

Prevalence of chronic cough and possible causes in the general population based on the Korean National Health and Nutrition Examination Survey

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Abstract

Although chronic cough is very common, its prevalence and causes have been rarely reported in the large general population including smokers. This study aimed to identify the prevalence of possible causes of chronic cough and their clinical impact.

From Korean National Health and Nutrition Examination Survey (KNHANES) data including 119,280 adults aged over 40 years, 302 individuals with chronic cough were recruited irrespective of smoking status. Data from questionnaire, laboratory tests including spirometry, chest radiographs, and otorhinolaryngologic examination were analyzed.

The prevalence of chronic cough in adults was $2.5\% \pm 0.2\%$. Current smokers occupied $47.7\% \pm 3.8\%$ of study population and $46.8\% \pm 3.9\%$ of the subjects showed upper airway cough syndrome (UACS). Based on spirometry, chronic obstructive pulmonary disease (COPD) was identified in $26.4\% \pm 3.5\%$. Asthma explained for $14.5\% \pm 2.8\%$ of chronic cough. Only $4.1\% \pm 1.6\%$ showed chronic laryngitis suggesting gastro-esophageal reflux-related cough. Abnormalities on chest radiography were found in $4.0\% \pm 1.2\%$. Interestingly, $50.3\% \pm 4.5\%$ of study subjects had coexisting causes. In multivariate analysis, only current smoking (odds ratio [OR] 3.16, $P < 0.001$), UACS (OR 2.50, $P < 0.001$), COPD (OR 2.41, $P < 0.001$), asthma (OR 8.89, $P < 0.001$), and chest radiographic abnormalities (OR 2.74, $P = 0.003$) were independent risk factor for chronic cough. This pattern was not different according to smoking status excepting the prevalence of COPD.

Smoking, COPD, and chest radiographic abnormalities should be considered as causes of chronic cough, along with UACS and asthma. Gastro-esophageal reflux-related cough is not prevalent in study population.

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Abbreviations: COPD = chronic obstructive pulmonary disease, GERD = gastro-esophageal reflux disease, KNHANES = Korean National Health and Nutrition Examination Survey, OR = odds ratio, UACS = upper airway cough syndrome.

Keywords: chronic cough, COPD, KNHANES, prevalence, smoking, upper airway cough syndrome

1. Introduction

Cough is an important defense mechanism in the airway and a common symptom of many pulmonary and extra-pulmonary diseases.^[1,2] However, for many patients, cough may be regarded merely as an annoyance, particularly if chronic.^[3-5]

Most guidelines on chronic cough emphasize the upper airway cough syndrome (UACS), asthma, and gastro-esophageal reflux disease (GERD) as usual causes of chronic cough in nonsmokers with normal chest radiographs.^[6-13] However, the data in these recommendations were reported a long time ago.^[3-11] Further, the prevalence of diseases that cause chronic cough, such as asthma, GERD, and other comorbidities, differs according to region and ethnicity.^[14] The prevalence of asthma is higher in urbanized communities adopting a Western lifestyle^[15]; notably, the prevalence of GERD is reported to be 10% to 20% in the Western area but less than 5% in Asia.^[16]

In clinical practice, a significant number of smokers complain of chronic cough; therefore, many clinicians have questions about the actual prevalence and clinical characteristics of diseases contributing to chronic cough. Nevertheless, reports on the possible causes of chronic cough are not up to date and any relevant data come from relatively small populations. Additionally, the prevalence study of chronic cough has been rarely reported in the large general population including smokers. Updated research on the prevalence of chronic cough and the impact that various conditions have on it is now mandatory. Moreover, many diseases affecting the respiratory tract show environmental, regional, and ethnic differences, and the same might apply to causes of chronic cough.

Recently published Korean guideline listed the various causes of chronic cough, placing emphasis on the major ones.^[17] However, there are still little data on the prevalence of possible causes or the impact of each diseases on chronic cough in general population including smokers.

This study aimed to identify the prevalence of chronic cough and its possible causes, along with the relative impact of each cause on the prevalence of cough in the general population using data from the Korean National Health and Nutrition Examination Survey (KNHANES).

2. Methods

2.1. Study population

The KNHANES is a collection of nationally representative, cross-sectional, population-based health, and nutritional surveys produced by the Korean Centers for Disease Control and Prevention.^[18] Briefly, participants in KNHANES were chosen by proportional allocation sampling with multistage stratification, based on geography, age, and sex. KNHANES includes a health interview, physical examination, laboratory tests, and nutritional questionnaires to assess the health and nutritional status of the noninstitutionalized civilian population of Korea. The health interview included an established questionnaire to determine the demographic and socioeconomic characteristics of the subjects including age, education level, occupation, income, marital status, smoking habits, alcohol consumption, exercise,

past and current diseases, and family history. A field survey team including otorhinolaryngologists performed the interviews and physical examinations in a mobile examination unit. All individuals participated voluntarily and provided their written informed consent. The KNAHENS protocol was approved by the Korean Centers for Disease Control and Prevention institutional review board.

2.2. Measurements

Spirometry was performed for subjects aged >40 years according to the guidelines of the American Thoracic Society/European Respiratory Society,^[19] using a spirometry system (model 1022; SensorMedics Corporation San Diego, CA). Predicted values were calculated using the predictive equation for the Korean population.^[20] Chest radiographs were evaluated and interpreted by a pulmonologist and a radiologist. Quality of life was measured using a validated Korean version of the 5-item self-administered EuroQOL (EQ-5D).^[21] An otorhinolaryngologic examinations were performed by trained otorhinolaryngologists according to standardized protocols. Examinations of the nasal cavity were performed using a 4 mm, 0° nasal endoscope before and after decongestion. Laryngoscopic vocal cord examinations were performed using a 4 mm 70° angled rigid endoscope with a CCD camera. The Epidemiologic Survey Committee of the Korean Otorhinolaryngologic Society prepared a protocol for the diagnosis of chronic laryngitis. This committee verified the quality of the survey by periodically visiting the mobile examination units, educating participating doctors, obtaining laryngeal examination data, and data-proofing using video documentation of the larynx throughout the study. Two otorhinolaryngologic surgeons from the Korean Otorhinolaryngologic Society subsequently confirmed the video documentation and assessed the disease decision protocol. Documentation of the video was obtained as 640 × 480-sized Audio Video Interleave files, which were compressed by DivX 4.12 codec using a compression rate of 6 Mb/s.

2.3. Definitions

Rhinitis and chronic sinusitis were diagnosed according to standardized protocols. If symptoms or physical examination indicated rhinitis or chronic sinusitis, UACS was diagnosed. Laryngoscopic findings of laryngitis and/or inflammation, including Reinke edema, pseudosulcus, erythema, or thick endolaryngeal mucus, were diagnosed as chronic laryngitis.

Chronic obstructive pulmonary disease (COPD) was defined as a spirometric result for forced expiratory volume in 1 second/forced vital capacity of <0.7 in adults aged >40 years. A history of asthma, tuberculosis, hypertension, diabetes, hyperlipidemia, and/or cardiac disease was obtained by a self-administered questionnaire asking “Have you been diagnosed with the disease by a doctor?” or “Do you take medicine or treatment for the disease?” Since, many Koreans with COPD are misdiagnosed as having asthma, asthma was only diagnosed if the subject reported a history of asthma but did not meet the criteria for COPD.

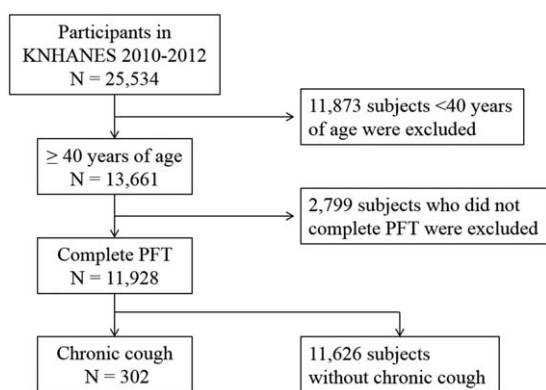


Figure 1. Flow chart of the study population.

Chest radiographic abnormalities included only conditions expected to contribute to chronic cough. Inactive lesions including healed condition or minimal extent were not regarded as abnormalities.

Hypertension was defined as blood pressure ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic, or the use of antihypertensive medications irrespective of the blood pressure status.^[22] Diabetes was defined as a fasting plasma glucose level ≥ 126 mg/dL or hemoglobin A1c $\geq 6.5\%$, and/or a current regimen for diabetes treatment.^[23] Hyperlipidemia was defined as an abnormal level of high density lipoprotein (< 40 mg/dL in male and < 50 mg/dL in female participants), a triglyceride level > 150 mg/dL, and/or currently taking lipid lowering agents.^[24]

2.4. Statistical analysis

KNHANES was designed using a complex, stratified, multistage probability sampling model, whereby the data were analyzed using the complex sample design to represent prevalence in the Korean population. The analysis was performed using SAS software (version 9.3, SAS Institute, Inc., Cary, NC).

The study population with chronic cough was compared with subjects without chronic cough. The common causes of chronic cough were described according to smoking status to identify the causes of cough in each group. The impact of each condition contributing to chronic cough was also analyzed, adjusting for age, sex, body mass index, smoking status, and comorbidities.

General linear regression was used for continuous variables and logistic regression for categorical variables. Data are shown as the mean \pm standard error or as the frequency (%). A P -value < 0.05 was considered to be statistically significant.

3. Results

3.1. Prevalence and clinical characteristics

Data from 11,928 adults aged > 40 years who completed spirometry in 2010 to 2012 were retrieved from KNHANES. Of these, 302 had chronic cough for more than 3 months (Fig. 1). The overall prevalence of chronic cough in the Korean population aged > 40 years was $2.5\% \pm 0.2\%$. When compared with people without chronic cough, those with chronic cough were older, male-predominant, and included more current smokers. Hypertension, hyperlipidemia, COPD, diabetes, history of tuberculosis, cardiac disease, asthma, and stroke were more prevalent in subjects with chronic cough. However, the prevalence of chronic laryngitis was not significantly different. The demographic and clinical characteristics of participants are summarized in Table 1.

Of the participants with chronic cough, $47.7\% \pm 3.8\%$ were current smokers, $45.1\% \pm 3.9\%$ had nasal symptoms, $42.2\% \pm 3.7\%$ had an identifiable problem in the nasal cavity, and $46.8\% \pm 3.9\%$ were suspected to UACS; $26.4 \pm 3.5\%$ were compatible with COPD by spirometry, and $14.5 \pm 2.8\%$ were compatible with asthma. Chronic laryngitis was used as an alternative to identify GERD-related cough and was presented in $4.1\% \pm 1.6\%$ of the population. On chest radiography, $4.0\% \pm 1.2\%$ had an abnormality implying a cause of chronic cough. Patients with chronic cough reported significantly lower quality of life (Table 1).

Table 1
Baseline characteristics of the study population according to the presence of chronic cough.

	Total (N = 11,928)	Chronic cough (-) (n = 11,626)	Chronic cough (+) (n = 302)	P
Age, year	55.4 \pm 0.2	55.3 \pm 0.2	58.0 \pm 0.9	0.002
Sex, male	48.6 \pm 0.4	48.1 \pm 0.4	64.7 \pm 3.5	<0.001
BMI, kg/m ²	24.1 \pm 0.04	24.1 \pm 0.04	23.9 \pm 0.2	0.15
Smoking status				<0.001
Never smoker	54.2 \pm 0.5	54.8 \pm 0.5	32.0 \pm 3.2	
Ex-smoker	23.0 \pm 0.5	23.1 \pm 0.5	20.3 \pm 2.9	
Current smoker	22.8 \pm 0.5	22.2 \pm 0.5	47.7 \pm 3.8	
Underlying disease				
Hypertension	26.8 \pm 0.6	26.5 \pm 0.6	36.9 \pm 3.5	0.003
Hyperlipidemia	13.4 \pm 0.4	13.3 \pm 0.4	18.4 \pm 3.3	0.001
COPD	12.2 \pm 0.4	11.8 \pm 0.4	26.4 \pm 3.5	<0.001
Diabetes mellitus	8.9 \pm 0.3	8.8 \pm 0.3	15.4 \pm 2.5	0.003
History of tuberculosis	6.4 \pm 0.3	6.1 \pm 0.3	15.8 \pm 2.7	<0.001
Angina or myocardial infarction	3.1 \pm 0.2	3.0 \pm 0.2	7.1 \pm 1.9	<0.001
Asthma	2.8 \pm 0.2	2.5 \pm 0.2	14.5 \pm 2.8	<0.001
Stroke	2.0 \pm 0.1	1.9 \pm 0.2	3.0 \pm 1.1	<0.001
Quality of life				
EQ5D-index	0.93 \pm 0.002	0.93 \pm 0.002	0.88 \pm 0.01	<0.001
EQ5D-VAS	87.4 \pm 1.6	87.6 \pm 1.7	78.0 \pm 6.1	0.001

Data were represented as mean \pm standard error, or frequency (%). BMI = body mass index, COPD = chronic obstructive pulmonary disease, EQ5D = EuroQOL instrument, VAS = visual analogue scale.

Table 2**Prevalence of chronic cough-related diseases in the study population.**

Contributing conditions to chronic cough	Chronic cough (-) (n=11,626)	Chronic cough (+)			P [†]	P [*]
		Total (n=302)	Ex- or current smoker (n=181)	Never smoker (n=121)		
Currently smoking status	22.2±0.5	47.7±3.8	70.1±4.1	0	–	<0.001
UACS	27.8±0.7	46.8±3.9	45.8±4.7	49.4±5.8	0.61	<0.001
COPD	11.8±0.4	26.4±3.5	31.8±4.7	13.7±4.7	0.02	<0.001
Asthma	2.5±0.2	14.5±2.8	13.0±3.6	19.3±5.0	0.31	<0.001
Chronic laryngitis	2.7±0.3	4.1±1.6	5.6±2.3	1.7±1.1	0.14	0.31
CPA abn	1.5±0.1	4.0±1.2	5.0±1.8	1.1±0.8	0.07	0.18

Data were represented as mean±standard error, or frequency (%). COPD=chronic obstructive pulmonary disease, CPA abn=chest X-ray abnormality, UACS=upper airway cough syndrome.

* P-values for comparisons between patients with and without chronic cough.

† P-values for comparisons between ex-smokers, current smokers, and never smokers.

When the study population was stratified according to smoking status, the following factors were not significantly different between never smokers and former/current smokers: the frequencies of UACS, asthma, chronic laryngitis, abnormal chest radiographs, hypertension, diabetes, hyperlipidemia, stroke, cardiac disease, and history of tuberculosis. However, the prevalence of COPD was higher in current smokers (Table 2 and Table S1, <http://links.lww.com/MD/B256>).

3.2. Prevalence of overlapped possible causes

Given the unified airway theory that causes of chronic cough frequently coexist, we identified the frequency of coexistence of possible causes. When possible causes were classified by current smoking status, UACS, COPD, asthma, and chest radiographic abnormality, 50.3%±4.5% of those with chronic cough had coexisting possible causes (Fig. 2). Additionally, 12.7%±3.2% of those with chronic cough were suspected to have 3 or more possible causes. However, no possible causes were noted in 14.7%±3.1% of subjects. The most highly overlapped conditions were UACS in subjects with asthma (66.9%±10.8%) and chest radiographic abnormalities in those with COPD (9.9%±4.3%) or asthma (9.4%±6.3%) (Table 3).

3.3. Relative impacts of possible causes

Since these possible causes, that is, current smoking, postnasal drip, COPD, asthma, and chest radiographic abnormality, are also

observed in the population without chronic cough, the odds ratios (ORs) were analyzed to evaluate the impact of these factors on chronic cough. In multivariable analysis, only current smoking status, UACS, COPD, asthma, and abnormal chest radiographs were independently associated with chronic cough, and the adjusted ORs were 3.16, 2.50, 2.41, 8.89, and 2.74, respectively (Table 4). Current smoking, UACS, COPD, asthma, and abnormal chest radiographs were sequentially observed in subjects with chronic cough; however, the impact of chronic cough was strongest for asthma, followed in descending order by current smoking status, chest radiographic abnormality, UACS, and COPD.

3.4. Comparison according to possible causes

We compared the clinical characteristics of the subjects according to current smoking status, UACS, COPD, asthma, and abnormal chest radiographs to determine whether associated symptoms could be used to differentiate causes of chronic cough. The most frequently associated symptom was phlegm (75.9%±3.0%). All groups showed a high frequency of chronic sputum production, but the frequency was significantly higher in current smokers (86.9%±3.7%). The UACS group reported more episodes of dyspnea and night sweats, and the COPD group reported more occurrences of blood-tinged sputum. However, there was no specific clinical characteristic suggesting asthma or chest radiographic abnormality (Table 5). When clinical characteristics were compared between subjects with a single cause and those with 2 or more causes, subjects with multiple causes complained more frequently of dyspnea and weight loss (Table S2, <http://links.lww.com/MD/B257>).

4. Discussion

Based on nationwide survey, we identified the prevalence of chronic cough in the Korean population and analyzed the prevalence of possible contributors.

To the best of our knowledge, our results are derived from a larger population including smokers than in previous reports^[25–35] and ours is the first report on the prevalence of chronic cough in the Korean population. We found the overall prevalence of chronic cough in the general adult Korean population to be 2.5%±0.2%, and the common possible causes, in descending order, to be current smoking, UACS, COPD, asthma, and chest radiographic abnormalities. This pattern was not different according to smoking status, although COPD was more prevalent in cigarette smokers.

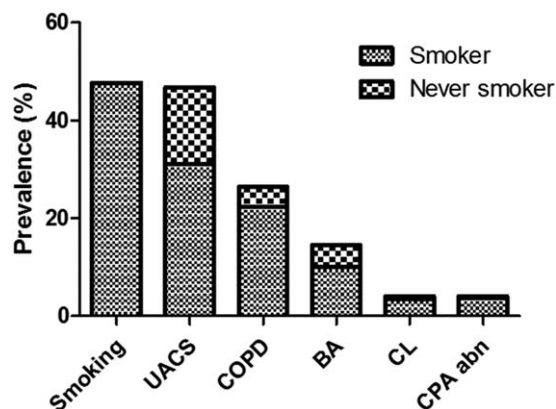


Figure 2. Prevalence of possible causes of chronic cough.

Table 3**Prevalence of overlapped conditions in patients with chronic cough.**

	Currently smoking status	UACS	COPD	Asthma	CPA abn
Prevalence	47.7±3.8	46.8±3.9	26.4±3.5	14.5±2.8	4.0±1.2
Currently smoking status	–	44.5±5.6	54.4±7.9	37.9±10.5	66.7±15.6
UACS	43.8±5.8	–	41.6±7.8	66.9±10.8	43.6±16.3
COPD	27.9±5.4	22.1±5.2	–	–	66.1±20.2
Asthma	11.0±3.8	19.6±4.1	–	–	33.9±20.2
CPA abn	5.4±2.3	3.6±1.8	9.9±4.3	9.4±6.3	–

Data were represented as mean ± standard error, or frequency (%). COPD=chronic obstructive pulmonary disease, CPA abn=chest X-ray abnormality, UACS=upper airway cough syndrome.

Individual causes of chronic cough may overlap. In this analysis, UACS frequently accompanied asthma, and chest radiographic abnormalities were frequently observed in subjects with both COPD and asthma. In multivariable analysis, the conditions that cause chronic cough were asthma, current smoking, chest radiographic abnormality, UACS, and COPD, in descending order. More frequently associated symptoms were chronic phlegm for current smokers, dyspnea and night sweats for those with UACS, and blood-tinged sputum for those with COPD.

We believe that our study have some merits and could contribute more to clinical practice. First, previous studies of causes of chronic cough were performed in a relatively small number of patients seen in a specific clinic, so risked selection bias. In this study, although the number of patients with chronic cough may seem small, the survey population selected is regarded as representative of the Korean general population. Second, most of the previous studies excluded smokers or patients with abnormal chest radiographs, and clinicians have had questions about the general frequency of chest radiographic abnormalities and the different characteristics of smokers. Our data showed not only a high prevalence of cigarette smoking (47.7%) in subjects with chronic cough, but also a strong impact of smoking (OR 3.16) on the prevalence of chronic cough independent of underlying diseases. Third, our study found that the prevalence of abnormal chest radiographs, which could be a cause of chronic cough, is 4.0% in the general population. However, the OR for chronic cough was higher than for COPD or UACS, underscoring

the importance of chest radiography, especially in a region with a high prevalence of tuberculosis.

Unlike previous research, which reported the prevalence of chronic bronchitis to be 5%,^[7] our study reported the prevalence of COPD to be as high as 26.4%. In a previous report, the overall prevalence of COPD in Koreans older than 40 years was 13.4% and increased to 19.4% in men.^[36] In our analysis, 12.2% of the total study population had COPD. Focusing on patients with chronic cough, the prevalence of COPD increased to 26.4%. Therefore, physicians should not underestimate the possibility of COPD in patients with chronic cough.

A diagnosis of GERD needs to be confirmed with 24-hour pH monitoring, so the KNHANES data could not show accurately the prevalence or clinical impact of this condition. However, GERD has been reported to be the 3rd most common cause of chronic cough and its frequency is estimated to be 10% to 21%.^[7,37] Otorhinolaryngologic examinations cannot completely replace pH monitoring for diagnosing GERD; however, we used reflux laryngitis as a clue for determining the presence of GERD. Surprisingly, the prevalence of chronic laryngitis was low (4.1% ± 1.6%) and not significantly different from the prevalence in the population without chronic cough (2.7% ± 0.3%). This may imply the fact that GERD-related cough may not be prevalent in the Korean population. Alternatively, the prevalence of GERD in Asian patients may be different from that in previous reports on Western patients with chronic cough.^[38] Our data may highlight a need for different algorithms to establish the etiology of chronic cough in different races.

Table 4**Risk factors contributing to chronic cough in univariable and multivariable analysis.**

	Univariable			Multivariable*		
	OR	95% CI	P	OR	95% CI	P
Age	1.21	1.08–1.37	0.002	0.97	0.78–1.20	0.29
Sex, male	1.97	1.45–2.67	<0.001	1.24	0.83–1.85	0.16
BMI	0.98	0.94–1.03	0.17	0.99	0.94–1.05	0.86
Current smoker	3.21	2.35–4.37	<0.001	3.16	2.11–4.74	<0.001
UACS	2.28	1.68–3.11	<0.001	2.50	1.75–3.56	<0.001
COPD	2.67	1.87–3.82	<0.001	2.41	1.59–3.66	<0.001
Asthma	8.45	5.22–13.69	<0.001	8.89	5.32–14.87	<0.001
Abnormalities on chest X-ray	2.75	1.44–5.25	<0.001	2.74	1.30–5.77	0.01
Chronic laryngitis	1.65	0.73–3.75	0.31	1.75	0.68–4.50	0.27
Hypertension	1.62	1.19–2.19	0.003	1.51	0.96–2.40	0.20
Hyperlipidemia	1.46	0.95–2.26	0.001	1.41	0.76–2.62	0.15
Diabetes mellitus	1.85	1.27–2.70	0.003	1.65	0.98–2.79	0.26
Angina or myocardial infarct	2.42	1.34–4.38	<0.001	1.38	0.59–3.22	0.70
Stroke	1.58	0.76–3.27	<0.001	0.79	0.22–2.83	0.80

Data were represented as mean ± standard error, or frequency (%). BMI=body mass index, CI=confidence interval, COPD=chronic obstructive pulmonary disease, OR=odds ratio, UACS=upper airway cough syndrome.

* Adjusted by age, sex, BMI, current smoking status, presence of UACS, COPD, asthma, chest X-ray abnormalities, chronic laryngitis, hypertension, hyperlipidemia, diabetes mellitus, and stroke.

Table 5
Comparing clinical characteristics between possible causes of chronic cough.

	Total	Currently smoking status	UACS	COPD	Asthma	CPA abn
Prevalence		47.7 ± 3.7	46.8 ± 3.9	26.4 ± 3.5	14.5 ± 2.8	4.0 ± 1.2
Age, years	57.9 ± 0.9	53.2 ± 1.2	58.2 ± 1.1	63.3 ± 1.8	54.3 ± 1.7	62.9 ± 1.6
Sex, male	64.7 ± 3.4	92.2 ± 3.0	68.6 ± 4.3	82.5 ± 6.0	54.5 ± 10.6	85.8 ± 9.2
Smoking status						
Never smoker	55.8 ± 0.6	–	33.7 ± 4.3	15.5 ± 5.3	38.6 ± 9.6	9.1 ± 7.0
Ex-smoker	21.7 ± 0.5	–	21.8 ± 4.1	30.2 ± 7.6	23.6 ± 9.9	24.3 ± 14.4
Current smoker	22.4 ± 0.5	100	44.5 ± 5.6	54.4 ± 7.9	37.9 ± 10.5	66.7 ± 15.6
Symptoms						
Sputum > 3 months	75.9 ± 3.0	86.9 ± 3.7*	71.3 ± 4.7	89.5 ± 4.6	69.4 ± 9.2	70.0 ± 16.2
Blood tinged sputum	3.8 ± 1.5	2.6 ± 2.0	3.7 ± 2.2	8.0 ± 5.2*	0	0
Chest pain	9.3 ± 2.3	13.9 ± 4.8	8.0 ± 2.9	12.7 ± 6.2	5.7 ± 4.2	6.0 ± 6.0
Dyspnea	11.4 ± 2.4	12.3 ± 4.2	15.9 ± 4.1*	7.6 ± 4.2	6.2 ± 4.5	14.5 ± 10.1
Weight loss	5.3 ± 1.5	4.5 ± 2.1	9.5 ± 2.9	2.4 ± 1.7	9.8 ± 5.5	12.6 ± 8.9
Fatigue	6.8 ± 1.7	6.0 ± 2.6	7.7 ± 2.5	6.5 ± 4.6	16.7 ± 8.4	6.0 ± 6.0
Fever	3.2 ± 1.0	0.4 ± 0.4	5.3 ± 1.9	2.4 ± 1.7	5.9 ± 4.0	6.0 ± 6.0
Night sweat	1.3 ± 0.7	0.3 ± 0.3	2.4 ± 1.4*	1.4 ± 1.4	0	0

Data were represented as mean ± standard error, or frequency (%). COPD=chronic obstructive pulmonary disease, CPA abn=chest X-ray abnormality, UACS=upper airway cough syndrome.

*Indicate statistical significance ($P < 0.05$).

Despite the interesting findings of this study, there are several potential limitations. First, as this study was a cross-sectional analysis, each cause was not confirmed by response to treatment. However, chronic cough is widely known to have multiple causes, and the relative risk for each of these was calculated. Describing the pattern of presentation and considering all possible causes in the general population would be meaningful for physicians encountering patients with chronic cough. Second, the prevalence of asthma was calculated using a self-reported questionnaire and not by a provocation test, so there is a risk of classifying a patient as false positive or as false negative. Although we categorized patients as having asthma diagnosed by their doctor, we acknowledge the possibility of misdiagnosis or underdiagnosis, and there is limitation in differentiating COPD from asthma or asthma-COPD overlap syndrome. Third, we used the prevalence of chronic laryngitis instead of pH monitoring to diagnose GERD frequently leads to chronic laryngitis,^[39–42] however, there are some differences in the mechanism of diseases, and these changes may also appear secondary to smoking, excessive alcohol, allergies, asthma, or voice abuse.^[37,42] Fourth, medication effects, such as those of angiotensin-converting enzyme inhibitors, were not evaluated since most participants did not know the exact name of their prescribed medication. Therefore, we could not determine the prevalence of angiotensin-converting enzyme inhibitor-related cough. Finally, we did not identify other diseases causing chronic cough that could be diagnosed by other methods, such as sputum analysis, computed tomography, or bronchoscopy. Therefore, the number of patients who cannot find the cause of cough may be overestimated.

In conclusion, GERD-related cough is not prevalent in Korean population, and more attention should be paid to smoking and COPD in subjects with chronic cough along with asthma or UACS. Further effort to develop a protocol for chronic cough is necessary for Asian populations.

References

- Irwin R, Boulet L-P, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. *Chest* 1998;114(suppl):133S–181S.
- Woodwell D. National Ambulatory Medical Care Survey: 1998 Summary. Hyattsville, MD:National Center for Health Statistics; 2000.
- Irwin R, Madison JM. The diagnosis and treatment of cough. *N Engl J Med* 2000;343:1715–21.
- Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med* 1996;156:997–1003.
- Palombini BC, Villanova CA, Araujo E, et al. A pathogenic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. *Chest* 1999;116:279–84.
- Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981;123:413–7.
- 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.
- Pratter MR, Bartter T, Akers S, et al. An algorithmic approach to chronic cough. *Ann Intern Med* 1993;119:977–83.
- Poe RH, Harder RV, Israel RH, et al. Chronic persistent cough: experience in diagnosis and outcome using an anatomic diagnostic protocol. *Chest* 1989;95:723–8.
- Smyrniotis NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Chest* 1995;108:991–7.
- McGarvey LP, Heaney LG, Lawson JT, et al. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax* 1998;53:738–43.
- Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):1S–23S.
- Morice AH, McGarvey L, Pavord I, et al. Recommendations for the management of cough in adults. *Thorax* 2006;61(Suppl 1):i1–24.
- Song WJ, Chang YS, Faruqi S, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J* 2015;45:1479–81.
- Global Initiative for Asthma (GINA). The global initiative for asthma. GINA report, global strategy for asthma management and prevention [cited 2013 January 24th]. Available from: www.ginasthma.org; 2012. Accessed October 2015.
- Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastroesophageal reflux disease: a systematic review. *Gut* 2005;54:710.
- Rhee CK, Jung JY, Lee SW, et al. The Korean Cough Guideline: Recommendation and Summary Statement. *Tuberc Respir Dis (Seoul)* 2016;79:14–21.
- National Health and Nutrition Examination Survey Report 2014. Ministry of Health and Welfare, Seoul, South Korea (in Korean). Available from: <https://knhanes.cdc.go.kr/knhanes/index.do>. Accessed January 2015.

- [19] American Thoracic Society Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–36.
- [20] Choi JK, Paek DM, Lee JO. Normal predictive values of spirometry in Korean population. *Tuberc Respir Dis* 2005;58:230–42.
- [21] The EuroQol Group EuroQol – a new facility for measurement of health related quality of life. *Health Policy* 1990;16:199–208.
- [22] Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;31:1281e357.
- [23] American Diabetes Association Standards of medical care in diabetes 2013. *Diabetes Care* 2013;36(Suppl 1):S11e66.
- [24] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III) final report. *Circulation* 2002;106:3143e421.
- [25] Barbee RA, Halonen M, Kaltenborn WT, et al. A longitudinal study of respiratory symptoms in a community population sample. Correlations with smoking, allergen skin-test reactivity, and serum IgE. *Chest* 1991;99:20–6.
- [26] Cerveri I, Accordini S, Corsico A, et al. Chronic cough and phlegm in young adults. *Eur Respir J* 2003;22:413–7.
- [27] Zemp E, Elsasser S, Schindler C, et al. Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). *Am J Respir Crit Care Med* 1999;159:1257–66.
- [28] Cullinan P. Aetiological factors in persistent sputum production: a case-control study. *J Epidemiol Community Health* 1993;47:27–31.
- [29] Janson C, Chinn S, Jarvis D, et al. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. *Eur Respir J* 2001;18:647–54.
- [30] Ford AC, Forman D, Moayyedi P, et al. Cough in the community: a cross sectional survey and the relationship to gastroin-testinal symptoms. *Thorax* 2006;61:975–9.
- [31] Chen RC, Lai KF, Liu CL, et al. An epidemiologic study of cough in young college students in Guangzhou. *Chin J Epidemiol* 2006;27:123–6.
- [32] Lundback B, Nystrom L, Rosenhall L, et al. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Respir J* 1991;4:257–66.
- [33] Ludviksdottir D, Bjornsson E, Janson C, et al. Habitual coughing and its associations with asthma, anxiety, and gastroesophageal reflux. *Chest* 1996;109:1262–8.
- [34] Coultas DB, Mapel D, Gagnon R, et al. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. *Am J Respir Crit Care Med* 2001;164:372–7.
- [35] Carter ER, Debley JS, Redding GR. Chronic productive cough in school children: prevalence and associations with asthma and environmental tobacco smoke exposure. *Cough* 2006;2:11.
- [36] Yoo KH, Kim YS, Sheen SS, et al. Prevalence of chronic obstructive pulmonary disease in Korea: the fourth Korean National Health and Nutrition Examination Survey, 2008. *Respirology* 2011;16:659–65.
- [37] Irwin RS, French CL, Curley FJ, et al. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. *Chest* 1993;104:1511–7.
- [38] Deng HY, Luo W, Zhang M, et al. Initial empirical treatment based on clinical feature of chronic cough. *Clin Respir J* 2015.
- [39] Toohill RJ, Kuhn JC. Role of refluxed acid in pathogenesis of laryngeal disorders. *Am J Med* 1997;103:100S–6S.
- [40] Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991;101(4 Pt 2 Suppl 53):1–78.
- [41] Branski RC, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. *Laryngoscope* 2002;112:1019–24.
- [42] Vaezi MF, Hicks DM, Abelson TI, et al. Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): a critical assessment of cause and effect association. *Clin Gastroenterol Hepatol* 2003;1:333–44.