



Perspectives on chronic cough in Korea

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Abstract: Chronic cough is a common condition, and generally affects about 3% of Korean adults with a significant influence on quality of life (QoL). Despite continued clinical and academic efforts, there are unmet needs for chronic cough prevention and management in Korea. Epidemiologically, there are two major challenges: an aging population and air pollution. Korea is one of the most rapidly aging countries, and the relative proportion of elderly to younger people is expected to double within the next two decades. Air pollution is a major concern, but there is very limited evidence on the effects of air pollutant on cough in Korean patients. Clinically, upper and lower airway diseases, such as rhinitis/rhinosinusitis and cough variant asthma/eosinophilic bronchitis, are reported to account for about 75% of chronic cough in Korean adults, which formed the basis in formulating clinical practice guidelines. However, further studies are warranted to resolve clinical uncertainty, particularly for the evaluation and treatment of upper airway conditions in chronic cough. The prevalence of gastroesophageal reflux disease (GERD) is increasing, thus its relevance to cough among Koreans may warrant re-evaluation. Infection-associated chronic cough, such as tuberculosis, is another continuing concern. The proportion of chronic refractory or unexplained cough is assumed to be 10–20% among patients visiting referral clinics for chronic cough. This review presents our perspectives on current epidemiological and clinical issues of chronic cough in Korea, and addresses major knowledge gaps and future research priorities.

Keywords: Chronic cough; Korea; epidemiology; etiology; review

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Introduction

Cough is a physiological reflex to protect the lower airways against aspiration and irritation, but it is also one of the most common medical problems in many parts of the world (1). In a study in Asian-Pacific countries, cough was the main reason for medical visits among patients with upper and lower respiratory diseases (2). In particular, chronic cough, usually defined as lasting eight or more weeks, has received much national and international attention, as it frequently persists for years, has significant physical, social,

and psychological consequences, and is often refractory to treatments (3–11).

Chronic cough is a globally prevalent condition, but its epidemiological and clinical considerations may be locally different (12–14). In Korea, since the first cough clinic was established in the 1990s, chronic cough has been one of the major research interests of allergy and respiratory specialists (9,15). Upper and lower airway diseases, such as rhinitis, sinusitis, asthma, or eosinophilic bronchitis, were found to be frequent in Korean adults with chronic cough (16,17), which formed the basis in setting priorities and formulating

Table 1 Prevalence of chronic cough in Korean community populations

Study	Study population	Survey year	Definition of chronic cough	Cough duration	Prevalence of chronic cough
Shin <i>et al.</i> , 2004, (26)	Participants of the KHG study; aged 40–69 years	2000	Period prevalence of chronic bronchitis (cough and phlegm on most days for a minimum of three months a year and for at least two successive years)	NA	3.5%
Song <i>et al.</i> , 2013, (27)	Participants of the KLoSHA study; aged ≥65 years	2005–2006	Period prevalence of chronic cough (cough on most days for three consecutive months or more during the year)	NA	4.6%
Kang <i>et al.</i> , 2017, (25)	Participants of the KNHANES; aged ≥18 years	2010–2012	Point prevalence of chronic cough (current cough lasting more than eight weeks)	1.6% had cough lasting for more than one year.	2.6%
Won <i>et al.</i> , 2020, (24)	Participants of the KNHANES; aged ≥40 years	2010–2016	Period prevalence of chronic cough (cough on most days for three months or more in the past year)	Mean duration of chronic cough; 7.8 years	3.5%

KHG, Korean Health and Genome; KLoSHA, Korean Longitudinal Study on Health and Aging; KNHANES, Korean National Health and Nutrition Examination Survey; NA, not available.

recent clinical practice guidelines in Korea (9). Despite these efforts, there are unmet clinical needs of patients in the community, particularly regarding diagnosis and treatment (18).

This review presents our perspectives on current epidemiological and clinical issues of chronic cough in Korea. Based on a recent paradigm shift and progress in mechanistic and clinical studies for cough (19–21), this review also describes major knowledge gaps and future research priorities for chronic cough in Korea.

Epidemiology of chronic cough: global and local perspectives

The global prevalence of chronic cough is estimated as approximately 10% in adults, but the regional prevalence in Asian countries is lower (4.4%) than that in Europe (12.7%) or America (11.0%) (12). Reasons for regional differences are not clear. However, host factors such as allergies, obesity, or gastroesophageal reflux may underlie the regional heterogeneity, because these conditions are less prevalent in Asian than in western populations (13). There is no comprehensive study on the roles of genetic factors in the epidemiology of chronic cough in adult populations. Only a few studies reported genetic polymorphisms in transient receptor potential vanilloid-1 (TRPV1) or neurokinin-2 receptor in relation to specific phenotypes of cough (22,23).

The Korean National Health and Nutrition Examination Survey (KNHANES) has enabled estimation of the nationwide prevalence of chronic cough in Korean adults (<https://knhanes.cdc.go.kr/knhanes/eng/index.do>). It is annually assessed using a structured questionnaire about a period prevalence (“Have you had a cough on most days for three months or more during the past year?”). The period prevalence of chronic cough in the KNHANES 2010–2016 has been estimated as 3.48%±0.17% among adults aged 40 years or older (24). Point prevalence (having current cough for two months or longer at the time of survey) is a preferred measure for studying cough epidemiology, as it is less subject to recall bias; however, it was only assessed for a limited period of the KNHANES surveys [2010–2012] and was noted as 2.6%±0.2% (25). Similarly, in two different regional community-based studies of middle-aged or older adult populations, period prevalences were approximately 4–5% (26,27) (Table 1).

Notably, chronic cough is more prevalent among older adults in many countries including Korea (28). It is

speculated that more frequent comorbidities in older adults may underlie the age-related prevalence patterns. Lung parenchymal diseases or structural changes may possibly be important in chronic cough among older adults; unlike in younger adults, abnormal chest X-ray findings were significantly more frequent in elderly patients (aged 65 or older) with chronic cough than in those without cough (45.5% *vs.* 25.1%; $P < 0.001$), and one outstanding finding was inactive tuberculosis (27.3% *vs.* 14.2%; $P < 0.001$) (28). However, in multivariate analyses of the KNHANES population dataset, the associations between chronic cough and old age were independent of comorbid conditions including asthma, chronic rhinosinusitis, or chest X-ray abnormalities (25), suggesting the need for further investigation of the age-related increase in prevalence. According to the World Population Prospects 2017 report, population aging is a globally emerging issue, but it is expected to be more dramatic in some Asia-Pacific countries like Korea, Japan, Singapore, and Thailand (29). Elderly people comprised 14.9% of the total Korean population in 2019, but this may increase to 46.5% (median age of 62.2 years old) in 2067 (<http://kosis.kr/index/index.do>). Due to frequent comorbidities and potential side effects from medications, chronic cough in older adults is more challenging to manage than that in younger patients (30). Therefore, prevention and management strategies for chronic cough problems in older adults should be developed further.

Given the high prevalence and impact on quality of life (QoL), the disease burden of chronic cough is expected to be substantial. However, it has not been formally estimated (11). In the recent KNHANES 2010–2016 analyses, chronic cough was significantly associated with lower EuroQoL 5-dimension (EQ-5D) index scores in Korean adults, independently of confounding factors (24). The mean difference in the EQ-5D index score between subjects with and without chronic cough exceeded the minimally important difference (0.79 ± 0.01 *vs.* 0.86 ± 0.00 ; $P < 0.001$); notably, the score difference was more remarkable in elderly women than in men or younger women, indicating that elderly women are the most susceptible demographic group warranting active interventions for chronic cough (24). Moreover, in a recent internet-based questionnaire survey of 15,000 adults in the UK, a mean EQ-5D index score was 0.71 in patients with chronic cough, which was significantly lower than 0.83 in healthy controls (31), confirming the impact of chronic cough.

Air pollution and chronic cough

Cough is a defensive reflex; thus, environmental factors should affect the epidemiology and clinical characteristics of chronic cough. In particular, air pollution is a major concern due to its considerable impact on respiratory health including cough (32). Unlike western countries, the annual mean concentrations of fine particulate matter with a diameter of $2.5 \mu\text{g}/\text{m}^3$ or less ($\text{PM}_{2.5}$), an indicator for ambient air pollution, are high ($\geq 25 \mu\text{g}/\text{m}^3$) in many Asian countries (32). Ironically, the prevalence of chronic cough in Asia is less than half of that in Europe or America (12). This discrepancy leads to speculation that air pollution is not a major determinant for the prevalence of chronic cough, although air pollutants are apparent triggers for provoking cough (33). Given acute effects of pollutant exposure on cough, the true impact of air pollution on chronic cough warrants longitudinal investigation, particularly for its long-term remnant effects (33). Meanwhile, recent animal experiments suggested some detail how air pollutant exposure may induce cough. In a recent study by Fang and colleagues, the experimental exposure to heavy traffic was significantly associated with cough reflex hypersensitivity and eosinophilic airway inflammation in guinea pigs (34). Another guinea pig model demonstrated that intranasal administration of $\text{PM}_{2.5}$ induced cough reflex hypersensitivity and up-regulated TRPV1 expression in airways and dorsal vagal complex (35).

However, so far, there is a very limited number of studies on the impact of air pollution on chronic cough in Korea. In a panel study during Asian sand dust seasons, high levels of PM_{10} , NO_2 , or ozone were related to weather-related cough in Korean patients with chronic obstructive pulmonary disease (COPD), as compared to control subjects without respiratory diseases (36). In a cross-sectional study of adult residents living near industrial complexes in Korea, cough was significantly more prevalent among the residents living near industrial complex cities, as compared to residents outside the influence of industrial complexes [odds ratio (OR), 1.18; 95% confidence interval (95% CI), 1.06–1.31] (37).

Clinical epidemiology of Korean patients

Demographics and cough sensitivity

The predominance of older women is a relatively well-known finding in chronic cough (4). A recent worldwide survey confirmed this observation, in a study which

consisted of 10,032 chronic cough patients recruited from 11 cough clinics in six countries (China, Holland, Korea, Sweden, UK, and the US) (38). Two-thirds of the participants were women and the most common age for clinical presentation was 60–69 years (mean age: 55 years); the demographic profile was mostly uniform across centers and countries, except for China (38). The female predominance is presumably attributed to sex differences in the following factors, including cough reflex sensitivity, central processing of cough, and impact of cough on QoL (or the complications with coughing) (24,38,39). It has been repeatedly found that women have a heightened cough sensitivity to tussigen inhalation than men (40–44). Also, in a functional brain imaging study, women showed greater activation of the somatosensory cortex than men, even with lower dose capsaicin inhalation (38). Estrogen hormone has been suggested as one of the mechanistic links to cough reflex sensitivity, as it may enhance the function of TRPV1 (45,46). However, estrogen hypothesis may not explain a large proportion of post-menopausal women among patients with chronic refractory or explained cough. Meanwhile, a reason for the difference in Chinese patients (roughly equal sex distribution and middle-aged predominance) is still unclear (14). There is no evidence for an ethnic difference in cough sensitivity (47).

Among Korean patients, the older female predominance appears to be more evident in unexplained or refractory chronic cough. In a recent multi-center study, the percentage of women was significantly higher in patients with unexplained chronic cough than in those newly referred with chronic cough (85.5% *vs.* 65.9%; $P=0.002$) (48). It utilized the Cough Hypersensitivity Questionnaire (CHQ) to assess a symptom profile related to cough hypersensitivity, and found that patients with unexplained chronic cough had significantly more cough triggers and laryngeal sensations than those with chronic cough (6.9±2.6 *vs.* 5.0±2.8; $P<0.001$; and 4.4±1.5 *vs.* 3.9±1.9; $P=0.049$, respectively), but suggested that cough hypersensitivity is not exclusive to refractory cough but that it is common to overall chronic cough patients. In addition, the CHQ score was significantly higher in women than in men (8.9±3.7 *vs.* 8.0±3.4; $P=0.013$) (48), also suggesting interactions between sex and cough hypersensitivity.

Rhinitis and rhinosinusitis: uncertainties

Upper airway symptoms or diseases are reportedly found

in about half of Korean adult patients with chronic cough, although their causal relationships are controversial (16). According to the specialist clinic data in Seoul, about 50% of the adult patients had nasal symptoms (rhinorrhea or nasal obstruction) or positive nasal endoscopic findings (defined by the presence of nasal polyps, mucopurulent discharge, or edema in the middle meatus) (44).

Specific diagnoses for upper airway conditions in these patients were not described in detail. Likewise, in a survey of Korean allergists in 2012, sinus X-ray was the second most common diagnostic tool in the daily practice of chronic cough management (70.1%), which was next only to chest X-rays (87%) (17). Rhinoscopy (22.1%) and laryngoscopy (12%) were also considered as a part of routine investigation in some clinics (17).

In this context, a short-term empirical trial with H1-receptor antagonists (H1RAs) (preferably first-generation agents) is strongly recommended for Korean adults with chronic cough, even in the absence of nasal symptoms or signs (*Figure 1*) (9). This recommendation is supported by randomized clinical trials (RCTs), and also by low costs, ease of accessibility, and known, expectable adverse reactions of H1RAs (9). However, there are controversies and uncertainties regarding the true benefits of H1RA treatment in chronic cough. First, the recommendation was based on a very low level of evidence. There were only three clinical trials with older generation H1RAs (diphenhydramine, loratadine, or oxatomide), which did not utilize validated cough measurement tools (9). Second, older generation H1RAs may exert anticholinergic side effects, such as sleep disturbance, inattention, disorganized speech, or alterations in consciousness, which can be more harmful in older adults (49). To our knowledge, there is no high quality evidence to confirm benefits of newer generation H1RAs using validated cough endpoints. Placebo-controlled trials are warranted to confirm this, as cough is frequently self-limiting and prone to placebo effects (50).

In the literature, there is a controversy regarding the clinical impact of assessing and controlling nasal diseases in chronic cough, even though they frequently overlap. Mechanistically, nasal inflammation does not directly trigger cough reflex via the vagus nerves, although it may sensitize the cough reflex through activation of the trigeminal nerves (51). In an observational study of 108 subjects with purulent postnasal drip, only 9 (8%) complained of cough in the absence of other pathology (52). In a prospective study of chronic cough patients ($n=36$), sinus imaging was not useful in determining the cause of cough (53).

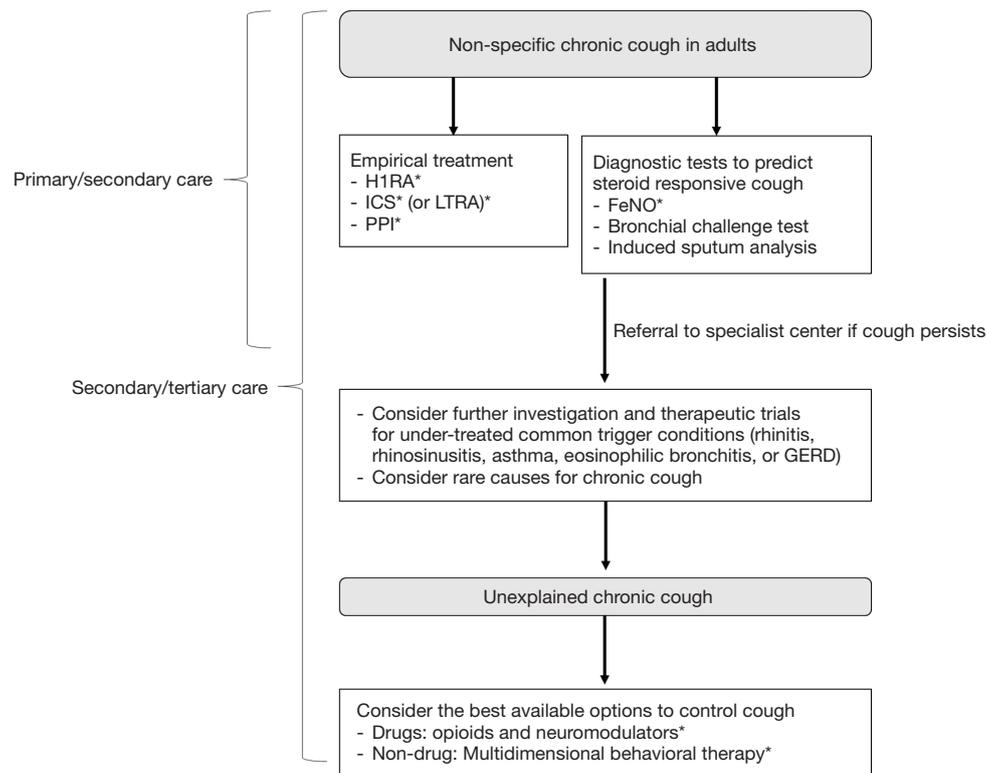


Figure 1 Management of non-specific chronic cough in Korean adults (age ≥ 15 years), recommended in the 2018 KAAACI Evidence-Based Clinical Practice Guidelines for Chronic Cough in Korea [reproduced from Song *et al.*, *Allergy Asthma Immunol Res* 2018;10:591-613, with permission of the journal] (9). Decision for empirical treatment and diagnostic tests may depend on clinical and instrument settings. Patients with chronic cough unresponsive to empirical trials or specific treatment should be referred to specialist centers for further diagnostic tests and therapeutic trials. If cough is still unexplained, pharmacological and non-pharmacological treatment options are considered to control cough. Asterisk (*) indicates the drug (or test) of interest in the present guidelines. KAAACI, Korean Academy of Asthma, Allergy and Clinical Immunology; H1RA, histamine-1 receptor antagonist; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; PPI, proton-pump inhibitor; GERD, gastroesophageal reflux disease; FeNO, fractional exhaled nitric oxide.

Cough variant asthma and eosinophilic bronchitis: diagnostic issues

Cough variant asthma and eosinophilic bronchitis are common type 2 airway inflammatory conditions presenting with chronic cough, accounting for about 25–50% of Korean adult patients (16). Notably, these are particular conditions in which objective diagnostic tests, such as bronchial challenge or induced sputum testing, are preferred to empiric treatment during the early stages of management (9). Both tests are commonly used at specialist centers, and consensus test protocols have been proposed by the working groups of the Korean Academy of Asthma, Allergy and Clinical Immunology (54,55). However, these tests are unavailable in most primary and secondary care

settings (18).

Recently, there is a growing interest regarding how to apply fractionated exhaled nitric oxide (FeNO) measurement in clinical management pathways in the primary clinics in Korea, as FeNO is quick, non-invasive and easy-to-perform. One major challenge in implementing FeNO tests in clinical practice is that it is difficult to determine reference values, as various factors including ethnicity, sex, age, or atopic status may considerably affect population or subgroup ranges (56-59). The American Thoracic Society (ATS) guidelines recommend the use of cutoff points rather than reference values, based on a specific clinical setting and the research question being addressed (60).

In adult patients with chronic cough, Yi and colleagues

found that FeNO levels ≥ 31.5 ppb indicate more likelihood of corticosteroid-responsive cough (including cough variant asthma, eosinophilic bronchitis, or atopic cough) (61). Our subsequent meta-analyses of 13 studies (2,019 patients) found that FeNO has moderate diagnostic utility as a rule-in test for detecting cough variant asthma (62). Summary area under the curve (AUC) was 0.87 (95% CI, 0.83–0.89), and notably, specificity was higher and more consistent than sensitivity (0.85, 95% CI, 0.81–0.88 and 0.72, 95% CI, 0.61–0.81, respectively) (62). The diagnostic characteristics of FeNO were consistently observed in later published studies of Japanese and Chinese patients with chronic cough (63,64).

However, for detecting non-asthmatic eosinophilic bronchitis, there is only limited evidence to guide the application of FeNO. Oh and colleagues found that the cutoff levels of 31.7 ppb have a sensitivity of 86% and a specificity of 76% for the detection of eosinophilic bronchitis among Korean patients with non-asthmatic chronic cough (65). Our meta-analysis identified four available studies (390 patients) including the study by Oh *et al.* (65), and estimated the summary AUC as 0.81 (95% CI, 0.77–0.84), sensitivity as 0.72 (95% CI, 0.62–0.80), and specificity as 0.83 (95% CI, 0.73–0.90) (62). However, neither sensitivity nor specificity appears to be an advantage of the FeNO test in the detection of eosinophilic bronchitis. Relatively poor accuracy of FeNO in detecting sputum eosinophilia was similarly found in a meta-analysis of asthmatic patients by Korevaar *et al.* (66), in that the summary AUC was 0.74 (95% CI, 0.70–0.78), and the sensitivity and specificity were only 0.66 (95% CI, 0.57–0.75) and 0.76 (95% CI, 0.65–0.85), respectively. The discrepancy between FeNO and sputum eosinophil counts may be attributed to different mechanisms of regulation (IL-4/IL-13 for FeNO *vs.* IL-5 for eosinophils), or to observer variability in conducting and interpreting induced sputum analyses. However, the predictability of treatment response is a clinically important outcome for a diagnostic test, and the FeNO test may be potentially useful in predicting inhaled corticosteroid (ICS) response in patients with chronic cough (67).

Despite these uncertainties, the Korean guideline committee agreed that a practical alternative test to induced sputum analyses should be introduced to clinics in daily practice, and decided to adapt the Korean patient data (65) to formulate a recommendation for the use of FeNO to predict asthma or eosinophilic bronchitis in Korean patients

with chronic cough (Figure 1) (9).

Natural course and optimal management of eosinophilic bronchitis

Although eosinophilic bronchitis is a common treatable trait in chronic cough, the natural course of patients with eosinophilic bronchitis is unclear. In a case series study of Korean patients with eosinophilic bronchitis, three of four cases followed up for more than six months re-developed eosinophilic bronchitis with cough and one patient developed asthma during 18 months of follow-up (68). In a prospective cohort study of 24 patients with eosinophilic bronchitis (observed up to 48 months), sputum eosinophilia recurred in five patients (21%) at between four and 24 months (69). Progressive forced expiratory volume in one second (FEV1) reduction $>20\%$ was observed in three of five patients with recurrent eosinophilic bronchitis, but not in those patients without recurrent eosinophilia (69). In a retrospective cohort study of Korean patients, chronic airflow obstruction developed in five of 48 patients with eosinophilic bronchitis, and exacerbations requiring systemic corticosteroids, antibiotics, or hospitalization occurred in 15 patients (70). However, in a prospective study of Chinese patients with eosinophilic bronchitis (followed for $>$ one year; median, 4.1 years), relapsing cases were reported in about 60% of the patients, and mild asthma developed in 5.7%, whereas progressive decline in lung function was not observed (71). In a UK-based prospective study of 32 patients with eosinophilic bronchitis with available longitudinal data for more than one year, three patients (9%) developed asthma and five patients (16%) developed fixed airflow obstruction (72).

These observational studies are not directly comparable due to considerable methodological and clinical heterogeneities. However, host factors may affect the natural course of eosinophilic bronchitis. Smoking may play a role in development of airflow obstruction. Concomitant blood eosinophilia might also increase the risk of recurrence (69), although larger studies are warranted to confirm this hypothesis.

Optimal management for eosinophilic bronchitis is unknown, although ICS is considered the mainstay treatment. In clinical experience, cough in patients with eosinophilic bronchitis usually responds to ICS treatment within 1 or 2 months (11). However, it is unknown how long the treatment should be maintained. In a recent randomized

open label trial of Chinese patients with cough >3 weeks and eosinophilic bronchitis, ICS treatment (budesonide 200 µg, twice daily) significantly reduced cough visual analogue scale scores (from 5.9±2.0 to 1.3±1.7) and sputum eosinophil counts [from 7.6% (4.5–13.0%) to 1.0% (0–3.2%)] in the one-month treatment group; however, the relapse rate was significantly associated with persistent sputum eosinophilia but was lower in the four-month treatment group than in the one-month group (10.7% vs. 41.9%; P=0.007) (73). Given the recurrence in some patients, a biomarker-driven ICS stepping-down strategy, based on repeated measures of FeNO or eosinophil counts, may be warranted.

Gastroesophageal reflux disease (GERD) and proton pump inhibitor (PPI) use

The prevalence of GERD in Korean patients with chronic cough was mostly determined using subjective criteria (16). One study at a tertiary hospital utilizing objective 24-hour esophageal pH monitoring found that only 1.7% of patients with chronic cough had acid-reflux-associated cough (74). Recent studies suggest that GERD is becoming more prevalent in East Asian populations (75–77), suggesting that the burden from GERD-associated cough may continue to increase.

Pathophysiology and management of GERD-associated cough are still controversial. It has been recently recognized that acid reflux may have a minor role in chronic cough (78). Recent guidelines recommend against the routine use of acid suppression therapy in chronic cough patients, in the absence of symptoms or signs suggestive of acid reflux (9,11,79). In a clinical trial of Korean patients with chronic cough, PPI treatment was associated with significant improvement in cough-specific QoL, as compared to placebo. However, these results warrant validation, because the baseline comparability was not met between different treatment groups (80).

There are no formal published data, but a considerable number of patients coming to our cough clinics have taken PPIs in the absence of clinical history or objective tests suggesting acid reflux. In observational studies, the use of PPIs is associated with risks of elderly prone diseases like pneumonia, *Clostridium difficile* infection, osteoporosis, bone fracture, or dementia (81,82); although the degree of associations is mostly modest, the summed impact may be substantial given the high number of patients exposed to PPIs.

Recent studies suggest potential relevance of non-acid

reflux in chronic cough (83–85). In a retrospective cohort study of Korean patients with chronic cough, baseline symptoms of non-acid reflux, such as coughing with eating or cough with certain foods, were associated with the risk of cough persistence at four years after systematic assessment at a tertiary clinic (86). In an open label, single arm intervention study in China, administration of baclofen as an add-on yielded a favorable response in 36.9% of patients with GERD-associated cough who were refractory to antacid therapy (87). However, causal relationships of non-acid reflux are not confirmed, as there are no published placebo-controlled RCTs examining pro-motility drugs in chronic cough patients (11).

Infection-associated chronic cough

In the literature published from Asian countries, infectious causes are still considered important in patients with chronic cough (13). The incidence of pulmonary tuberculosis is consistently decreasing, but the statistics report higher rates of incidence and mortality of tuberculosis in Korea among the Organisation for Economic Co-operation and Development (OECD) countries (88). Therefore, it is recommended to consider pulmonary tuberculosis as a differential diagnosis in Korean patients with cough lasting more than two to three weeks (15).

Pulmonary paragonimiasis is considered as a cause of persistent cough in some endemic areas of Southeast Asian countries (13). However, there are some cases reported in Korea; in a retrospective study of 36 Korean patients diagnosed with pulmonary paragonimiasis between 1994 and 2004, cough was the second common symptom (47%) (89). Paragonimiasis is frequently associated with endemicity and a dietary habit of eating raw crab, but may need to be suspected in immigrants or overseas travelers with chronic cough and highly suggestive history and abnormal chest radiographs (90,91).

There are studies investigating the incidence of pertussis in Korean adolescents or adults with bothersome cough (92–95). However, only one study (95) included subjects with cough lasting up to 12 weeks, in which no one with chronic cough (≥ eight weeks) reported positive polymerase chain reaction assay results for *Bordetella pertussis*. Given the concern about potential under-estimation of pertussis, more active surveillance might be needed particularly in Korean elderly with cough, due to waning effects of pertussis vaccination and increasing incidence in adults aged older than 70 years as reported by the Korea Centers for Disease

Control and Prevention (96).

Unexplained or refractory chronic cough

Unexplained or refractory chronic cough is a globally important target for novel drug development, due to its high impact on QoL and the lack of safe and effective treatments. Patients with chronic refractory cough experience unwanted social attention, personal isolation, depression, and feelings of helplessness (18,97). There is no comprehensive estimation on their healthcare utilization, but clinical experience suggests that these patients frequently undergo unnecessary investigations or treatments that are potentially harmful, such as oral corticosteroids, without adding any clinical benefits to controlling the cough. Currently available drugs have been empirically identified from centrally-acting drugs for pain or neuropathic conditions, such as opiates, gabapentin, or pregabalin (98-100); but they are only effective in a subset of patients with chronic refractory cough, and their frequent, sometimes serious, side effects limit their widespread use. In this regard, the success of P2X3 antagonists or other neuromodulators (such as neurokinin-1 receptor antagonists) in clinical trials (101-103) will be an important milestone.

The incidence of unexplained or refractory chronic cough has not been formally reported in Korean populations, although it is presumed 10–20% of patients with chronic cough attending specialist clinics (48). They are mostly non-smoking elderly women, characterized by hypersensitivity in cough reflex and abnormal laryngeal sensation (48). Approximately half of these patients have a cough that has persisted for more than five years (18,48). At present, codeine is considered as the best available drug for these patients in Korea (9). Speech language therapy is recommended in the recent Korean guidelines (9), but the service should be provided by experienced professionals; however, the pool of speech therapists qualified for this type of therapy is lacking. The burden of unexplained or refractory chronic cough has not been estimated yet. Healthcare utilization and future risk of adverse health outcomes should be also examined.

Role distributions between primary and referral clinics in the management of chronic cough

Korea has a universal health coverage system, and ensures easy access to referral clinics (104). The simple referral system helps patients visit specialist clinics or tertiary

hospitals without a long wait. In 2017, the annual number of doctor consultations per person was 16.6 in Korea, which is higher by far than the OECD average (6.8) (<https://www.oecd.org/health/health-data.htm>). This easier physician and treatment access may have attributed to a relatively short duration of cough among patients visiting specialist clinics in Korea (48). It is also presumed that there are considerable overlaps in the cough patient populations and clinical roles between primary clinics and referral centers in Korea.

In the recent Korean guidelines for chronic cough management (9), the concept of non-specific chronic cough was introduced, which indicates chronic cough in the absence of any symptoms, signs, history, or laboratory findings indicating a specific diagnosis for (specific cough pointers), such as use of angiotensin-converting enzyme inhibitors, current smoking, any evident symptoms indicating a specific diagnosis (fever, blood-tinged sputum, wheezing, dyspnea, rhinorrhea, nasal obstruction, or heartburn), abnormal physical findings (wheezing or crackles on auscultation), or abnormal findings on chest X-rays and/or spirometry. Then, three initial roles were assigned (but not exclusively) to primary and secondary cares: (I) screening of specific cough, based on history, physical examination, chest X-rays, or spirometry; (II) short-term empirical trials with H1RA or ICS in patients with non-specific chronic cough; and (III) FeNO tests to identify patients responsive to ICS. Referral to specialist center is recommended if a patient needs further diagnostic tests or management, or if cough is refractory to empirical trials (9) (*Figure 1*). However, studies are warranted to characterize patients with chronic cough in the community, and to validate the roles of primary care in the management of chronic cough Korea.

Knowledge gaps and future research directions

This section summarizes future research directions, based on the current status and knowledge gaps as discussed above (*Figure 2*).

- ❖ The burden of chronic cough in the elderly is expected to increase substantially in the near future. Further studies are warranted to reveal the mechanisms of the aging-related increase and to develop precise prevention and management strategies for cough in this population.
- ❖ Effects of air pollution on chronic cough problems should be investigated. Given the protective nature

Chronic cough in Korea	
<ul style="list-style-type: none"> • Nationwide prevalence: about 3% in adults (5% in the elderly) • Frequent overlaps with upper and lower airway diseases 	
Ongoing challenges	Uncertainties and knowledge gaps
<ul style="list-style-type: none"> • Aging population • Air pollution 	<ul style="list-style-type: none"> • Management of upper airway diseases-and reflux-associated cough • Precise roles of FeNO test • Burden and management of chronic refractory cough • Cough in primary care

Figure 2 Summary of current challenges, and major uncertainties and knowledge gaps in the management of chronic cough in Korea.

of cough, the true impact on chronic cough warrants longitudinal investigation, particularly for its long-term remnant effects.

- ❖ Clinical strategy should be revisited, particularly with respect to the efficacy and utility of diagnostic tests and therapeutic drugs for upper airway diseases in patients with chronic cough.
- ❖ FeNO is being incorporated into the clinical practice of chronic cough in Korean patients. However, further clinical evidence is required to confirm its use in the diagnostic pathways and longitudinal follow-ups of cough patients.
- ❖ Reflux-associated cough warrants further attention, given the recent increase of GERD in Asian populations. Meanwhile, there is a widespread use of PPI for patients with cough, which is unlikely to help patients in the absence of acid reflux.
- ❖ The disease burden of chronic cough should be measured.
- ❖ Cough patients in the community need to be characterized. Studies are also warranted to validate the roles of primary care in the management of chronic cough.

Conclusions

Chronic cough is a globally common condition, but also affects about 3% of the general adult population in Korea with a significant impact on QoL. Aging population and air pollution are major challenges from epidemiological perspectives. Clinically, upper and lower airway diseases—rhinitis/rhinosinusitis and cough variant asthma/eosinophilic bronchitis—are considered to be major comorbid conditions in Korean adults with chronic cough, which formed the basis in formulating clinical practice guidelines. However, there are uncertainties and unmet needs in how

to assess and manage these conditions more precisely and more effectively. GERD- and infection-associated cough problems are additional concerns. Further studies are warranted to refine our clinical strategy and reduce the disease burden.

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Footnote

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