Impact of anxiety and depression on respiratory symptoms

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Summary
Psychological factors such as anxiety and depression are prevalent in patients with asthma. The purpose of this study was to investigate the relationship between respiratory symptoms and psychological status and to estimate the importance of psychological status in comparison with other factors that are known to be associated with respiratory symptoms.

This study included 2270 subjects aged 20–44 (52% female) from Sweden, Iceland, and Norway. Each participant underwent a clinical interview including questions on respiratory symptoms. Spirometry and methacholine challenge were performed. Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS).

Eighty-two percent of the subjects reported no anxiety or depression whatsoever, 11% reported anxiety, 2.5% depression and 4% reported both anxiety and depression. All respiratory symptoms, such as wheezing, breathlessness and nightly symptoms, were more common, at a
Introduction

Respiratory symptoms are common. For instance the median prevalence of having had wheezing in the last 12 months was over 20% in a large international study of 20–44 year old adults [1]. Respiratory symptoms are often a manifestation of respiratory diseases such as asthma or Chronic Obstructive Pulmonary Disease (COPD), but can also exist in patient without any known respiratory disorder [2].

Respiratory symptoms are associated with bronchial responsiveness, allergy, obesity and exposures such as smoking and environmental factors [3]. Less is known about the association between psychological status and respiratory symptoms. Asthma has been associated with anxiety and depression [4]. But in one study having anxiety and depression was strongly associated with respiratory symptoms but not with asthma and bronchial responsiveness [5]. The nature of the relationship between psychological status and respiratory symptoms and the underlying mechanisms are still unknown [6]. In some studies, psychological symptoms have been related to a higher risk of developing asthma [7]. Other studies have indicated that poorly controlled asthma and respiratory symptoms such as breathlessness may lead to anxiety disorder [8] another study showed there is an association between generalized anxiety disorder and poor asthma control [9]. Some studies show, however, that respiratory symptoms and psychological symptoms are only loosely related to each other [10,11]. There are also studies that indicate that the association between psychological health and lung function differs between men and women [12].

The purpose of this study was to investigate the relationship between respiratory symptoms, such as wheezing and breathlessness, and psychological factors using Hospital Anxiety Depression Scale (HADS), and also to estimate the importance of psychological status in comparison with other well-known factors that are associated with respiratory symptoms, such as low lung function, bronchial responsiveness, smoking, body mass index (BMI) and atopy.

Material and methods

Study design

European Community Respiratory Health Survey (ECRHS) I and II were designed to determine the prevalence, incidence and risk factors for asthma and allergic disease in young and middle-aged adults living in Europe and other parts of the world. ECRHS I [13] was a multicenter study performed in 48 study centers during 1990–1993. Each participant was sent a brief questionnaire (Stage 1) and a random sample of responders was selected to undergo a more detailed clinical examination (Stage 2). In addition, a ‘symptomatic sample’ reporting symptoms of waking with shortness of breath, asthma attacks or using asthma medication in stage 1, was also studied. ECRHS II was a follow-up study, performed in 29 centers in 14 countries during 1999–2002, and comprised the participants in the second stage of ECRHS. The analyses presented here included 2270 subjects from Sweden, Iceland, and Norway who participated in ECRHS II (Fig. 1).

Measures

Questionnaires

Structured clinical interview. The screening questionnaire and the questionnaire used in the structured interview were based on the International Union against Tuberculosis and Lung Disease (IUATLD) questionnaire [14]. Each participant underwent a structured clinical interview including questions on the presence of asthma,
respiratory symptoms, and therapy. The full questionnaires can be found at http://www.ecrhs.org/Quests.htm.

Hospital Anxiety Depression Scale (HADS). Participants in Sweden, Iceland and Norway were also asked to fill out the self-reported Hospital Anxiety Depression Scale, HADS [15–17]. The HADS is a fourteen-item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression. Each item is rated on a 4-point scale: 0, not at all; 1, sometimes; 2, often; 3, all the time; this gives a maximum subscale score of 21 for anxiety and depression, respectively. HADS gives clinically meaningful results as a psychological screening tool in clinical group comparisons and correlation studies with several aspects of disease and quality of life [18].

In the validation of the questionnaire, a score of >7 in the two subscales has been found to discriminate non cases from suspected cases [17]. In the present study, we combined the depression and anxiety scale to obtain a combined measure of psychological status [19,20]. HADS has been validated for Swedish sample [21].

The European Community Respiratory Health Survey II main questionnaire. Respiratory symptoms were defined at follow up as answering "yes" to the questions:

- **Wheeze**
  Have you had wheezing or whistling in your chest at any time in the last 12 months?

- **Wheeze and breathlessness**
  Have you been at all breathless when the wheezing noise was present?

- **Wheeze when not having a cold**
  Have you had this wheezing or whistling when you did not have a cold?

- **Nocturnal chest tightness**
  Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?

- **Attack of breathlessness when at rest**
  Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?

- **Attack of breathlessness after activity**
  Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?

- **Nocturnal dyspnea**
  Have you been woken by an attack of shortness of breath at any time in the last 12 months?

Asthma

- Doctor’s diagnosed asthma was defined as a positive answer to both questions: “Have you ever suffered from asthma?” and “Was this confirmed by a doctor?” [1,22]

Smoking history

- Smoking history was investigated by asking subjects whether they were current smokers, smokers that quitted smoking between ECRHS I and II, ex-smokers (stopped smoking before ECRHS I) or never-smokers.

Clinical measurements

**Spirometry.** FEV1 (Forced expiratory volume in 1 s) was measured using a dry rolling seal Spirometry system (Sensor medics 2130, Sensor medics, Anaheim, CA, USA) after the structured interview. Up to five technically acceptable exhalations were determined. The results were expressed as percent of predicted using the European Community for Coal and Steel (ECCS) normal values for spirometry [23]. No bronchodilator was given before the spirometry.

**Bronchial responsiveness.** Methacholine challenge was performed with a Mefar dosimeter (Provacholine®, Methapharm, Inc., ON, Canada) after the structured interview. The participants first inhaled a diluent and doses of methacholine were then inhaled until a 20% fall in postdiluent FEV1 was observed or the maximum cumulative dose of 2 mg was reached. The degree of bronchial responsiveness was calculated using a previously described dose slope where a lower value indicates more responsiveness [24]. Standardization was assured through training seminars and quality control visits. A more detailed description of the methods use has been presented previously [25].

**Body mass index.** Height and weight was measured and BMI was calculated as weight in kilograms divided by the square of height in meters.

Atopy. Blood samples were collected for the measurement of serum-specific IgE and total IgE using the Pharmacia CAP System (Pharmacia Diagnostics, Uppsala, Sweden) after the interview. Serum samples were stored at –20 °C and transferred to a centralized laboratory where they were tested for specific IgE to house dust mite, grass, cat and Cladosporium. Atopy was defined as having IgE (≥0.35 kU/L) against at least one of the allergens investigated [26].

Statistical analysis

Associations between different respiratory-related symptoms and anxiety/depression were studied using binary logistic regression. Potential confounding variables were selected prior to the analyses, based on clinical knowledge and previous analyses of the ECRHS [3]. First, we fitted a flexible additive model for each outcome using restricted cubic splines with four degrees of freedom for the continuous determinants. Knowing that this model might be too flexible and overfit the data, we decided to either retain the nonlinear terms or model the determinant linearly, based on the determinant’s apparent predictive power. A determinant’s predictive power was defined as the χ² value obtained from the regression minus the determinant’s degrees of freedom [27]. The rationale behind this strategy is that it is less damaging to miss-specify the structure of a determinant whose predictive power is low than to miss-specify the structure of a powerful determinant.
We then tested three pre-specified interactions: anxiety/depression and sex, anxiety/depression and bronchial responsiveness, and anxiety/depression and atopy. Interaction terms were either retained or removed from the respective model, based on a global test of no interaction versus at least one interaction term not equal to zero. We performed a hierarchical cluster analysis using the fraction of missing values between any two variables to characterize the pattern of missing values in the data. Incomplete variables were then imputed under fully conditional specification [28]. Computations were done in R with 15 imputations created using the mice package [29].

Only variables with a Spearman correlation $>0.1$ with the variable being imputed were included in the imputation model for that variable [29].

Ethical approval

Ethical approval was obtained from each center’s regional research ethical committee. Each participant provided a written informed consent.

Results

HADS ($n = 2270$) was used to divide the study sample into the following groups: no anxiety or depression, anxiety, depression and both anxiety and depression. Eighty-two percent of the subjects reported no anxiety or depression whatsoever, 11% reported anxiety, 2.5% depression, and 4% both anxiety and depression.

All respiratory symptoms were more common in the group with anxiety and depression symptoms than in the group without anxiety and depression (Table 1). No association was found between psychological status and smoking, atopy, lung function or bronchial responsiveness. Anxiety was more common in women than men.

There was a significant association between psychological status and all respiratory symptoms studied, after adjusting for age, sex, smoking habits, atopy, BMI, bronchial responsiveness and FEV1 (Table 2). Participants with higher bronchial responsiveness were more likely to report respiratory symptoms. Also, atopy and BMI were significantly associated with all respiratory symptoms except for breathlessness at rest. Smoking was associated with prevalent wheeze. FEV1 was significantly lower in subjects with respiratory symptoms except in the group that experienced nocturnal chest tightness. In analyses of interactions between men and women, HADS score and respiratory symptoms showed no effect modifications ($p$-values = 0.37–0.76).

An analysis of the importance of the different determinants in predicting respiratory symptoms showed that the HADS score was the most important determinant for nightly symptoms (nocturnal chest tightness or breathlessness) and the prevalence of attacks of breathlessness at rest (Fig. 2). Bronchial responsiveness was the most important determinant for wheezing and breathlessness when wheezing. FEV1 was the most important determinant for attacks of breathlessness after activity, but the HADS score and bronchial responsiveness also had a strong association to this symptom.

Discussion

The main finding was a strong association between experiencing respiratory symptoms and psychological status, but this relationship varied depending on symptom.

| Table 1 | Characteristics of the study sample ($n = 2270$), % and Mean (±SD). |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | All             | No anxiety or depression | Anxiety | Depression | Anxiety and depression | p-Value |
| Women           | 52%             | 50.7%             | 64.8%             | 47.1%             | 63.2%             | <0.001            |
| Age             | 42.7 (7)        | 43 (±7)           | 42 (±7)           | 44 (±7)           | 42 (±7)           | 0.052             |
| Smoking habits  |                 |                   |                   |                   |                   |                   |
| Never-smokers   | 24%             | 24.2%             | 24.9%             | 26.1%             | 31.1%             | 0.097             |
| Ex-smokers      | 13%             | 12.5%             | 15.6%             | 11.6%             | 15.9%             |                   |
| Quitted smoking | 20%             | 19.9%             | 19.1%             | 20.3%             | 15.2%             |                   |
| Current smokers | 43%             | 45.2%             | 38.4%             | 42.0%             | 37.9%             |                   |
| Atopy           | 28%             | 28.2%             | 25.1%             | 28.1%             | 25.7%             | 0.747             |
| BMI ($\text{kg/m}^2$) | 25.7 (±4.2) | 25.7 (±4.3) | 25.7 (±4.3) | 26.7 (±6.0) | 26.4 (±5.1) | 0.021             |
| FEV1 (percent predicted) | 103 (±14) | 103 (±14) | 103 (±15) | 106 (±13) | 103 (±16) | 0.291             |
| Bronchial responsiveness | 7.92 (±2.1) | 7.49 (±1.8) | 7.76 (±1.8) | 7.8 (±1.8) | 7.23 (±2.2) | 0.232             |
| Doctor-diagnosed asthma | 19.9% | 18.9% | 22.4% | 22.4% | 30.5% | <0.01             |
| Wheeze          | 29%             | 26.8%             | 43.1%             | 35.7%             | 45.9%             | <0.001             |
| Nocturnal chest tightness | 16% | 13.2% | 25.5% | 20.0% | 34.6% | <0.001             |
| Attack of breathlessness after activity | 16% | 13.7% | 18.5% | 20.0% | 33.1% | <0.001             |
| Attack of breathlessness when at rest | 7% | 4.9% | 11.0% | 11.4% | 18.9% | <0.001             |
| Breathlessness when wheezing | 18% | 16.0% | 25.2% | 24.3% | 32.6% | <0.001             |
| Wheeze when not having a cold | 19% | 16.6% | 25.8% | 24.3% | 35.1% | <0.001             |
| Nocturnal dyspnea | 7% | 5.4% | 13.4% | 10.3% | 16.5% | <0.001             |
The HADS score was the most important determinant for nightly symptoms (nocturnal chest tightness or dyspnea) but also had a strong association with attacks of breathlessness at rest. This is in line with a study showing that symptoms related to anxiety and especially depression are important determinants for the development of respiratory symptoms as dyspnea [30]. The prevalence of physician-diagnosed asthma was very high in subjects with both anxiety and depression. Other studies have also shown that diagnosed asthma and current wheezing were associated with diagnosed depression and anxiety [31,32]. An increased risk of incident asthma at follow-up was found in adults who reported symptoms of anxiety or depression at baseline in a large prospective study on the general population of Norway [33].

Anxiety was more common in women than men in our study, which agrees with the results of another Swedish study [34]. However, an analysis of interaction between men and women in our study showed no significant effect modification. Current smokers had the highest prevalence of depression and current smoking was associated with wheezing and wheezing when not having a cold.

As expected, increased bronchial responsiveness was associated with all respiratory symptoms. Bronchial responsiveness was the most important determinant for wheezing and breathlessness. A close association between wheezing and bronchial responsiveness has been shown in other studies [35]. In the present study, FEV1 was a significant determinant for four out of seven respiratory symptoms (wheezing, breathlessness, wheezing when not having a cold and attack of breathlessness after activity) and atopy was associated with respiratory symptoms except for breathlessness at rest.

A high BMI was associated with an increased prevalence of most respiratory symptoms. In a large meta-analysis obesity was found to be independently associated with an increased risk of incidence asthma [36]. The association between obesity and asthma may, however, not be completely straightforward. An Australian study showed that subjects with severe obesity reported more wheezing and shortness of breath but obesity was not associated with atopy or airway hyper-responsiveness [37]. In a cross-sectional multicenter study from Spain obesity was not associated with a confirmed asthma diagnosis in patients with asthma symptoms and a positive methacholine test. However, obesity was suspected to be a risk factor for development of asthma among non-atopic subjects [38]. A Korean study of patients with an asthma diagnosis confirmed by asthma specialists and methacholine test showed that obesity was positively related to the prevalence of wheezing but inversely related to bronchial hyperresponsiveness [39]. There are relatively few interventional studies but Mansiscalco et al. found that laparoscopic adjustable gastric banding lead to an improvement in asthma symptoms in severely obese asthmatics [40] and an improvement in asthma control was found in recent study of a weight loss program for asthmatics [41].

The present study indicates that improving psychological status may be a way forward in reducing respiratory symptoms. Beneficial short and long-term effects of a brief cognitive behavioral therapy designed to reduce asthma-specific fear has been shown [42]. Behavioral therapeutic
programs may therefore offer an opportunity to reduce anxiety and to improve asthma self-management in some patients. It is, however, also likely that higher levels of respiratory symptoms may also increase psychological distress. The present study is cross sectional. It is therefore not possible to know whether the association between psychological status and respiratory symptoms is an effect of anxiety and depression causing respiratory symptoms or whether the cause and effect relationship is the opposite.

In conclusion, there is a strong association between respiratory symptoms and psychological status. There is therefore a need for interventional studies designed to improve depression and anxiety in patients with respiratory symptoms.

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