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Cough variant asthma patients are more depressed and anxious than classic asthma patients

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ABSTRACT

Objective: Many recent studies have indicated that depression and anxiety are more common in asthmatic patients than in the general population and psychological stress can lead to asthma exacerbations, but no study specifically targets cough variant asthma (CVA) patients. The purpose of this study was to evaluate depression and anxiety levels in CVA patients compared with classic asthma patients and to identify the psychological features of CVA patients.

Methods: Fifty-nine outpatients with CVA and 128 outpatients with classic asthma were interviewed about psychosomatic and psychiatric symptoms, and they underwent three psychological tests: Self-rating Depression Scale (SDS), State-Trait Anxiety Inventory (STAI), and Comprehensive Asthma Inventory (CAI). They were ultimately screened for major and minor depression, dysthymia, panic disorder, generalized anxiety disorder, social anxiety disorder, and other anxiety disorders.

Results: CVA patients showed higher SDS and STAI scores than classic asthma patients, and mood disorders and anxiety disorders were more common than in classic asthma outpatients. The psychological factors 'frustration', 'fright into illness', and 'distorted lifestyle' were more prominent in CVA patients than in classic asthma patients. **Conclusion:** CVA patients are on average more depressed and anxious than classic asthma outpatients. Though CVA appears pathologically to be just an early stage of typical asthma, the psychological stress may often be more serious than in asthma controlled by medication, which may explain why CVA cannot be controlled by a bronchodilator alone and patients often require no less intense therapy than for severe asthma.

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Introduction

Chronic cough has been reported to be the fifth most common complaint seen by primary care physicians [1]. For instance, in the USA, persistently troublesome chronic cough accounts for up to 38% of a pulmonologist's outpatient practice [2]. In Japan, cough is the most frequent reason (11.7% of all) for clinic visits [3].

Cough variant asthma (CVA) is the most common cause of prolonged/chronic cough (42.2%), followed by cough-predominant asthma (28.4%), in Japan [4]. In classic asthma, variable airflow obstruction typically leads to symptoms such as wheeze, dyspnea, and cough. In CVA, cough can be the sole presenting symptom. CVA remains one of the most common causes of chronic cough worldwide [5,6]. More importantly, in classic asthma, cough may be associated with a worse prognosis [7–9].

CVA is thought to be a precursor of classic asthma, because 30–40% of CVA patients have been found to develop classic asthma [1,10,11], and

pathologically, eosinophilic inflammation is involved in CVA as well as in classic asthma [10]. CVA is also characterized by airway hyper-responsiveness, and it usually responds to bronchodilators such as beta-agonists and theophyllines [12–14]. However, many pulmonologists often experience CVA patients who couldn't be controlled by a bronchodilator alone and therefore tend to administer inhaled corticosteroids (ICS) or a combination of inhaled corticosteroids and long acting beta-agonists (ICS/LABA). There are no data currently available regarding the choice of ICS, its dose or duration that should be used for the treatment of CVA. In very severe cases whose symptoms are refractory to ICS, even oral corticosteroids may be required. [15,16]. However, if CVA were just a precursor or a very mild phenotype of classic asthma, ICS, ICS/LABA or oral corticosteroids usually indicated for patients with moderate to severe asthma would rarely be necessary.

On the other hand, many recent studies have indicated that depression and anxiety are more common in asthmatic patients than in the general population [17–19].

We hypothesized that CVA patients might be more depressed and anxious than classic asthma patients. The purpose of this research was to evaluate the depression and anxiety levels in a population of 59 CVA patients and 128 classic asthma outpatients, and to identify the psychological features of CVA compared with classic asthma. This

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study is the first report to show that the psychological state of CVA patients is different from that of classic asthma patients.

Methods

Participants and procedure

Participants were recruited from adult patients (aged between 18 and 79 years old) presenting to Allergy and Respiratory Unit of Yokote Municipal Hospital from April 2009 to March 2013. Flowchart of patient

participation and procedure is shown in Fig. 1. They consulted or were referred to the unit with undiagnosed chronic cough, or for follow up treatment of asthma that had already been diagnosed in the past. Undiagnosed patients had a detailed examination such as basic blood tests, spirometry, X-ray and computed tomography of the chest, sputum examination including acid-fast stain, and serologic assays for *Mycoplasma pneumoniae*, *Bordetella pertussis* and other organisms, that ruled out other respiratory disease with chronic cough. Patients were excluded if they had any comorbid diagnosis of greater severity than asthma (e.g. chronic obstructive pulmonary disease, coronary artery

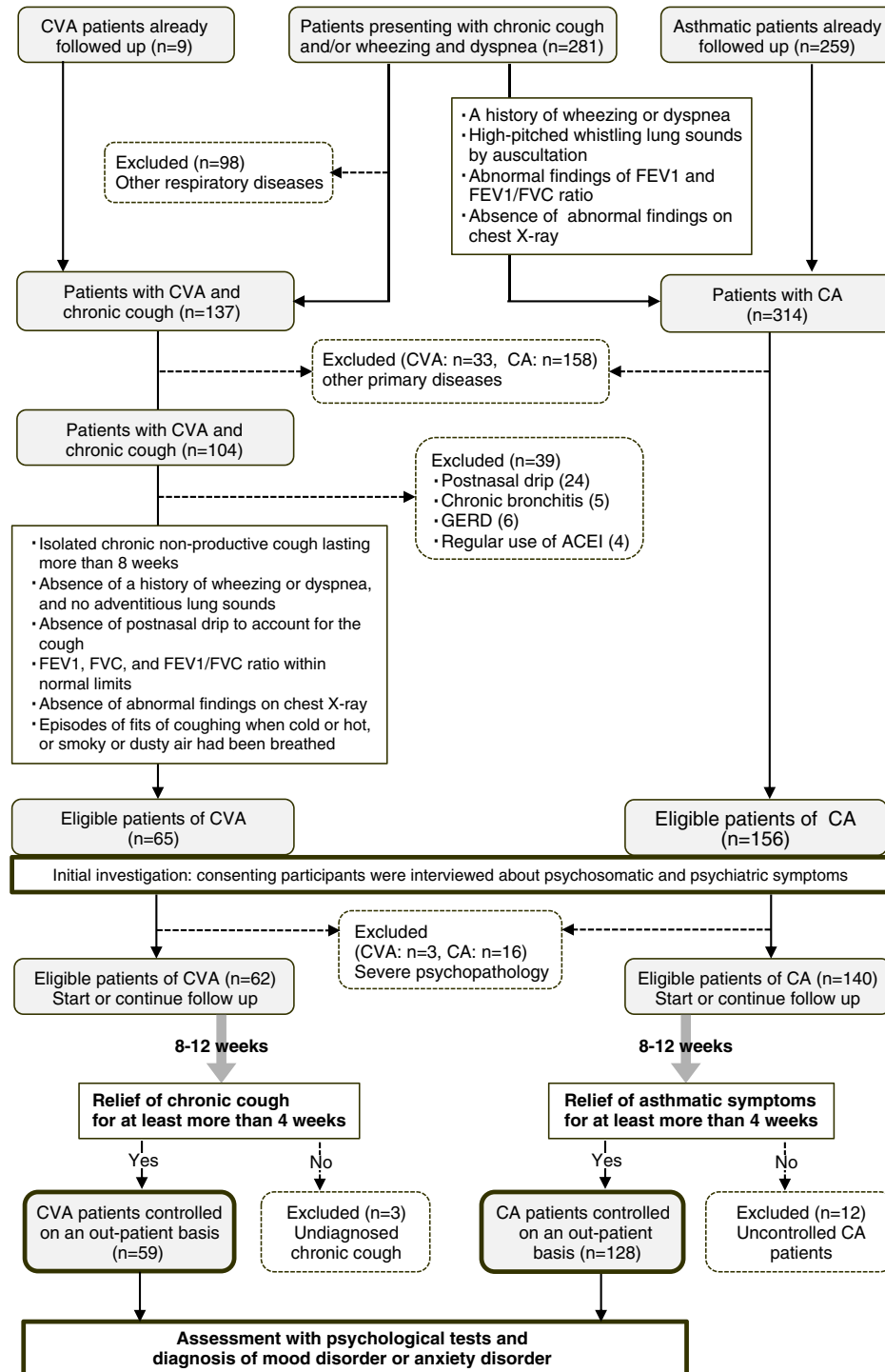


Fig. 1. Flowchart of patient participation and procedure. CVA = Cough variant asthma, CA = Classic asthma, GERD = Gastroesophageal reflux disease, ACEI = Angiotensin converting enzyme inhibitor.

disease, heart failure, cancer, dialysis patients). Patients with chronic cough due to post nasal drip, chronic bronchitis by environmental factors, gastroesophageal reflux disease (GERD) and regular use of angiotensin converting enzyme inhibitor (ACE inhibitor) were excluded. Eligible patients of CVA ($n = 65$) and classic asthma ($n = 156$) gave their written or oral consent for participation, the obtained consents were recorded in each patient's chart. Initially, they were asked about psychosomatic and psychiatric symptoms using Mini International Neuropsychiatric Interview (M.I.N.I.) [20] and diagnosed according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision (DSM-IV-TR) [21] by a single specialist in psychosomatic medicine. Patients were excluded if they had any cognitive deficits (e.g. dementia), severe psychopathology (e.g. schizophrenia, delusional disorder, delirium, acute mania), or current substance abuse. None of the eligible participants received psychotropic medication, but most of the undiagnosed patients had already received cough suppressants and/or mucolytic agents. Most of the asthmatic patients who had already been followed up had received leukotriene receptor antagonist, bronchodilators and/or inhaled corticosteroids.

They were followed up for more than eight weeks since they were newly diagnosed and medicated, or since patients who had already been followed up for CVA or classic asthma participated in this study. To investigate depression and anxiety disorder of patients with CVA and classic asthma who could be treated on an out-patient basis, the patients were excluded if they had not responded at all to treatment and/or required hospitalization.

When relief of their symptoms such as frequent cough and asthma attacks had lasted at least more than four weeks in eight to twelve weeks from the initial interview, patients underwent psychological tests: the Self-rating Depression Scale (SDS) [22,23], the State-Trait Anxiety Inventory (STAI) [24–26], and the Comprehensive Asthma Inventory (CAI) [27–30]. They were ultimately screened for major and minor depression, dysthymia, panic disorder, generalized anxiety disorder, social anxiety disorder, and other anxiety disorders.

The final subject population consisted of 59 CVA patients and 128 classic asthma patients who were able to fill out the self-administered questionnaires by themselves.

This study was approved by the ethics committee of Yokote Municipal Hospital.

Diagnosis

The diagnosis of classic asthma was based on the Global Initiative for Asthma (GINA) guidelines [31,32]. All classic asthma patients had a history of episodic dyspnea, wheezing, and cough.

CVA patients were referred to our clinic for chronic cough for longer than 8 weeks but without wheezing or shortness of breath. They did not have any signs or symptoms of postnasal drip or gastro-esophageal reflux, had not been taking angiotensin-converting enzyme inhibitors, and had normal chest X-rays. The diagnosis of CVA is commonly made according to the following seven criteria [11]:

- 1) Isolated chronic non-productive cough lasting more than 8 weeks.
- 2) Absence of a history of wheeze or dyspnea, and no adventitious lung sounds on physical examination.
- 3) Absence of postnasal drip to account for the cough.
- 4) FEV₁, FVC, and FEV₁/FVC ratio within normal limits.
- 5) Presence of bronchial hyperresponsiveness (by methacholine challenge test).
- 6) Relief of cough with bronchodilator therapy.
- 7) No abnormal findings indicative of cough etiology on chest X-ray.

The main features of CVA are 1), 2), and 6); these three features are also the simple criteria of CVA. To satisfy the strict full criteria, an inhaled methacholine challenge test is required to establish the degree of bronchial hyperresponsiveness. However, it seems difficult to recommend this potentially hazardous challenge test for all patients with

chronic cough, and they do not benefit clinically from the examination. Therefore, the presence of bronchial hyperresponsiveness was confirmed by episodes of fits of recurring coughing when cold or hot, or smoky or dusty air had been breathed, instead of the methacholine challenge test, and the diagnosis of CVA was made with the seven criteria in this study.

All psychiatric disorders were diagnosed (or ruled out) based on the DSM-IV-TR criteria [21], after the screening by a brief, structured psychiatric interview (M.I.N.I.) by a single specialist in psychosomatic medicine. The M.I.N.I. is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders [20].

Evaluation of depression and anxiety

The level of depression was scored by the Self-rating Depression Scale (SDS) [22,23], which is a self-report measure for assessing depression and consists of 20 items with negative and positive contents. A higher score is positively correlated with a higher level of depression (range of possible scores: 20–80). There are many self-rating depression scales, such as CES-D (Center for Epidemiologic Studies Depression Scale), SDS and HAM-D (Hamilton Rating Scale for Depression). SDS is a somewhat old scale, but has been translated into most languages, and especially Chinese and Japanese specialists in psychosomatic medicine often use it for rating depression even today [33–35]. Demura et al. reported the correlation of depression scale scores between SDS and CES-D in 563 Japanese was significant and comparable (correlation coefficient: 0.78, $p < 0.01$), and similarities in depression determination were found between SDS and CES-D [36].

The level of anxiety was scored by the State-Trait Anxiety Inventory (STAI) [24–26], which is a self-report measure for assessing anxiety and consists of 40 items. The STAI measures two types of anxiety: state anxiety, which is about an event at that time, and trait anxiety, which is an anxiety level as a personal characteristic. Higher scores are positively correlated with higher levels of anxiety (each range of possible scores: 20–80).

The Comprehensive Asthma Inventory (CAI)

The CAI, which was originally published by the Japanese Society of Psychosomatic Research on Respiratory Disease, is a questionnaire containing 18 questions designed to assess the involvement of psychological factors with asthmatic symptoms [27–30]. Using the CAI, psychological factors were categorized into nine categories: 'A: extent of conditioning', 'B: suggestibility', 'C: expected anxiety', 'D: dependency', 'E: frustration', 'F: fright into illness', 'G: distorted lifestyle', 'H: negative attitudes toward prognosis', and 'I: decreased motivation toward therapy'. They were measured as the CAI scores of each psychological factor, and the total CAI score was calculated as the average of all CAI scores. Each question is estimated to relate largely or moderately to some categories of psychological factors (A to I) (Table 1), with "times 1" allotted to psychological categories largely related and "times 0.5" allotted to categories moderately related in some cells. To measure the CAI score (%) of each psychological factor, "Yes" is converted to 2 points, "?" to 1 point, and "No" to 0 points, and the points are multiplied by 1 or 0.5 in the matched cells. All products for one category of psychological factor are summed, and a percentage of full marks is calculated for the category.

Data analysis

Differences between two groups were tested for significance using Student's *t*-test when the distribution of the data followed a normal distribution, and using Mann–Whitney's *U* test when the distribution did not follow a normal distribution. Significance was set at $p < 0.05$.

Table 1
The Comprehensive Asthma Inventory.

Questionnaire	Answer	A	B	C	D	E	F	G	H	I
1 Do you have your symptoms at a certain time of the day?	Yes / ? / No	×1	×1	×0.5		×0.5	×1	×0.5		
2 Do you have your symptoms on a certain day of the week?	Yes / ? / No	×1	×1	×1	×0.5	×0.5	×0.5	×0.5		
3 Do your symptoms occur when you notice that you do not have the drug with you?	Yes / ? / No	×0.5	×0.5	×1	×1				×0.5	
4 Will your symptoms occur usually when you only see something that once triggered your symptoms?	Yes / ? / No	×1	×1	×0.5						
5 Did you usually have your symptoms before some important activities?	Yes / ? / No	×1	×1	×1		×0.5	×1			
6 Do you usually have no symptoms when you leave home such as by hospitalization or traveling?	Yes / ? / No	×1				×1	×0.5	×0.5		
7 Do you often have symptoms when you leave home?	Yes / ? / No	×0.5	×0.5	×0.5		×1	×0.5	×1		
8 Are you apt to have your symptoms when you have certain feelings such as anger, sorrow, or hatred?	Yes / ? / No					×1		×0.5		
9 Did you ever think that your symptoms were punishment for your sins?	Yes / ? / No		×0.5	×0.5		×1		×0.5		
10 Do your symptoms always lead you to the same condition?	Yes / ? / No	×1	×1	×0.5			×0.5			
11 Do you find yourself more comfortable during your symptoms when someone is with you?	Yes / ? / No			×1	×1	×0.5	×0.5			
12 Do you ever think you would rather die when you have your symptoms?	Yes / ? / No					×0.5			×1	×0.5
13 Do you often think your asthma is incurable?	Yes / ? / No		×0.5	×0.5					×1	×0.5
14 Do you have other symptoms when you have no respiratory symptoms?	Yes / ? / No					×1	×0.5	×0.5		
15 Do you often think that your symptoms prevent you from starting new things?	Yes / ? / No		×0.5				×1			×0.5
16 Have you decided that you can't do anything unless you have no symptoms?	Yes / ? / No					×0.5	×1	×0.5	×0.5	×0.5
17 Are you often irritated as you wonder why you have to suffer the symptoms?	Yes / ? / No					×1	×0.5	×0.5		×0.5
18 Do you want many people to understand the pain you suffer during your symptoms?	Yes / ? / No				×1	×1			×0.5	
Points										
Full marks		14	15	14	7	20	15	10	7	5
CAI score		%	%	%	%	%	%	%	%	%
Total (average) CAI score										%

A: Extent of conditioning, B: Suggestibility, C: Expected anxiety, D: Dependency, E: Frustration, F: Fright into illness, G: Distorted lifestyle, H: Negative attitudes toward prognosis, I: Decreased motivation toward therapy.

Results

Clinical characteristics and present symptoms were shown in Table 2. They were identified when newly diagnosed CVA or classic asthma patients were interviewed at the initial investigation, or when patients who had been already followed up were interviewed at their arbitrary participating time. The data were compared with respect to total patients and limited newly diagnosed patients. The mean age of total CVA patients was 43.2 years, and 79.7% of patients were women; they were significantly younger with a greater proportion of women than total classic asthma patients (53.1 years; 60.9% women). In newly diagnosed patients, the mean age of CVA patients (43.1 years) had no significant difference with that of classic asthma patients (46.1 years). The pathology duration, which means the period from the onset of symptoms to their participating time, was far longer in classic asthma patients than in CVA patients. Smokers were significantly often in classic asthma patients. FEV1.0% at the initial investigation on this study was lower, and peripheral eosinophils (%) were higher in classic asthma patients. There were no significant differences between CVA and classic asthma patients with regard to %VC and serum IgE. These results were similar in newly diagnosed patients.

Detailed questioning about psychosomatic and psychiatric symptoms with the structured psychiatric interview showed more frequent anorexia, disturbed sleep, depressive mood, autonomic imbalance and anxiety in total CVA patients than in total asthma patients, while only depressive mood was significantly more frequent in newly diagnosed CVA patients.

SDS and STAI scores and the prevalence of mood disorders and anxiety disorders are shown in Table 3. Both total and newly diagnosed CVA patients showed higher SDS scores than classic asthma patients regardless of sex. In state anxiety of the STAI, both total and newly diagnosed CVA patients showed higher STAI-state scores than classic asthma patients, but there was no significant difference in females of total patients and in males of newly diagnosed patients. Similarly, in trait anxiety of the STAI, both total and newly diagnosed CVA patients showed higher STAI-trait scores than classic asthma patients, but there was no significant difference in females of total and newly diagnosed patients.

Collecting relevant features of their history, symptoms, and results of psychological tests and physical examination, mood disorder or anxiety disorder was diagnosed according to DSM-IV-TR criteria. Ultimately, a total of 57.6% of CVA patients met the diagnostic criteria for any mood disorder or anxiety disorder (including previous history in the last 12 months); they included major depression (13.6%), minor depression (11.9%), dysthymia (1.7%), panic disorder (3.4%), generalized anxiety disorder (16.9%), social anxiety disorder (8.5%), and other anxiety disorders (1.7%). In classic asthma, 28.1% of patients met the diagnostic criteria for a psychiatric disorder, including major depression (8.6%), minor depression (3.9%), dysthymia (0.8%), panic disorder (7.8%), generalized anxiety disorder (3.1%), social anxiety disorder (0.8%), and other anxiety disorders (3.1%). In total patients, CVA patients had significantly higher prevalence rates of total mood disorders (CVA: 27.1% versus classic asthma:13.3%), minor depression, total anxiety disorders (CVA: 30.5% versus classic asthma: 14.8%), generalized anxiety disorder, and social anxiety disorder than classic asthma patients. A similar tendency was seen in newly diagnosed patients as well, but there were significant differences only in total anxiety disorders in female, and in generalized anxiety disorder. Only panic disorder showed a trend toward higher prevalence rates in classic asthma patients than in CVA patients, and slightly significant difference was found only in newly diagnosed male patients, although the number was small.

SDS and STAI scores of CVA patients were compared with those of the subgroups of classic asthma patients who had or had not been hospitalized at least once, and compared with each group of the present therapeutic steps for asthma (Table 4). CVA patients

showed higher scores on the SDS and both state and trait anxiety in the STAI than classic asthma patients who had never been hospitalized, but no difference with those who were hospitalized at least once. A similar tendency was seen in the limited newly diagnosed patients as well.

CVA patients showed higher SDS scores than classic asthma patients at therapeutic steps 2–4, and higher scores on both state and trait anxiety in the STAI than asthma patients at therapeutic steps 3–4. In the limited newly diagnosed patients, the statistical analysis comparing CVA patients and asthmatics at therapeutic steps 1–2 could not be performed because of the smaller number of patients, but significantly higher scores in CVA patients were found in the SDS scores compared with asthmatics at therapeutic steps 3–4, on the STAI-state scores compared with asthmatics at therapeutic step 4, and on the STAI-trait scores compared with asthmatics at therapeutic steps 3–4.

The involvement of psychological factors with asthmatic symptoms including chronic cough was evaluated using the CAI. Nine categories of psychological factors were measured and compared between CVA and classic asthma patients (Table 5). CVA patients showed higher CAI scores for 'frustration', 'fright into illness', and 'distorted lifestyle', and higher total CAI scores than classic asthma patients. The score for 'frustration' was higher especially in males, and 'fright into illness' was higher especially in females. In newly diagnosed patients, there was no significant difference in any category (the data was not shown).

Discussion

The characteristics of CVA patients

The aim of this study was to investigate CVA patients' characteristics, including depression and anxiety, and compare them with those of classic asthma outpatients. The present results showed that CVA patients were generally younger and included more women than classic asthma patients, although there was no statistic difference in age of newly diagnosed patients. Given the previous report that CVA is a precursor of classic asthma and 30–40% of them have developed classic asthma [1,10,37], it is natural that CVA patients are less commonly elderly. Many studies have suggested that adult CVA patients are more likely to be females [10,11,37–39], while in children, CVA was identified in slightly more boys than girls [40,41].

Psychological symptoms identified by the interview were significantly more prominent in CVA patients than in classic asthma patients, especially for anorexia, disturbed sleep, depressive mood, autonomic imbalance, and anxiety. These data (Table 2) were taken at the initial investigation on this study, and most CVA patients (91.5%) had been referred as patients with undiagnosed persistent chronic cough for more than eight weeks, while many classic asthma patients (84.3%) had already been followed up and were aware of subjective asthma. Therefore, psychological stress with their respiratory symptoms is thought to be more integrated in CVA patients than in classic asthma

Table 2

Clinical characteristics and present symptoms at the initial interview.

	Cough variant asthma (Total) n = 59	Classic asthma (Total) n = 128	Cough variant asthma (Newly diagnosed) n = 54	Classic asthma (Newly diagnosed) n = 20
<i>Clinical characteristics</i>				
Female (%)	47 (79.7)*	78 (60.9)	42 (77.8)*	10 (50.0)
Age ± SD	43.2 ± 14.2**	53.1 ± 15.6	43.1 ± 14.8	46.1 ± 15.8
No. of patients who smoke (%)	1 (1.7)**	19 (14.8)	1 (1.9)**	3 (15.0)
Pathology duration (days) ± SD	133.7 ± 164**	2018.1 ± 1926	90.5 ± 72.9**	163.2 ± 104
%VC before treatment (%) ± SD	108.6 ± 15.3	104.8 ± 17.1	108.5 ± 15.9	106.7 ± 18.2
FEV1.0% before treatment (%) ± SD	82.9 ± 5.4**	69.0 ± 12.8	83.0 ± 5.6**	66.2 ± 13.3
Peripheral eosinophils (%) ± SD	2.9 ± 2.4**	6.5 ± 5.0	3.1 ± 1.9**	8.2 ± 4.6
IgE (IU/mL) ± SD	237 ± 458	342 ± 453	256 ± 474	320 ± 238
<i>Present symptoms</i>				
Anorexia (%)	11 (18.6)*	9 (7.0)	11 (20.4)	3 (15.0)
Disturbed sleep (%)	46 (78.0)*	77 (60.2)	44 (81.5)	13 (65.0)
Depressive mood (%)	31 (52.5)**	37 (28.9)	31 (57.4)*	6 (30.0)
Diminished motivation (%)	28 (47.5)	45 (35.2)	27 (50.0)	7 (35.0)
Guilt (%)	22 (37.3)	30 (23.4)	22 (40.7)	7 (35.0)
Autonomic imbalance (palpitation, dizziness, appendicular pain, or dysesthesia) (%)	45 (76.3)**	68 (53.1)	41 (75.9)	11 (55.0)
Anxiety (%)	25 (42.4)**	28 (21.9)	25 (46.3)	7 (35.0)

* p < 0.05: significance compared with classic asthma.

** p < 0.01: significance compared with classic asthma.

Table 3

Scores of SDS and STAI, and prevalence of mood disorders and anxiety disorders.

		Cough variant asthma (Total) n = 59	Classic asthma (Total) n = 128	Cough variant asthma (Newly diagnosed) n = 54	Classic asthma (Newly diagnosed) n = 20
		Female: 47 Male: 12	Female: 78 Male: 50	Female: 42 Male: 12	Female: 10 Male: 10
<i>Scores of psychological tests</i>					
SDS score	All	43.0 ± 9.1**	37.3 ± 9.4	43.6 ± 8.9**	35.9 ± 7.8
	Female	42.9 ± 9.4**	37.4 ± 9.2	43.5 ± 9.2*	35.6 ± 8.2
	Male	43.7 ± 8.2*	37.1 ± 9.8	43.7 ± 8.2*	36.1 ± 7.7
STAI score: state anxiety	All	47.0 ± 10.0**	42.6 ± 9.7	47.9 ± 9.8**	41.2 ± 8.9
	Female	46.3 ± 10.1	43.1 ± 9.6	47.4 ± 10.0*	39.0 ± 7.9
	Male	49.6 ± 9.4*	41.8 ± 9.9	49.6 ± 9.4	43.3 ± 9.7
STAI score: trait anxiety	All	47.1 ± 11.8*	42.9 ± 9.4	48.2 ± 10.6**	40.6 ± 8.9
	Female	46.3 ± 12.0	43.9 ± 9.3	47.7 ± 10.5	40.6 ± 9.6
	Male	49.8 ± 11.2**	41.3 ± 9.3	49.8 ± 11.2*	40.5 ± 8.7
<i>Prevalence of mood disorders and anxiety disorders</i>					
Any psychiatric disorder (%)	All	34 (57.6)**	36 (28.1)	33 (61.1)*	6 (30.0)
	Female	25 (53.2)**	21 (26.9)	24 (57.1)**	1 (10.0)
	Male	9 (75.0)**	15 (30.0)	9 (75.0)	5 (50.0)
Mood disorders (%)	All	16 (27.1)*	17 (13.3)	15 (27.8)	2 (10.0)
	Female	12 (25.5)	10 (12.8)	11 (26.2)	1 (10.0)
	Male	4 (33.3)	7 (14.0)	4 (33.3)	1 (10.0)
Major depression (%)	All	8 (13.6)	11 (8.6)	8 (14.8)	1 (5.0)
	Female	7 (14.9)	7 (9.0)	7 (16.7)	1 (10.0)
	Male	1 (8.3)	4 (8.0)	1 (8.3)	0 (0)
Minor depression (%)	All	7 (11.9)*	5 (3.9)	6 (11.1)	1 (5.0)
	Female	5 (10.6)	2 (2.6)	4 (9.5)	0 (0)
	Male	2 (16.7)	3 (6.0)	2 (16.7)	1 (10.0)
Dysthymia (%)	All	1 (1.7)	1 (0.8)	1 (1.9)	0 (0)
	Female	0 (0)	1 (1.3)	0 (0)	0 (0)
	Male	1 (8.3)	0 (0)	1 (8.3)	0 (0)
Anxiety disorder (%)	All	18 (30.5)*	19 (14.8)	18 (33.3)	4 (20.0)
	Female	13 (27.7)	11 (14.1)	13 (31.0)*	0 (0)
	Male	5 (41.7)	8 (16.0)	5 (41.7)	4 (40.0)
Panic disorder (%)	All	2 (3.4)	10 (7.8)	2 (3.7)	3 (15.0)
	Female	2 (4.3)	5 (6.4)	2 (4.8)	0 (0)
	Male	0 (0)	5 (10.0)	0 (0)*	3 (30.0)
Generalized anxiety disorder (%)	All	10 (16.9)**	4 (3.1)	10 (18.5)*	0 (0)
	Female	7 (14.9)	4 (5.1)	7 (16.7)	0 (0)
	Male	3 (25.0)**	0 (0)	3 (25.0)*	0 (0)
Social anxiety disorder (%)	All	5 (8.5)**	1 (0.8)	5 (9.3)	1 (5.0)
	Female	4 (8.5)**	0 (0)	4 (9.5)	0 (0)
	Male	1 (8.3)	1 (2.0)	1 (8.3)	1 (10.0)
Other anxiety disorder (%)	All	1 (1.7)	4 (3.1)	1 (1.9)	0 (0)
	Female	0 (0)	2 (2.6)	0 (0)	0 (0)
	Male	1 (8.3)	2 (4.0)	1 (8.3)	0 (0)

* p < 0.05: significance compared with classic asthma.

** p < 0.01: significance compared with classic asthma.

patients. In the limited newly diagnosed patients, only depressive mood was significantly more frequent in CVA patients, although a similar tendency was seen in general. The average SDS score after treatment was also higher in newly diagnosed CVA patients with a large significant difference regardless of sex, and the prevalence of mood disorders with CVA patients was higher than that with classic asthma patients (Table 3). These results imply that CVA patients tend to be more depressed in particular than classic asthma patients.

Depression and anxiety levels in CVA and classic asthma patients

When comparing the psychological state, including depression and anxiety, between CVA and classic asthma patients, it is very difficult to determine the best time to perform the psychological tests and diagnose such a psychiatric disease. In this study, they were performed and diagnosed when relief of their symptoms had lasted at least more than four weeks, and all patients had recognized their own illness and had good control at that time. Nevertheless, CVA patients showed significantly higher depression and anxiety scores than classic asthma patients. The average SDS and STAI scores of CVA patients were similar to those of classic asthma patients who had one or more hospitalizations

for a severe asthma attack, and were higher than those of classic asthma patients even at therapeutic steps 3–4 (Table 4). A similar tendency was seen in the limited newly diagnosed patients as well. There were so few asthma patients at therapeutic step 1 and step 2 that their SDS and STAI scores might not be significantly different from those of CVA patients.

The present study indicated that mood disorder and anxiety disorder were more prevalent in CVA patients than in classic asthma outpatients. It is interesting that generalized anxiety disorder and social anxiety disorder were especially more common in CVA patients, while panic disorder was, although not significantly different, more common in classic asthma patients (Table 3). There have been a number of reports regarding depression and anxiety in patients with asthma, but no study specifically targeted CVA patients. Lavoie et al. reported that 34% of 406 patients with asthma had one or more psychiatric disorders, including major depression (15%), minor depression (5%), dysthymia (4%), panic disorder (12%), generalized anxiety disorder (5%), and social phobia (4%) [42]. The WHO World Health Survey available for 245,404 participants from 60 countries reported that the prevalence of depression with adult asthma was 18.1%, while the overall prevalence of depression alone was 3.2%, and that of asthma alone was 3.3% [17]. Furthermore, 12 cross-sectional studies suggested that the prevalence

Table 4

SDS and STAI scores in CVA and CA patients by previous hospitalization and by therapeutic step for asthma.

		SDS score	STAI score: state anxiety	STAI score: trait anxiety
<i>Previous hospitalization</i>				
CVA (total)	Yes (0 patient)			
	No (59 patients)	43.0 ± 9.1	47.0 ± 10.0	47.1 ± 11.8
Classic asthma (total)	Yes (25 patients)	41.6 ± 8.0	45.0 ± 9.4	46.8 ± 9.9
	No (103 patients)	36.4 ± 9.6**	42.0 ± 9.7**	41.9 ± 9.0**
CVA (newly diagnosed)	No (54 patients)	43.6 ± 8.9	47.9 ± 9.8	48.2 ± 10.6
	Yes (5 patients)	39.4 ± 6.1	45.6 ± 9.2	43.4 ± 8.3
Classic asthma (newly diagnosed)	Yes (5 patients)	39.4 ± 6.1	45.6 ± 9.2	43.4 ± 8.3
	No (15 patients)	34.7 ± 8.1**	39.7 ± 8.5**	39.6 ± 9.2**
<i>Therapeutic steps of asthma when the psychological tests were performed</i>				
Classic asthma (total)	Step 1 (5 patients)	40.4 ± 10.0	45.2 ± 11.3	46.0 ± 7.0
	Step 2 (19 patients)	37.5 ± 9.3*	45.2 ± 10.6	44.8 ± 10.1
	Step 3 (74 patients)	37.7 ± 9.3**	42.0 ± 9.9**	42.7 ± 9.2*
	Step 4 (30 patients)	36.1 ± 10.3**	42.0 ± 8.6*	41.7 ± 9.7*
Classic asthma (newly diagnosed)	Step 1 (0 patients)			
	Step 2 (1 patients)	36.0 ± -	47.0 ± -	56.0 ± -
	Step 3 (12 patients)	36.8 ± 8.2*	42.0 ± 9.8	41.0 ± 8.6*
	Step 4 (7 patients)	34.1 ± 8.0**	38.9 ± 7.7*	37.6 ± 8.0*

CVA: cough variant asthma.

Plus-minus values are means ± SD.

* p < 0.05: significance compared with CVA (total or newly diagnosed).

** p < 0.01: significance compared with CVA (total or newly diagnosed).

of panic disorder among patients with asthma ranged from 6.5% to 24% [18], while that in community populations had been estimated at 1% to 3% [43].

Many studies indicated that having depression and/or anxiety is associated with an increased risk of developing a new asthma diagnosis and with more poorly controlled asthma, and having asthma is associated with an increased risk of developing a new depression or anxiety diagnosis [44,45]. It is a very contentious issue whether symptoms of

asthma would lead to depression and anxiety, or a complication of depression and/or anxiety would trigger or exacerbate asthma, but both are thought to be possible, and that may also be true for CVA. According to a 20-year prospective community study by Hasler et al. [46], active asthma predicted subsequent panic disorder (OR = 4.5; 95% CI, 1.1, 20.1), and the presence of panic disorder predicted subsequent asthma activity (OR = 6.3; 95% CI, 2.8, 14.0); thus, bidirectional longitudinal associations between the two conditions were seen.

On the other hand, inaccurate perception of respiratory symptoms is often found in asthma patients [47,48]. For example, the stable personality 'trait Negative Affectivity' reflecting the tendency to experience negative emotions [49], which may predispose to depression and anxiety, is positively related to elevated symptom levels in general, but also to specific respirator symptoms [50–52]. Therefore, the possibility should be considered that CVA patients with trait Negative Affectivity might become oversensitive to their symptoms and many of them might be included in this study sample.

In the present study, neither the scale of depression nor that of anxiety was associated with the intensity of the therapeutic step for asthma, since all patients with classic asthma had good control at that time. Trojan et al. reported that asthma was associated with current depressive symptoms and lifetime history of depression, but neither lung function nor asthma controller medications were associated with depression, and depression with asthma does not appear to be exclusively related to severe or poorly controlled asthma [53].

Psychological state of CVA and classic asthma patients

Many recent studies have indicated that not only depression and anxiety but also psychological stress can lead to asthma exacerbations [54,55]. Laboratory-based research has confirmed that induction of a negative emotional state is associated with a decline in lung function in individuals with asthma [56,57]. On the other hand, independent of reduced lung function, the perception of asthma symptoms occurs when changes in somatosensory information are detected and matched to mental models of asthma symptoms [47]. Experimental studies have shown that contextual information that is related to previous experience with asthma triggers can lead to the perception of asthma symptoms in the absence of the original asthma trigger [58]. Also, other factors such as memory, personality, gender, and cultural norms have been shown to influence perception and report of asthma symptoms [47,49,59].

Table 5

Comparison of psychological factors between CVA and classic asthma patients by the CAI.

		Cough variant asthma All: 59 Female: 47 Male: 12	Classic asthma All: 128 Female: 78 Male: 50
A. Extent of conditioning	Total	17.6 ± 13.5	14.5 ± 14.5
	Female	17.8 ± 13.4	14.6 ± 15.7
	Male	17.1 ± 14.5	14.4 ± 12.6
B. Suggestibility	Total	16.9 ± 12.7	14.2 ± 13.9
	Female	16.7 ± 12.3	14.2 ± 14.8
	Male	17.5 ± 14.7	14.1 ± 12.4
C. Expected anxiety	Total	17.1 ± 11.8	15.0 ± 14.4
	Female	17.0 ± 11.5	15.5 ± 15.4
	Male	17.6 ± 13.8	14.2 ± 12.7
D. Dependency	Total	22.6 ± 16.5	21.0 ± 22.1
	Female	21.9 ± 16.8	22.2 ± 23.9
	Male	25.3 ± 15.4	19.1 ± 19.0
E. Frustration	Total	17.7 ± 12.5*	14.2 ± 14.2
	Female	16.3 ± 11.2	14.3 ± 14.6
	Male	23.7 ± 16.0*	14.0 ± 13.6
F. Fright into illness	Total	17.2 ± 12.3**	13.3 ± 14.2
	Female	17.0 ± 11.2*	13.8 ± 15.3
	Male	18.2 ± 16.9	12.5 ± 12.2
G. Distorted life habits	Total	13.8 ± 11.9**	10.0 ± 12.8
	Female	13.1 ± 10.8	10.8 ± 13.0
	Male	16.4 ± 16.0	8.8 ± 12.5
H. Negative attitudes toward prognosis	Total	19.8 ± 19.4	19.5 ± 20.3
	Female	18.9 ± 19.4	20.5 ± 21.6
	Male	23.4 ± 19.7	17.9 ± 18.0
I. Decreased motivation toward therapy	Total	13.8 ± 17.1	14.1 ± 19.0
	Female	13.1 ± 17.7	15.1 ± 20.6
	Male	16.4 ± 15.0	12.4 ± 16.4
CAI score (total average)	Total	17.4 ± 11.3*	15.1 ± 14.2
	Female	16.9 ± 10.8	15.7 ± 15.2
	Male	19.5 ± 13.4	14.2 ± 12.4

Plus-minus values are means ± SD.

* p < 0.05: significance compared with CVA.

** p < 0.01: significance compared with CVA.

In this study, psychological factors were evaluated with respect to perceived symptoms of CVA and classic asthma using the CAI. The present results indicated that CVA patients had more frustration, fright into illness, distorted lifestyle, and overall more psychosomatic correlations to the perceived symptoms compared with classic asthma patients in general (Table 5). Use of the CAI has generally been limited to Japanese specialists in psychosomatic medicine who have a particular interest in respiratory disease, and is not widely available, since it was published only in Japanese articles [27–30] and requires complicated computations for scoring. However, there are few published tools for evaluation of psychosomatic correlations in patients with asthma or asthmatic chronic cough, and the scoring is very easy with a spreadsheet program that anyone can easily make. Ebana et al. [28] applied five psychological tests (Cornell Medical Index, SDS, Manifest Anxiety Scale, Yatabe-Guilford test, Seikenshiki Personality Inventory) and the CAI to 144 randomized patients with asthma and sampled 13 patients whose CAI scores were lower than the average, – 1SD in all categories of psychological state, and 15 patients whose CAI score was higher than the average, + 1SD in even one category of psychological state. Inevitably, many differences in psychological factors by CAI were found in the two groups, but neither a particular psychological factor nor a difference was found with five other psychological tests, which indicates that the CAI may be a more specific tool for evaluation of psychological factors in patients with asthma, including CVA, which cannot be evaluated using the above five common psychological tests. However, there is a vulnerability in the evaluation of psychological factors by the CAI which includes the issue with many overlapping question items in subscales, although there is a certain measure of difference in the allotment of marks of each factor. Furthermore, there is no study about the validity and reliability of the CAI, which might be difficult to be evaluated on its nature (e.g. psychological factor of ‘frustration’, ‘flight into illness’). The CAI leaves much to be improved, such as reducing question items or reconsidering some question sentences, and long-term and large-scale studies are required in the future.

Study limitations

Our study was limited in the diagnosis of CVA. Predisposing main factor to chronic cough in CVA is thought to be bronchial hyperresponsiveness by eosinophilic inflammation of airway as well as in classic asthma [10]. In the current study, the presence of bronchial hyperresponsiveness was confirmed by recurring cough episodes under conditions irritating the airway for reasons given in ‘Diagnosis’. However bronchial hyperresponsiveness is often not in accordance with the subjective experience and the methacholine challenge test is required to satisfy the strict full criteria, although most pulmonologists actually diagnose CVA on clinical judgment of airway hyperresponsiveness without methacholine challenge test after excluding other diseases with chronic cough. We therefore cannot exclude the possibility that patients with allergic chronic cough other than CVA (e.g. non-asthmatic eosinophilic bronchitis [60] and atopic cough [11,61]) were included in the CVA sample of this study.

Our study was also limited in that many classic asthma patients in this study sample were stable for far longer periods than CVA patients. Although the results were also compared in limited newly diagnosed patients, the pathology duration of classic asthma patients was still longer than that of CVA patients. Moreover, because this study was carried out in a self-selected sample of patients consulting at single respiratory medicine department, the possibility must be entertained that CVA patients who were more likely to feel not only physical symptoms but also depression and anxiety were more often at baseline than classic asthma patients as shown in the results in Table 2. Therefore, it should be considered that these differences of baseline characteristics might affect the results of psychological tests and prevalence of psychiatric disorders in Tables 3–4. However, it may be difficult to equalize the

comparison conditions at baseline, and there are actually few patients who remain as CVA patients followed up for a long time if they did not develop classic asthma, and there is no evidence about how long treatment should be continued for CVA patients who improved after a brief period of time. A longer term investigation for psychological state of CVA patients is required.

Finally, we had limited our study to an exploration of the comparison between CVA patients and classic asthma patients classified by the severity. Although SDS and STAI scores in CVA and classic asthma patients by previous hospitalization and by therapeutic step for asthma were shown in our study, the present therapeutic step neither means severity of asthma, nor is it correlated with symptom perception. There is an ambiguity of the term ‘severity of asthma’. GINA has described that asthma severity involves both the severity of the underlying disease and its responsiveness to treatment, and severity is not a static feature of an individual patient’s asthma but may change over months or years. For this reason, GINA has described the classification of severity only in exacerbation, and the levels of asthma control which are classified as ‘Controlled’, ‘Partly Controlled’ or ‘Uncontrolled’ by symptoms and lung function. In our study, limited patients with asthma classified as ‘Controlled’ independent of therapeutic step were recruited to compare with CVA patients whose symptoms were well under control. Although increased therapeutic step looks associated with reduced depression and anxiety in classic asthma patients in Table 4, the results do not mean an inverse relationship between their severity of asthma and psychological scales, but they might be affected by some social factors such as economic reasons in our prospective.

Conclusion

The present research demonstrated that CVA patients are on average more depressed and anxious than classic asthma outpatients. Though CVA can be thought of pathologically as just an early stage of typical asthma, the psychological stress may often be more serious than asthma controlled by medication, and this may explain why CVA cannot be controlled by a bronchodilator alone and patients often require no less intensive therapy than for severe asthma, such as inhaled corticosteroids or a combination of inhaled corticosteroids and long-acting beta-agonists. Physicians may have to monitor CVA patients over time and consider the comorbid psychological conditions, as for classic asthma patients.

Competing interest statement

The authors have no competing interests to report.

References

- [1] Braman SS, Corrao WM. Chronic cough. Diagnosis and treatment. *Prim Care* 1985; 12:217–25.
- [2] Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990;141:640–7.
- [3] Yamada T, Yoshimura M, Nago N, Asai Y, Koga Y, Inoue Y, et al. What is the common diseases and common health problems? The use of ICPC in the community-based project. *Jpn J Prim Care* 2000;23:80–9.
- [4] Niimi A, Ohbayashi H, Sagara H, Yamauchi K, Akiyama K, Takahashi K, et al. Cough variant and cough-predominant asthma are major causes of persistent cough: a multicenter study in Japan. *J Asthma* 2013;50:932–7.
- [5] 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.
- [6] French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. *Arch Intern Med* 1998;158:1657–61.
- [7] Mc Garvey LP, Heaney LG, Lawson JT, Johnston BT, Scally CM, Ennis M, et al. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax* 1998;53:738–43.
- [8] Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med* 1999;160:406–10.

- [9] Kastelik JA, Aziz I, Ojoo JC, Thompson RH, Redington AE, Morice AH. Investigation and management of chronic cough using a probability-based algorithm. *Eur Respir J* 2005;25:235–43.
- [10] Niimi A, Amitani R, Suzuki K, Tanaka E, Murayama T, Kuze F. Eosinophilic inflammation in cough variant asthma. *Eur Respir J* 1998;11:1064–9.
- [11] Fujimura M, Ogawa H, Nishizawa Y, Nishi K. Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma? *Thorax* 2003;58:14–8.
- [12] Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979;300:633–7.
- [13] Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. *Lancet* 2008;371:1364–74.
- [14] Manfreda J, Becklake MR, Sears MR, Chan-Yeung M, Dimich-Ward H, Siersted HC, et al. Prevalence of asthma symptoms among adults aged 20–44 years in Canada. *CMAJ* 2001;164:995–1001.
- [15] Millar MM, McGrath KG, Patterson R. Malignant cough equivalent asthma: definition and case reports. *Ann Allergy Asthma Immunol* 1998;80:345–51.
- [16] Niimi A. Cough and asthma. *Curr Respir Med Rev* 2011;7:47–54.
- [17] Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 2007;370:851–8.
- [18] Katon WJ, Richardson L, Lozano P, McCauley E. The relationship of asthma and anxiety disorders. *Psychosom Med* 2004;66:349–55.
- [19] Centanni S, Di Marco F, Castagna F, Boveri B, Casanova F, Piazzini A. Psychological issues in the treatment of asthmatic patients. *Respir Med* 2000;94:742–9.
- [20] Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59:34–57.
- [21] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text revision (DSM-IV-TR). Washington DC: American Psychiatric Press; 2000.
- [22] Zung WW, Richards CB, Short MJ. Self-rating Depression Scale in an outpatient clinic. Further validation of the SDS. *Arch Gen Psychiatry* 1965;13:508–15.
- [23] Magruder KM, Norquist GS, Feil MB, Kopans B, Jacobs D. Who comes to a voluntary depression screening program? *Am J Psychiatry* 1995;152:1615–22.
- [24] Spielberg CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologist Press; 1970.
- [25] Okun A, Stein RE, Bauman LJ, Silver EJ. Content validity of the Psychiatric Symptom Index, CES-Depression Scale, and State-Trait Anxiety Inventory from the perspective of DSM-IV. *Psychol Rep* 1996;79:1059–69.
- [26] Oei TP, Evans L, Crook GM. Utility and validity of the STAI with anxiety disorder patients. *Br J Clin Psychol* 1990;29:429–32.
- [27] Katsura T, Hayashi N, Sano S, Nakatani T, Kojima K, Okayasu M. Studies on comprehensive asthma inventory (CAI). History of CAI and its current use. *Arerugi* 1984;33:231–41 [Japanese].
- [28] Ebana S, Hayashi N, Katsura T, Okayasu M. Psychosomatic research on bronchial asthma — chiefly examined by the Comprehensive Asthma Inventory. *Shinshin Igaku* 1987;27:449–57 [Japanese].
- [29] Ono Y, Kondo T, Hirokawa Y, Moue Y, Kamio K, Kato H, et al. Efficacy and assessment of patient education as related to morbidity from asthma. *Nihon Kyobu Shikkan Gakkai Zasshi* 1995;33:293–9 [Japanese except abstract].
- [30] Yokota S, Mifune T, Mitsunobu F, Hosaki Y, Ashida K, Tsugeno H, et al. Psychological investigation on spa therapy in patients with bronchial asthma. *Arerugi* 1997;46:511–9 [Japanese except abstract].
- [31] Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention; 2011[Updated].
- [32] Pocket guide for asthma management and prevention (for adults and children older than 5 years). Global Initiative for Asthma (GINA); 2011[Updated].
- [33] Liu S, Wu R, Li L, Liu L, Li G, Zhang X, et al. The prevalence of anxiety and depression in Chinese asthma patients. *PLoS One* 2014;9:e103014.
- [34] Yin W, Pang L, Cao X, McGoogan JM, Liu M, Zhang C, et al. Factors associated with depression and anxiety among patients attending community-based methadone maintenance treatment in China. *Addiction* 2015;110:51–60.
- [35] Sawa M, Yamashita H, Fujimaki K, Okada G, Takahashi T, Yamawaki S. Negative correlation between affective symptoms and prefrontal activation during a verbal fluency task: a near-infrared spectroscopy study. *Neuropsychobiology* 2013;67:103–10.
- [36] Demura S, Sato S, Tada N, Matsuzawa J, Hamasaki H. Agreement in depression determination among four self-rating depression scales applied to Japanese community-dwelling elderly. *Environ Health Prev Med* 2006;11:177–83.
- [37] Nakajima T, Nishimura Y, Nishiuma T, Kotani Y, Funada Y, Nakata H, et al. Characteristics of patients with chronic cough who developed classic asthma during the course of cough variant asthma: a longitudinal study. *Respiration* 2005;72:606–11.
- [38] Niimi A, Matsumoto H, Minakuchi M, Kitaichi M, Amitani R. Airway remodelling in cough-variant asthma. *Lancet* 2000;356:564–5 (12).
- [39] Takemura M, Niimi A, Matsumoto H, Ueda T, Yamaguchi M, Matsuoka H, et al. Atopic features of cough variant asthma and classic asthma with wheezing. *Clin Exp Allergy* 2007;37:1833–9.
- [40] Koh YY, Chae SA, Min KU. Cough variant asthma is associated with a higher wheezing threshold than classic asthma. *Clin Exp Allergy* 1993;23:696–701.
- [41] Tokuyama K, Shigeta M, Maeda S, Takei K, Hoshino M, Morikawa A. Diurnal variation of peak expiratory flow in children with cough variant asthma. *J Asthma* 1998;35:225–9.
- [42] Lavoie KL, Cartier A, Labrecque M, Bacon SL, Lemièr C, Malo JL, et al. Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respir Med* 2005;10:1249–57.
- [43] Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8–19.
- [44] Rank MA, Shah ND. Multiple chronic conditions and asthma: implications for practice and research. *J Allergy Clin Immunol Pract* 2014;2:518–24.
- [45] Di Marco F, Verga M, Santus P, Giovannelli F, Busatto P, Neri M, et al. Close correlation between anxiety, depression, and asthma control. *Respir Med* 2010;104:22–8.
- [46] Hasler G, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D, et al. Asthma and panic in young adults: a 20-year prospective community study. *Am J Respir Crit Care Med* 2005;171:1224–30.
- [47] Janssens T, Verleden G, De Puter S, Van Diest I, Van den Bergh O. Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. *Clin Psychol Rev* 2009;29:317–27.
- [48] Janssens T, Ritz T. Perceived triggers of asthma: key to symptom perception and management. *Clin Exp Allergy* 2013;43:1000–8.
- [49] Watson D, Pennebaker JW. Health complaints, stress, and distress: exploring the central role of negative affectivity. *Psychol Rev* 1989;96:234–54.
- [50] Put C, Demedts M, Van Den Bergh O, Demyttenaere K, Verleden G. Asthma symptoms: influence of personality versus clinical status. *Eur Respir J* 1999;13:751–6.
- [51] Put C, Van den Bergh O, Van Ongeval E, De Puter S, Demedts M, Verleden G. Negative affectivity and the influence of suggestion on asthma symptoms. *J Psychosom Res* 2004;57:249–55.
- [52] Van Diest I, De Puter S, Eertmans A, Bogaerts K, Victoir A, Van den Bergh O. Negative affectivity and enhanced symptom reports: differentiating between symptoms in men and women. *Soc Sci Med* 2005;61:1835–45.
- [53] Trojan TD, Khan DA, Defina LF, Akpotaire O, Goodwin RD, Brown ES. Asthma and depression: the Cooper Center Longitudinal Study. *Ann Allergy Asthma Immunol* 2014;112:432–6.
- [54] Ritz T, Simon E, Trueba AF. Stress-induced respiratory pattern changes in asthma. *Psychosom Med* 2011;73:514–21.
- [55] Ritz T. Airway responsiveness to psychological processes in asthma and health. *Front Physiol* 2012;3 (Article 343).
- [56] Ritz T, Steptoe A. Emotion and pulmonary function in asthma: reactivity in the field and relationship with laboratory induction of emotion. *Psychosom Med* 2000;62:808–15.
- [57] Ritz T, Kullowatz A, Goldman MD, Smith HJ, Kannies F, Dahme B, et al. Airway response to emotional stimuli in asthma: the role of the cholinergic pathway. *J Appl Physiol* 2010;108:1542–9.
- [58] De Puter S, Put C, Lemaigre V, Demedts M, Verleden G, Van den Bergh O. Context-evoked overperception in asthma. *Psychol Health* 2007;22:737–48.
- [59] Fritz GK, McQuaid EL, Kopel SJ, Seifer R, Klein RB, Mitchell DK, et al. Ethnic differences in perception of lung function: a factor in pediatric asthma disparities? *Am J Respir Crit Care Med* 2010;182:12–8.
- [60] Niimi A, Matsumoto H, Mishima M. Eosinophilic airway disorders associated with chronic cough. *Pulm Pharmacol Ther* 2009;22:114–20.
- [61] Magni C, Chellini E, Zanasi A. Cough variant asthma and atopic cough. *Multidiscip Respir Med* 2010;5:99–103.