Habitual Coughing and Its Associations With Asthma, Anxiety, and Gastroesophageal Reflux*

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**Study objective:** Coughing was studied in relation to different disorders and objective variables indicative of airway inflammation.

**Setting:** A random sample of 800 persons, aged 20 to 44 years, was chosen from a larger cohort of participants in the European Community Respiratory Health Survey in Uppsala Sweden; of these, 623 participated. This sample was enriched with 201 individuals who reported asthma-related symptoms or the use of asthma medication.

**Methods:** The study comprised a structured interview, including questions about habitual (productive and nonproductive) and nocturnal coughing and spirometry, methacholine challenge, peak flow diary, skin prick tests, and measurements of blood eosinophil count and serum eosinophil cationic protein (S-ECP).

**Results:** A significant positive correlation was found between productive coughing and asthma (adjusted odds ratios [OR]=2.0), allergic rhinitis (OR=1.9), gastroesophageal reflux (OR=4.4), smoking (OR=1.9), and anxiety (OR=1.8), while nonproductive coughing was related to female gender (OR=1.8) and anxiety (OR=1.7). Nocturnal coughing was positively correlated to female gender (OR=1.8), smoking (OR=1.9), and asthma (OR=2.2). Bronchial hyperresponsiveness was positively related to productive coughing (p<0.001), nonproductive coughing, and nocturnal coughing (p<0.05). S-ECP was significantly higher in individuals with nonproductive coughing compared with subjects without habitual coughing (p<0.01).

**Conclusions:** We conclude that habitual coughing has a significant association with different disease categories.

(CHEST 1996; 109:1262-68)

**Key words:** epidemiology; habitual coughing; productive and nonproductive coughing; variables of inflammation

**Abbreviations:** B-EOS=blood eosinophil count; BHR=bronchial hyperresponsiveness; ECRHS=European Community Respiratory Health Survey; GER=gastroesophageal reflux; PEF=peak expiratory flow; S-ECP=serum eosinophil cationic protein; S-IgE=serum immunoglobulin E

Chronic and prostrating coughing is a common problem, both in pulmonary medicine and general practice. The cough reflex is initiated by a stimulation of sensory nerves beneath and between the epithelium of the larynx and the tracheobronchial tree. Receptors coupled to the vagal and the superior laryngeal nerve pathways can also induce coughing, when stimulated by airway secretions, foreign bodies, or tumors.1 An abnormal increase in the sensitivity of cough receptors may lead to a reduced threshold for coughing and therefore persistent coughing. This mechanism has been ascribed to the cough associated with angiotensin-converting enzyme inhibitors.2,3 Coughing is also common in asthma and may be its sole manifestation.4,5 By utilizing an anatomic, diagnostic protocol, Irwin et al6 found that chronic coughing was most commonly due to a single cause (82%) and, in most cases (96%), was caused by one of four disorders: asthma, chronic bronchitis, gastroesophageal reflux (GER), or the postnasal drip syndrome.

In this study, we have exploited the opportunity afforded by participation in the European Community Respiratory Health Survey (ECRHS), to look into coughing from an epidemiologic perspective and clarify its associations to different diseases. Previously reported data from the first part of the ECRHS in Sweden showed that nocturnal and long-term coughing...
were found to be more frequent among women than men.7 The aim of this report from the second part of the ECRHS in Uppsala was to investigate whether the various types of coughing, habitual coughing, productive and nonproductive coughing, and nocturnal coughing, are associated with different disease categories and inflammatory parameters in blood.

MATERIALS AND METHODS

Study Population

An extensive study of the prevalence of asthma and allergies was conducted at 48 centers around the world, as part of the ECRHS.8 Sweden contributed data from three such centers, one of which is in Uppsala. In December 1990, a questionnaire on asthma-related symptoms was mailed to 3,600 persons, men and women, aged 20 to 44 years, randomly selected from the population register of the municipality of Uppsala.

From this cohort, a random sample of 800 persons was invited to participate in a further investigation; of these, 78% (n=623) participated. In order to enrich the sample with symptomatic individuals, all persons from the main sample who reported the use of asthma medication, attacks of asthma, or awakening because of shortness of breath were invited to participate and 93% (n=201) were accepted. Thus, a total of 824 participants were interviewed and 722 were examined by specially trained nurses. This part of the study was conducted from April 1991 to February 1992. The investigations took place from 8 AM to 5 PM each day. The same investigation sequence was applied to all participants. All subjects gave their informed consent. The protocol of the study was approved by the Ethics Committee of the Medical Faculty of Uppsala University.

Questionnaires and Disease Definitions

The interview questionnaire used was a modified version of the International Union Against Tuberculosis and Lung Disease Questionnaire.9,10 It contained a total of 71 questions concerning airway symptoms, housing, social situation, education, environmental exposure during childhood, etc.

Habitual coughing was defined as answering yes to one or more of the following questions: “Do you usually cough first thing in the morning in the winter?” and “Do you usually cough during the day or at night in the winter?”

Productive coughing was defined as habitual coughing in addition, a positive answer to at least one of the following questions: “Do you usually bring up any phlegm from your chest during the day or at night in the winter?” and “Do you usually bring up any phlegm from your chest first thing in the morning in the winter?”

Nonproductive coughing was defined as habitual coughing and additionally a negative answer to both of the questions concerning phlegm.

Nocturnal cough was defined as answering yes to the following question: “Have you been awakened by an attack of coughing at any time during the last 12 months?”

Current asthma was defined as answering yes to both of the questions: “Have you ever had asthma?” and “Have you had asthma in the last 12 months?”

Allergic rhinitis was defined as answering yes to the following question: “Do you have any nasal allergies, including hay fever?”

Questionnaire on Psychological Status: To examine psychological status, all subjects were asked to fill in a separate questionnaire, including the Hospital Anxiety and Depression Scale11 that consists of 14 questions in which the severity of anxiety and depression is rated on a four-point scale (0 to 3). A score of 8 or greater has been found to discriminate definitive and possible cases of anxiety and depression from non-cases. Reports from the ECRHS about anxiety and depression in relation to asthma-related symptoms and asthma have been published elsewhere.12

Sleep Questionnaire: All subjects were asked to fill in a separate questionnaire on the quality of their sleep and any sleep-related symptoms. They were also asked to estimate the frequency of different symptoms during the past few months on a five-point scale. The questionnaire consisted of 14 multiple-choice questions, including the following: “Do you have any heartburn or belching when you have gone to bed?”

In this study, GER was defined as reporting this symptom at least once a week.

Lung Function and Bronchial Hyperresponsiveness

FEV1 was measured in 720 persons using a computerized dry-rolling seal spirometer system (Spiro Medics 2130; Sensor Medics; Anaheim, Calif). The predicted values were calculated for each patient.13

Methacholine challenge was performed on 667 individuals using a dosimeter (Mefar; Brescia, Italy).15 Patients with a decrease in FEV1 of 20% with an accumulated methacholine dose of 2 mg or less were defined as having bronchial hyperresponsiveness (BHR).16

Peak expiratory flow (PEF) (best of three measurements) was recorded twice daily during 1 week with a flowmeter (Mini-Wright Peak Flow Meter; Clement Clarke; London, UK). The number of patients who managed to perform PEF measurements twice a day on at least 4 of 7 days was 552. Peak flow variability was calculated by dividing the difference between the highest and lowest daily PEF reading by the daily mean PEF value.17

Skin Prick Tests

Skin prick tests were carried out in a carefully standardized way by using allergen-coated lancets (Phazets; Pharmacia Diagnostics; Uppsala, Sweden). The following allergens were used: Dermato-phagoides pteronyssinus, cat, birch, dog, Cladosporium, olive, ragweed, mugwort, timothy, and alternaria with histamine as a positive control. Atopy was defined as a positive prick test reaction to at least one allergen with a mean diameter of 3 mm or greater and no dermatographism.18

Blood Samples

The following venous blood samples were collected from each subject: (1) Five milliliters supplemented with edetic acid (0.34 mol/L), which is used for analyzing the blood eosinophil count (B-Eos) (Technicon H*1, Technicon Chemicals Company; Tournai, Belgium). (2) Twenty milliliters from which serum was collected and thereafter kept frozen at −70°C until analyzed for serum eosinophil cationic protein (S-ECP); the concentration of S-ECP was assayed by means of a double antibody radioimmunoassay (Pharmacia Diagnostics AB; Uppsala, Sweden).19 (3) Ten milliliters, from which serum was collected and analyzed for total serum immunoglobulin E (S-IgE).

Statistics

The statistical analysis was performed with a software package (Statistica 4.0; StatSoft Inc; Tulsa, Okla). Comparisons of B-Eos and S-ECP between subgroups of the population were made by the unpaired Student’s t test and analysis of variance. Multiple logistic and linear regression analyses were used for investigating the correlation of more than one variable with B-Eos, S-ECP, or asthma prevalence. For all statistical tests, S-ECP, B-Eos, and S-IgE were log transformed to achieve an approximately normal distribution. A p value of <0.05 or an odds ratio with the lower limit of the 95% confidence interval greater than 1.0 were regarded as statistically significant.
Table 1—Age, Gender, and Smoking Habits of Subjects With and Without Habitual and Nocturnal Coughing

<table>
<thead>
<tr>
<th>Age, yr mean ± SD</th>
<th>Habitual Coughing</th>
<th>No</th>
<th>Yes</th>
<th>Nocturnal Coughing</th>
<th>Nonproductive</th>
<th>Productive</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>33±7</td>
<td>32±7</td>
<td>33±7</td>
<td>33±7</td>
<td>33±7</td>
<td>33±7</td>
<td>33±7</td>
</tr>
<tr>
<td>Female, %</td>
<td></td>
<td>49</td>
<td>62*</td>
<td>52</td>
<td>45</td>
<td>39*</td>
<td>59*</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker, %</td>
<td></td>
<td>26</td>
<td>17</td>
<td>15*</td>
<td>26</td>
<td>20*</td>
<td>21</td>
<td>35*</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td>25</td>
<td>32</td>
<td>39*</td>
<td>21</td>
<td>35*</td>
<td>14*</td>
<td>16*</td>
</tr>
</tbody>
</table>

*p<0.05.
1*p<0.01.
1*P<0.001.

**RESULTS**

Of the 623 randomly selected subjects, 52 (8%) reported productive and 70 (11%) reported nonproductive habitual coughing. Nocturnal attacks of coughing during the last 12 months were reported by 234 (38%) of the subjects.

**Gender, Smoking, and Age**

Women coughed significantly more than men: habitual coughing (p<0.01), nonproductive coughing (p<0.01), and nocturnal coughing (p<0.001). Smokers experienced significantly more coughing than ex-smokers and nonsmokers: habitual coughing (p<0.001), productive coughing (p<0.05), and nocturnal coughing (p<0.001) (Table 1). No significant correlation was found between age and coughing.

**Asthma, Allergic Rhinitis, and GER**

A total of 109 subjects reported having current asthma, and of these, 101 had asthma diagnosed by a physician. A significant positive correlation was found between asthma and coughing: habitual coughing (p<0.001), productive and nonproductive coughing (p<0.05 and 0.001), and nocturnal coughing (p<0.001). Allergic rhinitis was positively correlated to habitual coughing (p<0.001) and productive coughing (p<0.001), and GER was positively correlated to habitual coughing (p<0.001), productive coughing (p<0.001), and nocturnal coughing (p<0.01) (Table 2).

**Psychological Factors**

Anxiety and depression had a positive significant correlation to coughing; anxiety was correlated to all four types of coughing (habitual coughing [p<0.001], nocturnal coughing [p<0.05], productive and nonproductive coughing [p<0.001 and p<0.01]), and depression was positively correlated to habitual coughing (p<0.001) and productive coughing (p<0.01) (Table 2).

**Multivariate Analysis**

The results of a logistic regression analysis with gender, age, asthma, rhinitis, and anxiety as independent variables and productive, nonproductive, and nocturnal coughing as dependent variables are presented in Table 3. A significant positive correlation was found between productive coughing and asthma (p<0.05), allergic rhinitis (p<0.05), GER (p<0.001), smoking (p<0.05), and anxiety (p<0.05), while nonproductive coughing was related to female gender and anxiety (p<0.05). Nocturnal coughing was positively correlated to female gender (p<0.001), smoking (p<0.001), and asthma (p<0.01).

Table 2—Asthma, Rhinitis, GER, and Psychological Disorders in Subjects With and Without Habitual and Nocturnal Coughing

<table>
<thead>
<tr>
<th>Asthma, %</th>
<th>Rhinitis, %</th>
<th>GER, %</th>
<th>Anxiety, %</th>
<th>Depression, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habitual Coughing</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nonproductive</td>
<td>10</td>
<td>21*</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>Productive</td>
<td>24*</td>
<td>45</td>
<td>52*</td>
<td>20</td>
</tr>
</tbody>
</table>

*p<0.05.
1*p<0.01.
1*P<0.001.
**BHR, FEV₁, and PEF Variability**

BHR was positively related to productive coughing (p<0.001), nonproductive coughing, and nocturnal coughing (p<0.05). FEV₁ was significantly related to productive coughing (p<0.001) and PEF variability was significantly related to nonproductive, productive, and nocturnal coughing (p<0.05) (Table 4). When adjusting for BHR by means of logistic regression, no significant relationship was found between reported coughing and FEV₁ or PEF variability.

**Variables of Inflammation**

There were no significant differences in the prevalence of productive, nonproductive, or nocturnal coughing between atopic and nonatopic subjects. S-ECP was significantly higher in individuals with nonproductive coughing (p<0.001) than in subjects with no habitual cough. S-IgE was positively correlated to productive coughing (p<0.05) while no correlations are found between alterations in the eosinophil count and coughing (Table 4). The relationship between S-ECP and nonproductive coughing was significant (p<0.01), while the association between S-IgE and productive cough was not significant after adjusting for BHR by means of logistic regression.

**Discussion**

The aim of this study was to establish the relationship between coughing and various disorders. It was found that habitual coughing was a common symptom that was reported by one fifth of the random population of Uppsala; this figure is similar to other population studies.19,20 Productive coughing was significantly related to asthma, allergic rhinitis, smoking, and GER, while nonproductive coughing was related to female gender. Both types of habitual coughing were significantly related to anxiety. Nocturnal coughing was significantly related to female gender, smoking, and asthma.

In this study, as in our previous report from the first phase of the ECRHS in Sweden,17 women reported coughing more often than men. The reason for this has not been clarified. Treatment with angiotensin-converting enzyme inhibitors is often complicated by

**Table 4—BHR, Atopy, Inflammatory Variables, IgE, and Lung Function (Mean±SD) in Subjects With and Without Habitual and Nocturnal Coughing**

<table>
<thead>
<tr>
<th>Coughing</th>
<th>Nonproductive</th>
<th>Productive</th>
<th>Nocturnal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.94(0.80-1.11)</td>
<td>1.03(0.86-1.23)</td>
<td>1.03(0.92-1.15)</td>
</tr>
<tr>
<td>Female</td>
<td>1.82(1.10-3.00)</td>
<td>1.39(0.83-2.32)</td>
<td>1.76(1.26-2.44)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.27(0.75-2.17)</td>
<td>1.85(1.11-3.19)</td>
<td>1.92(1.34-2.76)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.41(0.72-2.78)</td>
<td>2.00(1.07-3.74)</td>
<td>2.18(1.34-2.76)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1.41(0.85-2.35)</td>
<td>1.91(1.13-3.21)</td>
<td>1.14(0.82-1.60)</td>
</tr>
<tr>
<td>GER</td>
<td>1.33(0.47-3.82)</td>
<td>4.44(2.02-9.75)</td>
<td>1.86(0.93-3.69)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.73(1.03-2.92)</td>
<td>1.79(1.04-3.08)</td>
<td>1.29(0.89-1.57)</td>
</tr>
<tr>
<td>Depression</td>
<td>2.08(0.96-4.54)</td>
<td>1.91(0.85-4.28)</td>
<td>1.07(0.58-1.96)</td>
</tr>
</tbody>
</table>

*p<0.05.

1p<0.01.

1p<0.001.

ECP=eosinophil cationic protein.
coughing and the mechanism may involve an abnormal increase in the sensitivity of cough receptors. This side effect is more common in women than in men and thus, it is possible that women have more sensitive cough receptors.

Less surprising was the relationship found between current smoking and productive and nocturnal coughing. Numerous studies have shown chronic coughing and chronic phlegm production to be more frequent in smokers than in nonsmokers. In the Framingham cohort, cigarette smoking was observed to be the prime determinant of chronic coughing. Current smoking, however, was not related to nonproductive coughing in this study; this perhaps indicates that bronchial secretion induced by cigarette smoking is the main determinant of coughing in smokers.

The symptom triad of dyspnea, coughing, and wheezing is characteristic of asthma. These symptoms are thought to be caused by physiologic responses to various stimuli, superimposed on a background of eosinophilic inflammation. In the early stages of asthma, inflammatory events may precede the development of BHR, another cardinal feature of asthma, which would account for the coughing tendency to antedate other symptoms of asthma, such as wheezing.

Cough variant asthma is a well-defined entity, characterized by persistent, nonproductive coughing without wheezing. A higher wheezing threshold, ie, wheezing becoming audible at a greater degree of airway obstruction, may explain this variation in symptoms. In a recent study, however, no significant correlation was found between cough sensitivity and BHR. Furthermore, coughing and bronchoconstriction can be both induced and inhibited by drugs. Gibson et al found that nonsmoking subjects with a corticosteroid-responsive cough but without BHR had sputum that contained eosinophils and metachromatic cells in similar numbers to those seen in asthmatics and significantly higher levels than in subjects with chronic bronchitis. Similarly, Tollerud et al found eosinophils to be an independent risk factor for coughing and phlegm production. These findings suggest that airway inflammation with eosinophilia is not always associated with BHR or asthma.

In addition to total levels of eosinophils in blood, we measured S-ECP because S-ECP levels reflect the involvement of the eosinophil granulocyte in the asthmatic process. This has been documented by various studies in which increased numbers of eosinophils in the lungs, either measured as eosinophils in the BAL fluid, sputum samples, or as seen in biopsy specimens were shown. S-ECP levels have also been shown to correlate with asthma severity as measured by different means such as FEV1, bronchial hyperresponsive-ness, the propensity to develop late asthmatic reactions after allergen challenge, and the propensity to develop exercise-induced asthma.

In our study, asthma was an individual risk factor for both productive and nonproductive coughing as well as nocturnal coughing, whereas S-ECP was independently associated with nonproductive coughing, but not productive or nocturnal coughing. It is possible that asthma entails a dual stimulation to coughing, both through the induction of airway secretions and BHR and through eosinophilic inflammation that may lower the coughing threshold. This, however, is speculative.

The same mechanisms may apply to individuals with allergic rhinitis who have an increased prevalence of BHR, without concomitant asthma symptoms. Alternately, as suggested by Irwin et al, postnasal dripping may be the cause of chronic coughing in these subjects. We found that allergic rhinitis was related to productive coughing but not nonproductive coughing. As our questions about habitual coughing were limited to the winter months, the number of individuals who had allergic rhinitis and postnasal drip as a cause of habitual coughing may have been underestimated. Typical symptoms of GER are often associated with respiratory symptoms. GER can be the sole cause of chronic coughing and is most likely due to stimulation of the distal esophageal mucosal receptors rather than aspiration. This could be due to a esophageal-bronchial reflex mechanism with cholinergic efferents in the tracheobronchial tree, which may explain the beneficial effects of ipratropium bromide on chronic coughing without asthma. Cholinergic discharge would result in fluid secretion from submucosal glands, which is consistent with the findings of this study that symptoms of GER were related to productive, but not nonproductive, coughing.

In a previous report from the ECRRS, a significant correlation was found between anxiety and depression and reports of wheezing or breathlessness; however, there was no relationship to the self-reported diagnosis of asthma or objective asthma-related variables. In this study of the same population sample, the analysis was extended to include habitual coughing. Anxiety was found to be an independent risk factor for both productive and nonproductive coughing, which may reflect an increased awareness of physical symptoms in anxious individuals. An association between psychological factors and coughing was also reported by Hutchings et al. In their study, subjects with obsessional personalities had greater difficulties in maintaining voluntarily cough suppression.

Our study has certain limitations that should be recognized. A potential disadvantage was that it was not designed to address coughing in particular; the questionnaire was limited to the standardized version of the Clinical Investigations.
ACKNOWLEDGMENTS: We wish to thank S. Swedberg Brandt and E. Rydelén, our nurses, who did all the field work, and L. Larsson and M. Medéen for help with many practical details.

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