<0.001). When CRI subjects were excluded from the analyses, lung function parameters of subjects with pertussis (after the same adjustments) were lower than those of NOCRI subjects, though the difference was not statistically significant.

![Fig. 1. Percentage predicted lung function parameters adjusted for sex, age and smoking in CRI, PT and NOCRI groups. The difference was evaluated by analysis of variance (**: p<0.001; *: p<0.05). The number of subjects in each group is smaller than that reported in table 3 because some were not able to correctly perform lung function tests. See legends to tables 1 and 6 for abbreviations. □: NOCRI=1,475; Ⓡ: PT=1,000; ■: CRI=290.](image)

The prevalence rate of ARI (i.e., recurrent chest colds and/or pneumonia after 12 yrs) was significantly higher in subjects who reported CRI both in smokers (34.1% vs 13.1% in PT and 11.6% in NOCRI) and in nonsmokers (31.6% vs 8.4% in PT and 7.2% in NOCRI). Hence, we have investigated the presence of respiratory symptoms, diseases and lung function impairment in subjects who reported: 1) both CRI and ARI (CRI-ARI); 2) CRI per se; 3) ARI per se or in association with PT (ARI-PT); and 4) no CRI, no ARI with or without PT (since PT per se did not show in the previous analyses an important effect on respiratory symptoms and lung function) (PT-NODIS).

In table 5, the prevalence rates of symptoms and diseases are reported in smokers and nonsmokers of all ages for the groups mentioned above. In smokers, all symptoms and diseases were significantly more prevalent in subjects of the CRI-ARI group. Also subjects who complained of ARI singly or in combination with PT (PT-ARI) showed higher prevalence rates with respect to subjects of CRI, PT-NODIS groups. Smokers with CRI still had higher prevalences of SOBWHZ and asthma than those of PT-NODIS. In nonsmokers, prevalence rates were consistently lower; subjects of CRI-ARI and PT-ARI groups showed the highest prevalence rates, followed by those of CRI and PT-NODIS groups. Again, CRI subjects also showed higher prevalence rates when compared to those of PT and NODIS groups; prevalence rates for all symptoms and diseases were significantly different.

![Fig. 2. Percentage predicted lung function parameters adjusted for sex, age and smoking in CRI-ARI, PT-ARI, CRI-ARI and PT-NODIS. The difference was evaluated by analysis of variance (**: p<0.001; *: p<0.05). The number of subjects in each group is smaller than that reported in table 3 because some were not able to correctly perform lung function tests. See legends to tables 1 and 6 for abbreviations. □: PT-NODIS=1,925; Ⓡ: CRI=169; ■: CRI-ARI=79.](image)
Table 6. Multiple logistic models for different risk factors related to respiratory symptoms, diseases and lung function

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Dependent variables</th>
<th>Odds ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cough</td>
<td>Phlegm</td>
</tr>
<tr>
<td>Age</td>
<td>1.22</td>
<td>1.22</td>
</tr>
<tr>
<td>CRI</td>
<td>1.55*</td>
<td>1.67</td>
</tr>
<tr>
<td>ARI</td>
<td>3.48</td>
<td>2.76</td>
</tr>
<tr>
<td>Smoke§</td>
<td>2.86</td>
<td>2.59</td>
</tr>
<tr>
<td>Pack-years§</td>
<td>1.28</td>
<td>1.27</td>
</tr>
</tbody>
</table>

SOBWHZ: shortness of breath associated with wheeze; COLD: chronic obstructive lung disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; Vmax_50: maximum flow at 50% FVC; DLcosb: single-breath diffusing capacity for carbon monoxide; CRI: recurrent chest colds, pneumonia or croup, singly or in combination, with or without pertussis (all subjects); ARI: recurrent chest colds, pneumonia or both (age >12 yrs); §: considering "non-normals", those with values below 95th percentile [28, 29], except for FEV_1/FVC (see text). *: smoker vs nonsmoker.

Mean values of percentage predicted FEV_1, Vmax_50, and DLcosb adjusted for age, sex and smoking habits are reported in figure 2 for the four groups. Lower values of %FEV_1 and %DLcosb were present in subjects with both CRI and ARI, PT-ARI and ARI alone; percentage predicted Vmax_50 was lower in PT-ARI, CRI-ARI and ARI alone. Analysis of variance showed significant difference for all the parameters.

In order to evaluate the role of the different risk factors for OAD, multiple logistic models were performed, considering respiratory symptoms, diseases, and lung function impairment as dependent variables. Age, smoking habits (smokers vs nonsmokers and pack-years), CRI and ARI were the independent variables. Odds ratios are reported in table 6. CRI and ARI were selected in the models for the symptoms and diseases, and the coefficients were significant for almost all the dependent variables; the highest odds ratios were present for ARI, especially in relation to the presence of COLD, SOBWHZ, asthma and wheeze. The role of smoking variables and of age was confirmed. With regard to lung function parameters, cases were those with percentage predicted values below the 95th percentile [28, 29], with the exception of FEV_1/FVC% when values below 70% were considered as abnormal. Smoking habits, pack-years and age (as expected) were significantly selected in the models with the exception of smoke for FEV_1%, FEV_1/FVC% and Vmax_50. ARI and CRI showed significant coefficients except for DLcosb.

Discussion

The results of the present study support the hypothesis that both CRI and ARI may affect the presence of respiratory symptoms, asthma, COLD and reduced lung function in adulthood. This cross-sectional analysis confirms the previous cross-sectional observations of Burrows et al. [19, 20] and Lebowitz et al. [13] also obtained in a general population sample.

Our analyses were also performed in subjects aged 8–20 yrs, thus a short-term effect of CRI on the development of respiratory symptoms and lung function impairment has been evaluated. CRI in young nonsmokers was associated with the presence of wheeze, SOBWHZ and asthma suggesting that the presence of bronchial lability may be related to the history of respiratory diseases in childhood. Our observations confirm the results of Weiss et al. [9], and support the hypothesis that the pathological changes caused by CRI may be responsible for acquired bronchial hyperresponsiveness. Some of these subjects may have an individual host susceptibility to develop bronchial hyperreactivity and respiratory infections may be the initiating cause. Another possible explanation is that respiratory diseases (recurrent chest colds, pneumonia) may cause anatomical changes which may alter the threshold response to irritants and thus lead to bronchial hyperresponsiveness.

The association between wheeze, SOBWHZ, asthma and CRI was not present in smokers of the same age possibly due to self-selection. However, asthma was significantly higher in smokers with CRI in the 21–44 yrs age group, and SOBWHZ was significantly higher in nonsmokers of the same age. In this age group, chronic cough and phlegm were higher in smokers and nonsmokers implying some continued mucus hypersecretion even in the absence of smoking [34], as suggested also by the only significantly higher prevalence of chronic phlegm in nonsmokers aged 45–64 yrs. The effect of smoking and its association with CRI is even more evident in the oldest age group, where older subjects smoked more pack-years, as found by Burrows et al. [19]. In nonsmokers of the oldest ages, the relationships of CRI and respiratory symptoms were not present. This suggests that the absence of smoking in those subjects with CRI appears to prevent the negative effects of respiratory diseases in childhood. In the exsmokers of the older age groups, the effect of smoking cessation is evident by the reduction of symptoms and diseases.

Our cross-sectional results are in accordance with the
recent longitudinal data of Britten et al. [27], after a follow-up of thirty years, subjects with respiratory infections in childhood showed higher prevalence rates of respiratory symptoms and reduced lung function.

The high prevalence rate of pertussis in our sample may be ascribed to the absence of a national immunization programme in our country. However, the PT data might be biased since our data are derived from a questionnaire and not from serological or cultural diagnoses. Nevertheless, family practitioners are well trained in the clinical detection of "whooping cough". We did not find relationships between the presence of PT per se and respiratory symptoms and diseases. The question on pertussis was based on the presence of the disease before 12 yrs of age, and probably the sequelae caused by pertussis are important only in subjects who complained of this disease in very early childhood. Indeed, a recent paper of Johnston et al. [35] based on a case-control study, where the cases were children admitted to the hospital for pertussis in the first year of life, pointed out no important respiratory consequences nine years after the episode (they observed only a minor effect on respiratory symptoms).

In our study, the presence of CRI, after having taken into account age, sex and smoking, is associated with a reduced level of lung function parameters such as FEV₁, Vmax₉₀ and CO diffusing capacity. This result supports the hypothesis that functional impairment may be caused by anatomical lesions in childhood since the lungs during growth are more susceptible to the insult of infectious diseases [3-5]. Therefore, lower FEV₁ and Vmax₉₀ may reflect the presence of airflow obstruction related to the "sequelae" of CRI and to the subsequent damage that can be caused by cigarette smoking. The presence of lower Dlcosb values probably reflects early ventilation/perfusion inequalities and/or diffusion limitation caused by anatomical changes, as observed in asymptomatic smokers [36, 37]. A similar result, though not statistically significant, was obtained when the analyses were performed excluding CRI subjects, indicating that the history of PT per se may be related to reduced lung function values, though to a minor degree.

Our results point out the strong association of respiratory symptoms and diseases with the presence of a past history of recurrent chest colds and pneumonia in all age groups. The effects of ARI also appear to be important during adolescence-adulthood. It was not surprising to find the additional effect of smoking in the 45-64 yrs age group with ARI, since a higher susceptibility to infectious episodes has been reported in smokers [38, 39]. In the older age group especially, ARI may be considered as a manifestation of underlying chronic disease or exacerbations of current disease. The higher prevalence rates of both chronic cough and phlegm in older smokers with ARI may indicate that probably many "recurrent chest colds" are not diagnosed as "chronic bronchitis" by physicians. On the other hand, significant associations between respiratory symptoms, diseases and ARI were also found in nonsmokers. This result may imply a role of individual host susceptibility as an important risk factor in the complex multifactorial process of the development of OAD.

We observed a significantly higher prevalence of ARI in subjects who reported CRI, both in smokers and nonsmokers. In addition, the highest prevalence rates of symptoms, diagnoses and reduced lung function were found in subjects who reported both these conditions, especially in smokers (table 5, fig. 2).

The higher prevalence of ARI in subjects with CRI may be ascribed to an increased susceptibility to bronchial irritants after the insults of CRI or to altered lung growth (due to CRI); these changes probably facilitate respiratory infections. We may also consider subjects who reported CRI as those "sick" during adolescence-adulthood, and the presence of ARI reflects this "chronic condition". In an attempt to clarify this aspect, we looked at the age of onset of asthma (as assessed by the questionnaire) in subjects who reported both CRI and ARI (n=85). There were 17 subjects (20.0%) who reported the diagnosis of asthma before 15 yrs and 10 (11.7%) after 15 yrs. In the former, the presence of ARI probably reflects the consequence of a chronic condition since childhood; in the latter, ARI may be responsible in part for the development of asthma or asthmatic bronchitis later in life.

Furthermore, the analyses of lung function suggest that the subjects with CRI-ARI may be at higher risk of developing OAD. Indeed, they have reduced lung function and the highest prevalence of subjects with FEV₁/FVC% less than 70% was observed in this group: 32.1% vs 24.0%, 18.2%, 16.7%, in PT-ARI, CRI, and PT-NODIS groups, respectively. This implies some consistencies, since Burrows et al. [40] have recently demonstrated that FEV₁/FVC% at the onset of study is significantly related to the longitudinal decline of FEV₁.

The results from the multiple logistic models (table 6) were able to point out the role of CRI and ARI among the well known risk factors, such as age and smoking variables. The coefficients were significant for the reported symptoms and diagnoses, and for lung function. The use of this more complex and powerful statistical method showed the effect of CRI and ARI especially for the wheezy syndromes.

Our findings regarding the effect of ARI on respiratory symptoms and lung function confirm the importance of infectious episodes among the risk factors related to the pathogenesis of OAD. Infectious episodes do not necessarily reflect mucus hypersecretion and vice versa and consequently the presence of airway obstruction as demonstrated by Fletcher et al. [41]. In fact, our results point out the association of wheezy symptoms with ARI in nonsmokers also, confirming the effect of respiratory infections on bronchial reactivity [7-11]. Thus, our observations suggest that the "British hypothesis" should be reconsidered only with regard to the importance of infectious episodes in determining inflammatory changes which may lead to increased bronchial hyperreactivity in association with or without mucus hypersecretion.

The results of the present study are based on the retrospective analysis of the presence of CRI and ARI. Thus, they may be biased by the "preferential recall" of subjects who reported respiratory symptoms and diagnoses. Indeed, the mean age of subjects who reported CRI
was significantly lower than that of subjects in the PT and NOCRI groups, suggesting a better recall of those who had recent respiratory events. This possible effect was present in previous epidemiological studies dealing not only with childhood respiratory diseases but also with respiratory symptoms and diseases [1, 6, 9, 13, 19–20]. In addition, it is a limitation present in all cross-sectional studies. This result was also present in the cross-sectional analysis of Burrows et al. [19]. However recent cross-sectional and longitudinal analyses of children [13, 27, 42–45] indicate otherwise, and confirm the importance of CRI and ARI. In addition, in our questionnaire, the presence of different respiratory diseases with paediatric age, as well as in adolescence-adulthood, were investigated separately in the attempt to focus attention to each single disease using precise temporal allocations as pointed out by Samet et al. [46]. Therefore, analyses performed after age stratification (i.e. similar age-related recall characteristics) and precise assessments of respiratory diseases, should have been able to reduce this possible error.

In conclusion, our results, obtained by a cross-sectional study in a large general population sample, confirm the relationships between CRI, ARI and the presence of respiratory symptoms, diseases and lung function impairment. In addition our observations indicate that certain subjects have a susceptibility to develop “respiratory sequelae” (the presence of CRI and ARI later in life) and that these subjects are those with lung function impairment and are probably those who may develop OAD. Finally, the ongoing follow-up of these subjects will allow the possible confirmation of these results.

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