Urban Residence Is Associated With Bronchial Hyperresponsiveness in Italian General Population Samples*

Sara Maio, BSc; Sandra Baldacci, BSc; Laura Carrozzi, MD; Eva Polverino, MD; Anna Angino; Francesco Pistelli, MD; Francesco Di Pede; Marzia Simoni, BSc; Duane Sherrill, BSc; and Giovanni Viegi, MD

Background: The role of different risk factors for bronchial hyperresponsiveness (BHR), such as gender, atopy, IgE, and environmental factors (smoking, occupational exposure, infections), has been described. Indoor and outdoor pollution play an important role too, but few studies have analyzed the association with BHR. The aim of this study was to assess the effect of urban residence on BHR.

Methods: We studied two general population samples enrolled in two cross-sectional epidemiological studies performed in Northern Italy (Po Delta, rural area) and Central Italy (Pisa, urban area). We analyzed 2,760 subjects (age range, 8 to 74 years). We performed analysis of variance and logistic regression analysis using ln slope of the dose-response curve of the methacholine challenge test as dependent variable, and sex, age, smoking habits, respiratory symptoms, skin-prick test results, IgE value, residence, and airway caliber as independent variables.

Results: The mean value of ln slope of the dose-response curve adjusted for initial airways caliber (by baseline FEV1 percentage of predicted value) was significantly higher in female subjects, in smokers, in subjects with respiratory symptoms, in younger and older ages, in subjects with high values of IgE, and in subjects with positive skin-prick test results. After controlling for the independent effects of all these variables, living in urban area was an independent risk factor for having BHR (odds ratio, 1.41; 95% confidence interval, 1.13 to 1.76).

Conclusion: Living in urban area is a risk factor for increased bronchial responsiveness.

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Key words: bronchial responsiveness; epidemiology; general population; methacholine; risk factors; urban

Abbreviations: ANOVA = analysis of variance; BHR = bronchial hyperresponsiveness; BR = bronchial responsiveness; CI = confidence interval; CNR = National Research Council; MCT = methacholine challenge test; OR = odds ratio; PD20 = provocative dose of methacholine inducing a fall of 20% in FEV1

Bronchial responsiveness (BR) to nonspecific agents has been widely used in both clinical and epidemiological studies. Bronchial hyperresponsiveness (BHR) appears related to the development of COPD\(^1\); it is also an important characteristic of asthma according to the American Thoracic Society definition criteria\(^2\) and Global Initiative for Asthma guidelines.\(^3\)

*From the Pulmonary Environmental Epidemiology Unit (Ms. Maio, Ms. Baldacci, Ms. Angino, Ms. Simoni, and Mr. Di Pede, and Dr. Polverino), Institute of Clinical Physiology, National Research Council, Pisa, Italy; Cardiopulmonary Department (Drs. Carrozzi and Pistelli), University and Hospital, Pisa, Italy; College of Public Health (Mr. Sherrill), University of Tucson, Tucson, AZ; and Institute of Biomedicine and Molecular Immunology (Dr. Viegi), National Research Council, Palermo, Italy. The authors have no financial or other potential conflicts of interest to disclose.

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Correspondence to: Giovanni Viegi, MD, CNR Institute of Clinical Physiology, Via Trieste 41, 56126 Pisa, Italy; e-mail: viegig@ifc.cnr.it

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Many studies have described the role of different risk factors for BHR, such as host factors (gender, age) and environmental factors (smoking habits, occupational exposure, infections). Atopy, defined as a genetic predisposition toward developing immediate hypersensitivity reactions against environmental allergens and indicated by positive skin-prick test result or elevated IgE concentration, has a close association with BHR.\(^6\)\(^5\)

We observed a significant father/son correlation in the slope of methacholine dose-response curve in an Italian general population sample; moreover, when performing a segregation analysis in families of smokers, evidence of Mendelian inheritance of BHR was found. This suggests a gene/environment (smoking habit) interaction in the inheritance of BHR.\(^6\)

As for the relationship between BHR and respiratory symptoms, in a cross-sectional study performed in approximately 1,900 Dutch subjects, those with airway responsiveness were more likely to be symptomatic than nonresponders, regardless of smoking habit.\(^7\) Moreover, Palmer et al\(^8\) showed that airway responsiveness to inhaled histamine in early life predicts asthma development, lower respiratory tract symptoms, and reduced spirometric indexes by school age.

Indoor and outdoor pollution may play an important role, but few studies analyzed the association with BHR.\(^9\)\(^-\)\(^11\) The aim of our study was to evaluate the relationship between BHR and living in different Italian areas (urban vs rural).

### Materials and Methods

#### Populations

We analyzed two general population samples enrolled in two cross-sectional epidemiological studies performed in Northern and Central Italy: the Po Delta and Pisa studies.\(^12\) Among the 2,841 survey participants in the Po Delta study, 1,602 subjects (56%) performed the MCT,\(^2\) while 1,239 subjects did not perform it or interrupted the maneuver (Table 1).

#### Data Collection

All subjects completed an interviewer-administered standardized respiratory questionnaire, developed by the CNR. According, subjects were classified for the analysis into three mutually exclusive categories following a priority order: (1) asthma-like subjects, with diagnosis of bronchial asthma confirmed by a physician, or persistent wheezing, or lifetime breathlessness attacks associated with wheezing; (2) chronic bronchitis-like subjects, with chronic cough, or chronic phlegm, or diagnosis of chronic bronchitis or emphysema confirmed by a physician; and (3) "others," without bronchitic or asthmatic symptoms.

In addition, the investigated subjects performed skin-prick tests to common airborne allergens,\(^13\)\(^,\)\(^14\) serum IgE determination,\(^15\) lung function tests,\(^16\)\(^-\)\(^18\) and BR to MCT.\(^6\)\(^,\)\(^18\) Details are described in the Web-only material.

**Atopy:** Total serum immunoglobulin E (IgE) were measured using a direct paper radioimmunosorbent test and were transformed in logarithm\(_{10}\) values (log IgE) to obtain a normal distribution.\(^13\) The sensitization to 12 local allergens (pollens, house dust mites, animal danders, molds) was assessed by skin-prick test reactivity using a standardized protocol.\(^14\) A skin-prick test result was considered positive if it yielded a mean wheal diameter ≥ 3 mm than that determined by the negative control.

**Lung Function Tests:** A pneumotachograph and a water-sealed spirometer were used for measuring flows and volumes in the Po Delta and in Pisa studies, respectively.\(^16\)\(^-\)\(^17\) Each subject performed slow vital capacity, single-breath diffusing capacity for carbon monoxide, FVC, and derived forced expiratory flows. For the latter, reference equations derived from normal subjects within the samples were used to calculate predicted values.\(^19\)\(^,\)\(^20\)

**MCT:** Among the tests used for assessing BR, we selected the nonspecific bronchial challenge test with methacholine, which is the most commonly used in clinical settings because it is standardized, easy to perform, not expensive, reproducible, and able to elicit a dose-response curve. As subsequently indicated by the American Thoracic Society statement, the MCT has a very good sensitivity.\(^21\)

Incremental doses of methacholine were administered up to the maximum of 4.8 mg or when the fall of FEV\(_1\) percentage compared to the post-saline solution value was > 20%.\(^6\)\(^,\)\(^18\) The results were expressed using a continuous variable to characterize BR, the slope of dose-response curve, as suggested by O'Connor et al\(^22\): the percentage decrement of FEV\(_1\)/dose, \(ie\), the fall in FEV\(_1\) (from the post-saline solution value) after the final administered methacholine dose divided by the final administered cumulative dose.

The slope was transformed using the natural logarithm (ln slope) because the data distribution was highly skewed, and a small constant (+ 2.57) was added to allow ln transformation of negative and zero values. Values of ln slope were adjusted for the initial airway caliber by FEV\(_1\) percentage.

#### Statistical Analysis

Analyses were performed using statistical software (SPSS 13.0 for Windows; SPSS; Chicago, IL). The dependent variable was the slope (ln transformed) of the dose-response curve. Analysis of variance (ANOVA) was used to compare mean values of ln slope, adjusted for initial airway caliber (by FEV\(_1\) percentage), between gender, decades of age, respiratory symptoms, smoking groups, log IgE (dichotomized through the 75th percentile value: 1.93 kU/L), skin-prick test reaction (negative, positive), and residence (urban, rural). We also performed logistic regression models by using the same independent variables and ln slope (dichotomized through the 75th percentile value: 2.21) as dependent variable.

### Results

#### Selection of the Samples

**Po Delta Sample:** Among the 2,841 survey participants, 1,602 subjects (56%) performed the MCT, while 1,239 subjects did not perform it or interrupted the maneuver (Table 1).

**Pisa Sample:** Among the 2,841 survey participants, 2,556 subjects were eligible because subjects > 75
years old (n = 285) were invited to answer the questionnaire only. Among the eligible participants, 1,158 subjects (45%) performed the MCT, while 1,398 subjects did not perform it or interrupted the maneuver (Table 1).

There were significant differences among the two samples. When considering subjects performing MCT, in Po Delta there were a lower prevalence of male gender and of symptoms, a higher prevalence of smokers, and people were younger with a lower FEV₁ percentage of predicted. Except for the latter and for gender, the same results were found when considering the subjects not performing or refusing the test (Table 2). Moreover, within each sample, subjects either not performing or refusing the MCT were significantly older, had a lower prevalence of smokers, had a higher prevalence of respiratory symptoms, and had a higher prevalence of female gender with lower mean value of FEV₁ percentage of predicted, with respect to those performing MCT (Table 2).

The use of dose-response curve slope allows to determine a measure for all subjects, avoiding the censoring effect inherent in the provocative dose of methacholine inducing a fall of 20% in FEV₁ (PD₂₀). Indeed, in our data the slope was significantly related to PD₂₀ values, supporting its usefulness in epidemiological studies. The results showed that 41% of subjects with a slope > 2.21 reached a PD₂₀ with a dose of methacholine < 1 mg and 54% reached it with a dose of methacholine from 1 to 4.8 mg (Table 3). Using a cutoff of 4.8 mg of methacholine for PD₂₀ considered as a “gold standard,” we have evaluated that the 75th percentile of ln slope has a sensitivity of 80% and a specificity of 98% for indicating the presence of BHR.

### BHR Values and Determinants

The mean ln slope value of the dose-response curve adjusted for initial airways caliber was signifi-

| Table 1—Reasons for Not Performing or Interrupting the MCT* |
|---------------------------------|----------------|----------------|
| Variables                        | Po Delta       | Pisa           |
| Not performed                    |                |                |
| Refusal                          | 774 (62.4)     | 763 (54.6)     |
| Inability to perform the test    | 109 (8.8)      | 87 (6.2)       |
| Baseline FEV₁ < 70%              | 41 (3.3)       | 50 (3.6)       |
| Reported cardiac or hypertensive | 228 (18.4)     | 384 (27.5)     |
| or neurologic disorders or       |                |                |
| recent infectious episodes        |                |                |
| Interrupted                      |                |                |
| Decrement ≥ 10% in FEV₁          | 39 (3.2)       | 70 (5.0)       |
| percentage after receiving buffer solution | |                |
| Medical or technical reasons     | 48 (3.9)       | 44 (3.1)       |
| Total                            | 1,239 (100)    | 1,398 (100)    |

*pData are presented as No. (%).

| Table 2—Characteristics of Subjects Performing, Not Performing, and Refusing the MCT* |
|---------------------------------|----------------|----------------|
| Characteristics                | Po Delta       | Pisa           |
|                                | (n = 1,239)    | (n = 1,398)    |
| Male gender                    | 51.8‡,§         | 55.6‡,§**      |
| Age, yr                        | 33.1 ± 14.9‡,§ | 37.5 ± 16.1‡,§ |
| Smokers                        | 31.6‡,§ NS      | 26.9‡,**       |
| Ex-smokers                     | 25.2            | 29.0           |
| Any symptoms                   | 28.7‡,§ NS      | 33.2‡         |
| FEV₁, % of predicted           | 103 ± 12.4‡,§ | 107.5 ± 13.4‡,** |

*pData are presented as % or mean ± SD. NS = not significant.

†p < 0.05, comparison of subjects who performed MCT vs those who did not in Po Delta sample.
‡p < 0.001, comparison of subjects who performed MCT vs those who did not in Po Delta sample.
§p < 0.001, comparison of subjects who performed MCT vs those who refused in Po Delta sample.
¶p < 0.01, comparison of subjects who performed MCT vs those who did not in Pisa sample.
†p < 0.01, comparison of subjects who performed MCT vs those who did not in Pisa sample.
‡p < 0.01, comparison of subjects who performed MCT vs those who refused in Pisa sample.
**p < 0.001, comparison of subjects who performed MCT vs those who refused in Pisa sample.

| Table 3—Comparison Between BHR Assessed by PD₂₀ and By Dose-Response Curve Slope |
|---------------------------------|----------------|----------------|
| PD₂₀                            | ln Slope < 2.21 | ln Slope ≥ 2.21 |
|                                | (n = 2,081) %  | (n = 679) %    |
| High (< 1 mg of methacholine)   | 40.9*           |                |
| Medium (1 to 4.8 mg of methacholine) | 7.6†          | 54.1†          |
| Nonresponders                   | 92.4            | 5.0            |

*Median PD₂₀, 0.54 mg
†Median PD₂₀, 1.75 mg
‡Median PD₂₀, 3.90 mg

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cantly higher in Pisa than in Po Delta in both genders (Fig 1a–1b). Mean ln slope values by gender, age, smoking habits, respiratory symptoms/diseases, skin-prick test, and IgE, stratified by residence, are shown in Table 4.

The mean ln slope value was significantly higher in female than in male subjects in both samples. Mean slope values showed a “U” pattern from the youngest to the oldest 10-year age group, in both samples. In Pisa, the slope values began to go up from 25 to 34 years, while in Po Delta from 45 to 54 years. Moreover, in Pisa, the highest slope values were reached at 65 to 74 years while in Po Delta at 8 to 14 years. “Current smokers” showed mean slope values significantly higher than “ex-smokers” and “never-smokers” in Po Delta; the same difference, although not significant, was observed in Pisa. In both samples, mean ln slope values showed a significantly increasing trend from the “others” through the “chronic bronchitis-like subjects” up to the “asthma-like subjects”; further, mean ln slope values were significantly higher in atopic subjects (high values of IgE or positive skin-prick test reaction).

By logistic regression analysis, the risk factors significantly associated with an elevated ln slope value were as follows: female gender, younger age (8–14 years and 15–24 years), current smokers, asthma-like subjects, positive skin-prick test reaction, and elevated log IgE value (Table 5). Moreover, airway caliber had a significant protective relationship with BHR. After controlling for the independent effects of all these variables, people living in the urban area had an odds ratio (OR) of 1.41 of getting BHR with respect to people living in the rural area (Table 5). No significant association was found between BHR and either work or passive smoking exposure.

**Discussion**

We have confirmed the important role of several risk factors for BHR. The significantly higher risk of an elevated ln slope of the dose-response curve in female subjects is in agreement with previous studies on adults19,23,24 and on children.25 Possible mechanisms, as reported by Paoletti et al.,18 are a higher cholinergic irritability in female subjects and hormonal differences related to sex (such as pregnancy and menstrual cycle).

The distribution of BR by age showed a “U” pattern, with the highest values corresponding to the youngest and oldest ages. Sparrow and Weiss26 had already indicated larger BHR values at the age extremes. These results were confirmed partially by Renwick and Connolly,27 who described a weak positive association between BHR and age in a population sample aged 45 to 86 years, and by Schwartz et al.,28 who found the highest BHR values in the younger subjects within a sample aged 18 to 60 years.

Current smokers in both our samples had the largest BHR values, with an OR of 1.39 for getting an elevated slope. The tendency to an increased BR for smokers has been observed in previous studies,23,29 and it has been supported by pathological evidences of important changes in large and peripheral airways induced by smoke, which lead to different degrees of airway obstruction. Moreover, Mitsunobu and associates30 reported that the cumulative dose of methacholine causing a significant increase in total respiratory resistance was significantly lower in asthmatics with a smoking history than in those without it.

We also showed a strong relationship between chronic bronchitis-like or asthma-like symptoms and the risk for BHR (OR, 1.30 and OR, 2.65, respectively), bringing further evidence to a reappraisal of the Dutch hypothesis.31,32 Furthermore, our findings underline the association of a positive skin reactivity (OR, 1.32) or of higher total IgE values (OR, 1.61) with an enhanced BR, according to other studies.24,33–35

We also confirmed the inverse relationship between airway caliber and BHR,28,36,37 which could be ascribed
to anatomic, mechanical, and mathematical factors: the flow resistance in a tube is inversely proportional to the radius of the tube to the fourth power. This leads to a proportionally greater resistance for a narrow airway. Hence, the influence of baseline lung function must be accounted for when analyzing BHR.

**BHR and Urban Residence**

In our investigation, after controlling for the independent effects of gender, age, smoking habits, respiratory symptoms/diseases, and atopic status, residence in an urban area appears to be an independent risk factor for BHR (OR, 1.41; 95% confidence interval [CI], 1.13 to 1.76). Interestingly, such an OR is of the same magnitude as the one for active smoking (1.39).

Likely, there is higher outdoor air pollution in urban than in rural areas. Indeed, when we had evaluated pollutants (sulfur dioxide, total suspended particulate) from the two areas, we had found higher mean annual levels in Pisa than in Po Delta, with differences of 40 µg/m³ for total suspended particulate (94 µg/m³ and 54 µg/m³, respectively) and 7 µg/m³ for sulphur dioxide (15 µg/m³ and 8 µg/m³, respectively). The Study on Air Pollution and Lung Diseases in Adults also found that the annual average concentration of air pollutants was higher in urban areas than in rural/alpine areas. Moreover, it showed a relationship between annual average air pollution concentration and decrement in lung function parameters: for example, a 1.59% reduction in FEV₁ was estimated in healthy never-smokers for a 10 µg/m³ increase of particulate matter with aerodynamic diameter ≤ 10 µm.

The prevalence rates of respiratory symptoms and the chromosome aberrations baseline frequency were significantly higher in Pisa than in Po Delta. These findings might be due to the larger exposure to air pollution in Pisa. An indication of this hypothesis comes from the data regarding the self-perception of air pollution exposure: 55% of the Pisa subjects reported exposure to air pollution sources (industrial fumes/gases and traffic), while only 15% of Po Delta subjects did so. A study in Scotland highlighted that urban residence is associated with worse respiratory health status or quality of life among subjects reporting respiratory symptoms/diseases than rural residence. Moreover, people living in the urban area of Pisa had a higher value of serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts than people living in the suburban area of Pisa.

### Table 4—Mean Values of ln Dose-Response Slope Adjusted for FEV₁ Percentage of Predicted by the Independent Variables in the Two Samples

<table>
<thead>
<tr>
<th>Variables</th>
<th>Po Delta (n = 1,602)</th>
<th>95% CI</th>
<th>p Value</th>
<th>Pisa (n = 1,158)</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.75 (n = 830)</td>
<td>1.70–1.81</td>
<td>&lt; 0.001</td>
<td>1.80 (n = 644)</td>
<td>1.73–1.87</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.98 (n = 772)</td>
<td>1.92–2.04</td>
<td>2.01 (n = 514)</td>
<td>1.92–2.09</td>
<td></td>
</tr>
<tr>
<td>Age group, yr</td>
<td>8–14</td>
<td>2.02 (n = 139)</td>
<td>1.86–2.19</td>
<td>2.09 (n = 77)</td>
<td>1.82–2.35</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>15–24</td>
<td>1.90 (n = 425)</td>
<td>1.81–1.98</td>
<td>1.78 (n = 237)</td>
<td>1.66–1.90</td>
<td>0.441</td>
</tr>
<tr>
<td></td>
<td>25–34</td>
<td>1.82 (n = 367)</td>
<td>1.73–1.90</td>
<td>1.80 (n = 217)</td>
<td>1.67–1.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35–44</td>
<td>1.76 (n = 277)</td>
<td>1.67–1.85</td>
<td>1.86 (n = 203)</td>
<td>1.74–1.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45–54</td>
<td>1.83 (n = 227)</td>
<td>1.74–1.93</td>
<td>1.89 (n = 210)</td>
<td>1.77–2.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55–64</td>
<td>1.95 (n = 128)</td>
<td>1.82–2.08</td>
<td>2.04 (n = 173)</td>
<td>1.89–2.19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65–74</td>
<td>1.94 (n = 38)</td>
<td>1.66–2.23</td>
<td>2.18 (n = 41)</td>
<td>1.89–2.46</td>
<td></td>
</tr>
<tr>
<td>Smoking habits</td>
<td>Never-smoker</td>
<td>1.87 (n = 692)</td>
<td>1.81–1.93</td>
<td>1.89 (n = 510)</td>
<td>1.80–1.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ex-smoker</td>
<td>1.78 (n = 403)</td>
<td>1.71–1.86</td>
<td>1.86 (n = 336)</td>
<td>1.76–1.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current smoker</td>
<td>1.92 (n = 506)</td>
<td>1.84–2.00</td>
<td>1.93 (n = 312)</td>
<td>1.82–2.04</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms/diseases</td>
<td>Others</td>
<td>1.78 (n = 1,260)</td>
<td>1.74–1.82</td>
<td>1.79 (n = 893)</td>
<td>1.73–1.85</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Chronic bronchitis</td>
<td>1.99 (n = 199)</td>
<td>1.86–2.12</td>
<td>1.94 (n = 131)</td>
<td>1.79–2.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>2.40 (n = 142)</td>
<td>2.19–2.60</td>
<td>2.51 (n = 134)</td>
<td>2.28–2.74</td>
<td></td>
</tr>
<tr>
<td>Skin-prick test result</td>
<td>Negative</td>
<td>1.80 (n = 1,114)</td>
<td>1.76–1.85</td>
<td>1.81 (n = 798)</td>
<td>1.75–1.87</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>2.01 (n = 436)</td>
<td>1.92–2.10</td>
<td>2.05 (n = 321)</td>
<td>1.93–2.17</td>
<td></td>
</tr>
<tr>
<td>Log IgE values</td>
<td>&lt; 1.58*</td>
<td>1.79 (n = 866)</td>
<td>1.74–1.84</td>
<td>1.86 (n = 757)</td>
<td>1.80–1.93</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>≥ 1.93</td>
<td>2.04 (n = 337)</td>
<td>1.93–2.15</td>
<td>2.06 (n = 199)</td>
<td>1.89–2.22</td>
<td></td>
</tr>
</tbody>
</table>

*Corresponding real number is 85.11 kU/L.
Few recent studies analyzed the relation between BHR and air pollution indicators, confirming our findings. Jang and colleagues\textsuperscript{10} found a significant increase in BHR and atopy in children living near a chemical factory with respect to those in rural/coastal areas. A similar result has been shown in a study about BHR in urban, periurban, and rural South African children.\textsuperscript{11} Furthermore, Longhini and colleagues\textsuperscript{45} showed that normal children living in an air-polluted area had a higher prevalence of BHR, compared with those living in mountain valleys.

BHR can be considered an efficacy indicator of air quality intervention. Indeed Wong and colleagues\textsuperscript{46} showed that 1 year after a governmental intervention on air quality by reducing the sulfur content of fuels to 0.5\% in a polluted area, showed that BHR diminished in children living in the polluted district and, to a lesser extent, in the less polluted one; this trend continued in the polluted district 2 years after the intervention.\textsuperscript{46}

Boezen and colleagues\textsuperscript{47} showed that in adults with airway lability (as either peak expiratory flow variability or BHR), there was a significant relationship between the increase of air pollutant concentration levels and the prevalence of respiratory symptoms. Manfreda and colleagues\textsuperscript{9} suggested that BHR may reflect susceptibility to outdoor as well as indoor air quality.

Validity of the Study

When comparing the subjects who refused or were excluded from the analysis of BR to those who were submitted to it, similar characteristics were observed in both samples. In particular, subjects not performing the test had an older age, a higher prevalence of respiratory symptoms, and a worse respiratory function (Table 2). This is likely the result of both a self-selection process and the BR inclusion criteria. This phenomenon is systematic and does not affect the comparability of the urban and the rural samples.

Moreover, the strengths of this study are the large sample sizes, the standard protocols,\textsuperscript{16,17} which already had passed the scrutiny of independent reviewers,\textsuperscript{12,38,48} and the analyses in two representative populations living in rural and in urban geographic areas.\textsuperscript{12} According to the Hill postulate,\textsuperscript{49} the validity of our study is enhanced by the confirmation in different populations of biologically plausible relationships between BHR and various determinants.

Conclusion

We have brought further epidemiological evidences on factors influencing BHR, such as age, female gender, airway caliber, presence of respiratory symptoms/diseases, and atopy. Moreover, we have shown new evidences of the detrimental effect (ie, increased risk for BHR) of living in an urban area with respect to living in a rural area.

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