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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

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statistically significant level, in participants who had depression and anxiety, even after adjusting for confounders (ORs 1.33—1.94). The HADS score was the most important determinant for nightly symptoms and attacks of breathlessness when at rest whereas bronchial responsiveness was the most important determinant for wheezing, and breathlessness when wheezing. The probability of respiratory symptoms related to HADS score increased with increasing HADS score for all respiratory symptoms.

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.

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 badly 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,

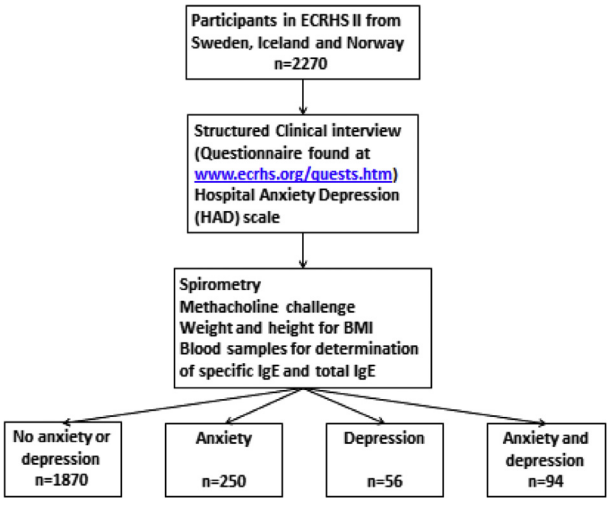

Figure 1 Study design.

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. FEV_1 (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 (Provocholine®, 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 FEV_1 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 ($\geq$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 χ^2-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 FEV_1 (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. FEV_1 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. FEV_1 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 $n = 1870$	Anxiety $n = 250$	Depression $n = 56$	Anxiety and depression $n = 94$	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%	22.4%	26.9%	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 (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
FEV_1 (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%	41.3%	35.7%	45.9%	<0.001
Nocturnal chest tightness	16%	13.2%	25.5%	20.0%	34.6%	<0.001
Attack of breathlessn. after activity	16%	13.7%	18.5%	20.0%	33.1%	<0.001
Attack of breathlessn. 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

Table 2 Importance of the determinants in predicting respiratory symptoms expressed as adjusted odds ratio (95% CI). Odds ratios are for an interquartile range increase in continuous variables. Significant results are written with bold numbers (n = 2270).

	Wheeze	Nocturnal chest tightness	Attack of breathlessness after activity	Attack of breathlessness when at rest	Wheeze and breathlessness	Wheeze when not having a cold	Nocturnal dyspnea
Age[a]	1.09(0.92–1.28)	1.00(0.82–1.20)	1.17(0.97–1.41)	1.05(0.79–1.38)	1.10(0.92–1.33)	1.19(0.98–1.44)	**1.31(1.01–1.71)**
Female gender		0.81(0.65–1.02)	0.87(0.70–1.08)	**0.61(0.43–0.86)**	0.90(0.73–1.12)	1.15(0.92–1.45)	0.84(0.62–1.15)
HADS[a]	**1.43(1.22–1.67)**	**1.82(1.50–2.21)**	**1.33(1.19–1.49)**	**1.61(1.38–1.88)**	**1.40(1.17–1.68)**	**1.43(1.20–1.71)**	**1.94(1.43–2.64)**
Smoking history							
Never-smokers	1	1	1	1	1	1	1
Ex-smokers	1.15(0.89–1.49)	0.71(0.52–0.97)	0.97(0.72–1.32)	1.13(0.74–1.73)	1.01(0.75–1.36)	1.01(0.74–1.39)	0.67(0.43–1.05)
Quitted smoking	1.05(0.78–1.41)	0.96(0.70–1.33)	1.19(0.86–1.64)	1.07(0.67–1.70)	1.04(0.74–1.45)	0.81(0.57–1.16)	0.82(0.51–1.30)
Current smokers	**2.91(2.34–3.62)**	0.94(0.72–1.23)	1.23(0.95–1.61)	0.93(0.62–1.38)	1.32(1.02–1.70)	**2.29(1.79–2.94)**	0.96(0.66–1.38)
Atopy	**2.03(1.57–2.63)**	**1.49(1.15–1.93)**	**1.33(0.97–1.81)**	1.34(0.83–2.17)	**1.98(1.50–2.61)**	**2.27(1.70–3.04)**	**1.55(1.06–2.28)**
BMI[a]	**1.53(1.30–1.81)**	**1.24(1.08–1.42)**	**1.23(1.08–1.39)**	1.13(0.95–1.35)	**1.28(1.12–1.46)**	**1.43(1.19–1.71)**	**1.20(1.01–1.43)**
Bronchial responsiveness[a]	**0.69(0.51–0.92)**	**0.78(0.66–0.91)**	**0.78(0.67–0.91)**	**0.52(0.39–0.70)**	**0.61(0.44–0.84)**	**0.54(0.39–0.75)**	**0.80(0.65–0.99)**
FEV1[a]	**0.71(0.61–0.83)**	0.93(0.80–1.07)	**0.70(0.59–0.83)**	0.96(0.76–1.21)	**0.73(0.62–0.86)**	**0.69(0.58–0.81)**	0.95(0.74–1.22)

[a] OR for an inter-quartile range (IQR) increase.

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 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 Mansiscalclo 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

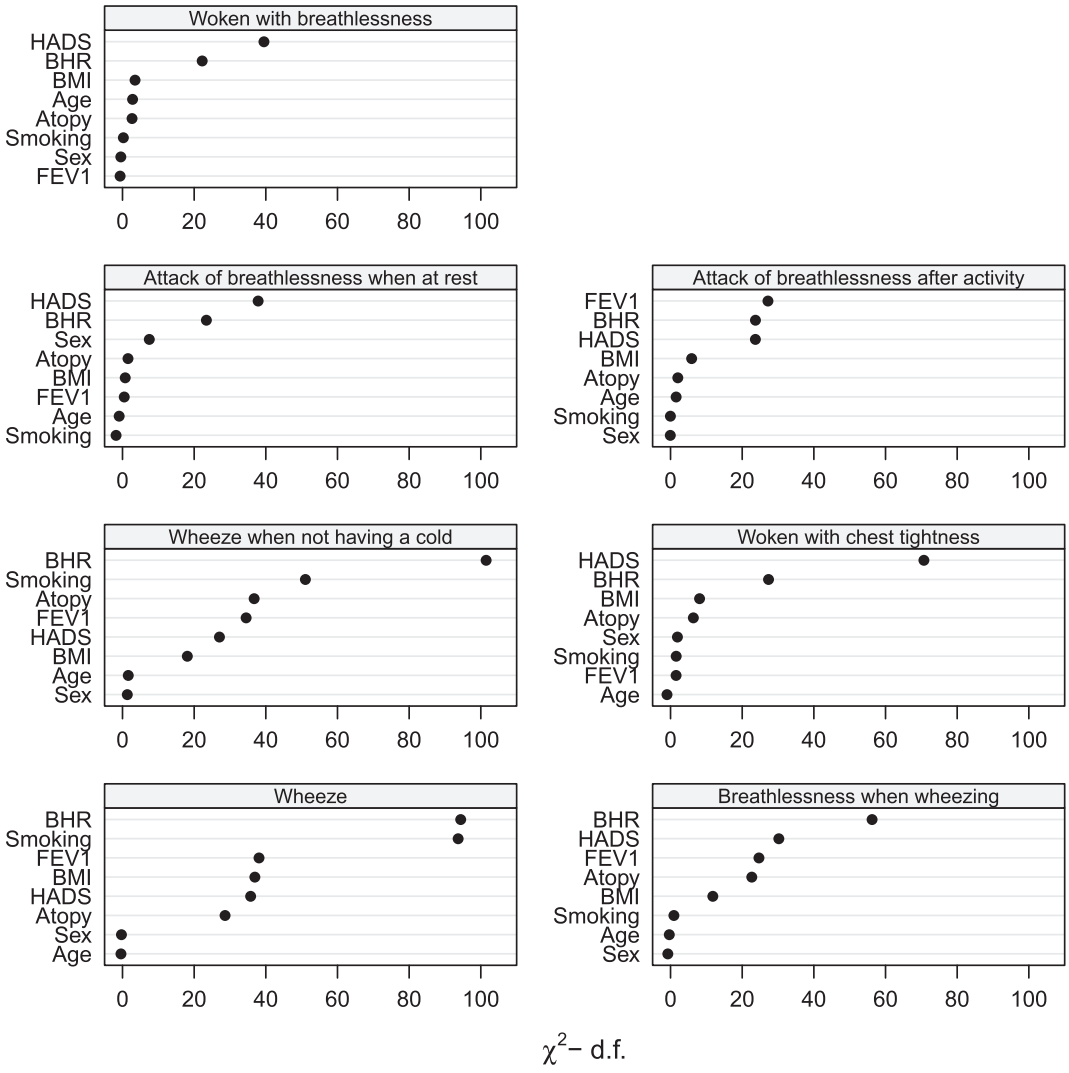

Figure 2 Variable importance for the different outcomes as judged by Wald χ^2-predictor degrees of freedom.

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.

Acknowledgments

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References

[1] Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J 1996;9(4):687—95.

[2] Burney PG, et al. Validity and repeatability of the IUATLD (1984) bronchial symptoms questionnaire: an international comparison. Eur Respir J 1989;2(10):940—5.

[3] Janson C, et al. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. Eur Respir J 2001;18(3):598—611.

[4] Oraka E, King ME, Callahan DB. Asthma and serious psychological distress: prevalence and risk factors among US adults, 2001—2007. Chest 2010;137(3):609—16.

[5] Janson C, et al. Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Med 1994; 149(4 Pt 1):930—4.

[6] Thomas M, et al. Asthma and psychological dysfunction. Prim Care Respir J 2011;20(3):250—6.
[7] Wang G, et al. Relationship between current psychological symptoms and future risk of asthma outcomes: a 12-month prospective cohort study. J Asthma 2011;48(10):1041—50.
[8] Vieira AA, et al. Anxiety and depression in asthma patients: impact on asthma control. J Bras Pneumol 2011;37(1):13—8.
[9] Lavoie KL, et al. Association between generalized anxiety disorder and asthma morbidity. Psychosom Med 2011;73(6): 504—13.
[10] Johansson A, Millqvist E, Bende M. Relationship of airway sensory hyperreactivity to asthma and psychiatric morbidity. Ann Allergy Asthma Immunol 2010;105(1):20—3.
[11] Wang G, et al. Psychological status in uncontrolled asthma is not related to airway hyperresponsiveness. J Asthma 2010; 47(1):93—9.
[12] Hayatbakhsh MR, et al. Association of psychiatric disorders, asthma and lung function in early adulthood. J Asthma 2010; 47(7):786—91.
[13] Burney PG, et al. The European Community Respiratory Health Survey. Eur Respir J 1994;7(5):954—60.
[14] Burney P, Chinn S. Developing a new questionnaire for measuring the prevalence and distribution of asthma. Chest 1987;91(6 Suppl.):79S—83S.
[15] Sundberg R, et al. Asthma in men and women: treatment adherence, anxiety, and quality of sleep. Respir Med 2010; 104(3):337—44.
[16] Lindberg E, et al. Sleep disturbances in a young adult population: can gender differences be explained by differences in psychological status? Sleep 1997;20(6):381—7.
[17] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361—70.
[18] Herrmann C. International experiences with the hospital anxiety and depression scale—a review of validation data and clinical results. J Psychosom Res 1997;42(1):17—41.
[19] Harter M, et al. Screening for anxiety, depressive and somatoform disorders in rehabilitation—validity of HADS and GHQ-12 in patients with musculoskeletal disease. Disabil Rehabil 2001;23(16):737—44.
[20] Mitchell AJ, Meader N, Symonds P. Diagnostic validity of the Hospital Anxiety and Depression Scale (HADS) in cancer and palliative settings: a meta-analysis. J Affect Disord 2010; 126(3):335—48.
[21] Saboonchi F, et al. Examination of the construct validity of the Swedish version of Hospital Anxiety and Depression Scale in breast cancer patients. Qual Life Res 2013;22(10):2849—56.
[22] ten Thoren C, Petermann F. Reviewing asthma and anxiety. Respir Med 2000;94(5):409—15.
[23] Quanjer PH, et al. Lung volumes and forced ventilatory flows. Eur Respir J 1993;6(Suppl. 16):5—40.
[24] Chinn S, et al. Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). Eur Respir J 1997;10(11):2495—501.
[25] European Community Respiratory Health Survey, I.I.S.C. The European Community Respiratory Health Survey II. Eur Respir J 2002;20(5):1071—9.
[26] Bousquet PJ, et al. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. Allergy 2007;62(3):301—9.
[27] Harrell JFE. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. Springer series in statistics. New York: Springer; 2001. xxii, 568 s.
[28] van Buuren S, et al. Fully conditional specification in multivariate imputation. J Statistical Comput Simul 2006;76(12): 1049—64.
[29] van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by Chained Equations in R. J Statistical Softw 2011;45(3):1—68.
[30] Neuman A, et al. Dyspnea in relation to symptoms of anxiety and depression: a prospective population study. Respir Med 2006;100(10):1843—9.
[31] Sembajwe G, et al. National income, self-reported wheezing and asthma diagnosis from the World Health Survey. Eur Respir J 2010;35(2):279—86.
[32] Wong KO, et al. Asthma and wheezing are associated with depression and anxiety in adults: an analysis from 54 countries. Pulm Med 2013;2013:929028.
[33] Brumpton BM, et al. The joint association of anxiety, depression and obesity with incident asthma in adults: the HUNT study. Int J Epidemiol 2013;42(5):1455—63.
[34] Carlsson AC, et al. High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden — a challenge for public health. BMC Public Health 2013;13(1):670.
[35] Blomstrand P, Ekedahl S, Schmekel B. Bronchial responsiveness to dry air hyperventilation in smokers may predict decline in airway status using indirect methods. Lung 2013; 191(2):183—90.
[36] Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007;175(7):661—6.
[37] Schachter LM, et al. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. Thorax 2001;56(1):4—8.
[38] Barranco P, et al. Obesity is not associated with mild asthma diagnosis in a population of Spanish adults. J Asthma 2009; 46(9):867—71.
[39] Kwon JW, et al. Airway hyperresponsiveness is negatively associated with obesity or overweight status in patients with asthma. Int Arch Allergy Immunol 2012;159(2):187—93.
[40] Maniscalco M, et al. Weight loss and asthma control in severely obese asthmatic females. Respir Med 2008;102(1): 102—8.
[41] Dias-Junior SA, et al. Effects of weight loss on asthma control in obese patients with severe asthma. Eur Respir J 2014;43(5): 1368—77.
[42] Parry GD, et al. Cognitive behavioural intervention for adults with anxiety complications of asthma: prospective randomised trial. Respir Med 2012;106(6):802—10.