Review Article on Novel Insights into Chronic Cough

Worldwide prevalence, risk factors and burden of chronic cough in the general population: a narrative review

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Background and Objective: Chronic cough is one of the commonest complaints requiring medical attention that significantly impacts on the patient's quality of life. In this review, we focus on chronic cough prevalence, risk factors, and health burden among the general adult population based on recent reports, which will be helpful for a better understanding of the global burden of chronic cough.

Methods: A narrative search of Medline was performed for articles and their lists of references published using the keywords "chronic cough", "chronic bronchitis", "epidemiology", "prevalence", "risk factor", "burden", "quality of life", "adult" and "general population".

Key Contents and Findings: Although there is a growing literature on the prevalence of chronic cough in the general population from different countries, the prevalence of chronic cough in different populations cannot be directly compared because of the use of varying definitions of chronic cough. Generally, the prevalence of chronic cough is higher in Europe and North America than in Asia. Regarding the risk factors for chronic cough, several have been identified, including age, smoking, asthma, allergic rhinitis, and rhinosinusitis, whereas for other imputed factors, such as occupational exposure, air pollution, and obesity, these remain inconclusive. Although chronic cough is usually not life-threatening, the physical and psychological impact of chronic cough is obvious, leading to substantial healthcare resource utilization, especially for the elderly or those with comorbidities.

Conclusions: Chronic cough is a common symptom in the general population that can be associated with a deterioration of quality of life and with increased burden. The identification of risk factors and associated co-morbidities will help towards an improved management of this condition. There is an urgent need to apply the standard definition of chronic cough in future research, so that comparisons of the prevalence and other findings across populations can be made.

Keywords: Chronic cough; prevalence; risk factor; burden; quality of life

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Introduction

Cough is a vital protective reflex of the respiratory tract important for upper airway clearance (1-3). However, chronic cough may cause physical and psychological adverse effects on patients, when the cough is persistent (1). Chronic cough is one of the most frequent reasons for patients to request for a medical consultation (1,4), for example, accounting for more than one-third of the outpatient visits to respiratory clinics in China (5).

Chronic cough is present in many pulmonary conditions

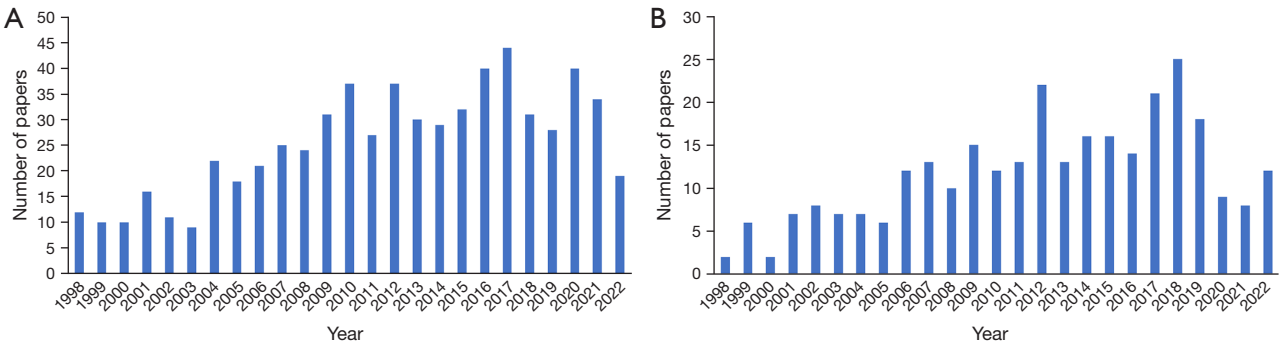

Figure 1 The number of papers on the prevalence of cough in the general population since 1998. (A) The number of papers on the prevalence of cough. A systematic search was performed using the terms in PubMed, as "Humans"[Mesh] AND "Cough"[Mesh] AND "Prevalence"[Mesh] AND ("1998/01/01"[Date - Publication]: "2022/10/08"[Date - Publication]). (B) The number of papers on the prevalence of chronic cough. A systematic search was performed using the terms in PubMed, as "Humans"[Mesh] AND "Prevalence"[Mesh] AND ("Bronchitis, Chronic"[Mesh] OR ("Chronic Disease"[Mesh] AND "Cough"[Mesh])) AND ("1998/01/01"[Date - Publication]: "2022/10/08"[Date - Publication]).

such as asthma, pulmonary fibrosis, lung cancer, or chronic obstructive pulmonary disease (COPD), but it is not easy to fit into these diagnostic labels for most of patients with chronic cough (6). Although the most common causes of chronic cough are considered to be upper airway cough syndrome from rhino-sinus conditions, asthma, gastro-oesophageal reflux disease (GORD), and non-asthmatic eosinophilic bronchitis (7), in up to 42% patients, no cause can be identified (8). On the other hand, there is increasing evidence that chronic cough is a clinical syndrome with distinct pathophysiology characterized by neuronal hypersensitivity (3,6,9,10). Additionally, the adverse impact of chronic cough on quality of life is under-recognized by clinicians, according to a European Respiratory Society (ERS) survey (11).

In view of this, chronic cough has gained increasing attention in the late 20 years, with an increase in studies of the epidemiology, etiology, diagnosis, treatment, and management of chronic cough carried out worldwide since the first Cough Guideline published in 1998 (12), leading to increasing numbers of publications on the prevalence of cough in the general population that confirm an increased trend (*Figure 1*). Based on these reports, Song and colleagues reported that the global prevalence of chronic cough was 9.6% by pooled analyses in 2015 (13). Since then, some data from epidemiological surveys on chronic cough conducted in different countries have been published. In this review, we focus on chronic cough prevalence, risk factors, and health burden among the general adult population based on recent reports, that provide data for a better understanding of the burden of chronic cough in the general adult population. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1435/rc).

Methods

We searched Medline (PubMed interface) for relevant articles and their lists of references published in English using the key words of "chronic cough", "chronic bronchitis", "epidemiology", "prevalence", "risk factor", "burden", "quality of life", "adult" and "general population". Citations from 2015 to 2022 were preferably referenced whenever possible. Further details of the literature search are described in *Table 1*.

Discussion

Prevalence

There have been different definitions of chronic cough. Earlier studies (14,15) used the definition of chronic cough as lasting for at least 3 months based on the Medical Research Council definition of chronic bronchitis (16), while more recently, both the ERS and the American College of Chest Physicians (CHEST) guidelines adopted a definition of cough of more than 8 weeks' duration (2,7). Defining chronic cough based on different duration of chronic cough is an arbitrary paradigm (2), that increases

Table 1 The search strategy summary

Items	Specification
Date of search	8 October 2022
Databases and other sources searched	Medline (PubMed interface)
Search terms used	"Chronic cough", "chronic bronchitis", "epidemiology", "prevalence", "risk factor", "burden", "quality of life", "adult" and "general population"
Timeframe	From 1 January 2015 to 8 October 2022
Inclusion and exclusion criteria	Inclusion criteria: Original Article, Research Article, Review, English language only
	Exclusion criteria: Editorial, Comments, Letters, Proceedings, Case reports, Full paper, Non-English papers
Selection process	Xuwen Yang did the initial literature search with subsequent help from all authors

the difficulty of comparing the prevalence of chronic cough in different studies using different definitions. The prevalence of chronic cough in the general population in different countries from recent studies is shown in *Table 2*.

Several studies have adopted the definition of cough lasting for at least 3 months (17,18). Abozid and colleagues (17) used cross-sectional baseline data from the Lung, hEart, sociAl, boDy (LEAD) cohort conducted in Austria, and found that the prevalence of chronic cough was 9% in subjects aged 18 to 80 years and that it increased with age. No sex predominance in the total study population was observed, but women were predominant in never smokers with 68.4% prevalence. The study also identified that almost 66% of chronic cough individuals were overweight or obese, and the prevalence of chronic cough in participants taking an angiotensin-converting enzyme inhibitors (ACEI) was 13.6%.

In the Rotterdam Study (18), the overall baseline period prevalence of chronic cough was 10.9% and increased with age among subjects aged ≥45 years. There were no significant sex-specific differences in the overall study population, but in subjects aged <70 years chronic cough was more common in women.

A meta-analysis based on several Chinese studies showed that the prevalence of chronic cough was 6.22% in Chinese adults (5). However, the studies included in this pooled analysis were of small sample sizes often conducted in specific regions of China and used different diagnostic criteria and sampling methods. Therefore, this reported prevalence may not represent the real prevalence of chronic cough in China. The China Pulmonary Health (CPH) (19), a national cross-sectional study enrolled 57,779 Chinese adults aged 20 years or older, which defined chronic cough as lasting for >3 months each year, and found that its prevalence was 3.6%, increasing with age from 2.4% in individuals aged 20–49 years to 6.0% in those aged 50 years or older. They also observed a higher prevalence of 4.6% in men compared to 2.6% in women, while the higher prevalence of chronic cough in men was likely to be partly due to the much higher smoking rate of 47.2% in men compared to only 2.7% in women (29).

There are an increasing number of studies that have defined chronic cough based on a duration of more than eight weeks (20-22). The Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2012 reported the prevalence of chronic cough of 2.6% in the general population in Korea (20). Similarly, based on the data from the 2018 National Health and Wellness Survey (NHWS) in the USA through a web-based survey panel, Meltzer and colleagues (21) reported a weighted prevalence of 5.0% of chronic cough defined as cough ≥8 weeks in the past 12 months for those aged 18 years or older. They also found that respondents with chronic cough were older and more predominantly women than those without. A cross-sectional study based on the German NHWS found that the lifetime prevalence of chronic cough was 6.5% and the 12-month prevalence defined as reporting it in the past 12 months was 4.9%, with a higher prevalence in those aged 50 years and older (22).

The Copenhagen General Population Study reported that the prevalence of chronic cough was 4% increasing with age overall among the general population (23). Kubo and colleagues (24) based on the data from the 2019 Japan NHWS and a supplemental chronic cough survey, showed that the 12-month prevalence of chronic cough was 4.29%. Domínguez-Ortega and colleagues (25) reported prevalence

Table 2 Prevalence of chronic cough in the general population in different countries

First author, publication year	Study name	Country	Study year	Population	Sample size	Chronic cough definition	Chronic cough prevalence			
							Overall	Sex	Age	Smoking status
Abozid H, 2022 (17)	The LEAD study	Australia	2012–2016	18–80 years	10,057	Coughing nearly every day for ≥3 months during the last 12 months	9%	Women: 8.3%, men: 9.0% (no P value reported)	NA	Never: 6.0%, former: 7.8%, current: 14.7% (no P value reported)
Arinze JT, 2020 (18)	The Rotterdam Study	The Netherlands	2002–2008	≥45 years	9,824	Coughing for ≥3 months duration during the preceding 2 years	10.9%	Women: 11.2%, men: 10.6% (P=0.369)	45–70 years: 9.5%, ≥70 years: 13.3% (P<0.001)	Never: 8.6%, past: 9.7% (P=0.620), current: 18.6% (P<0.001)
Huang K, 2022 (19)	The CPH study	China	2012–2015	≥20 years	57,779	Coughing last for >3 months in each year	3.6%	Women: 2.6%, men: 4.6% (P=0.0005)	20–49 years: 2.4%, ≥50 years: 6.0% (P<0.0001)	Never: 2.5%, ever: 5.9% (P<0.0001)
Kang MG, 2017 (20)	The KNHANES 2010–2012	South Korea	2010–2012	≥18 years	18,071	Coughing last for ≥8 weeks	2.6%	Women: 2.0%, men: 3.3% (P<0.001)	NA	NA
Meltzer EO, 2021 (21)	The 2018 NHWS	USA	2018	≥18 years	74,977	Coughing last for ≥8 weeks in the past 12 months	5%	Women: 5.2%, men: 4.7% (P=0.01)	18–49 years: 4.4%, 50–64 years: 5.7%, ≥65 years: 5.8% (P<0.001)	Never: 3.4%, current or former: 7.3% (P<0.001)
Virchow JC, 2022 (22)	The German 2020 NHWS	German	2019–2020	≥18 years	15,020	Coughing last for ≥8 weeks and coughing last for ≥8 weeks in the past 12 months	Lifetime: 6.5%; the 12-month: 4.9%	Lifetime: women: 6.7%, men: 6.4% (P=0.412); the 12-month: women: 5.1%, men: 4.7% (P=0.223)	Lifetime: 18–29 years: 8.3%, 30–39 years: 5.6%, 40–49 years: 5.1%, 50–64 years: 6.5%, 65–74 years: 7.0%, ≥75 years: 6.4% (P<0.001); the 12-month: 18–29 years: 4.8%, 30–39 years: 3.9%, 40–49 years: 3.7%, 50–64 years: 5.4%, 65–74 years: 5.7%, 75 years: 5.7% (P<0.001)	Lifetime: never: 4.8%, current or former: 8.0% (P<0.001); the 12-month: never: 3.1%, current or former: 6.4% (P<0.001)
Çolak Y, 2017 (23)	The Copenhagen General Population Study	Denmark	2013–2014	20–100 years	14,669	Coughing last for >8 weeks	4%	NA	20–50 years: 2%, 70–100 years: 5% (no P value reported)	Never: 3%, former: 4%, current: 8% (no P value reported)
Kubo T, 2021 (24)	The 2019 Japan NHWS and a Chronic cough survey	Japan	2019	≥20 years	24,015	Coughing last for >8 weeks in the past 12 months	4.29%	NA	NA	NA
Domínguez-Ortega J, 2022 (25)	The 2020 Spanish NHWS	Spanish	2019–2020	≥18 years	7,074	Coughing last for >8 weeks and coughing last for >8 weeks in the past 12 months	Lifetime: 8.2%; the 12-month: 5.5%	Lifetime: women: 8.6%, men: 7.8% (P=0.229); the 12-month: women: 6.0%, men: 4.9% (P=0.049)	Lifetime: 18–29 years: 10.8%, 30–39 years: 10.6%, 40–49 years: 7.4%, 50–64 years: 7.7%, 65–74 years: 5.7%, ≥75 years: 10.3% (P<0.001); the 12-month: 18–29 years: 5.8%, 30–39 years: 6.4%, 40–49 years: 5.5%, 50–64 years: 5.7%, 65–74 years: 4.1%, ≥75 years: 6.7% (P=0.267)	Lifetime: never: 5.9%, current or former: 9.6% (P<0.001) the 12-month: never: 3.5%, current or former: 6.7% (P<0.001)
Satia I, 2021 (26)	The CLSA Study	Canada	2011–2015	45–85 years	29,972	Self-identified as having coughed most days within the past 12 months	15.8%	Women: 14.5%, men: 17.2% (no P value reported)	NA	Never: 12.5%, former: 15.6%, current: 37.3% (no P value reported)
Maio S, 2019 (27)	A study in Pisa	Italy	Baseline (1991–1993) followed-up 18 years	≥20 years, general population	970	Self-reported usual cough apart from common colds	18.5%	NA	NA	Never: 15.9%, persistent: 21.3%, remittent for <18 years: 13.8%, remittent for ≥18 years: 14.9%, incident: 20.8% (P=0.562)
Wang G, 2021 (28)	The BAMSE study	Sweden	Baseline (1994–1996) followed-up 24 years	General population	2,890	Coughing with phlegm as soon as waking up in the winter morning	5.5%	Women: 5.5%, men: 5.5% (no P value reported)	NA	Never: 4.2%, former: 8.5%, current sometimes: 8.3%, current every day: 18.4% (P<0.001)

LEAD, Lung, hEart, sociAl, boDy; CPH, China Pulmonary Health; KNHANES, Korean National Health and Nutrition Examination Survey; NHWS, National Health and Wellness Survey; CLSA, Canadian Longitudinal Study on Aging; BAMSE, Child (Barn), Allergy, Milieu, Stockholm, Epidemiological; NA, not applicable.

during their lifetime or the previous 12 months in Spanish adults was respectively 8.2% and 5.5%.

There are also a few reports on the prevalence of chronic cough base on no objective definition for the duration of cough (26-28). For example, in the Canadian Longitudinal Study on Aging (CLSA) conducted in Canadians from the general population aged 45–85 years based on self-reported daily cough in the past 12 months (26), the prevalence of chronic cough was 15.8%, which increased with age and current smoking, and was higher in Caucasians compared to participants in the black population and in those with South Asian, Asian and Arab background.

Considering the difference in the definitions of chronic cough used, it is difficult to directly compare the prevalence of chronic cough among different countries or ethnicities. However, one can surmise that the prevalence of chronic cough in Europe and North America is higher than in Asia, which is consistent with the systematic review performed by Song and colleagues in 2015 (13).

Risk factors

Risk factors for chronic cough have been investigated from population-based studies. The risk factors of chronic cough from recent studies are listed in *Table 3*.

Ethnicity

As mentioned above, the prevalence of chronic cough varies among different races or the sexes (13). Nevertheless, whether or not the difference in prevalence is attributed to race or sex itself needs to be determined further. Dicpinigaitis and colleagues (36) evaluated ethnic and sex differences in cough reflex sensitivity measured by capsaicin cough challenge in 182 healthy volunteers of three distinct ethnic groups: Caucasian (white, non-Hispanic, of European origin), Indian (originating from the Indian subcontinent) and Chinese. They found no significant ethnic differences in cough reflex sensitivity, suggesting that the difference in prevalence among different races may be attributed to the influence of other factors, such as asthma, allergy, or environmental factors.

Sex

Women are always over-represented in specialist cough clinics (6,37). Although some studies have shown opposite results in univariate analysis (10,19,20,26), the positive association between male and chronic cough is statistically insignificant after adjustment for smoking status (20), suggesting that it is not appropriate to analyze the influence of gender on the risk of chronic cough separately from the smoking status of the population.

To further clarify whether there is a sex difference in cough sensitivity, cough challenge testing was conducted using capsaicin, citric acid, or tartaric acid in healthy volunteers (6,36,38) and patients with chronic cough (39,40). The results confirmed that there were lower cough thresholds in women than in men. Using functional magnetic resonance imaging (fMRI), Farrell and colleagues (41) measured the brain responses during inhalation of saline and a low and high dose of capsaicin in healthy participants. The study showed that activation in the somatosensory and mid-cingulate cortices correlated with ratings of urge-to-cough and displayed sex-related differences. Women were more sensitive to capsaicin challenge, and even a lower stimulus could create a magnitude of activation in the somatosensory cortex almost twice that of men (6).

Age

Studies from different countries have demonstrated that the prevalence of chronic cough in the adult general population increased significantly with age. For example, the KNHANES 2010–2012 found the prevalence of chronic cough increased from 18–39 years to those aged 65 years or older (OR 2.20, 95% CI: 1.53–3.16) (20). The CPH study also showed that the prevalence of chronic cough is 2.4% among individuals aged 20–49 years and 6.0% among those aged 50 years or older (OR 1.43, 95% CI: 1.26–1.61) (19). Similarly, the Copenhagen General Population Study also observed that the prevalence of chronic cough increased from almost 2% in the age groups 20–50 years to 5% in the age groups between 70–100 years (23). In a worldwide survey on chronic cough patients from cough specialist clinics, 60–69 years was the most frequent age group of presentation (6), while the Rotterdam Study (18) found the prevalence of chronic cough increased with age and peaked in the eighth decade. Besides, Hedlund and colleagues (42) found that age was a significant risk factor for chronic cough with phlegm but not for asthma or other symptoms.

Smoking

Most studies report that smoking is an important risk factor for chronic cough (2,17,18,26,27,43-45). The CPH study reported that ever-smokers defined as having smoked equal to or more than 100 cigarettes in the lifetime had double to triple the risk of chronic cough compared with never-smokers (OR 2.61, 95% CI: 2.10–3.25) (19). Similarly, the

Table 3 Risk factors of chronic cough from different studies

First author, publication year	Study name	Country	Study year	Population	Sample size	Chronic cough definition	Risk factors of chronic cough	Other investigated non-risk factors
Abozid H, 2022 (17)	The LEAD study	Australia	2012–2016	18–80 years, general population	10,057	Coughing nearly every day during the last 12 months for ≥3 months	Age, smoking (former smokers, current smokers), low socioeconomic status, asthma, GORD, upper airway cough syndrome, obesity, obstructive sleep apnea, COPD	Gender, residence area
Arinze JT, 2020 (18)	The Rotterdam Study	The Netherlands	Baseline (2002–2008) followed-up 6 years	≥45 years, general population	6,245	Coughing for ≥3 months during the preceding 2 years	Smoking (current smokers), GORD, asthma, COPD, obstructive airway disease, obesity, chronic rhinosinusitis	Age, gender, smoking (past smokers)
Huang K, 2022 (19)	The CPH study	China	2012–2015	≥20 years, general population	57,779	Coughing last for >3 months in each year	Age, ever-smoking, occupational exposure, history of pneumonia or bronchitis during childhood, allergic rhinitis	Gender, rural resident, biomass use, annual mean PM2.5, educational level, visible mould spots in the current residence, parental history of respiratory diseases, BMI
Kang MG, 2017 (20)	The KNHANES 2010–2012	South Korea	2010–2012	≥18 years, general population	18,071	Coughing last ≥8 weeks	Age, smoking (current smokers), chest X-ray abnormality, chronic rhinosinusitis, asthma, diabetes mellitus	Gender, smoking (former smokers), blue-collar occupation, high household income, pulmonary tuberculosis
Çolak Y, 2017 (23)	The Copenhagen General Population Study	Denmark	2013–2014	20–100 years, general population	14,669	Coughing last >8 weeks	Bronchiectasis, asthma, occupation exposure to dust/fumes, airflow limitation, GORD, upper airway cough syndrome, low income, smoking, low vegetable intake, abdominal obesity, gender	Allergy, pulmonary fibrosis, daily exposure to passive smoking, use of medication for hypertension, overweight, low education, high and low intake of various types of food (red meat, white meat, fast-food and fruits) and beverages (tea, coffee, milk, soda, and alcohol)
Maio S, 2019 (27)	A study in Pisa	Italy	Baseline (1991–1993) followed-up 18 years	≥20 years, general population	970	Self-reported usual cough apart from common colds	Smoking (persistent smoking, incident smoking), occupational exposure (persistent, incident)	Smoking (remittent smoking), occupational exposure (remittent), vehicular traffic exposure
Wang G, 2021 (28)	The BAMSE study	Sweden	Baseline (1994–1996) followed-up 24 years	General population	2,890	Coughing with phlegm as soon as waking up in the winter morning	Parental education, parental smoking during childhood, childhood asthma, pollution at 1–4 years (nitrogen oxides, black carbon)	Gender, age, BMI, electronic cigarette smoking, parental occupation, parental asthma, maternal smoking during pregnancy, premature birth, low birthweight, respiratory syncytial virus infection/pneumonia during infancy, bronchitis during infancy, pneumonia at age 0–4 years, exclusive breastfeeding for ≥4 months
Lytras T, 2019 (30)	The ECRHS study	Europe, USA, Australia and New Zealand	Baseline (1991–1993) followed-up 20 years	20–44 years, general population	8,794	Coughing during the day, or at night, in the winter, and on most days for ≥3 months annually	Occupational exposures (metals, mineral dust, herbicides, chlorinated solvents), smoking	Occupational exposures (biological dust, gases and fumes, vapours, gases, dusts and fumes, insecticides, fungicides, all pesticides, aromatic solvents, other solvents)
Doiron D, 2021 (31)	The Lifelines cohort study	The Netherlands	2006–2013	18–93 years, general population	132,595	Coughing in winter when getting up, during daytime or at night almost daily for ≥3 months a year	Ambient air pollution exposure (black carbon)	Ambient air pollution exposure (PM2.5, nitrogen dioxide)
Landt EM, 2022 (32)	The Copenhagen General Population Study	Denmark	2003–N/A	20–100 years, general population	33,577	Coughing last for >8 weeks	BMI	NA
Kim TH, 2022 (33)	The 2019 KNHANES	South Korea	2019	≥40 years, general population	4,217	Self-reported coughing for ≥3 months	Age, smoking (current-smoker), asthma history, FEV_1%pred, house income, educational level, economic activity	Gender, BMI, hypertension, diabetes mellitus, allergic rhinitis history, sinusitis history
Arinze JT, 2021 (34)	The Rotterdam Study	The Netherlands	Baseline (2009–2014) followed-up 2016	≥45 years, general population	2232	Coughing daily for ≥3 months	Chronic pain status (weekly, monthly, daily)	NA
Saeed MA, 2020 (35)	The NHANES study	USA	2007–2012	20–79 years, general population	13,147	Coughing on most days for ≥3 consecutive months during the year	Dietary fiber intake	NA

LEAD, Lung, hEart, sociAl, boDy; GORD, gastro-oesophageal reflux disease; COPD, chronic obstructive pulmonary disease; CPH, China Pulmonary Health; PM2.5, particulate matter with a diameter of less than 2.5 μm; BMI, body mass index; KNHANES, Korean National Health and Nutrition Examination Survey; BAMSE, Child (Barn), Allergy, Milieu, Stockholm, Epidemiological; ECRHS, European Community Respiratory Health Survey; FEV_1%pred, FEV_1 %predicted; NHANES, National Health and Nutrition Examination Survey; NA, not applicable.

Copenhagen General Population Study (23) showed that smoking was not only a risk factor of chronic cough at the level of the individuals (OR 1.5, 95% CI: 1.2–1.8), but also was the first ranked risk factor for the chronic chough at the level of the community with a 20% of attributable risks (PARs). A systematic review (46) recently showed that compared with never smoking, current smoking at baseline was strongly associated with higher odds of chronic cough [pooled adjusted RR (aRR) =1.97, 95% CI: 1.68–2.27].

Several longitudinal cohort studies lasting more than 10 years have observed the relationship between changes in smoking habits and the cumulative incidence of chronic cough, and found that current smokers at follow-up (i.e., none-to-current and current-to-current smokers) had higher incidence of cough than never-to-never smokers, while ex-to-ex and current-to-ex smokers were not significantly different from never-to-never smokers (14,27). Meanwhile, the above studies showed that the incidence of chronic cough was dependent on the total smoking consumption, with a dose-dependent response relationship. Furthermore, these studies demonstrated that those with chronic cough could benefit from quitting smoking. Wang and colleagues assessed the role of second-hand tobacco smoking in chronic cough, and observed that parental smoking during childhood was slightly associated with a higher risk of chronic cough with phlegm in early adulthood (28).

Occupational exposure

The evidence for high-risk occupational exposures for chronic cough remains limited and inconsistent. The long-term health consequences of inhalation exposures in these jobs remain largely unexplored and need further investigation to draw firmer conclusions. The data of approximately 3-year follow-up from the Atherosclerosis Risk in Communities (ARIC) study showed that risks of new-onset chronic cough were elevated in mechanics and repairers (RR 1.81, 95% CI: 1.02–3.21) and cleaning and building service workers (RR 1.85, 95% CI: 1.01–3.37), compared to a referent category of managerial and administrative support occupation (47). The CPH study also showed that occupational exposure defined as exposure to dust, allergens, and noxious gases (e.g., mining, forging, chemical industry, cement, greenhouse planting) for >3 months increased the risk of chronic cough by 40% (OR 1.41, 95% CI: 1.10–1.80) (19).

However, the European Community Respiratory Health Survey (ECRHS) (30) reported that any exposure to metals (RR 1.70, 95% CI: 1.16–2.50), mineral dust (RR 1.35, 95% CI: 0.99–1.83), and chlorinated solvents (RR 1.21, 95% CI: 0.81–1.81) was associated with the higher incidence of chronic cough patients with phlegm, while the associations were generally weaker for chronic cough patients without phlegm, except for exposure to metals (RR 1.29, 95% CI: 1.02–1.64).

Air pollution

Chhabra and colleagues (44) found that the pollution zone defined by total suspended particulates was not an independent determinant for chronic cough. Likewise, the CPH study showed that exposure to high concentrations of particulate matter with a diameter of less than 2.5 μm (PM2.5) ≥75 μg/m^3 and biomass use was not associated with the prevalence of chronic cough (19). However, the Lifelines cohort study showed weak associations for chronic cough with exposure to ambient black carbon (BC) (aOR 1.05, 95% CI: 1.02–1.08), compared to exposure to nitrogen dioxide (NO_2) and PM2.5 (31).

As for the pollution caused by traffic, Maio and colleagues (27) found that self-reported state of the vehicular traffic exposure change during an 18-year follow-up was not a risk factor for chronic cough. On the contrary, using the distances between home addresses and the nearest major roads as the dose indicator for traffic-related air pollution exposure, Hu and colleagues (48) observed that people who live near major roads in Beijing have a higher prevalence of chronic cough, suggesting the risks of long-term exposure to traffic-related air pollution.

In addition, little is known about the effect of a reduction in air pollutants on chronic cough. Schikowski and colleagues (49) used data from the Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) cohort study conducted in Germany, and found that the decreased ambient air concentrations of particulate matter with aerodynamic size <10 microns (PM10) during the study period was associated with a decrease in prevalence of chronic cough among middle-aged women.

In general, the correlation between air pollution and chronic cough has been inconclusive, and there may be several reasons for the inconsistency. One of the reasons is that the air pollution in these studies was mainly defined by only one measure of PM2.5 or PM10 level averaged over a certain period of time within the geographical region of the participant, but the amount of personal exposure to PM2.5 or PM10 and to other constituents of air pollution may be more important in relation to the underlying cough response. Thus, the impact of air pollution on chronic

cough needs to be investigated further.

Body weight

Obesity has been regarded as a potential risk factor for chronic cough (18,23,26,32), particularly abdominal obesity (OR 1.4, 95% CI: 1.2–1.7) (23). It is also a common risk factor for asthma, GORD, obstructive sleep apnoea, upper airway cough syndrome and type 2 diabetes, which are all related to some extent to chronic cough (50-52). Landt and colleagues (32) reported there was a dose-response relationship between body mass index (BMI) and chronic cough, and chronic cough risk was two- to three-fold higher in obese individuals from the general population from the Copenhagen General Population Study, and this increased risk was partly mediated by GORD, low vegetable intake and occupational exposure. However, the CPH study (19) demonstrated that BMI was not associated with the prevalence of chronic cough in the general adult population, and these results were consistent with another study conducted in Korea. Using the data from the 2019 KNHANES, Kim and colleagues (33) reported there was no significant relationship between BMI and the occurrence of chronic cough using a multivariate analysis. These inconsistent findings between Eastern and Western populations may be attributed partly by the higher proportion of vegetables in Eastern diet compared to the Western diet (53), because vegetables and fruits are the major food sources of antioxidants which are helpful to protect the lung from oxidative stress (54) and independently associated with less symptoms of cough with phlegm (55). A recent study also showed that against the background of abdominal obesity, the risk of chronic cough with phlegm increased with the serum levels of some adipokines such as lipocalin-2 and glucose-dependent insulinotropic polypeptide (GIP) and tumor necrosis factor-alpha (TNF-α) (56). We therefore cannot exclude the potential link between the various fat components and chronic cough, which needs to be further studied in the future.

Although lifestyle therapy such as losing weight is an effective treatment for patients with asthma (58) and GORD (56) in improving symptoms, weight loss is not recommended in the latest guideline for chronic cough (2,7). Therefore, further longitudinal studies are urgently needed, focusing on the potential interactions between obesity, weight loss, asthma, GORD, obstructive sleep apnoea, upper airway cough syndrome, and diabetes, as well as chronic cough.

Socioeconomic status and education

The ECRHS (59) study found that chronic cough with phlegm was associated with low educational level (OR 1.9, 95% CI: 1.4–2.8). Besides, Eagan and colleagues (15) demonstrated that subjects with a primary educational level have a higher risk of chronic cough (aOR 1.4, 95% CI: 0.9–2.3), compared to subjects with a university educational level. Based on the LEAD longitudinal study conducted in the general Austrian population, Abozid and colleagues (17) found that participants with chronic cough were associated with lower socioeconomic status (OR 1.6, 95% CI: 1.2–2.0). Accordingly, a systematic review (46) recently concluded that there was a significant association between low education level and high risks of chronic cough (aOR 2.06, 95% CI: 1.42–2.88). Thus, all the above studies have reached a consistent conclusion that socioeconomic status and education level are closely related to chronic cough.

Asthma or atopy

Cough variant asthma is the top-ranked cause of chronic cough (60). On the other hand, asthma and bronchial hyper-responsiveness (BHR) were also one of the most common risk factors for developing chronic cough (18,46). Airway inflammation characterized by upregulated IL-5 expression has been regarded as the potential mechanism for BHR in asthma, and studies have shown that chronic cough and eosinophilic bronchitis may have the same mechanism (61,62). In addition, Hedlund and colleagues (42) found that a family history of asthma was significantly associated with the incidence of chronic cough with phlegm (OR 1.6, 95% CI: 1.3–2.1) in middle age.

Atopy is one of the common reasons for chronic cough, which could take the form of allergic rhinitis and atopic dermatitis, as examined by skin prick tests or serum IgE levels. Using cross-sectional data, Terho and colleagues (45) observed that chronic cough with phlegm was related to allergic rhinitis or allergic dermatitis diagnosed by a doctor (RR 1.41, 95% CI: 1.20–1.65). Similarly, Guerra and colleagues (63) also found that rhinitis was associated with an increased risk for chronic cough (OR 1.7, 95% CI: 1.1–2.6) apart from colds among adults. The CPH study showed that people with allergic rhinitis had nearly triple the risk for chronic cough compared with those without allergic rhinitis (OR 2.84, 95% CI: 1.98–4.09) (19). However, several longitudinal studies showed that there was no evidence of the association between skin prick tests or serum IgE levels and chronic cough (64,65).

COPD, GORD, ACEI, and sleep-disordered breathing

The Rotterdam Study (18) showed that the risk of developing chronic cough was significantly increased in subjects with GORD (OR 1.34, 95% CI: 1.01–1.78) and COPD (OR 2.52, 95% CI: 1.70–3.71), suggesting they were independent risk factors for chronic cough. However, how precisely causative this relationship remains open to confirmation, and further longitudinal data are needed to determine whether COPD without chronic bronchitis itself is an independent cause of cough (46). The use of ACEI is a common cause of chronic cough. The Rotterdam Study showed that the prevalence of chronic cough was significantly higher in ACEI users (13.3%, 95% CI: 11.8–14.9) than in non-users (10.4%, 95% CI: 9.7–11.1) (18). Chan and colleagues (66) demonstrated that chronic cough is a common symptom associated with sleep-disordered breathing. Another study conducted in Korea found that persons snoring 5 times per week or less (RR 1.25, 95% CI: 0.95–1.64) and those snoring 6 to 7 times per week (RR 1.68, 95% CI: 1.17–2.42) had an increased risk of chronic cough with phlegm compared with never snorers (67). Additionally, Arinze and colleagues (34) also identified that prevalent chronic pain was significantly associated with incident chronic cough (OR 1.47, 95% CI: 1.08–1.99) after adjustment for potential confounders, indicating a shared mechanism between the two conditions.

Other factors

Unlike most studies mentioned above, there were also some studies focusing on the protective factors for the occurrence of chronic cough. For example, a systematic review showed beneficial associations of fresh fruit and vegetable intake with chronic cough (46), which may be attributed to the antioxidant vitamins in fresh vegetables and fruits (54). Additionally, a cohort study of 63,257 middle-aged Chinese population in Singapore demonstrated that the intake of more non-starch polysaccharides, a major component of dietary fiber, certain non-citrus fruits (e.g., apples, grapes) and total soya isoflavones was independently associated with reduced development of cough with phlegm (55). Similarly, based on the National Health and Nutrition Examination Survey (NHANES) from the USA, Saeed and colleagues (35) found that a diet with low fiber intake was associated with an increased odds of chronic cough (OR 1.7, 95% CI: 1.2–2.3) compared to high fiber intake. Besides, exclusive breastfeeding for more than 4 months was found to be a protective factor with lower odds of chronic cough (aOR 0.66, 95% CI: 0.44–0.99), however, it became nonsignificant after excluding the subjects with current asthma (28).

Disease burden of chronic cough

Chronic cough is believed to have a high disease burden both directly (economic burden, healthcare resource utilization) and indirectly (comorbidities and concomitant symptoms, lung function, impact on life quality).

Economic burden

Health costs resulting from having chronic cough has been evaluated both in high income and low income countries. A case-control study (68) based on the data from the PharMetrics Integrated Database in the US reported that chronic cough patients with phlegm had high total costs for 12 months prior to diagnosis and 24 months post-diagnosis. The heaviest economic burden for chronic cough patients with phlegm compared to those without occurred during the 6 months post-diagnosis (US$12,781 *vs.* US$3,862). Sichali and colleagues (69) based on the general population in Malawi reported that the mean care-seeking cost per patient with chronic cough was US$3.90 in a 12-month period, and it was 2.3 times the average per capita expenditure on health of US$1.69. The largest costs for the patient with chronic cough were due to transport (US$1.4), followed by drugs (US$1.3).

Healthcare resource utilization

Using the Kaiser Permanente Southern California (KPSC) Research Data Warehouse, Zeiger and colleagues (37) found that the patients with chronic cough had more healthcare resource utilization, including emergency department (ED) visits from all causes (28.4% *vs.* 23.4%) and respiratory causes (12.9% *vs.* 5.0%), and had more visits to at least 2 different specialty departments (39.6% *vs.* 5.7%) compared with the patients without cough. In addition, the frequency of laboratory examination in patients with chronic cough is higher, including spirometry, allergy radioallergosorbent test, advanced chest imaging, laryngoscopy, and sinus imaging. Further, those with chronic cough used more respiratory and non-respiratory medications.

Similarly, a case-control study based on the data from the PharMetrics Integrated Database in US found that chronic cough patients with phlegm had 5.6 times more hospitalizations and 3.1 times more ED/urgent care visits (68). The CPH study (19) showed that 3.5% or 5.5% of people with chronic cough reported at least one emergency

room visit or hospital admission in the past 12 months respectively due to an exacerbation of respiratory symptoms, which were significantly higher than those without chronic cough of 0.5% for emergency room visit and 0.4% for hospital admission respectively, and the impact of chronic cough on hospital admission was significantly among those with COPD or small airway dysfunction (SAD) than those without COPD or SAD. A similar finding was reported by Çolak and colleagues (70) who investigated the role and impact of chronic cough in individuals with asthma from the general population, and found that those with chronic cough versus those without chronic cough in individuals with asthma had greater health care utilization.

Comorbidities and concomitant symptoms

Using administrative pharmacy and medical data from the KPSC Research Data Warehouse, Zeiger and colleagues (37) reported that the most common cough comorbidities for patients with chronic cough were respiratory disease and GORD. In more detail, the non-respiratory comorbidities of chronic cough were 44.1% for GORD, 41.9% for hypertension, 24.3% for obesity, and 20.3% for depression, while the respiratory comorbidities attained a frequency of 32.7% for allergic rhinitis, 31.5% for chronic rhinitis, 31.2% for asthma. Other surveys from Finland and Denmark reported similar results (23,71).

The Copenhagen General Population Study (23) reported that the concomitant symptoms accompanying chronic cough were dyspnoea (54%), sputum production (47%), wheezing (40%), and chest pain or tightness (8%). In China, the most common concomitant symptom of chronic cough was sputum production (67.5%), secondly dyspnea (24.6%), and wheezing (21.0%), with only 22.6% of subjects with a chronic cough having neither phlegm nor dyspnoea and wheeze based on the CPH study (19). A study from the KNHANES 2010–2016 showed that the concomitant symptoms accompanying chronic cough increased with age, suggesting a large impact on the quality of life in the elderly (72).

Fatigue, disturbed sleep, anger, frustration, anxiety, and depression were also commonly reported concomitant symptoms or comorbidities in patients with chronic cough (21,73,74). In addition, urinary incontinence was a commonly reported concomitant symptom in women with an occurrence of 55% (73). All concomitant symptoms or comorbidities seriously interfere with the social life of patients with chronic cough.

Lung function

A previous study from a small asthma cohort reported that cough frequency was not associated with airflow obstruction measured by spirometry (75). However, the CPH study based on a large general population showed that chronic cough was associated with lower lung function, including forced expiratory volume in one second/forced vital capacity (FEV_1/FVC), FEV_1 %predicted (FEV_1%pred), and small airway function, such as maximal mid-expiratory flow (MMEF) %pred, forced expiratory flow (FEF) 50%pred, FEF 75%pred (19). Çolak and colleagues (70) also reported that among individuals with asthma, those with chronic cough versus those without had more often an FEV_1%pred of less than 60% (14% *vs.* 7%). The BOLD study (76) also showed similar findings, with an association between chronic bronchitis symptoms defined as chronic cough and phlegm on most days for ≥3 months each year for ≥2 years and worse lung function (FEV_1%pred), after adjustment for potential confounders.

Impact on life quality

An internet survey based on the Europe general population (77) reported that 96% of participants with chronic cough felt there was a major decrement in their quality of life, leading to social isolation, depression, and difficulties in relationships.

The CPH study (19) showed that individuals with a chronic cough had an impaired physical component summary (PCS) score based on the 12-item Short Form Health Survey (SF-12) questionnaire. Moreover, the impact of chronic cough on PCS score was more significant in participants aged 50 years or older, or with COPD than those aged 20–49 years, or without COPD. Similarly, a survey based on an elderly community population in Korea showed that chronic cough was detrimental to the quality of life on both PCS and mental component summary (MCS) measured by the Short Form 36 Health Survey (SF-36) questionnaire (78).

Based on the Lovelace Smokers' Cohort (LSC) and the Chronic Obstructive Pulmonary Disease Gene Cohort (COPDGene), Meek and colleagues (79) observed that those with COPD and chronic cough with phlegm presented worse symptoms and impact scores measured by the St. George's Respiratory Questionnaire (SGRQ) and emotional and social scores measured by the SF-36 questionnaire than those with chronic airflow obstruction only. Similarly, the BOLD study showed that chronic cough with phlegm had a significant adverse impact on the quality

of life of the general population aged ≥40 years measured by SF-12, both physically and mentally (76).

Chronic cough also has adverse effects on social life. A cross-sectional postal UK survey (73) showed that 64% of respondents felt that cough interfered with their social life, including reduced frequency to the cinema/bingo or restaurants avoiding things that trigger the cough, affecting phone calls, hobbies and less frequent visits to friends or relatives. Using the data from the Respiratory Health In Northern Europe (RHINE) III cohort, Johansson and colleagues (80) found that participants with chronic cough at baseline reported lower work ability and more often had >7 days of sick leave at follow-up, compared to those without cough.

Conclusions

Chronic cough is a common complaint in the clinic that is drawing more attention worldwide. The reported prevalence varies widely among the general population, mainly due to geographical differences, as well as the variable definition of chronic cough. Thus, there is an urgent need for epidemiological surveys using a standard definition of chronic cough (e.g., cough ≥8 weeks) in representative populations from different countries.

Several risk factors of chronic cough have been identified, including sex, age, persistent or current smoking status, asthma, and allergic rhinitis. Other factors which are frequently mentioned empirically, such as ethnicity, smoking cessation, occupational exposures, air pollution, body weight, diet, and breastfeeding need to be further investigated.

This review also highlights the need to pay attention to the wide spectrum of disease burden of chronic cough, including numerous comorbidities and concomitant symptoms, impaired lung function, impaired quality of life and substantial healthcare resource utilization, especially for those vulnerable populations, such as the elderly and people with chronic respiratory disease. In conclusion, chronic cough is a common symptom in the general population that can be associated with a deterioration of quality of life and with increased burden. The identification of risk factors and associated co-morbidities will help towards an improved management of this condition.

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