

# Defining Chronic Cough: A Systematic Review of the Epidemiological Literature

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**Purpose:** Recent evidence suggests a global burden of chronic cough in general populations. However, the definitions vary greatly among epidemiological studies, and none have been validated for clinical relevance. We aimed to examine previous epidemiological definitions in detail and explore the operational characteristics. **Methods:** A systematic review was conducted for epidemiological surveys that reported the prevalence of chronic cough in general adult populations during the years 1980 to 2013. A literature search was performed on Pubmed and Embase without language restriction. Epidemiological definitions for chronic cough were classified according to their components, such as cutoff duration. Meta-analyses were performed for the male-to-female ratio of chronic cough prevalence to explore operational characteristics of epidemiological definitions. **Results:** A total of 70 studies were included in the systematic review. The most common epidemiological definition was identified as 'cough  $\geq$  3 months' duration without specification of phlegm ( $n=50$ ); however, it conflicted with the cutoff duration in current clinical guidelines (cough  $\geq$  8 weeks). Meta-analyses were performed for the male-to-female ratio of chronic cough among 28 studies that reported sex-specific prevalence using the most common definition. The pooled male-to-female odds ratio was 1.26 (95% confidence interval 0.92-1.73) with significant heterogeneity ( $I^2=96\%$ ,  $P<0.001$ ), which was in contrast to clinical observations of female predominance from specialist clinics. Subgroup analyses did not reverse the ratio or reduce the heterogeneity. **Conclusions:** This study identified major issues in defining chronic cough in future epidemiological studies. The conflict between epidemiological and clinical diagnostic criteria needs to be resolved. The unexpected difference in the gender predominance between the community and clinics warrants further studies. Clinical validation of the existing definition is required.

**Key Words:** Cough; epidemiology; definition

## INTRODUCTION

Cough is an essential mechanism for protecting airways, but is also one of the most common symptoms that lead patients to seek medical attention.<sup>1</sup> In particular, chronic cough has a high global health burden, affecting about 10% of general adult populations.<sup>2</sup> Chronic cough is a significant health issue due to its substantial impact on quality of life,<sup>3</sup> and it causes many clinical challenges.<sup>4,5</sup>

In the past, chronic cough was understood to be a consequence of several diseases affecting airway sensory nerve terminals, such as rhinitis, gastroesophageal acid reflux, and eo-

sinophilic airway diseases.<sup>4,5</sup> However, many patients with these diseases do not report cough,<sup>6,7</sup> suggesting that chronic cough,

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although associated, may be a separate condition. Moreover, diagnostic and therapeutic failures have been reported in a substantial proportion of patients with the classic causes of chronic cough (12%-44%).<sup>8</sup> Therefore, cough hypersensitivity syndrome, a new paradigm has recently been formulated to understand chronic cough as a clinical syndrome with a common intrinsic pathophysiology (cough hypersensitivity).<sup>9-12</sup>

This recent paradigm shift in understanding chronic cough warrants further epidemiological characterization. However, in our recent meta-analyses of prevalence studies, substantial methodological heterogeneity was found among the existing epidemiological definitions.<sup>2</sup> Moreover, to the best of our knowledge, none of these definitions have been validated for clinical relevance. To further advance understanding of this disease, a consensus definition needs to be developed. Using a systematic literature review, this study examined previous epidemiological definitions utilized in general population surveys reporting the prevalence of chronic cough and explored the operational characteristics of the most common definition. We hope to open a field of discussion toward consensus development for the definition of chronic cough in further epidemiological studies.

## MATERIALS AND METHODS

### Data sources and searches

A systematic search was conducted of the Pubmed and Em-

base databases for the literature that measured the prevalence of chronic cough in community-based adult populations, as previously described.<sup>2</sup> The search terms were “cough AND (epidemiology OR epidemiologic OR epidemiological OR prevalence OR incidence)” for articles published in peer-reviewed journals between January 1980 and December 2013. Additional searches were performed in Google Scholar (<http://scholar.google.com>) and via cross-referenced articles. Language was not restricted. In cases where full-text links were not available, we contacted the corresponding authors by email for the full text. The systematic review process followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 1).<sup>13</sup>

### Study selection

Studies were initially included if they met the following criteria: (1) cross-sectional or longitudinal studies conducted in community-based or unselected adult populations and (2) reported prevalence of chronic cough. Various definitions of chronic cough were accepted due to the lack of a validated definition. However, here we ultimately included studies only if their diagnostic terms were chronic cough, or other conceptually equivalent terms, such as long-term, longstanding, or persistent cough. We excluded studies with bronchitis, or cough but without including any conceptual terms for chronicity in their diagnostic labels. Other exclusion criteria were as follows: (1) no relevant analyses, (2) convenience sample studies without detailed

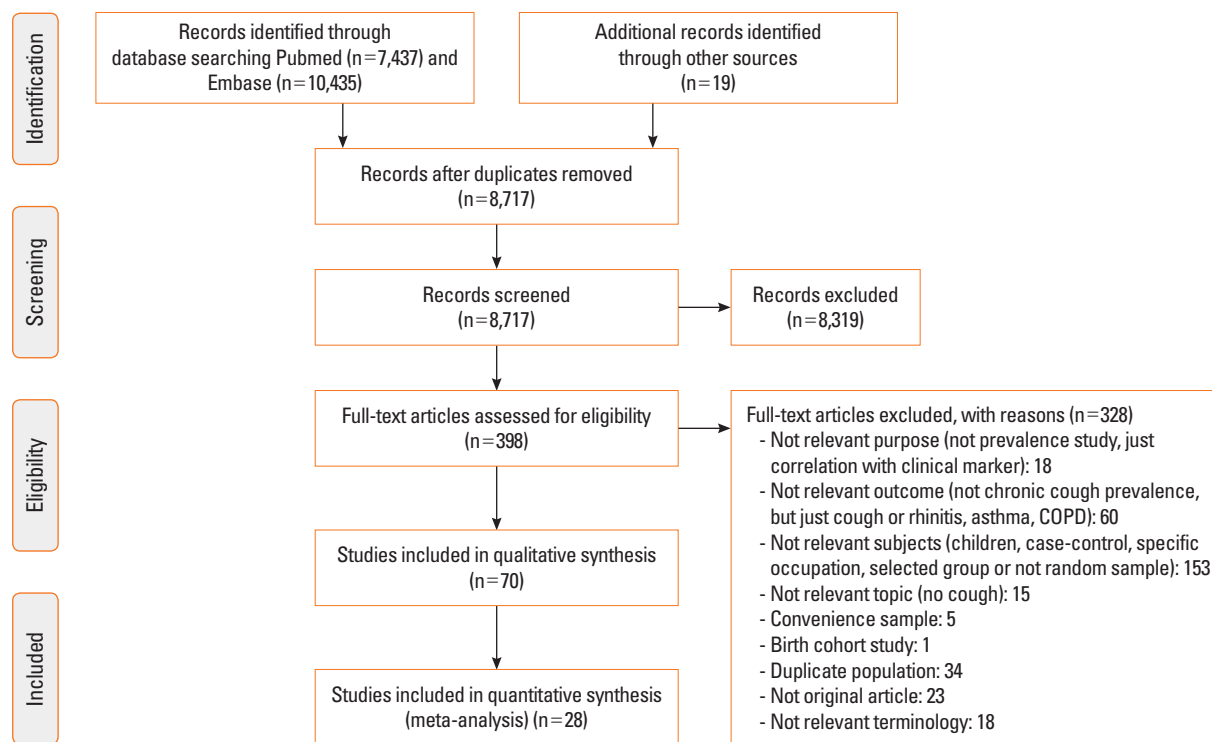


Fig. 1. PRISMA for study selection.

information on demographic characteristics, (3) birth cohort studies confined to specific ages, (4) studies confined to specific occupations, (5) studies using duplicate samples, or (6) non-original papers (reviews and case reports). In determining eligibility, discrepancies were resolved through consensus conference.

#### Data extraction and quality assessment

For all of the included articles, we extracted and confirmed the data. The extracted outcomes included study design, study region, study year, participant characteristics, smoking rate, and definition and prevalence of chronic cough. Sex-specific prevalence of chronic cough was also extracted in as many cases as possible, including email contact of the corresponding authors. In addition, according to text excerpts of research purposes described in original papers, individual studies were classified as studies with chronic cough as the primary outcome or not.

Quality was assessed by 2 reviewers using a quality scoring system in a quality effects model.<sup>14</sup> Briefly, the scores were calculated by summing 6 measurements: (1) definition of the study population, (2) use of reported diagnostic criteria, (3) method of case ascertainment, (4) administration of measurement protocol, (5) characteristics of catchment area, and (6) prevalence measure. Discrepancies in scoring were resolved by consensus conference.

#### Data analyses

Definitions were classified according to the diagnostic terms and questions as utilized in original papers. Definitions were also examined by their components, such as cutoff duration, phlegm, or prevalence measure. Time trends in the definitions were also examined by each decade (1980-1990, 1991-2000, and 2001-2013). These evaluations were repeated for a subgroup of studies that had chronic cough as the primary outcome.

Operational characteristics of the most common definition were examined in relation to sex ratio, as female predominance was a representative finding among patients visiting cough clinics in several countries.<sup>15</sup> A quality effects model was primarily used to calculate a pooled male-to-female odds ratio (OR) and 95% confidence interval (95% CI) of chronic cough prevalence. Heterogeneity was assessed using the  $I^2$  test, with a cutoff of 50%<sup>16</sup> and the chi-squared test with a  $P$  value  $<0.10$ . We adapted the quality effects model due to a considerable heterogeneity in our previous meta-analyses of prevalence,<sup>2</sup> probably due to a combination of true variance of the prevalence and variability produced by the methodological differences used to measure the outcome.<sup>14</sup> The quality effects model gives greater weight to studies of high quality than those of low quality, as it uses the quality scores assigned to individual studies; however, the random effects model assigns more weight to smaller studies in cases of heterogeneity.<sup>17</sup> Therefore, we determined that the quality effects model was a more appropriate statistical method

to obtain a pooled ratio. However, we also presented the pooled estimates by the random effects model for comparison.

Subgroup analyses were performed to explain the heterogeneity, according to study year (before vs after 2000), region, age group (non-elderly vs elderly), and study quality (quality score  $\leq 9$  vs  $\geq 10$ ). Evidence of publication bias was assessed by applying the Peters test to funnel plots of the natural log of OR.<sup>18</sup> Quality effects meta-analyses were performed using MetaXL software version 2.0 (<http://www.epigear.com>), and all other statistical analyses were conducted using Stata software package release 12.0 (Stata Corp., College Station, TX, USA).

## RESULTS

### Baseline description

A total of 70 articles met the inclusion criteria<sup>19-88</sup> (Fig. 1). Nineteen articles<sup>89-107</sup> that had been included in previous meta-analyses for prevalence<sup>2</sup> were excluded here because their diagnostic terms were determined not to specifically intend chronic cough (such as 'chronic bronchitis', 'frequent cough', or just 'cough' in their terms). The characteristics of the 70 articles included and the 19 article excluded are summarized in Appendix Tables S1 and S2, respectively. The quality scores of the included studies are described in Appendix Table S3.

### Cutoff duration for defining chronic cough

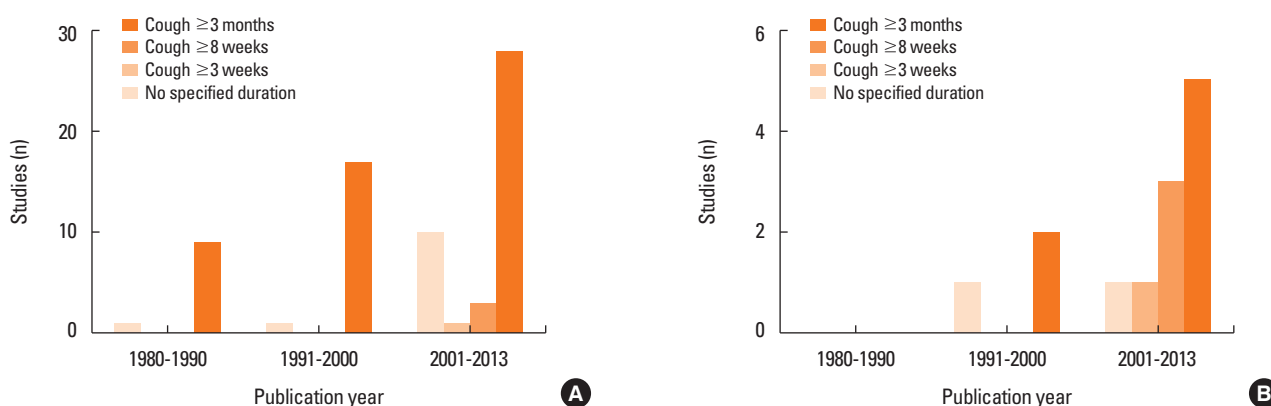
Several diagnostic terms were identified from the 70 studies included, such as chronic cough ( $n=56$ ), chronic cough with phlegm ( $n=4$ ), long-standing cough ( $n=5$ ), long-term cough ( $n=2$ ), and persistent cough ( $n=3$ ) (Appendix Table S4). By cutoff duration, cough  $\geq 3$  months was by far the most common criterion ( $n=55$ ), and cough  $\geq 8$  weeks was the second ( $n=3$ ) most common. Eleven studies did not specify a cutoff duration for defining chronic cough (Table 1).

Based on the research purpose of individual articles (Appendix Table S3), 13 studies were classified as having chronic cough as the primary outcome. Cough  $\geq 3$  months was again the most common cutoff criterion ( $n=7$ ), and cough  $\geq 8$  weeks was the second ( $n=3$ ) most common. One study used cough  $\geq 3$  weeks, and the remaining 2 studies did not use a cutoff duration for cough (Table 1).

Time trends in the utilization of cutoff duration for defining chronic cough were examined (Fig. 2). Over the last 3 decades, the overall number of epidemiological studies for chronic cough had continuously increased, but cough  $\geq 3$  months remained the most frequently used criterion. Other cutoff criteria, such as 8 or 3 weeks, have only been found in recent studies published during 2001-2013. In a subgroup analysis of 13 studies with chronic cough as the primary outcome, cough  $\geq 3$  months remained the most common criterion, but the proportion of cough  $\geq 8$  weeks was higher than in the analysis of all studies (Fig. 2).

**Table 1.** Component of chronic cough definitions utilized in epidemiological studies

Component	All studies (n=70)	Studies with chronic cough as primary outcome (n=13)
<b>Duration</b>		
≥3 months	19,21,23,24,27,28,30,32,33,36-47,49,50,52-55,60-65,67-81,83-88	19,23,24,30,53,73,81
≥8 weeks or 2 months	31,34,35	31,34,35
≥3 weeks	25	25
No specific description	22,26,29,48,51,56-59,66,82	22,29
<b>Combined phlegm</b>		
Yes (productive cough)	24,26,47,50,61	24
No (dry cough)	74	
No specific description	19,23,25,27-46,48,49,51-60,62-73,75-88	19,22,23,25,29-31,34,35,53,73,81
<b>Prevalence measure</b>		
12-month prevalence	20,21,23,24,26-33,36-55,58,60-65,67-71,73-88	23,24,29-31,53,73,81
Point prevalence	19,22,25,34,35,72	19,22,25,34,35
No specific description	56,57,59,66	

**Fig. 2.** Time trends in the utilization of definitions in epidemiological studies. (A) Time trends among all articles which reported the prevalence of chronic cough (n=70). (B) Time trends among a subgroup of articles which reported the prevalence of chronic cough as the primary outcome (n=13).

### Other components for defining chronic cough

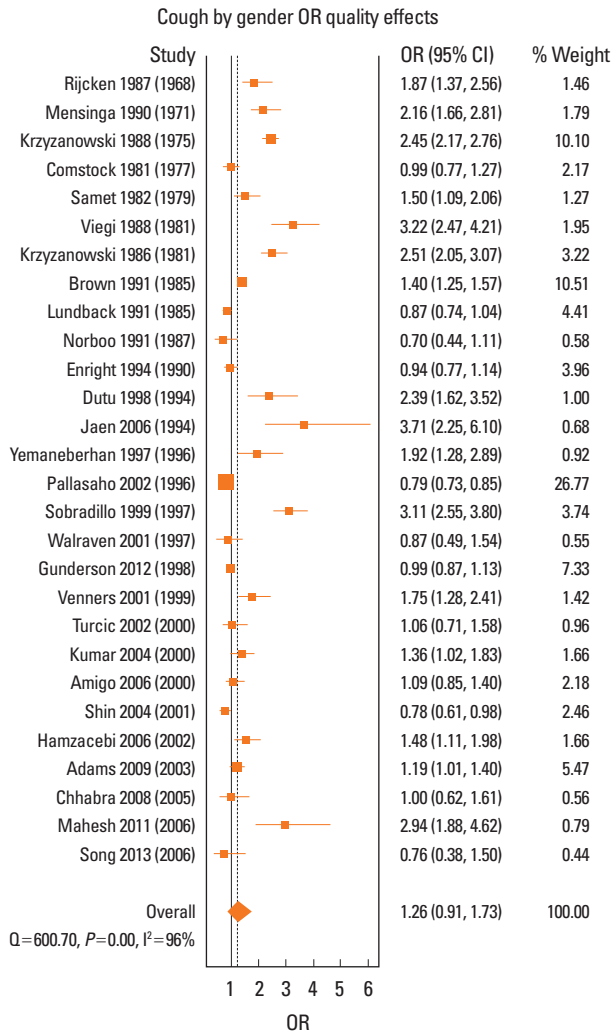
Most studies did not differentiate by the presence of phlegm in their reporting the prevalence of chronic cough (n=64). This preponderance was similarly observed in a subgroup analysis of 13 studies with chronic cough as the primary outcome (Table 1). Of 6 studies that utilized a phlegm component, none quantified or specified the diagnostic criteria for phlegm in detail. Based on the ways of measuring prevalence, the majority of studies (n=60) were classified as using period prevalence (12-month prevalence), whereas 6 studies used point prevalence (Table 1). The proportion of using point prevalence was higher in the subgroup of studies that analyzed chronic cough as the primary outcome (5 of 13).

### Chronic cough by gender

Next, we examined the operational characteristics of the most common definition (n=50, cough ≥ 3 months [12-month prevalence] with no specification on phlegm, *i.e.*, using a question,

“Do you usually cough on most days for 3 consecutive months or more during the year?”) in relation to a male-to-female ratio of chronic cough prevalence because female predominance is a common finding among patients visiting cough clinics in several countries.<sup>15</sup> This meta-analysis included 28 studies (56%) that specified sex-specific prevalence.<sup>19,20,23,27,28,32,33,36,37,42,44-46,52,53,55,60,64,67,68,70,72,73,76,77,79,81,88</sup> Sex-specific pooled prevalence was 9.6% (95% CI 6.0-14.1%,  $I^2=99%$ ,  $P<0.001$ ) in males, and 8.6% (95% CI 5.2-12.8%,  $I^2=99%$ ,  $P<0.001$ ) in females by the quality effects model. The pooled male-to-female ratio of chronic cough prevalence was OR 1.26 (95% CI 0.92-1.73) (Fig. 3) with a significant level of heterogeneity ( $I^2=96%$ ,  $P<0.001$ ) but no significant funnel plot asymmetry (Peters test,  $P=0.592$ ). Male preponderance was also observed by random effects model analyses (OR 1.45, 95% CI 1.20-1.75; Appendix Fig. S1).

The current smoking rate was correlated with chronic cough prevalence at population levels ( $r=0.378$ ,  $P=0.009$ ), and was markedly higher among males than females ( $40.8 \pm 13.3%$  vs



**Fig. 3.** Forest plots for male-to-female ratio in 28 epidemiological studies using a ‘cough ≥3 months’ definition and quality effects model. Study name indicates the first author and publication year, and they were ordered according to the study year (the number within the parenthesis). OR, odds ratio; 95% CI, 95% confidence interval.

13.7 ± 17.7%,  $P < 0.001$ ). Thus, smoking was presumed to be a confounder in the association between gender and chronic cough prevalence. However, meta-regression analyses for sex-smoking-cough interactions were not performed here, as only 15 studies reported a sex-specific rate of current smoking.

We performed subgroup analyses as follows, to explore confounders affecting the gender/cough association. In subgroup analyses by study year, the male-to-female ratio was slightly lower in recent studies conducted after 2000, compared to studies before 2000 (Table 2); however, significant heterogeneity still remained among recent studies after 2000 ( $I^2 = 76\%$ ,  $P < 0.001$ ). In subgroup analyses by age group, elderly-specific studies<sup>33,73,76</sup> had a lower heterogeneity than non-elderly studies<sup>20,23,36,42,44,45,52,55,64,67,70,72,79</sup>; however, the number of elderly-specific studies was small ( $n = 3$ ). Subgroup analyses by study qual-

ity score or region also did not significantly reduce heterogeneity (Table 2).

## DISCUSSION

In previous analyses, we found a global pooled prevalence of chronic cough of 9.6% with a wide geographical distribution.<sup>2</sup> Here, we examined previous epidemiological definitions and their differences, and explored the operational characteristics of the most common definition in relation to the male-to-female ratio.

The high frequency of using 3 months as the cutoff for chronic cough in epidemiological studies may be attributed to the use of major standardized questionnaires in respiratory epidemiology. The British Medical Research Council (BMRC) questionnaire was the first one, particularly developed for the epidemiology of chronic bronchitis in the 1960s.<sup>108</sup> A reference paper stated that to define “chronic,” *quantitative terms must be introduced into the definition, and at present this must be done more or less arbitrarily, and that the phrase “chronic or recurrent” has usually been accepted as implying that expectoration has occurred on most days during at least three consecutive months for more than 2 successive years.*<sup>108</sup> This cutoff duration for “chronic” remained in use in later major protocols of the European Community for Coal and Steel (ECSC)-87 and the American Thoracic Society with the Division of Lung Diseases (ATS-DLD)-78.<sup>109</sup> The ECSC-87 and ATS-DLD-78 questionnaires had modified the BMRC questionnaire by asking for a seasonal association of cough, from in the winter to no specification of season, but not the cutoff duration for chronicity in cough and phlegm. The use of 3 months’ cutoff duration has been maintained in recent large-scale population surveys in Europe, including the European Community Respiratory Health Survey (ECRHS) since the 1990s.<sup>110</sup>

It may be advantageous to utilize these major questionnaires in further population surveys for chronic cough, as they have been extensively validated and have presented little risk for bias from the mode of administration. However, a major dilemma is that the questionnaires were not developed or validated for chronic cough specifically. Moreover, the criterion of 3 months’ duration conflicts with the criterion of 8 weeks’ duration used in major clinical guidelines for chronic cough in adults.<sup>4,5</sup> However, because neither of them was evidence-based, but rather arose from expert opinions, neither can be viewed as “correct.” Before the publication of current clinical guidelines, a ≥3 weeks’ duration had often been utilized in clinical studies of chronic or persistent cough,<sup>111-113</sup> as common colds were considered to usually resolve within 3 weeks; however, a later consensus was made as 8 weeks<sup>114</sup> because post-infectious cough often persists longer than 3 weeks. Meanwhile, in a recent international qualitative study, significant variation was still observed in the definition of chronic cough used in clinical prac-

**Table 2.** Sub-group analyses for sex associations of chronic cough

Classification	Parameter	Number of studies	Number of subjects	Quality effects	Random effects	$I^2$	Pvalue for $I^2$
				OR (95% CI)	OR (95% CI)		
Among studies using 'cough $\geq$ 3 months' definition							
All		28	135,327	1.26 (0.92-1.73)	1.45 (1.20-1.75)	96%	<0.001
Study year	1980-1999	19	107,160	1.28 (0.85-1.91)	1.58 (1.23-2.02)	97%	<0.001
	2000-2013	9	28,167	1.17 (0.91-1.50)	1.20 (0.97-1.48)	76%	<0.001
Region	Africa	2	18,265	1.47 (0.66-3.28)	1.33 (0.61-2.88)	80%	0.027
	America	4	9,811	1.05 (0.87-1.27)	1.08 (0.90-1.30)	54%	0.091
	Asia	7	24,366	1.16 (0.76-1.79)	1.18 (0.81-1.71)	86%	<0.001
	Europe	14	78,825	1.31 (0.82-2.08)	1.77 (1.31-2.38)	98%	<0.001
	Oceania	1	4,060	NA	NA		
Age group	Elderly-specific ( $\geq$ 60-70 years)	3	6,619	0.94 (0.79-1.11)	0.95 (0.80-1.12)	0%	0.700
	Non-elderly-specific (< 60-70 years)	13	84,658	1.27 (0.80-2.00)	1.64 (1.21-2.23)	98%	<0.001
	Others (all ages)	12	44,050	1.35 (1.07-1.71)	1.40 (1.15-1.70)	76%	<0.001
Quality score	$\leq$ 9	22	77,492	1.34 (1.03-1.75)	1.45 (1.18-1.77)	91%	<0.001
	$\geq$ 10 (max: 11)	6	57,835	1.20 (0.68-2.12)	1.45 (0.93-2.27)	99%	<0.001

OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable.

tice, even among specialist clinicians.<sup>115</sup> We suggest that the discrepancy on cutoff duration needs to be resolved by prospective studies on the natural course of self-limiting cough and the characteristics of the minority of patients who go on to prolong chronic cough.

As another component, phlegm may need to be discussed. Productive cough could suggest a likelihood of cough associated with infection or smoking. However, it is difficult to quantify or characterize phlegm objectively in large-scale population surveys. Moreover, among chronic cough patients, the history of excessive sputum production did not indicate different natures of cough.<sup>113</sup> In our unpublished data, the population-level correlations between current smoking and chronic cough prevalence did not significantly differ between chronic cough subjects with and without phlegm. Collectively, the informative value of classifying chronic cough as dry or productive may be questioned in epidemiological surveys.

Our meta-analysis found a slightly higher proportion of males than females, and a high level of heterogeneity in the sex ratio, among chronic cough subjects in the community. These findings were unexpected, as a homogeneous demographic profile was observed among chronic cough patients visiting specialist clinics, where two-thirds of patients were females.<sup>15</sup> The female-predominant profiles of chronic cough patients are considered plausible, as females have enhanced cough responses to tussigen inhalation compared to males, irrespective of being cough patients or healthy controls.<sup>116-120</sup>

With regard to this discrepancy between community and clinics, socioeconomic or individual factors need to be prospectively investigated first. These may include disease characteristics, health-seeking behaviours, or other non-medical factors.

Smoking may be one of these factors; smoking is more prevalent among males than among females (males 40.8%  $\pm$  13.3% vs females 13.7%  $\pm$  17.7% in the present data) and is correlated with chronic cough prevalence, but smokers are less likely to seek medical care for their health problems.<sup>121</sup> Moreover, smoker's cough may be resolved by smoking cessation alone,<sup>114</sup> also possibly leading to less medical attendance among them. Meanwhile, females have more frequent complications from cough, such as incontinence.<sup>122</sup>

The discrepancy in sex-specific associations of chronic cough between community and clinics also leads to the speculation that the current duration-based definition does not easily differentiate clinically relevant cough from a protective cough response. As suggested by the cough-smoking correlations,<sup>2,34,37,53,55,75,78</sup> chronic cough among smokers may be a protective response against irritant inhalation. However, chronic cough patients are frequently never smokers<sup>122,123</sup> and have troublesome cough in response to various trivial triggers, such as cold air, singing/talking, or fatigue/stress,<sup>123-125</sup> which represents a hypersensitive cough response. Thus, if we aim to identify subjects with chronic cough that is clinically relevant, we may need to add some components to detect this hypersensitivity. Conventional tussigen inhalation cough reflex tests have limited utility, as there is a significant overlap between chronic cough patients and normal controls.<sup>11</sup> It would be ideal to have an objective cough reflex test to define cough hypersensitivity for use in epidemiological surveys.

This study has several limitations. First, our meta-analysis of gender ratio included relatively few studies ( $n=28$ ; 56%) and thus could not confirm the gender associations of chronic cough prevalence in the community populations. We attempted to

contact the corresponding authors by email, but could add sex-specific data in only a few cases. Second, the reasons for the heterogeneity in the pooled gender ratio were not clearly explained by our subgroup analyses. The heterogeneity may arise from the variability in the study designs, protocols, or demographic characteristics of included studies and participants. Among demographic factors, in particular, we suppose age and smoking could influence the gender ratio of chronic cough; however, the lack of available information did not allow us to perform meta-regression tests for smoking, or further subgroup analyses by age groups in detail.

Despite these limitations, this study has strength in that it is the first systematic review on the epidemiological definitions of chronic cough. We had no language restriction in retrieving the relevant publication from major databases, enabling the inclusion of non-English literature and the comprehensive review of existing definitions. Our meta-analysis had explorative nature for the reasons described above, but could identify the unexpected but clear heterogeneity and discrepancy in the gender preponderance between the community and clinics.

In conclusion, this study identified major issues for further epidemiological studies of chronic cough. First, cough  $\geq 3$  months' duration was the most common definition, but it conflicts with the criterion of current clinical guidelines (cough  $\geq 8$  weeks). Moreover, both criteria were determined by expert opinions rather than clinical evidence. Thus, we may need to develop objective evidence for defining chronicity in cough. Second, we found unexpected discrepancies in the demographic profiles of chronic cough subjects between the community and clinics. This discrepancy needs to be comprehensively explained in further prospective studies, but also may raise a question about the appropriateness of using a duration-based definition for identifying clinically relevant chronic cough.

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