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Real-world effect of gastroesophageal reflux disease on cough-related quality of life and disease status in asthma and COPD

Toshihiro Shirai [a,*], Masashi Mikamo [b], Tomoyoshi Tsuchiya [c], Yuichiro Shishido [a], Takefumi Akita [a], Satoru Morita [a], Kazuhiro Asada [a], Masato Fujii [a], Takafumi Suda [b]

[a] Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan
[b] Second Department of Internal Medicine, Hamamatsu University School of Medicine, Shizuoka, Japan
[c] Department of Respiratory Medicine, Shizuoka City Shimizu Hospital, Shizuoka, Japan

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is one of the most common causes of chronic cough and often coexists with asthma or chronic obstructive pulmonary disease (COPD); however, it is unknown whether there are differences in the effect of GERD on these diseases. The purpose of this study was to assess the difference in the effect of GERD on cough-related quality of life and disease status in asthma and COPD in a real-world setting.

Methods: Subjects were 132 patients with overall controlled asthma and 102 patients with stable COPD. They completed the frequency scale for symptoms of GERD (FSSG), a validated Japanese questionnaire for GERD, the Leicester Cough Questionnaire (LCQ), and the Asthma Control Test (ACT) or COPD assessment test (CAT) questionnaires.

Results: We found that 29 (22.0%) patients with asthma and 22 (21.6%) patients with COPD had GERD. There was no difference in the FSSG scale between the diseases. The patients with GERD, regardless of having asthma or COPD, had lower LCQ scores affecting all health domains and lower ACT or higher CAT scores than those without GERD. Overall, the patients with COPD had lower LCQ scores regardless of the presence or absence of GERD. The FSSG scale was negatively correlated with the LCQ total score in asthma and in COPD. In contrast, the FSSG scale was positively correlated with the CAT score but not with the ACT score.

Conclusions: Patients with GERD had impaired cough-related quality of life, poor asthma control or more symptoms and impacts of COPD.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common causes of chronic cough[1] and often coexists with asthma or chronic obstructive pulmonary disease (COPD).[2,3] A systematic review reported the prevalence of GERD symptoms to be 45%–71% in patients with asthma,[2] whereas a Korean survey from the National Health Insurance Database found the prevalence of GERD to be 28% in patients with COPD.[3] The current asthma guidelines recommend medical management of GERD in patients with symptoms of reflux and poorly controlled asthma, particularly those who have nocturnal symptoms.[4] Previous studies demonstrated that COPD exacerbations were associated with GERD symptoms.[5,6] GERD not only causes coughing but also affects the disease status in asthma and COPD, in both of which coughing is a common symptom in itself; however, very few have studied the differences in the effect of GERD on these diseases.[7]

The prevalence of GERD varies depending on the diagnostic modalities. Upper gastrointestinal endoscopy is a conventional test but cannot definitively diagnose GERD if there is no erosive lesion. Esophageal pH monitoring is the current gold standard but cannot detect reflux events with a pH similar to that of the normal esophagus.[8] Several questionnaires have been developed for the symptom-based diagnosis of GERD, including a questionnaire for the diagnosis of reflux disease (QUEST)[9] and a frequency scale for symptoms of GERD (FSSG).[10] FSSG is the standard questionnaire used in Japan for the diagnosis of GERD and assessment of the response to treatment. GERD symptoms can be quantified with FSSG but not with QUEST.

* Corresponding author. Department of Respiratory Medicine, Shizuoka General Hospital, 4-27-1 Kita-Ando, Aoi, Shizuoka, 420-8527 Japan.
E-mail address: toshihiro-shirai@i.shizuoka-pho.jp (T. Shirai).
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Symptoms related not only to acid reflux but also to gastric dysmotility can be evaluated with FSSG.[10] We hypothesized that the effect of GERD would differ between asthma and COPD. In this cross-sectional real-world study we assessed the effect of GERD, which was diagnosed by FSSG, on the cough-related quality of life and disease status in patients with asthma and COPD. We used the Leicester Cough Questionnaire (LCQ)[11] to assess the cough-related quality of life, and the Asthma Control Test (ACT)[12] or COPD assessment test (CAT)[13] questionnaires to assess the disease status.

Methods

Subjects

One hundred and thirty-two patients with bronchial asthma and 102 patients with COPD who attended outpatient clinics at Shizuoka General Hospital for routine check-ups between 2009 and 2011 were enrolled in this study.

The patients with asthma satisfied the definition of asthma of the Global Initiative for Asthma (GINA)[14] and were receiving inhaled corticosteroids with or without other medications, including long-acting β2-agonists, leukotriene receptor antagonists, or sustained release theophylline for at least 3 months. Patients were excluded from the study if they[1] had had any acute viral infections within at least 1 month before the study[2]; had a smoking history of >10 pack-years[3]; had COPD[4]; had been diagnosed with cough variant asthma; or[5] were receiving proton pump inhibitors.

The patients with COPD satisfied the definition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[15] They were clinically stable and had no exacerbations, defined as increased dyspnea associated with a change in the quality and quantity of sputum, for at least one month before the study. They were excluded from the study if they[1] had had any acute viral infections within at least 1 month before the study[2]; had any history of asthma; or[3] were receiving proton pump inhibitors.

Study design

On the examination day, the patients completed the FSSG, LCQ, and ACT or CAT questionnaires and underwent pulmonary function tests. The protocols were approved by the Institutional Review Board of Shizuoka General Hospital (SGH 13-01-42) and informed consent was obtained from all subjects prior to the study.

FSSG

GERD was diagnosed by the FSSG questionnaire,[10] a validated questionnaire in the Japanese population. The FSSG consists of 12 items, each of which is quantified on a scale ranging from 0 to 4 points and the cut-off score for GERD is set at 8 points.

LCQ

Cough-related quality of life was assessed by the LCQ,[11] which comprises 19 items and three domains: physical, psychological and social. Each item is scored between 1 and 7, with a higher score indicating better quality of life. The total score ranges from 3 to 21. The Japanese version was developed by Dr Akio Niimi (Nagoya City University Graduate School of Medical Sciences) and Dr Haruhiko Ogawa (Ishikawa-ken Saiseikai Kanazawa Hospital).

ACT

The ACT (Japanese version, supplied by GlaxoSmithKline Japan) questionnaire consists of 5 items assessing the impact of asthma on everyday functioning at school or work, shortness of breath, nocturnal asthma symptoms, use of rescue medication, and the patient's self-rating of asthma control during the previous 4 weeks.[12]

CAT

The CAT (Japanese version, supplied by GlaxoSmithKline Japan) questionnaire consists of 8 items (cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep, and energy) assessing and quantifying the symptoms and impacts of COPD.[13] Each item is scored from 0 to 5, giving a total score range from 0 to 40, corresponding to the best and worst health status, respectively.

Pulmonary function tests

Spirometry was performed using computerized equipment (model CHESTAC-33; CHEST MI, Inc., Tokyo, Japan) according to the standards of the American Thoracic Society.[16]

Statistical analysis

Comparisons between groups were made using the Kruskal–Wallis test. The chi-square or Fisher's exact test was used to test significance in group differences with respect to the percentage of patients in various categories. Correlations between variables were performed using the Spearman rank correlation coefficient. The analysis of covariance (ANCOVA) was used to adjust for age and gender. Stat View Version 5.0 (SAS Institute, Cary, NC, USA) was used for statistical calculations. A p value of <0.05 was considered significant, and all tests were 2 sided.

Results

Characteristics of study patients

The characteristics of study patients are shown in Table 1. The patients with asthma were younger and female-dominant, had a

Table 1
Characteristics of study patients.

	Patients with asthma ($n = 132$)	Patients with COPD ($n = 102$)
Age, y	60 (17–81)‡	73 (57–86)
Male/female	62/70‡	92/10
Body mass index, kg/m^2	23.1 (16.0–46.9)‡	20.9 (13.9–32.6)
Non/ex/current smokers	72/49/11‡	3/87/12
Pack-years	0 (0–9.5)†	51.0 (0–300.0)
FEV1, % of predicted	87.6 (23.0–145.7)‡	50.2 (17.0–109.0)
FEV1/FVC, %	72.2 (25.2–100.0)‡	50.2 (20.8–69.9)
ACT score†	22.9 (9–25)	NA
CAT score†	NA	11.8 (0–32)
FSSG scale†	4.7 (0–33)	5.1 (0–34)
LCQ		
Total score†	20.2 (9.5–21.0)‡	18.8 (7.5–21.0)
Physical domain†	6.6 (3.6–7.0)‡	6.2 (2.6–7.0)
Psychological domain†	6.8 (2.6–7.0)‡	6.2 (2.1–7.0)
Social domain†	6.8 (2.3–7.0)‡	6.4 (2.5–7.0)

Data are expressed as the median (range) or No.
Abbreviations: ACT, Asthma Control Test; CAT, COPD assessment test; FEV1, forced expiratory volume in 1 s; FSSG, frequency scale for the symptoms of GERD; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; LCQ, Leicester Cough Questionnaire; NA, not applicable.
† Data are expressed as the mean (Range).
‡ $p < 0.05$ versus patients with COPD.

higher body mass index and pulmonary function, included more nonsmokers, and had fewer pack-years than those with COPD. The mean ACT score of 22.9 indicated that study patients with asthma were overall controlled. There was no difference in the mean FSSG scale between the two groups; however, the LCQ scores in the patients with COPD were significantly lower than those in the patients with asthma. These results were reanalyzed using ANCOVA adjusting for age and gender; however, the results were the same.

Comparison between patients with asthma and GERD and those without GERD

We found that 29 of 132 (22.0%) patients with asthma and 22 of 102 (21.6%) patients with COPD had GERD. Table 2 shows the comparison of characteristics between patients with and without GERD. The patients with asthma and GERD were younger and had a lower ACT score and more impaired cough-related quality of life affecting all health domains than those without GERD. There was no difference in the body mass index or pulmonary function.

Comparison between patients with COPD and GERD and those without GERD

The patients with COPD and GERD had a higher CAT score and more impaired cough-related quality of life affecting all health domains than those without GERD; however, there was no difference in the body mass index or pulmonary function.

Comparison between patients with asthma and GERD and those with COPD and GERD

Concerning the LCQ scores, the patients with COPD had a more impaired psychological domain than those with asthma; however, there was no difference in the body mass index, FSSG scale, and LCQ total scores and other domains between the two groups.

Comparison between patients with asthma and without GERD and those with COPD and without GERD

Concerning the LCQ scores, the patients with COPD had a more impaired cough-related quality of life affecting all health domains than those with asthma.

Correlation between FSSG scale and LCQ score and disease status

In patients with asthma, the FSSG scale was negatively correlated with the LCQ total score ($r = -0.328$, $p = 0.0002$) but not with the ACT score ($r = -0.164$, $p = 0.0610$) (Fig. 1). In contrast, the FSSG scale was negatively correlated with the LCQ total score ($r = -0.351$, $p = 0.0004$) and positively correlated with the CAT score ($r = 0.543$, $p < 0.0001$) (Fig. 2).

Discussion

In this cross-sectional study we assessed whether the effect of GERD on cough-related quality of life and disease status differs between patients with asthma and those with COPD in a real-world clinical setting. We found that patients with GERD had significantly more impaired cough-related quality of life that affected all health domains and poorer asthma control and more symptoms and impacts of COPD than those without GERD. We also found that patients with COPD had more impaired cough-related quality of life than those with asthma, regardless of the presence or absence of GERD.

Previous studies using FSSG reported the prevalence of GERD to be 25.0%[7] and 27.4%[17] in Japanese patients with asthma and 26.8%,[5] 32.5%,[7] and 34.0%[18] in those with COPD, which were slightly higher proportions than in the present study. In the comparison between asthma and COPD, the prevalence of GERD was comparable and there was no difference in the mean FSSG scale between the two groups in the present study, whereas a previous study revealed a higher prevalence in patients with COPD than in those with asthma (32.5% versus 25.0%), but did not describe the difference in the mean scale.[7] Possible explanations for these discrepancies may be

Table 2
Comparison of characteristics between patients with and without GERD.

	Patients with asthma		Patients with COPD	
	GERD (+) ($n = 29$)	GERD (−) ($n = 103$)	GERD (+) ($n = 22$)	GERD (−) ($n = 80$)
Age, y	45 (17–78)*,**	62 (20–81)***	74 (62–84)	73 (57–86)
Male/female	12/17**	50/53***	19/3	73/7
Body mass index, kg/m^2	21.2 (17.2–45.4)	21.9 (16.0–46.9)***	21.6 (13.9–32.6)	20.9 (14.7–30.1)
Non/ex/current smokers	14/9/6**	58/40/5***	1/20/1	2/67/11
Pack-years	0 (0–9.5)**	1.1 (0–9.0)***	45.0 (0–150.0)	51.3 (0–300)
FEV1, % of predicted	89.9 (23.0–116.6)**	87.3 (29.6–145.7)***	56.5 (17.8–109.0)	46.5 (17.0–108.0)
FEV1/FVC, %	75.7 (45.6–100.0)**	71.3 (25.2–98.7)***	56.3 (32.2–68.1)	49.5 (20.8–69.9)
ACT score †	21.2 (9–25)*	23.4 (15–25)	NA	NA
CAT score†	NA	NA	18.1 (0–32)*	10.0 (0–30)
FSSG scale†	15.0 (8–33)*	1.8 (0–7)	15.3 (8–34)*	2.4 (0–7)
LCQ				
Total score†	18.9 (13.0–21.0)*	20.5 (9.5–21.0)***	16.9 (7.5–21.0)*	19.4 (10.6–21.0)
Physical domain†	6.0 (3.6–7.0)*	6.8 (3.8–7.0)***	5.5 (2.6–7.0)*	6.4 (4.5–7.0)
Psychological† domain	6.4 (3.7–7.0)*,**	6.9 (2.6–7.0)***	5.5 (2.1–7.0)*	6.4 (3.1–7.0)
Social domain†	6.5 (4.8–7.0)*	6.8 (2.3–7.0)***	5.9 (2.8–7.0)*	6.6 (2.5–7.0)

Data are expressed as the median (range) or No.
Abbreviations: ACT, Asthma Control Test; CAT, COPD assessment test; FEV1, forced expiratory volume in 1 s; FSSG, frequency scale for the symptoms of GERD; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; LCQ, Leicester Cough Questionnaire; NA, not applicable.
*$p < 0.05$ versus patients without GERD.
**$p < 0.05$ versus patients with COPD and GERD.
***$p < 0.05$ versus patients with COPD and without GERD.
† Data are expressed as the mean (Range).

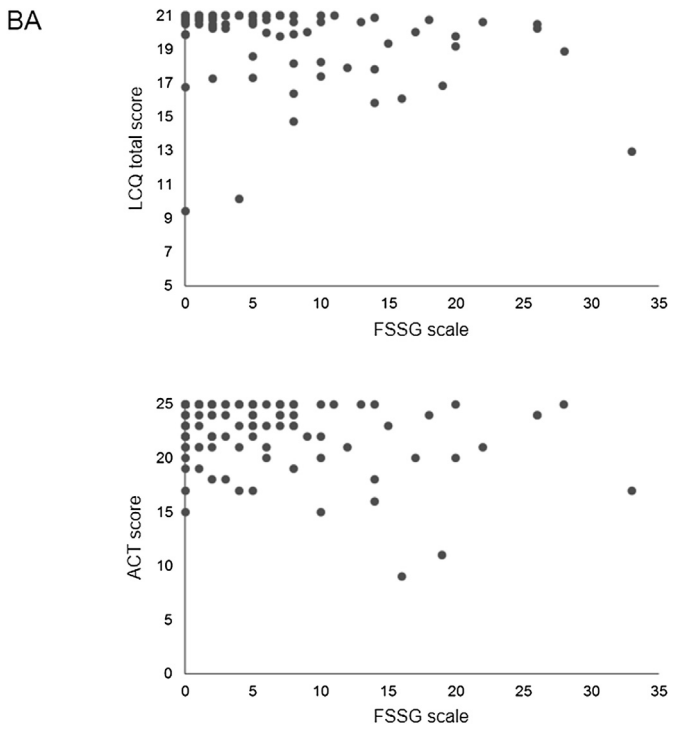

Fig. 1. Correlations between FSSG scale and LCQ total score (upper panel) and ACT score (lower pane) in patients with asthma. FSSG scale was negatively correlated with LCQ total score ($r = -0.328$, $p = 0.0002$) but not with ACT score ($r = -0.164$, $p = 0.0610$). Abbreviations: FSSG, frequency scale for symptoms of GERD; LCQ, Leicester Cough Questionnaire; ACT, Asthma Control Test.

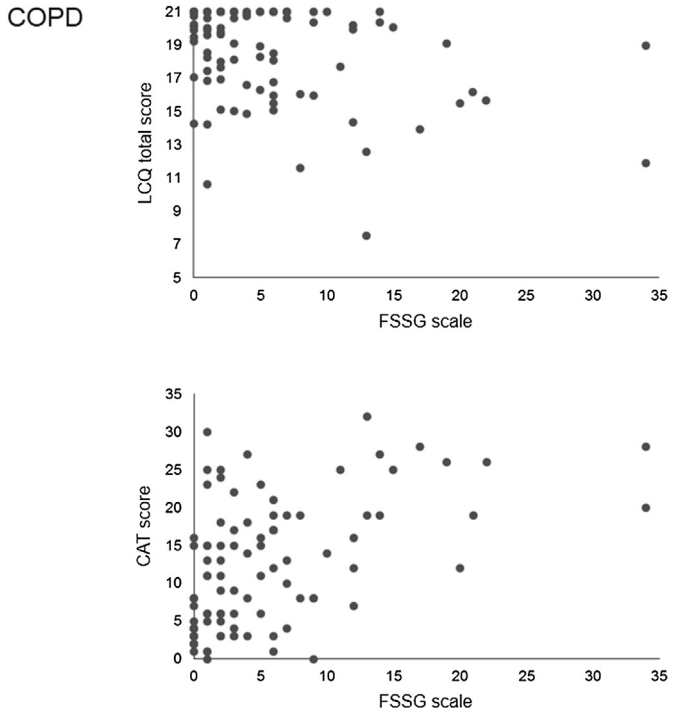

Fig. 2. Correlations between FSSG scale and LCQ total score (upper panel) and CAT score (lower panel) in patients with COPD. FSSG scale was negatively correlated with LCQ total score ($r = -0.351$, $p = 0.0004$) and positively correlated with CAT score ($r = 0.543$, $p < 0.0001$). Abbreviations: FSSG, frequency scale for symptoms of GERD; LCQ, Leicester Cough Questionnaire; CAT, COPD assessment test.

the difference in the sample size and the studied population, including asthma control levels and the backgrounds of the patients.

Previous studies reported the relationship between GERD and asthma control. Cheung et al.[19] identified that the patients with GERD had worse asthma control than those without GERD (mean ACT score, 19.2 versus 20.2) and that more patients with GERD had poor asthma control. They also demonstrated that GERD was associated with a poorer quality of life, as shown by the highly significant difference in all domain scores of the SF-36, a comprehensive measure of quality of life. Liang et al.[20] found that the independent association of GERD with not well-controlled asthma (ACT score <20) after other established contributors to asthma control were adjusted in multivariate logistic regression analyses. In the present study, we found that the patients with GERD not only had significantly lower ACT scores than those without GERD but also significantly more impaired cough-related quality of life that affected all health domains for the first time. Further, we demonstrated a negative correlation between the FSSG scale and LCQ total score. The lack of correlation between the FSSG scale and ACT score may reflect overall controlled patients with asthma in the present study. If we had recruited more uncontrolled patients, there would have been a significant correlation between the FSSG scale and ACT score. We previously assessed the effect of rabeprazole, a proton pump inhibitor, 10 mg/day on FSSG scale, ACT score, and LCQ total score in 13 patients with asthma in an uncontrolled, open-label pilot study.[21] We found that each parameter improved significantly after 4 months of treatment, suggesting the correlations between FSSG scale, ACT score, and LCQ total score.

A recent study analyzed the comorbid factors that increase CAT scores and found that the presence of GERD, depression, arrhythmia, and anxiety was significantly associated with a higher CAT score in patients with COPD than in those without comorbidities (mean CAT score: GERD, 16.3 versus 10.5).[18] In the present study, we found that patients with COPD and GERD had a higher CAT score (mean CAT score: 18.1 versus 10.0) and more impaired cough-related quality of life affecting all health domains than those without GERD. The correlation between the FSSG scale and LCQ total score or CAT score suggests that coexisting GERD may affect not only cough-related quality of life but also the COPD-specific health status.

Previous studies have shown that patients with GERD have high scores of psychological distress. Rey et al.[22] found that one-third of GERD patients with typical symptoms as the main complaint attending a gastroenterologist office were psychological distressed compared to the age- and sex-matched healthy controls. Cheung et al.[19] reported that the asthmatic patients with GERD had more anxiety and depression as reflected by the Hospital Anxiety and Depression Scale than those without GERD. Also, depression and anxiety are well-known comorbidities in COPD.[18] A recent study compared the psychological aspects between asthma and COPD, and found that patients with COPD, but not those with asthma, exhibited significantly higher levels of depressive and anxiety symptoms than healthy controls.[23] Also, in the present study, we confirmed that the patients with GERD had more impaired cough-related quality of life affecting the psychological domain than those without GERD in both asthma and COPD. Compared to patients with asthma and GERD, patients with COPD and GERD had a more impaired psychological domain of the LCQ, suggesting the difference in the psychological aspects of the diseases.

Cough is identified by asthmatic patients as a symptom that significantly interferes with activities of daily life.[24] Cough is also recognized by physicians as a very important symptom in determining asthma control, although less so than shortness of breath and wheezing.[25] In COPD, chronic coughing and sputum

production are present in a subset of patients and are related to disease progression.[26] Patients with asthma or COPD in the present study were clinically well controlled or stable; however, the LCQ scores in patients with COPD were significantly lower than in patients with asthma. This difference was also observed in the comparison between patients with asthma and without GERD and those with COPD and without GERD. A previous study compared the LCQ between clinically stable patients with asthma or COPD who did not report coughing as a prominent or troublesome symptom and found no difference in the total LCQ score (13.3 versus 13.2).[27] The small sample size in their study may explain the discrepancy but the findings in the present study may suggest a difference in the degree of coughing between asthma and COPD, even in a stable condition.

The relationship between GERD and age or BMI is controversial in Japan. Some investigators[28,29] reported old age (over 80 years) and obesity ($\geq$25 kg/m^2) as risk factors, whereas others found different results. Watanabe et al.[30] found that of the total 4139 subjects the prevalence of GERD diagnosed by the FSSG was highest in the 20–29 years age group and lowest in the 70–79 years group. Furukawa et al.[28] failed to show any significant difference in the proportion of esophagitis between patients with BMI ($\geq$25 kg/m^2) and those with BMI (<25 kg/m^2). In the present study, the asthma patients with GERD were younger than those without GERD. And there was no difference in the BMI between the two groups. Different populations may produce different results.

The major limitation of this study is that group characteristics, such as age and gender, did not match between the two groups, and it would be difficult to compare the effects of GERD between the groups directly; however, the purpose of this study was to evaluate the effect of GERD on cough-related quality of life and disease status in asthma and COPD in a real-world setting. We believe we could clarify the clinical features of patients with GERD both in asthma and COPD. Concerning the difference in GERD symptoms and the impact of GERD symptoms on exacerbation between age-matched patients with asthma and those with COPD, Shimizu et al.[7] found that patients with asthma had more regurgitation-related symptoms than those with COPD, whereas patients with COPD had more dysmotility-related symptoms than those with asthma. They also found that the presence of GERD influenced the exacerbation of COPD, but not asthma. Real-world effect of GERD in the present study should be interpreted in conjunction with the findings reported by Shimizu et al.

In conclusion, patients with GERD and asthma or COPD had impaired cough-related quality of life and poor asthma control or more symptoms and impacts of COPD.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Pratter MR. Overview of common causes of chronic cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**:59S–62S.
2. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. *Gut* 2007;**56**:1654–64.
3. Kim J, Lee JH, Kim Y, Kim K, Oh YM, Yoo KH, et al. Association between chronic obstructive pulmonary disease and gastroesophageal reflux disease: a national cross-sectional cohort study. *BMC Pulm Med* 2013;**13**:51.
4. National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute; 2007. Publication No. 08–4051.1.
5. Terada K, Muro S, Sato S, Ohara T, Haruna A, Marumo S, et al. Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. *Thorax* 2008;**63**:951–5.
6. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;**363**:1128–38.
7. Shimizu Y, Dobashi K, Kusano M, Mori M. Different gastroesophageal reflux symptoms of middle-aged to elderly asthma and chronic obstructive pulmonary disease (COPD) patients. *J Clin Biochem Nutr* 2012;**50**:169–75.
8. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**:80S–94S.
9. Carlsson R, Dent J, Bolling-Sternevald E, Johnsson F, Junghard O, Lauritsen K, et al. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol* 1998;**33**:1023–9.
10. Kusano M, Shimoyama Y, Sugimoto S, Kawamura O, Maeda M, Minashi K, et al. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol* 2004;**39**:888–91.
11. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;**58**:339–43.
12. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;**113**:59–65.
13. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J* 2009;**34**:648–54.
14. Global Initiative for Asthma (GINA). *Global strategy for asthma management and prevention*. December 2012. Available from: www.ginasthma.org [accessed 29.01.14].
15. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global strategy for diagnosis, management, and prevention of COPD*. January 2014. Available from: www.goldcopd.org [accessed 29.01.14].
16. Standardization of spirometry, 1994 update. American thoracic society. *Am J Respir Crit Care Med* 1995;**152**:1107–36.
17. Takenaka R, Matsuno O, Kitajima K, Ono E, Hiroshige S, Nishitake T, et al. The use of frequency scale for the symptoms of GERD in assessment of gastro-oesophageal reflex symptoms in asthma. *Allergol Immunopathol Madr* 2010;**38**:20–4.
18. Miyazaki M, Nakamura H, Chubachi S, Sasaki M, Haraguchi M, Yoshida S, et al. Analysis of comorbid factors that increase the COPD assessment test scores. *Respir Res* 2014;**15**:13.
19. Cheung TK, Lam B, Lam KF, Ip M, Ng C, Kung R, et al. Gastroesophageal reflux disease is associated with poor asthma control, quality of life, and psychological status in Chinese asthma patients. *Chest* 2009;**135**:1181–5.
20. Liang B, Yi Q, Feng Y. Association of gastroesophageal reflux disease with asthma control. *Dis Esophagus* 2013;**26**:794–8.
21. Shirai T, Mikamo M, Mori K, Shishido Y, Akita T, Morita S, et al. Association of asthma control, cough-related quality of life, and gastroesophageal reflux disease symptoms [abstract]. *Am J Respir Crit Care Med* 2011;**183**:A4323.
22. Rey E, García-Alonso M, Moreno-Ortega M, Almansa C, Alvarez-Sanchez A, Díaz-Rubio M. Influence of psychological distress on characteristics of symptoms in patients with GERD: the role of IBS comorbidity. *Dig Dis Sci* 2009;**54**:321–7.
23. Bratek A, Zawada K, Beil-Gawełczyk J, Beil S, Sozańska E, Krysta K, et al. Depressiveness, symptoms of anxiety and cognitive dysfunctions in patients with asthma and chronic obstructive pulmonary disease (COPD): possible associations with inflammation markers: a pilot study. *J Neural Transm*. Epub 2014 Feb 15.
24. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;**47**:76–83.
25. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini asthma quality of life questionnaire. *Eur Respir J* 1999;**14**:32–8.
26. Pelkonen M, Notkola IL, Nissinen A, Tukiainen H, Koskela H. Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged men. *Chest* 2006;**130**:1129–37.
27. Polley L, Yaman N, Heaney L, Cardwell C, Murtagh E, Ramsey J, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. *Chest* 2008;**134**:295–302.
28. Furukawa N, Iwakiri R, koyama T, Okamoto K, Yoshida T, Kashiwagi Y, et al. Proportion of reflux esophagitis in 6010 Japanese adults: prospective evaluation by endoscopy. *J Gastroenterol* 1999;**34**:441–4.
29. Sakaguchi M, Oka H, Hashimoto T, Asakuma Y, Takao M, Gon G, et al. Obesity as a risk factor for GERD in Japan. *J Gastroenterol* 2008;**43**:57–62.
30. Watanabe T, Urita Y, Sugimoto M, Miki K. Gastro-esophageal reflux disease symptoms are more common in general practice in Japan. *World J Gastroenterol* 2007;**13**:4219–23.