A Comparison of Risk Factors for Wheeze and Recurrent Cough in Preschool Children

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In a study of 2,978 Danish children aged 5 years from two suburban counties of Copenhagen, carried out in 1998, the authors compared risk factor profiles for wheeze and recurrent cough without wheeze by using polytomous logistic regression to clarify whether the two conditions are likely to have the same etiology. Data were obtained 1) by a mailed parental questionnaire (International Study of Asthma and Allergies in Childhood questions and supplementary questions on cough, sociodemography, perinatal factors, and environmental exposure); 2) through general practitioners (familial allergic disease); and 3) from the National Medical Birth Register (birth weight). Wheeze (WH) was defined as more than one episode of wheeze within the last 12 months (irrespective of cough status) and recurrent cough without WH (RC) as cough occurring outside colds and usually lasting for periods of more than 1 week in children with no more than one attack of wheeze within the last 12 months. Risk factors for comparison were selected as those that, after repeated stepwise logistic regression, remained significant for children with WH or RC. Significant differences were found for gender ($p = 0.003$), gestational age ($p = 0.0002$), maternal history of asthma ($p = 0.0008$), and standard of housing condition ($p = 0.04$)—all risk factors for WH but not RC. Results may suggest that the two conditions have different etiologies.

asthma; child; cough; diagnosis; health surveys; questionnaires; risk factors

Abbreviations: WH, more than one attack of wheeze within the last 12 months; RC (recurrent cough without WH), cough occurring outside colds and usually lasting for periods of more than 1 week in children with no more than one attack of wheeze within the last 12 months.

The role of cough in asthma has been debated in recent decades, with “cough variant asthma” being defined by some as monosymptomatic, chronic, repetitive cough outside periods with colds (1–3). Cough variant asthma is characterized by both the physical examination and the baseline pulmonary function being normal (1). However, this condition is susceptible to beta-2-agonists (4) or steroids (5), and some have advocated that it be considered and treated as asthma (5). Others question its existence, because studies on this subject have been based largely on selected inpatient materials (6). Recent epidemiologic surveys have found that children with monosymptomatic cough resemble asymptomatic children with respect to tests for allergy and respiratory health later in childhood (7–9).

The present study was based on a large representative sample of preschool children. It addressed whether the two conditions of wheeze and recurrent cough without wheeze may have the same etiology by testing the similarity of risk factors for the two conditions.
MATERIALS AND METHODS

Study population

The present study was based on a survey, carried out in 1998, of children aged 5 years in two suburban counties of Copenhagen, Denmark. All general practitioners in the study area were invited to participate; 191, equivalent to one third of all available practitioners in the area, agreed to do so (118 from the county of Copenhagen and 73 from the county of Frederiksborg). Sampled were all children who reached age 5 years in a 1-year period starting on February 20, 1996, and who were patients of the volunteering general practitioners. Personal identification numbers of the children, their names, and their addresses were obtained from the Danish Civil Registration System via their general practitioner’s identification code. The participating physicians differed from the remaining physicians in the study area because they had practiced medicine for a shorter period of time, worked as single practitioners more rarely, and more often were members of the Danish College of General Practitioners. In a previous Danish survey, similar findings regarding characteristics of volunteering physicians were suggested to reflect a higher-than-average working capacity (10).

Of a total of 4,117 children eligible for the study, 3,728 had a Danish background. Children with a non-Danish background were excluded because the response rate for these children was less than 50 percent and parents’ answers were hampered by low comprehension. Before it was initiated, the study was approved by the ethical committees of the counties and by the Data Protection Agency. Overall, parental information was obtained on 3,052 of the children with a Danish background, corresponding to 82 percent of the children included. A total of 74 children for whom data on the wheeze or cough variables were incomplete were excluded, leaving data on 2,978 children available for analysis.

Data instrument

A questionnaire was mailed to the parents 1 month prior to the day on which the child reached age 5 years. Non-responding parents were contacted again after 2 weeks. Questions on wheeze from the questionnaire validated by the international ISAAC committee (10) were included, as were supplementary questions on cough and asthma medication. In addition, information was collected on factors that previously have been associated with the risk of asthma, such as gestational age, mode of delivery, breastfeeding, day care, siblings, and parents’ educational, occupational, and marital status. Parents’ smoking habits in the child’s first and fifth years of life were reported, as was maternal smoking during pregnancy. Also recorded was environmental exposure during the child’s first and fifth years regarding housing conditions, including questions about moisture and carpeting and about pets in the household. The part of the questionnaire regarding cough and exposure was slightly modified from the one used in repeated surveys of respiratory symptoms in children in Leicestershire, United Kingdom (11). Usability was ensured in a pilot study, in which the parents of 14 children were interviewed after filling out the questionnaire. Information on parental history of asthma, atopic dermatitis, allergic rhinitis, and childhood bronchitis was obtained from a separate questionnaire completed by the parents and the general practitioner together and was based on their mutual recall and the physician’s medical record. Birth weight was collected from the Danish Medical Birth Register.

Definitions

We defined wheeze (WH) as more than one attack of wheeze within the last 12 months. We labeled troublesome, potentially asthmatic cough “recurrent cough” and defined it to be present in children fulfilling both criteria: “cough occurring outside colds” and “cough usually lasting for periods of more than 1 week” within the last 12 months. In the study, we compared WH and recurrent cough without wheeze (RC) because wheeze is considered the hallmark in asthma; the issue of major interest in asthma research is whether children suffering cough alone without wheeze might be categorized as asthmatics (12, 13).

Statistical analysis

Risk factors for WH and RC were compared by using polytomous logistic regression with adjustment, as described below (14). To facilitate identification of these risk factors, the polytomous logistic regression in all analyses prior to the final comparison was performed by using individualized logistic regression (15), that is, a logistic regression analysis for each of two outcomes with the reference outcome taken as the group with neither of the two outcomes. This approach is highly efficient as long as the probability of the reference outcome category occurring is not too low (15). The results of these analyses carried out prior to the final comparison are considered intermediate and are not presented in this paper. However, they are of interest because they show the process used; thus, this supplementary material is posted on the Journal’s website (http://aje.oupjournals.org/).

Initially, all variables were divided into seven subject-specific groups: 1) background variables, 2) birth characteristics and breastfeeding, 3) contact with other children, 4) family history of atopic diseases, 5) smoking exposure, 6) housing conditions, and 7) pets in the household. In the first step, the unadjusted association with the two outcomes for each variable was assessed. A large number of combined variables (e.g., parental smoking in the first and fifth years of the child’s life) were also considered. All variables significantly related to at least one of the two outcomes and variables of special interest were considered in the second step, when a backward elimination was performed for each of the two outcomes in each of the subject-specific groups of variables. In a third step, all variables remaining significant for at least one outcome in the second step were included in a backward elimination for each of the two outcomes. In a fourth step, all previously excluded variables were evaluated for each of the two outcomes, with adjustment for the significant variables identified in the third step.
In a final step, the significant variables from the third and fourth steps were included in a backward elimination for each of the two outcomes, excluding, however, only those effects that were insignificant for both outcomes. Variables significantly related to at least one of the two outcomes after the final backward elimination was performed were identified as risk factors significantly related to WH and/or RC. The only exception was “furry pet in the household other than a cat or dog,” where an association with RC and WH in the “first year” of life was found to be slightly significant (refer to the supplementary material on the Journal’s website [http://aje.oupjournals.org/]). No such effect was found in the “fifth year” or from exposure to “cat or dog,” both known as major allergens. We decided to disregard this effect; evidence suggests our findings to be a matter of reverse causality due to a general avoidance of pets by well-informed parents (16). When adjusted for all other significant risk factors identified after the final backward elimination, any other variable was found to be nonsignificantly related to the two outcomes.

The logistic regression analyses were performed by using the SAS procedure PROC GENMOD (Statistical Analysis System; SAS Institute, Inc., Cary, North Carolina). The final comparison in a polytomous regression of the risk factors found to be of significance for WH and/or RC was performed by using the Stata command mlogit (Stata statistical software; Stata Corporation, College Station, Texas) (table 1).

RESULTS

The median age of the 2,978 children in the present study was 4.94 years (95 percent confidence interval: 4.88, 5.10). The male/female ratio was 1.05. Overall, 579 (19.4 percent) children had at least one episode with wheeze during the last year, and 428 (14.4 percent) had WH (more than one wheezing episode). Recurrent cough was reported for 294 (9.9 percent). RC was reported for 184 (6.2 percent) of the study population, and 2,366 (79.4 percent) children suffered from neither RC nor WH. Of the children with WH, 25.7 percent had recurrent cough. The distribution of selected items reflecting respiratory distress in the three groups suffering WH, RC, and neither WH nor RC, respectively, was as follows: “ever reported by a doctor to have asthma”: 41 percent, 13 percent, and 5 percent; “exercise cough within the last 12 months”: 50 percent, 41 percent, and 9 percent; “cough with specific exposures”: 68 percent, 52 percent, and 15 percent; “beta-2-agonists mixture ever”: 72 percent, 53 percent, and 39 percent; “beta-2-agonists at present”: 42 percent, 20 percent, and 5 percent; and “asthma medication within the last 12 months”: 55 percent, 28 percent, and 9 percent.

Through the elaborate multivariate analyses described above in the Materials and Methods section, we found that the effects of the variables on WH or RC could be expressed sufficiently by the few variables listed in table 1. A detailed description of the results from these multivariate analyses is provided in an online data supplement posted on the Journal’s website [http://aje.oupjournals.org/]. The risk of WH was found to be higher for boys than for girls, and it increased with decreasing level of maternal education. Furthermore, we found WH to be more common in children of low (less than age 39 weeks) and high (more than age 41 weeks) gestational age than in children whose gestational age was 39–41 weeks at birth. Likewise, maternal history of asthma, parental history of allergic rhinitis or atopic dermatitis, and parental childhood bronchitis were associated with WH in the offspring. Finally, the risk of WH in children was found to increase with increasing number of parents currently smoking and with decreasing standard of housing condition. Regarding RC, only a parental history of childhood bronchitis and number of parents currently smoking increased the risk (table 1).

When comparing the effects of the risk factors found to be of significance for WH or RC, we found significant differences between WH and RC for gender ($p = 0.003$), gestational age ($p = 0.0002$), maternal history of asthma ($p = 0.0008$), and standard of housing condition ($p = 0.04$) (table 1). There were no significant differences for maternal education ($p = 0.09$), parental history of atopic dermatitis or allergic rhinitis ($p = 0.97$), parental history of childhood bronchitis ($p = 0.51$), or number of parents currently smoking ($p = 0.59$) (table 1).

DISCUSSION

We found that WH and RC in preschool children differ regarding risk factor profile and thus do not appear to have a similar etiology. Significant differences were found for the effects of gender, maternal history of asthma, gestational age, and housing condition. These factors were all risk factors for WH but not for RC.

Categorizing children as asthmatics who suffer from recurrent cough as their sole symptom has contributed to the recent increase in asthma prevalence and treatment (17, 18). However, justification for such classification derives from inpatient materials (2–4) and uncontrolled trials (5, 19). In population-based surveys, Timonen et al. (8) suggested that children with monosymptomatic night cough were an intermediate group between asymptomatic and asthmatic children. Over a period of 3 years, Brooke et al. (12) found that the majority of children with recurrent cough grew out of their symptoms, and the proportion developing asthma seemed no different from that of asymptomatic children. On the basis of a prospective survey, Wright et al. (7) reported that wheezers differed significantly from children with cough as the sole symptom with regard to lung function, measures of allergic response, and prognosis; furthermore, they appeared to have different risk factors. However, to our knowledge, it has not previously been tested whether the risk factors for the two conditions differ significantly from each other.

We consider the present findings to have high validity. All but a small percentage of the inhabitants of Denmark choose a general practitioner. The study sample was fully identified, and the response rate was 82 percent. Furthermore, the size of the study population ensured high discrimination, uniformity of age increased the precision, and seasonal bias was reduced by adding children to the study evenly over a 1-year period (20).
## TABLE 1. Adjusted odds ratios* for WH† and recurrent cough‡ without WH (RC†) compared with neither in Danish children aged 5 years, 1998

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. WH (n = 2,978)</th>
<th>WH (n = 428)</th>
<th>OR†</th>
<th>95% CI</th>
<th>p value§</th>
<th>OR</th>
<th>95% CI</th>
<th>p value§</th>
<th>Similarity p value€</th>
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<tr>
<td>Male</td>
<td>1,521</td>
<td>252</td>
<td>87</td>
<td>1.6</td>
<td>1.3, 1.9</td>
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<td>0.7, 1.2</td>
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<td>1,457</td>
<td>176</td>
<td>97</td>
<td>1</td>
<td>Ref†</td>
<td>&lt;0.0001</td>
<td>1</td>
<td>Ref</td>
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<td>Maternal educational level</td>
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<td>No education</td>
<td>312</td>
<td>67</td>
<td>23</td>
<td>1.8</td>
<td>1.3, 2.6</td>
<td>1.3</td>
<td>0.8, 2.1</td>
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<tr>
<td>&lt;3 years</td>
<td>967</td>
<td>165</td>
<td>56</td>
<td>1.5</td>
<td>1.2, 2.0</td>
<td>0.9</td>
<td>0.6, 1.3</td>
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<tr>
<td>3–4 years</td>
<td>1,311</td>
<td>156</td>
<td>80</td>
<td>1</td>
<td>Ref†</td>
<td>1</td>
<td>Ref</td>
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<td>&gt;4 years</td>
<td>357</td>
<td>35</td>
<td>24</td>
<td>0.9</td>
<td>0.6, 1.3</td>
<td>0.0001</td>
<td>0.9</td>
<td>0.5, 1.5</td>
<td>0.72</td>
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<td>Gestational age (weeks)</td>
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<td>&lt;38</td>
<td>384</td>
<td>82</td>
<td>16</td>
<td>1.8</td>
<td>1.3, 2.4</td>
<td>0.6</td>
<td>0.4, 1.1</td>
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<tr>
<td>39–41</td>
<td>2,094</td>
<td>264</td>
<td>143</td>
<td>1</td>
<td>Ref†</td>
<td>1</td>
<td>Ref</td>
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<tr>
<td>≥42</td>
<td>449</td>
<td>77</td>
<td>23</td>
<td>1.4</td>
<td>1.0, 1.9</td>
<td>0.0003</td>
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<td>Maternal history of asthma</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2,328</td>
<td>305</td>
<td>153</td>
<td>1</td>
<td>Ref†</td>
<td>1</td>
<td>Ref</td>
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<tr>
<td>Yes</td>
<td>163</td>
<td>50</td>
<td>6</td>
<td>2.2</td>
<td>1.5, 3.3</td>
<td>0.002</td>
<td>0.6</td>
<td>0.2, 1.3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Parental history of atopic dermatitis or allergic rhinitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1,725</td>
<td>219</td>
<td>102</td>
<td>1</td>
<td>Ref†</td>
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<tr>
<td>Yes</td>
<td>766</td>
<td>136</td>
<td>57</td>
<td>1.4</td>
<td>1.1, 1.8</td>
<td>0.01</td>
<td>1.4</td>
<td>1.0, 2.0</td>
<td>0.08</td>
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<td></td>
<td></td>
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<tr>
<td>Parental history of childhood bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2,358</td>
<td>316</td>
<td>143</td>
<td>1</td>
<td>Ref†</td>
<td>1</td>
<td>Ref</td>
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<tr>
<td>Yes</td>
<td>133</td>
<td>39</td>
<td>16</td>
<td>2.1</td>
<td>1.4, 3.3</td>
<td>0.002</td>
<td>2.7</td>
<td>1.4, 5.0</td>
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<tr>
<td>No. of parents smoking in the fifth year of the child’s life#</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>None</td>
<td>1,487</td>
<td>176</td>
<td>80</td>
<td>1</td>
<td>Ref†</td>
<td>1</td>
<td>Ref</td>
<td></td>
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<tr>
<td>One</td>
<td>858</td>
<td>119</td>
<td>58</td>
<td>1.1</td>
<td>0.9, 1.5</td>
<td>1.4</td>
<td>0.9, 2.0</td>
<td></td>
<td></td>
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<tr>
<td>Both</td>
<td>570</td>
<td>123</td>
<td>41</td>
<td>2.0</td>
<td>1.5, 2.6</td>
<td>&lt;0.0001</td>
<td>1.7</td>
<td>1.1, 2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Trend (%)</td>
<td>38</td>
<td>20, 59</td>
<td></td>
<td>&lt;0.0001</td>
<td>29</td>
<td>6.58</td>
<td>0.01</td>
<td>0.59</td>
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<tr>
<td>Lowest standard of housing condition during the first and fifth years of the child’s life</td>
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<td></td>
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<tr>
<td>Low</td>
<td>83</td>
<td>23</td>
<td>3</td>
<td>1.8</td>
<td>1.1, 3.2</td>
<td>0.6</td>
<td>0.2, 2.1</td>
<td></td>
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<tr>
<td>Medium</td>
<td>672</td>
<td>127</td>
<td>41</td>
<td>1.5</td>
<td>1.2, 1.9</td>
<td>1.0</td>
<td>0.7, 1.5</td>
<td></td>
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<tr>
<td>High</td>
<td>2,185</td>
<td>271</td>
<td>135</td>
<td>1</td>
<td>Ref†</td>
<td>0.001</td>
<td>1</td>
<td>Ref</td>
<td>0.74</td>
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</tbody>
</table>

* All variables in the table were adjusted for each other.
† WH, more than one attack of wheeze within the last 12 months; RC (recurrent cough without WH), cough occurring outside colds and usually lasting for periods of more than 1 week in children with no more than one attack of wheeze within the last 12 months; OR, odds ratio; CI, confidence interval; Ref, referent.
‡ Periods of cough lasting for more than 1 week occurring outside colds.
§ p value for similarity between WH and RC.
¶ p value for homogeneity.
# The variable describing parental smoking is shown in classes for illustrative purposes, but, in the adjustments for parental smoking in the polytomous comparison, the trend (the relative increase in odds per increase in number of parents smoking) is used.
We acknowledge a potential bias from increased parental attention to symptomatic children, which may, however, affect reports on asthmatics and coughing children in the same direction. The well-known recall bias of retrospective designs is considered of no major consequence to the information on exposure because this information is widely factual and was collected in ways previously used by others. Regarding our outcomes, the question on wheeze has previously been validated against a physician’s physical examination for a sensitivity of 85 percent, a specificity of 81 percent, and positive and negative predictive values of 61 percent and 94 percent, respectively (21). We increased the predictive value of wheeze by restricting the outcome to more than one attack of wheeze within the last 12 months, and this measure has been found to be preferable to parent-reported, physician-diagnosed asthma in identifying current asthma (21). We found a prevalence of wheeze comparable to that in our neighboring countries of Sweden (22) and Norway (23) but somewhat lower than that in Great Britain, Australia, and New Zealand (24). Parental questionnaire information on cough is potentially more vulnerable to recall bias than information on wheeze. Still, it is the source of choice when measuring cough in populations (25–27). When established criteria are lacking, troublesome potentially asthmatic cough is described by using labels such as “chronic cough,” “persistent cough,” or “recurrent cough” based mostly on the measure “cough outside colds” specified for either duration or frequency (7, 28–30). Because, as has been established, parents report the mere presence of “cough outside colds,” but not the frequency, fairly accurately, we chose the parental report of “cough occurring outside periods with colds within the last 12 months” to be the one criterion for recurrent cough in this study (27). Choosing the other criterion, “more than 1 week,” was motivated by the findings from an observational study that infectious coughing may last from 7 to 9 days, with durations of longer than that pointing toward other types of diseases (31). According to these criteria, we found that children with RC constitute an intermediate group between children with WH and those with neither of the symptoms with regard to a number of items reflecting major respiratory symptoms and distress in general. Both WH and RC may at this age include childhood bronchitis with risk factors of its own, but this possibility may have affected our comparison of WH and RC only in favor of the null hypothesis.

Finally, the statistics used in the present study were comprehensive and refined. After identifying significant risk factors among a large number of potential risk factors for asthma, we compared WH and RC by testing for similarity of risk factors. We used polytomous logistic regression, which is considered appropriate for this purpose. Furthermore, although many tests were performed, we do not consider multiple testing to be a concern because we specifically focused on risk factors generally considered of possible importance in asthma.

We found the two outcomes, WH and RC, to differ significantly with regard to four risk factors. The strong effect of male gender and maternal history of asthma on WH parallels findings by others (32, 33), as does the finding of no such effect on RC (29). Although the significant differences found for gestational age and housing condition are less easily interpreted, both are risk factors known to be of importance in asthma (34, 35), which speaks in favor of the two conditions, WH and RC, having different etiologies. This conclusion is further supported by the inverse action on the two outcomes of maternal history of asthma and gestational age. Finally, the risk factor profiles for the two outcomes are very different, and the one for WH resembles that known for asthma (33). This finding suggests that WH, as opposed to RC, may reflect asthma. As such, our findings call for caution in using recurrent cough as a sufficient criterion for the asthma diagnosis in daily clinic and in epidemiologic studies.

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