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Current Review

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# Epidemiology of adult chronic cough: disease burden, regional issues, and recent findings

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## ABSTRACT

Chronic cough is a common medical condition that has a significant impact on patients' quality of life. Although it was previously considered a symptom of other disorders, it is now regarded as a pathologic state that is characterized by a deviation from the intrinsic protective functions of the cough reflex, especially in adults. There are several factors that may underlie the cough reflex hypersensitivity and its persistence, such as age, sex, comorbidities, viral infection, exposure to irritants or environmental pollutants, and their interactions may determine the epidemiology of chronic cough in different countries. With a deeper understanding of disease pathophysiology and advanced research methodology, there are more attempts to investigate cough epidemiology using a large cohort of healthcare population data. This is a narrative overview of recent findings on the disease burden, risk factors, Asia-Pacific issues, and longitudinal outcomes in adults with chronic cough. This paper also discusses the approaches utilizing routinely collected data in cough research.

**Keywords:** Cough; Epidemiology; Burden of disease; Risk factor; Asia-Pacific; Longitudinal outcome

## INTRODUCTION

Epidemiology is a study of the distribution and determinants of a disease, as well as the application of the results obtained to disease control [1]. The results of epidemiological studies may not only help physicians to understand the pathophysiology of the disease but

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also guide decision-making in economics and politics by providing information about the socioeconomic impact of the disease and its treatment at the population level.

In the past, chronic cough was considered merely as a symptom or consequence of other chronic disorders; thus, less attention was paid to chronic cough itself. However, it is now regarded as a pathologic state on its own that deviates significantly from the intrinsic functions of the human cough reflex to protect the lower airways against aspiration [2]. In the 2010s, the concept of "cough hypersensitivity syndrome" was proposed and endorsed by the European Respiratory Society (ERS) task force [3-5]. The views have been adopted in the recent ERS cough guidelines, which defined chronic cough as a distinct clinical syndrome characterized by hypersensitivity in the cough reflex, especially in adults [6, 7].

With this paradigm shift in the definition of chronic cough, there have been recent attempts to explore some hidden aspects of chronic cough epidemiology. At the same time, there are growing interests in the disease burden, regional issues, and longitudinal outcomes of chronic cough. The present review aimed to provide an overview of the recent literature with the following topics: the disease burden, novel risk factors, regional issues, longitudinal outcomes, and novel approaches utilizing routinely collected data (RCD) in chronic cough research.

## DEFINITIONS FOR CHRONIC COUGH IN EPIDEMIOLOGICAL STUDIES

The first challenge encountered is how to define chronic cough in epidemiological studies since there is no consensus on a definition for this condition. In previous studies of chronic cough, various questionnaires were utilized, and a duration-based definition was most widely used to define the disease [8]. However, this definition using the duration of cough is controversial. The duration-based definition is useful in clinical practice of cough (as it helps to guide a differential diagnosis); however, it may not be valid for use in prevalence or incidence studies. Simply asking about the presence and duration of cough may not suffice to differentiate protective cough responses (i.e., coughing in response to chronic or repeated exposure to irritants such as cigarette smoke) from the cough problems encountered in clinical practice. There is a middle-aged female predominance in chronic cough patients attending specialist clinics [9]; however, this demographic pattern is not consistently observed in general population studies that use the duration-based definition [8]. Females have enhanced sensitivity to capsaicin inhalation in coughing and urge-to-cough sensation [9]; however, chronic cough is more frequently found in smoking men in general population studies [8]. Also, the duration alone might not properly represent the severity, impact, or burden of chronic cough. Further investigations are warranted to confirm the identities of the key components that define chronic cough as a disease condition, which will help us to revise the disease definition for use in epidemiological studies and also to further understand the risk factors, natural course, and burden of the disease (**Table 1**).

## BURDEN AND IMPACT OF CHRONIC COUGH

Disease burden is defined as the impact of a health problem on a given population. It can be assessed using several indicators, such as mortality, morbidity, or disease cost [10]. The

**Table 1.** Methodological issues and questions in chronic cough epidemiology research

| Issue | Remarks and questions |
|---|---|
| How to define chronic cough in general population surveys using questionnaires | Limitation: The duration-based definition is useful in clinical practice of patients who attended clinics but may not be valid for use for prevalence and incidence studies because (1) it may not differentiate protective cough responses (e.g., coughing in response to environmental irritant exposure) from clinical cough problems, and (2) it may not properly represent the severity, impact, or burden of chronic cough.<br>Question: What are key components that define chronic cough as a disease? |
| How to capture chronic cough patients in routinely collected data (RCD) | Limitation: RCD records are a promising tool to study a longitudinal disease course in a large patient population. However, the use of RCD is still limited in cough research, because there was no unique diagnostic code for chronic cough in the previous International Classification of Disease systems-9 and -10.<br>Question: What should be the optimal operational definition for detecting patients with chronic cough in RCD analyses? |
| Longitudinal outcomes and measurements in chronic cough cohort studies | Limitation: Cough may persist for years despite treatment efforts. However, the future risks in patients with chronic cough are unknown.<br>Questions: (1) How should we define cough persistence or remission in cohort studies? (2) Would there be other long-term health consequences that result from chronic cough, such as the risk of morbidity, mortality, or treatment-related complications? |

prevalence, incidence, and quality of life (QoL) are also useful as they reflect the burden of a disease in a given population [10].

There are a number of studies reporting the prevalence of chronic cough in general adult populations, although cough was reported mostly as one of the secondary outcomes [8]. The worldwide prevalence of chronic cough was estimated as 9.6% (95% confidence intervals [CI], 7.6%–11.7%; $I^2$ = 99%) in previous systematic reviews in 2014 [11]. However, there were substantial regional variabilities in the prevalence, generally being higher in Western than in Eastern countries; the reasons for the regional differences remain largely unclear because there is no direct comparison study. Some host factors such as obesity or gastroesophageal reflux disease (GERD) are speculated [12]. Although incidence data are scarce, according to recent studies, the incidence of chronic cough ranges from 1.16 to 5.70 per 100 person-years [13, 14].

The impact of chronic cough on QoL is widely recognized, as it is being utilized as one of the key outcomes in clinical decision-making and guideline recommendations [6]. A prospective study carried out in the United States was the first to describe the comprehensive impact of chronic cough [15]. Cough affects the physical, psychological, and social domains of QoL, and can be quantified using validated questionnaires such as the Cough-specific Quality-of-Life Questionnaire or the Leicester Cough Questionnaire (LCQ) [16, 17].

Although generic health-related QoL questionnaires such as the EuroQoL questionnaire are not specific to cough in content; they may help us to evaluate the comparative impact of chronic cough relative to those of other disorders. In the Korean National Health and Nutrition Examination Survey (KNHANES) carried out in 2010–2016, the 3-level EuroQoL 5-dimension component (EQ-5D-3L) index score was significantly lower in subjects with than without chronic cough (0.79 ± 0.01 vs. 0.86 ± 0.00, $p < 0.001$), and the difference exceeded the minimally important difference score of 0.05 in the scale. The EQ-5D-3L index score in patients with chronic cough was comparable to those with arthritis, stroke, asthma, or chronic obstructive pulmonary disease, especially in elderly women [18]. Similarly, in the National Health and Wellness Surveys (NHWS), subjects with chronic cough reported significantly lower health-related QoL than the matched controls as indicated by scores on the EQ-5D-5L (0.71± 0.18 vs. 0.81 ± 0.16, $p < 0.001$) and the Medical Outcomes Study 36-item Short Form Survey v2, including the 6-dimensional health state short form (0.62 ± 0.12 vs. 0.71 ± 0.14, $p < 0.001$), SF-36 physical (42.9 ± 10.8 vs. 48.8 ± 10.2, $p < 0.001$), and the mental component (41.7 ± 12.8 vs. 47.4 ± 11.6, $p < 0.001$) [19].


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Cough-related complications are another factor contributing to the disease burden, such as exhaustion, insomnia, or syncope [20]. In particular, older women are vulnerable to chronic cough and also to cough-induced stress urinary incontinence; thus, they require more attention [21]. In a recent study of women presenting to a specialist cough clinic in the US, 63% of them reported urinary stress incontinence induced by coughing [22]. The health-related QoL in patients with chronic cough is more impaired in elderly women than in men or younger women, and cough-induced stress urinary incontinence may be a major cause of the morbidity [18].

Chronic cough constitutes a financial burden not only by reducing the work productivity of patients suffering from it but also by increasing their medical expenses (for medications and diagnostic testing). In European studies, chronic cough was associated with an increase in the number of visits to doctors and sick leaves [23-25]. In the NHWS in Japan and the United States, patients with chronic cough reported more impaired work productivity and higher healthcare resource utilization compared to those without chronic cough [19, 26]. However, a formal estimation of the disease burden of chronic cough is needed.

## EMERGING OR NOVEL RISK FACTORS

### Chronic cough, pain, and pruritus

Results from epidemiological studies may provide clues to mechanical links between individual diseases. Given that hypersensitivity or hyper-sensation is a key component in the pathogenesis of chronic cough, it has been postulated that the condition is associated with chronic pain syndromes [27]. Chronic cough and chronic pain may share an impaired central inhibitory pathway and heightened sensory neuronal sensitivity. Recently, their interrelationships were suggested in a prospective population-based cohort study in the Netherlands. In a follow-up study for 4 years, baseline chronic pain was associated with incident chronic cough (odds ratio [OR], 1.56; 95% CI, 1.16–2.10), and the baseline presence of chronic cough was also associated with incident chronic pain (OR, 1.69; 95% CI, 1.06–2.70) [28]. In the Canadian Longitudinal Study on Aging, there was a higher incidence of chronic cough among subjects with chronic pain compared to those without chronic pain (5.5 per 100 person-years [95% CI, 5.1–5.9 person-years] vs. 4.3 per 100 person-years [95% CI: 4.0–4.6 person-years]) [13]. However, the causal or mechanistic relationships between chronic cough and pain warrant further investigation.

Pruritus is a sensory response that not only helps the host to localize and remove harmful or irritating stimuli but also becomes a clinical problem when it persists. Although the pathophysiology of chronic pruritus remains largely unclear, which leads to the lack of effective treatment [29], it is speculated that chronic cough and chronic pruritus have similarities in pathophysiology, especially regarding the involvement of neuropeptides, neurokinin receptors, or transient receptor potential channels [30]. In clinics, gabapentin and pregabalin are often prescribed for patients with chronic intractable pruritus, which also showed therapeutic benefits in patients with chronic refractory cough [31-33]. In a recent large-scale adult population study in France (n = 4,050), the risk of chronic cough (defined by cough lasting longer than 3 weeks) was higher among the participants having sensitive skin compared to those without it (OR, 1.88; 95% CI, 1.49–2.37) [34]. Although the presence of sensitive skin was self-reported, the study findings implicate potential relationships between this condition and chronic cough.


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### Chronic cough and diabetes mellitus

Previous studies have reported positive associations between chronic cough and diabetes mellitus (DM). In the Korean Longitudinal Study on Health and Aging, uncontrolled DM (defined as glycosylated hemoglobin ≥ 8%) showed positive associations with chronic cough (OR, 11.0; 95% CI, 2.56–47.6; $p = 0.001$) in a community-based cohort of elderly people (aged ≥ 65 years) in Seongnam, Korea [35]. Similarly, in the KNHANES study (2010–2012), adult subjects with chronic cough significantly more frequently had histories of physician-diagnosed DM than those without current cough (13.1% ± 1.8% vs. 6.1% ± 0.2%, $p < 0.001$) [36]. In line with these, in a 3-year follow-up of adult participants aged 45–85 years in the Canadian Longitudinal Study on Aging, participants with DM reported a higher incidence of chronic cough compared to those without DM, even after adjusting for age, sex, and smoking (5.5 per 100 person-years [95% CI, 5.0–6.1 person-years] vs. 4.6 per 100 person-years [95% CI, 4.3–5.0 person-years]) [13]. In the Copenhagen General Population Study, the prevalence of DM was higher in those having chronic cough compared to those without chronic cough both in non-obese (6% vs. 3%, $p < 0.001$) and obese patients (19% vs. 11%, $p < 0.001$) [25].

Although their associations were consistently observed in different populations, the mechanisms remain speculative but might be explained either by their shared abnormal neuronal physiology or neuropathic changes or by the risk of reflux. Various factors such as obesity, glycemic control status, diabetic complications, esophageal dysmotility, gastropathy, or other neuropathic conditions should be taken into consideration when investigating their relationships further [37].

### COVID-19

The ongoing coronavirus disease 2019 (COVID-19) pandemic was declared by the World Health Organization in March 2020. Given the limited supply of vaccines and rapidly developed genetic mutations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it is expected that the number of infected individuals will keep growing [38, 39]. Together with the loss of smell and taste, cough is a hallmark symptom of acute COVID-19. However, it is now apparent that there is a substantial number of patients who complain of chronic symptoms, including cough that persists for months or a year even after recovery from acute COVID-19, a phenomenon known as “post-COVID syndrome” or “long COVID.” Cough is one of the common symptoms of the post-COVID syndrome, along with fatigue, anosmia, and dyspnea. The pooled prevalence of persistent cough was calculated with 18% (95% CI, 12%–24%; $I^2 = 93\%$) from 14 studies of hospitalized patients at 8 weeks to 4 months after discharge [40].

Cough in viral infection is important as it is not only distressing to patients but also increases the risk of transmission. During the COVID-19 pandemic, patients with cough (of any etiology) can get stigmatized and socially isolated due to the fear of contagion among people [41]. Despite the significance, the mechanisms of COVID-19-related cough remain largely unknown. COVID-19-related cough might result from the invasion of vagal sensory neurons by SARS-CoV-2 or a neuroinflammatory response, or both, leading to peripheral and central hypersensitivity in the cough regulation pathways [40]. Patients with the post-COVID-19 syndrome may have central sensitization, as many of them have an array of symptoms such as pain, cough, breathlessness, or fatigue, in the absence of persistent tissue injuries. However, further studies on why this phenomenon occurs are warranted [40, 42].


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## UNDER-RECOGNIZED REGIONAL ISSUES IN THE ASIA-PACIFIC REGION

### Indoor air pollution

The associations between ambient air pollution and chronic cough were previously reviewed [43]. However, household air pollution is another ongoing issue in developing countries, including those in the Asia-Pacific region. Indoor air pollution is associated with various respiratory and cardiovascular diseases, along with increased mortality. Especially in low-to-middle-income countries, the use of biomass fuels for cooking and heating threatens children and women [44]. In particular, the South-East Asia region reported a mean value of 23.3 (95% CI, 13.7–34.4) million disability-adjusted life-years lost, which was the highest among the WHO regions, and 0.57 (0.34–0.84) million deaths [45]. A significantly higher frequency of cough in biomass fuel users than in clean gas fuel users (7.8% vs. 1.6%, $p = 0.002$) was noted in Bangladesh women. In never-smoking women in India, chronic bronchitis was associated with cooking with solid biomass fuel (OR, 1.96; 95% CI, 1.06–3.64; $p = 0.031$). Meanwhile, exposure to indoor air pollutants is also a relevant issue in high-income countries [46]. Although solid fuel is less used, cooking and heating produce various air pollutants. Moreover, indoor smoking, cleaning chemicals, and mold consist of indoor air pollution. One can speculate that the older female predominance among patients with chronic cough might be attributed to cumulative exposure to household air pollution [47]. However, research on the impact of household air pollution has largely focused on the development of respiratory diseases and decline of pulmonary function rather than that of chronic cough [48, 49].

It remains uncertain whether the exposure finally leads to the status of persistent hypersensitivity in the cough reflex although there are explicable mechanisms of respiratory diseases induced by indoor air pollution, such as neutrophilic inflammation, oxidative stress, and increased matrix metalloproteinase activity [48]. There is also a methodological challenge in studying causal relationships between exposure to air pollutants and chronic cough; with a cross-sectional study design, it is difficult to differentiate whether coughing is a physiologic response against pollutant exposure or the long-term result of neuronal inflammation and subsequent hypersensitivity. Individual susceptibility may also be attributed to genetic factors. The risk of the development of asthma and the decline of lung functions after the long-term exposure to indoor air pollution reportedly varied according to glutathione S-transferase gene polymorphism [49, 50]; however, there is no such study on chronic cough so far.

### Increasing prevalence of reflux disease in East Asian countries

The etiologies of chronic cough may change over time. The prevalence of reflux-associated cough was reported to be less than 5% in East Asian countries; however, the prevalence of reflux-related cough has been anticipated to steadily increase given the increase in the prevalence of obesity, GERD, and the number of people adopting the Western lifestyle and diet in the region [51, 52]. In a retrospective review of patients with chronic cough from 2009 to 2016 at a single respiratory clinic in China, the proportion of reflux cough increased significantly from 15.4% to 40.7% (the diagnosis was made based on the combination of daytime cough, results of the intraluminal impedance-pH monitoring, and responsiveness to anti-reflux medication or additional neuromodulators) [53]. Similarly, studies from Japanese cough clinics reported a rise in the prevalence of GERD in patients with chronic cough from 2% to 11.5% over 2 decades, when diagnosed by treatment response to proton-pump inhibitors (PPIs) and/or positive results of 24-hour ambulatory esophageal pH monitoring [54].


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The limited efficacy of PPIs on cough and even on reflux symptoms suggests a minor contribution of acid reflux to chronic cough but rather larger roles of nonacid or gaseous reflux and the involvement of neuronal hypersensitivity both in cough and typical esophageal symptoms [55, 56]. Recent randomized clinical trials evaluating the efficacy of bile acid sequestrant, IW-3718, as an add-on therapy of PPIs in patients with refractory GERD reported improvements in both the frequency and severity of cough, despite the uncertainty of clinical significance [57]. When further classifying GERD into reflux esophagitis and nonerosive reflux disease, the latter is associated with female predominance, enhanced perceptions of reflux in the presence of gas in refluxate, and a poor response to PPIs, which gain more attention due to challenging management among gastroenterologists [58, 59]. In a study of Japanese patients with subacute or chronic cough, coexisting GERD was associated with a longer duration of cough, slower treatment response, and poorer QoL [60]. Although there is no simple method of confirming causal relationships between reflux and cough, detailed phenotyping of reflux disease and chronic cough may help to identify a common pathophysiology and potential therapeutic targets in reflux cough.

### Pulmonary tuberculosis

A number of Asian countries are still endemic areas of pulmonary tuberculosis (TB) with the additional burden of drug-resistant cases [61]. In pulmonary TB, coughing is a key manifestation suggesting current infection and means of transmission [62]. Therefore, for those from populations of high TB prevalence, active case finding is recommended for patients with cough to improve clinical outcomes and reduce transmission [63]. Despite the important roles of cough at the early phase of TB infection, its clinical relevance and longitudinal course have been rarely described. The recent introduction of cough monitors enabled an objective analysis of the clinical relevance of cough frequency in patients with pulmonary TB, reporting that cough frequency was positively related to the volume and proximity to the airway of the cavity, as well as the bacillary load [64]. Appropriate treatment significantly reduced cough frequency along with microbiological conversion, although cough persisted in some participants after anti- TB treatment [65]. However, the longitudinal course or clinical significance of post-TB cough is largely unknown, especially in relation to the development of drug resistance, pulmonary sequelae, or relapse. Structural changes in the lungs that develop post-TB, such as bronchiectasis, may be associated with cough; in the KNHANES 2007–2009, cough was significantly more frequent in post-TB patients with bronchiectasis than in those without bronchiectasis (23.9% vs. 6.7%, $p = 0.033$) [66]. Considering the increasing awareness of cough as a key symptom of TB, the clinical relevance, impact, and longitudinal course of cough needs to be evaluated in patients with current or past pulmonary TB [67].

### Pulmonary paragonimiasis

Although parasitosis is an unusual cause of chronic cough [68], pulmonary paragonimiasis may be one of the differential diagnoses that should not be neglected in some Asian countries, which might be mistaken for pulmonary TB or lung cancer due to similarities in initial clinical presentation [69]. The consumption of raw freshwater crabs and crayfish leads to relatively frequent cases of paragonimiasis in some Asian countries such as Korea, China, Japan, Taiwan, and the Philippines [70]. Although the majority of cases are combined with abnormal chest images, according to the retrospective studies in Korea, chest x-rays can be normal in approximately 4.2%–8% of infected patients [69, 71]. Considering the endemicity, dietary habit and history of immigration or travel is required not to overlook paragonimiasis in patients with cough that have a history of suspected exposure.


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## ROUTINELY COLLECTED DATA AS A POTENTIAL RESEARCH TOOL IN COUGH EPIDEMIOLOGY

RCD is now an increasingly popular tool to obtain large-scale longitudinal epidemiological data. The most widely used RCD include administrative medical databases and electronic healthcare databases. Administrative medical databases are massive repositories of data collected on a large national or regional healthcare population scale. These databases contain comprehensive information on the relevant healthcare services including medical claims for reimbursement, records of health services, medical procedures, prescriptions, and information on patients' diagnoses [72, 73]. In recent years, they have been increasingly utilized for studies in various scientific disciplines, and data linkage between administrative data and other data sources opens new research opportunities by combining highly reliable administrative records with detailed surveys [74, 75].

Electronic Health Records (EHRs) are secure, private, and lifetime records containing patient-health and points-of-care histories within the healthcare system [76]. EHRs are increasingly used for research, and their fundamental goal is to create a longitudinal patient record with complete information about patients across all aspects of care [77]. Given the growing deployment of EHRs enabling large practice-based longitudinal data mining, advancement in artificial intelligence approaches such as natural language processing (NLP) may also capture unstructured data, analyze the grammatical structure, determine the meaning of the information, and summarize the information. As a result, NLP techniques can extract the information stored in unstructured and nonstandardized formats and potentially enable us to provide in-depth big data analytics [78, 79]. There are studies on the use of EHR/NLP in the field of respiratory medicine, such as childhood asthma and incidental lung nodules [80-83].

Recently, EHRs were integrated by thorough NLP to identify and examine chronic cough [84]. The use of the EHR system of Indiana enabled the identification of patients aged 18 to 85 years from 2005 through 2015. They identified 23,371 patients suffering from chronic cough with a positive predictive value of 97% in the sampled reviews. Notably, NLP alone identified 74% of a cohort of 23,371 patients, whereas the utilization of either the International Classification of Diseases (ICD)-9 or ICD-10 codes for cough (as a symptom code) or medication records specific to cough, such as benzonatate or dextromethorphan alone, only identified 15% of the cases. The use of the NLP improved the rate of detection of patients nearly 7-fold. However, the low yield in identifying the cases using diagnostic or medication codes alone indicates that the use of RCD is currently limited in chronic cough research. Whether RCD can be useful in chronic cough research will rely on the introduction of a proper code for “chronic cough” in the forthcoming ICD system and the demonstration of high-quality data (**Table 1**).

## LONGITUDINAL OUTCOME OF CHRONIC COUGH

It is unknown which future risks are present in patients with chronic cough (**Table 1**). Regarding the long-term persistence of cough, there are a few longitudinal studies [24, 85-88]. The study carried out on 42 patients with unexplained chronic cough in the UK was the first to document longitudinal outcomes [87]. At their 7-year follow-up appointments, only 14% of the patients had complete resolution of symptoms and 26% had significant


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improvements defined by a decrease in the cough visual analog scale score by more than 10 mm. They had an increased rate of decline in forced expiratory volume in 1 second ($FEV_1$), and approximately 10% of them developed fixed airflow obstruction ($FEV_1$/forced vital capacity less than 0.7 from a postbronchodilator test). However, there were no outstanding predictors identified for the persistence or resolution of cough.

In Finland, Koskela et al. [86] undertook a study to investigate the long-term prognosis and its determinants in 68 subjects with chronic cough. After 5 years from the initial assessment, continuing regular cough (on most days of the week) and impairment in cough-related QoL (less than 1.3 point's increase in the LCQ total score) were reported in 46% and 47% of the subjects, respectively. Continuing regular cough and impaired QoL were significantly associated with the number of background disorders such as esophageal reflux disease, asthma, and rhinitis. The baseline mild airway responsiveness to histamine, and strong cough responsiveness to hypertonic saline were also associated with continuing regular cough. Potential determinants of a persistent impairment in cough-related QoL were obesity and atopy.

In a subsequent study of 975 Finnish patients with current cough, cough phenotypes were analyzed using the clustering approach. Two cough phenotypes were identified: cluster A presenting a tendency to heal by itself and cluster B that is more persistent. Interestingly, cluster B was characterized by more cough triggers, more background disorders, and a poorer cough-related QoL. After 12 months of follow-up, 27.0% of the patients in cluster A and 46.1% in cluster B suffered from persistent cough [88].

We conducted a 4-year retrospective cohort study of 323 patients who had newly visited a tertiary cough clinic in Korea [85]. Of them, 19.8% had chronic persistent cough (defined as the presence of current troublesome cough) and 59.8% had remitted cough (having no trouble with their cough during the last 1 year). There were several significant differences between patients with remitted cough and patients with chronic persistent cough, including a family history of chronic cough, cold air-sensitive cough, and 2 items (cough with eating and cough with certain foods) in the Hull Airway Reflux Questionnaire.

In a recent prospective study carried out in Northern Europe involving 13,500 participants in the community, 41.3% of participants with nonproductive or productive cough at baseline also reported chronic cough at the 10-year follow-up [24]. One-third of the participants with nonproductive cough and half of the participants with productive cough at baseline reported chronic cough at follow-up. However, this study did not identify the predictors of cough persistence.

To summarize, there are only a few studies that have reported the long-term outcomes (mostly cough persistence) of patients with chronic cough (**Table 2**). It is difficult to draw any firm conclusion due to the heterogeneity of the study population, outcome definition, or measured risk factors; however, the study findings suggest that (1) a considerable proportion of patients (20%–60%) may persistently suffer from chronic cough for longer than several years and (2) certain clinical characteristics such as background disorders or cough hypersensitivity (as measured by the number of cough triggers or hypertonic saline responsiveness) might influence the persistence of cough for years. Further prospective studies are warranted to confirm these results.


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**Table 2.** Summary of patient cohort studies reporting longitudinal outcome in patients with chronic cough

| Study | Country | Study design and recruitment setting | Patients, n | Follow-up duration | Outcomes | |
|---|---|---|---|---|---|---|
| | | | | | Follow-up of cough | Risk factors for cough persistence, with odds ratios (95% confidence intervals) |
| Yousaf et al. 2012 [87] | UK | Retrospective cohort, based on a specialist cough clinic | 42 Patients with unexplained chronic cough | 7 Years | • Complete resolution: 14%<br>• Improvement: 26%<br>• No change: 24%<br>• Worsening: 36% | - |
| Koskela et al. 2017 [86] | Finland | Prospective cohort, based on a tertiary referral clinic, with newspaper advertisements | 68 Patients with chronic cough (>8 weeks) | 5 Years | • Continuing regular cough (on most days of the week at follow-up): 46%<br>• Continuing impairment in cough-related QoL: 47% | For continuing regular cough (vs. no)<br>• Response-to-dose ratio to histamine at initial assessment (calculated per one %/mg): 0.19 (0.06–0.65)<br>• Coughs-to-dose-ratio to hypertonic saline at initial assessment (calculated per one cough/Osm/kg): 2.4 (1.0–5.6)<br>• Chronic rhinitis or reflux disease: 8.0 (2.2–29)<br>For continuing impairment in cough-related QoL (<1.3 points increase in the LCQ) (vs. no)<br>• Body mass index at initial assessment (calculated per one kg/m$^2$): 1.5 (1.2–2.0)<br>• Atopy (vs. no atopy): 0.19 (0.04–0.84) |
| Koskela et al. 2020 [88] | Finland | Prospective cohort, based on a community-based survey of public service employees | 975 Patients with current cough | 1 Year | • Continuing cough at 12 months (that continued without interruptions): 36%<br>27% in cluster A<br>46.1% in cluster B* | For continuing cough at 12 months (vs. no)<br>• Cluster B*: 2.31 (1.52–3.53) |
| Kang et al. 2020 [85] | Korea | Retrospective cohort, based on a specialist cough clinic | 323 Patients with chronic cough (>8 weeks) | 4 Years | • Chronic persistent cough (troublesome cough that is persistent for longer than 25% of the last 1 year): 20%<br>• Remitted cough (no trouble with cough during the last 1 year): 60% | For chronic persistent cough (vs. remitted cough)<br>• Cough duration (months): 1.003 (1.000–1.006)<br>• Cough with certain foods (0–5; HARQ, Q10†): 1.08 (0.89–1.33)<br>• Cough with eating (0–5; HARQ, Q9†): 1.22 (1.02–1.45)<br>• Cold air-sensitive cough (vs. no): 2.01 (1.09–3.73)<br>• Family history of chronic cough (vs. no): 4.27 (1.35–9.89) |

QoL, quality of life; RDR, response-to-dose ratio; CDR, coughs-to-dose-ratio; LCQ, Leicester Cough Questionnaire; HARQ, Hull Airway Reflux Questionnaire. *Two clusters were identified using k-means method. Compared to cluster A, cluster B was characterized by more cough triggers, more background disorders, and poorer cough-related QoL. †Each item in the HARQ is scored between 0 and 5 (0, no problem; 5, severe/frequent problems).

## CLOSING REMARKS

Here, we reviewed recent epidemiological studies for chronic cough, focusing on the disease burden, risk factors, regional issues (indoor air pollutant, reflux, TB, and parasitosis), and longitudinal outcomes. Chronic cough is a prevalent condition with a significant impact on the QoL, and the disease burden is increasingly evaluated and quantified. With the introduction of a concept of cough reflex hypersensitivity and central sensitization in chronic cough, its associations with pain, pruritus, or neuropathic conditions have been explored in community-based population studies. Also, there have been attempts to investigate the epidemiology of chronic cough using a longitudinal cohort or large healthcare databases. However, there are several methodological issues that should be resolved before further progress can be made, especially in case definitions and outcome definitions.

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