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Risk factors for chronic cough in adults: A systematic review and meta-analysis

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ABSTRACT

Despite the challenges of diagnosing and managing adult patients with chronic cough, a systematic synthesis of evidence on aetiological risk factor is lacking. We systematically searched PUBMED and EMBASE to synthesize the current evidence for longitudinal associations between a wide range of risk factors and chronic cough in the general adult population, following the meta-analysis of observation studies in epidemiology (MOOSE) guidelines. The Newcastle-Ottawa scale was used to assess the quality of the included studies. Fixed-effect meta-analysis was conducted where appropriate. Of 26 eligible articles, 16 domains of risk factors were assessed. There was consistent evidence that asthma (pooled adjusted OR (aOR) = 3.01; 95%CI: 2.33-3.70; I^2=0%, number of articles (N)=3) and low education levels/socioeconomic status (SES) (pooled aOR=1.46; 95%CI: 1.20-1.72; I^2=0%; N=3) were associated with an increased risk of chronic cough after adjusting for smoking and other confounders. While continuous smoking was associated chronic cough (aOR =1.81; 95%CI: 1.36,2.26; I^2=57%; N=3), there was too little evidence to draw conclusions for occupational exposures, outdoor air pollution, early-life exposures, diet, snoring and other chronic conditions, including obesity, chronic obstructive pulmonary disease (COPD), gastro-oesophageal reflux disease (GORD) and chronic pain. Asthma, persistent smoking and lower education/SES were associated with increased risk of chronic cough. Longitudinal associations between other factors frequently mentioned empirically (i.e. occupational exposures, air pollution, chronic respiratory conditions) need further investigation, ideally with objective and standardized measurement.

Short title: Risk factors for adult chronic cough

Keywords: Asthma, bronchitis, risk of chronic cough, meta-analysis, occupational exposure.

Abbreviation List

ACE: angiotensin-converting enzyme

COPD: chronic obstructive pulmonary disease

CI: confidential interval

CRS: chronic rhinosinusitis

GORD: gastro-oesophageal reflux disease

HR: hazard ratio

MOOSE: meta-analysis of observation studies in epidemiology

NOS: Newcastle-Ottawa scale

OAD: obstructive airway disease

OR: odds ratio

PM: particular matter

RR: risk ratio

SES: socioeconomic status

US: United States

INTRODUCTION

Cough is one of the most common reasons patients present to primary and secondary health care. (1) Although often self-limiting, chronic cough causes substantial health burden and impaired quality of life. (2-4) In the most recent European Respiratory Society and the American College of Chest Physicians guidelines, chronic cough in adults is defined as cough for more than eight weeks duration, whereas earlier guidelines defined it as cough duration of more than three months. (5, 6) Chronic cough is a significant public health burden, with prevalence ranging from 9% to 33% globally. (7) This burden is even greater when considering that chronic cough can be the first symptom of chronic obstructive pulmonary disease (COPD) (8), a major source of morbidity in adults. (9) (10) Further, chronic cough with phlegm is associated with increased all-cause mortality, even when lung function is not impaired. (11-13)

Although chronic cough is a common symptom of various diseases, such as asthma, rhinitis, post-nasal drip and gastro-oesophageal reflux disease (GORD), (6) 46% of patients with chronic cough presenting to specialist clinics do not have any apparent underlying condition even after clinical investigations. (14) These patients are considered to have “undiagnosed” or “idiopathic” chronic cough. (1) The diagnosis and management of patients with chronic cough are often challenging, largely due to insufficient understanding of the aetiology and pathological mechanisms, and lack of effective therapies. The concept of “cough hypersensitivity syndrome” has also been proposed to describe hypersensitive cough responses, with the suggestion that this may arise from a neuropathic disorder. (15)

Many studies have recruited patients from clinics or certain industries, and evaluated risk factors for cough cross-sectionally. Findings of such studies are subject to multiple biases. (16-20) Few population-based studies have investigated risk factors for chronic cough longitudinally (12, 21-24)

and their findings have not yet been systematically synthesised. Such a synthesis would extend understanding of the pathophysiological mechanisms, potential treatments, and avenues for prevention for chronic cough. We undertook a systematic review to identify and synthesise the current evidence for longitudinal associations between a range of risk factors and chronic cough (with or without phlegm) in the general adult population.

METHODS

We followed the meta-analysis of observational studies in epidemiology (MOOSE) reporting guidelines for this review (Table S1 in the Supporting Information).(25) Methods were specified and documented in a protocol a priori, and published on PROSPERO (ID: CRD42020161973).

We systematically searched the MEDLINE and EMBASE electronic databases from inception to our last search date (2nd of May 2021). The search strategy included key words for risk factors and chronic cough (Table S2 in the Supporting Information).

Articles with longitudinal designs assessing risk factors for chronic cough, with and without chronic phlegm, were included. See Table S3 in the Supporting Information for detailed inclusion and exclusion criteria. For articles reporting chronic cough both with and without phlegm, both sets of results were extracted and treated separately. We included articles regardless of the measure of association used (i.e. odds ratios (OR), risk ratios or relative risks (RR), hazard ratios (HR)).

Two authors (JZ and NSI) independently screened titles and abstracts of all identified articles after duplicates were removed. Eligible articles were retrieved in full text for further assessment. We

screened the reference lists of these full-texts for additional articles which met our criteria and consulted experts in the field for any grey literatures. Any disagreements during the process were settled by consultation and consensus with other authors (SD, JP or CL).

Data extraction and statistical analysis

Relevant data were extracted using a pre-defined table (Table S4 in the Supporting Information). The quality of the articles was assessed using a form (Table S5 in the Supporting Information) based on the Newcastle-Ottawa scale (NOS).(26)

Articles were grouped according to the type of exposures. Forest plots were used to present results within similar exposure groups, but only estimates from ≥3 articles using the same effect estimate measure (i.e. OR, RR, HR or prevalence) and similar exposure measurements were meta-analysed. ORs and RRs underwent meta-analysis together following conversion: $RR = OR \div (1- p + (p \times OR))$, where p is the prevalence of chronic cough in the reference group. Adjusted effect estimates with 95% confidence intervals (CIs) were reported where available. If multiple results were reported from one article, only estimates with the most similar characteristics (i.e. set of confounders adjusted, age group, cough definitions) were pooled while other results were presented in tables or figures without pooling. Heterogeneity of associations was assessed using I^2 and was considered minimal if $I^2 < 25\%$, moderate if $25\% \leq I^2 \leq 75\%$, and substantial if $I^2 > 75\%$. Due to too few articles, fixed-effect models were used;(27, 28) funnel plots were not undertaken; heterogeneity and publication bias were explored narratively; interactions were listed in tables without further exploration. All statistical analyses were performed using STATA, version 16 (Stata Corp LP, College Station, TX, USA).

RESULTS

Study selection and characteristics

Our search identified 4051 records from electronic databases (last performed May 2nd, 2021) and an additional 105 records sourced from manual reference searches, no grey literature has been identified. No attempts were made to contact the authors of the records as all relevant information were available. Of the total articles identified, 26 met the eligibility criteria (Figure S1 in the Supporting Information).

The 26 eligible articles reported results from 19 studies, including two retrospective studies (29, 30)and 17 prospective studies.(31-51) Seven of these 19 studies generated multiple articles, all reporting different risk factors from the same cohort and there was no duplication in our analyses (Table 1).

The 26 articles were heterogeneous in terms of study population, definition of chronic cough, and potential risk factors, as well as in their statistical analyses (Table 1). The study populations came from 24 countries, mostly in Europe and the United States (US) , but five studies (six articles) were from Asian countries.(29, 30, 41, 42, 47, 48) Notably, articles from Europe and the US mostly focused on smoking, occupational exposures, and asthma, while articles from Asia mostly focused on air pollution and personal factors (i.e. diet and snoring). Cohorts were generally large (median: 3099; Q1=1796, Q3=8749), with a long follow-up period (median: 11 years; Q1=7 years, Q3=13 years). Participants were aged from 15 to over 75 years at baseline, except for two articles, (47, 51) which measured risk factors in childhood for adult chronic cough.

Quality assessment

Using the NOS scale, overall quality was found to be good with 22 out of 26 articles graded ≥ 7 (out of 9) and four articles graded 6 (Table S6 in the Supporting Information). All articles reported results for self-reported cough, while only one reported physician-diagnosed chronic bronchitis (in addition to self-reported chronic cough as a separate outcome) .(44) Ten articles(31-37, 43, 49, 52) measured exposures through postal surveys only, and nine articles(29, 30, 37-39, 44-47) reported a follow-up rate of less than 60%. Six articles (29, 30, 42, 44, 47, 51) did not exclude people with chronic cough at baseline. Confounding was considered in all articles and adjusted effect estimates were considered for meta-analysis. However, the adjusted confounders were often heterogenous across articles.

Risk factors for adult chronic cough

Overall, 15 domains of potential risk factors were extracted from the 26 eligible articles, including: asthma; atopy and allergy; smoking; occupation; air pollution; socioeconomic status (SES) or education; early-life environmental exposure; diet; snoring; obesity; chronic rhinosinusitis (CRS); COPD; GORD; obstructive airway disease (OAD); chronic pain and clinically relevant depressive symptoms. These factors were summarised in Figure 1. Three risk factors: smoking, education/SES and asthma, met the criteria to be included in the meta-analyses.

Asthma, atopy or allergic disease

Nine articles (33, 37, 43, 45, 46, 49-53) measured asthma or asthmatic features (i.e. clinical disease, airway hyper-responsiveness, childhood asthma or family history of asthma) and all found some evidence for positive associations between these factors and chronic cough (Table S7 in the Supporting Information). Our pooled effect estimate showed associations between doctor diagnosed

asthma and chronic cough with minimal heterogeneity (pooled adjusted OR (aOR)=3.01; 95%CI: 2.33-3.70; I^2=0%, number of articles (N)=3), as well as airway hyper-responsiveness and chronic cough (aOR=2.11; 95%CI: 1.35-2.87; I^2=18.6%; N=2). Two articles also found the hazard ratios of chronic bronchitis increased for people with asthma.(33, 43) (Figure 2). Interestingly, one article(49) found family history increased the risk of chronic cough in middle-aged while another article(51) found no association between parental asthma at 2-month-old and chronic bronchitis in early 20s. Different ages (for both participants and their families), family members and cough definitions may all contribute to the inconsistency. One article that defined atopy as atopic dermatitis or hay fever found no associations between atopy and chronic cough.(43) while two articles found rhinitis and/or allergic dermatitis associated with chronic cough.(37, 52) There was no evidence of a relationship between skin prick tests (33, 47) or serum IgE levels(33) and chronic cough.

Smoking

Compared with never smoking, four articles found that persistent smoking was consistently associated with higher odds of chronic cough (pooled aOR =1.81; 95%CI: 1.36,2.26; I^2=57%; N=3) (Table S8(A) in the Supporting Information, Figure 3). (34, 38, 49) Three articles that investigated associations between past smoking (quitting prior to baseline), remitted smoking (smoker at baseline but quit during follow-up) and chronic cough, found no association,(38) a positive association,(49) and a negative association,(34) respectively. The substantial heterogeneity (remitted smoking: I^2=76%; past smoking: I^2=83%) may be explained by different study designs and populations (Figure 3). Associations between incident smoking and chronic cough were also inconsistent (pooled aOR=1.28; 95%CI: 0.65, 1.90; I^2=64%; N=2), (34) (38) but small number of events (only 25 participants were incident smokers) may explain some of this inconsistency (Table S8(A) in the Supporting Information).(38)

Six articles investigated the association between baseline smoking status and subsequent chronic cough without accounting for any change in smoking status at the time of follow-up (Table S8(B) in the Supporting Information). All found some evidence for a positive association between current smoking at baseline and chronic cough (pooled aRR=1.97; 95%CI: 1.68, 2.27; I^2=64%; N=3). (33, 37, 43, 44, 52, 53) There was no evidence for an association between ex-smoking at baseline and chronic cough (pooled aRR=1.06; 95%CI: 0.88-1.24; I^2=0%; N=3, Figure 3).

A dose-response relationship between years of smoking/pack years of smoking and chronic cough was verified by three articles(34, 40, 43) but their study designs were too heterogenous to be pooled (Table S8(B) in the Supporting Information).

Occupation, SES and education

A range of occupations and/or occupational exposure to certain agents were assessed differently in ten articles, reporting inconsistent results (Table S9 in the Supporting Information). As these articles varied in their stratification approaches and/or confounders considered, results are presented in the forest plot but were not pooled (Figure S2 in the Supporting Information). High-risk occupations and/or occupational exposures for chronic cough were identified by only one article each (Figure 1).

Three articles assessed associations between SES and chronic cough and were included in the meta-analysis (Figure 4, Tables S9 in the Supporting Information).(30, 35, 39) Low education level was associated with higher risks/odds of chronic cough with minimal heterogeneity (Model 1: pooled aOR=2.06; 95% CI: 1.42-2.88; I^2=0%; N=2). The findings were similar for middle levels of SES/education when compared to higher levels (Model 2: pooled aOR=1.43, 95%CI: 1.18-1.67; I^2=0%; N=3) (Figure 4).

Outdoor air pollution

Five articles (29, 30, 38, 44, 51) assessed associations between air pollution and chronic cough with four found associations between outdoor air pollution and chronic cough (Table S10 in the Supporting Information), but their study designs were heterogeneous to be pooled. Two of the five articles measured polluted substances: one article found black carbon exposure from age 1-4 years were associated with higher risks of chronic bronchitis in early adulthood;(51) the other article found the decreased particulate matter (PM_{10}) during the study period might reduce chronic cough among middle-aged women.(44)

Other risk factors

Obesity, COPD, GORD, obstructive airway disease (OAD), chronic pain and snoring were all found to be associated with increased risk of chronic cough, while high intakes of non-starch polysaccharides, fruit and total soy isoflavones, exclusive breastfeeding for more than 4 months were associated with lower odds of chronic cough. (41, 48, 50, 51, 53, 54) Lower parental education and parental smoking during childhood (0-16 years) were also marginally related to higher risk of chronic bronchitis in early adulthood while maternal smoking during pregnancy and respiratory health during infancy were not associated with chronic bronchitis.(51) There was no evidence supporting associations between CRS, low birthweight, premature birth and chronic cough. (51, 53) Notably, however, each risk factor was only assessed in one article (Table S11 in the Supporting Information). Further, none of the above risk factors were strongly associated with chronic cough, indicating that smaller studies may not have enough power to detect any associations thus not published.

Many articles reported results for factors unrelated with chronic cough (Figure 1) with only one article(47) reported all non-significant associations. Several articles reported inconsistent results, but only for factors related to smoking and occupational exposures.

DISCUSSION

This systematic review has comprehensively investigated articles describing longitudinal risk factors for adult chronic cough. We confirmed that persistent smoking increased the risk of chronic cough. In addition, our review observed chronic cough to be consistently associated with asthma and low education/SES. We found some evidence that air pollution was associated with chronic cough, but the measurements and levels of air pollution varied across studies. Interestingly, several risk factors suggested in the clinical literature as risk factors for chronic cough had quite limited evidence in general populations, with only one article on each risk factor identified. These included occupational exposure to metals and certain occupations (farmers, cleaning services, manual workers etc), snoring, obesity, COPD, GORD, chronic pain and parental smoking. We also identified potentially protective factors against chronic cough, including a diet with high soy isoflavone, fruit and non-starch polysaccharides intake, exclusive breastfeeding for more than 4months and reduced concentrations of PM_{10} in ambient air. However, these protective factors too were only assessed in one article each, and further studies are needed to draw firmer conclusions.

Not unexpectedly, we found strong evidence that asthma is associated with increased risk of chronic cough. Increased airway responsiveness in asthma is frequently associated with airway inflammation, potentially through up-regulated interleukin-5 (IL-5) expression and studies have shown that chronic cough and eosinophilic bronchitis may have the same mechanism.(55) Asthma can initially present as

chronic cough and the two can co-exist. All articles related to asthma excluded chronic cough at baseline and were longitudinally conducted. Further, one article conducted a sensitivity analysis excluding participants with current asthma at follow-up and found congruent results.(29) However, we cannot confirm temporality of the observed association since both cough and asthma have the potential to be mis- or under-diagnosed because of their diagnostic overlap.

While smoking is a well-established risk factor for chronic cough,(5, 56) our review identified that the effect of smoking cessation (compared to never smoking) on chronic cough was extremely heterogeneous across the articles. Compared to non-smokers, smokers have down-regulated cough sensitivity,(57) which rebounds in quitters at 2-weeks after cessation, although this enhancement diminishes with time.(58) If the majority of ex-smokers were in the "cough reflex enhancement" period, quitting may be incorrectly identified as a risk factor for chronic cough. The fact that ex-smokers at baseline (regardless of their smoking status afterwards) were not significantly different from non-smokers in terms of chronic cough risk further supports this hypothesis.(33, 37, 52) Ex-smokers, in these articles, may have suppressed or enhanced cough reflexes depending on their time since quitting, generating inevitable heterogeneity between articles that have followed-up participants at different times after smoking cessation. Therefore, a detailed smoking history with date of cessation is a vital design consideration for future studies investigating associations between smoking cessation and chronic cough. Besides, parental smoking during childhood could increase the risk of chronic bronchitis in early adulthood. Smoking is also a known trigger for cough, either first- or second-hand, further investigations are needed to assess the role of second-hand tabaco smoking in chronic cough.

Occupational lung diseases such as work-related asthma and chronic bronchitis are common,(59) but there are relatively few longitudinal population studies that have investigated occupational risk factors for chronic cough without phlegm. The articles used different job exposure matrices and often reported results stratified by age, gender and/or exposure levels without sufficient justification. The current evidence remains limited and inconsistent for chronic cough per se, although we identified some high-risk occupations (e.g. cleaning, farming, manual work) which need further investigation to draw firmer conclusions. Interestingly, the association between lower SES and/or education levels and higher chronic cough risks were consistent.

Environmental pollutants have been suggested as airway irritant triggering chronic cough.(15) Four of the five articles found some evidence for this link between air pollution and chronic cough, but all four did not exclude participants with chronic cough at baseline, limiting the quality of the evidence.(29, 30, 44) Specifically, the reduction of PM_{10} levels during follow-up was found to attenuate the increased prevalence of chronic cough as the study population aged.(44) Higher black carbon exposure at age 1-4 years old increased the risk of chronic bronchitis in early 20s.(29) Further, longitudinal studies using objective measurements of air pollution (i.e. PM_{10}, $PM_{2.5}$, NO_2 concentrations) and effective adjustment for confounders (i.e. smoking) are needed. Background air quality and major sources of outdoor air pollution should also be measured and reported.

Data in our review of the association between cough and chronic health conditions (COPD, GORD, obesity and chronic pain) were limited to a single study.(50, 53) This study also identified a higher prevalence of chronic cough among ACE (angiotensin-converting enzyme)inhibitor users.(53) The second article generated from this study found bi-directory associations between chronic cough and chronic pain, indicating a shared mechanism of the two conditions.(50) Patients with COPD and

GORD can present with cough, but how precisely causative this relationship remains open to objective confirmation. Obesity has been considered as a potential risk factor for chronic cough and other conditions such as diabetes, asthma, and GORD,(5, 60-62) and previous cross-sectional studies have found some evidence for obesity-related chronic cough.(48) Weight loss has been found effective for the treatment of asthma(63) and GORD, (64, 65) and further longitudinal studies are needed to explore potential interactions between obesity, weight loss, ACE inhibitor usage, COPD, and GORD in relation to chronic cough. Nevertheless, although it is undisputed that there is an overlap between chronic bronchitis and COPD related to cigarette smoking,(66) understanding of this overlap is far from complete. Whether COPD itself without chronic bronchitis is an independent cause of cough is far from clear and needs further longitudinal data for better precision.

Interestingly, life-style factors such as diet and snoring have only been formally assessed in Asian populations. Future studies are needed to assess associations and interactions between diet, physical activity, sleeping disturbance and chronic cough in different ethnic and geographic settings, and especially taking into account differing lifestyle setting. This is in contrast to factors such as smoking and occupational exposures which were mostly conducted within non-Asian and high-income Western life-style countries.

Our review has highlighted the paucity of high-quality data directly relating chronic cough to supposed risk factors. Following a pre-registered protocol, we conducted a comprehensive search with two independent reviewers. We included longitudinal studies to establish the temporality between risk factors and chronic cough and followed the MOOSE guidelines for reporting meta-analysis of epidemiological observation studies. The quality of studies included was critically assessed using the NOS in addition to a pre-defined standard to interpret and apply the scale.

However, we faced major challenges pooling effect estimates. This was, in part, because of the limited number of studies, but also, because of variations on cough definitions, reference groups, and effect-estimate measures used in different studies. Meta-analysis could only be conducted across a few studies for any risk factor. Tables and figures were used instead to help interpret our findings. Similarly, we were unable to present informative funnel plots or subgroup analysis to quantify degrees of publication bias or heterogeneity, as per our protocol.

Evidence for relationships between potential confounders and chronic cough remained controversial and inadequate, except for smoking. Therefore, unrelated factors may have been over-adjusted and true confounders unadjusted, thus biasing the results. Non-English language records were excluded from our review, and so our conclusions should be generalised to non-English speaking populations with caution.

In conclusion, given the high burden of chronic cough, as distinct from its associated chronic lung disease, large epidemiological studies that can identify relevant risk factors in the general adult populations are surprisingly few. In this systematic review, we found consistent evidence that asthma, persistent smoking, and lower education are related to chronic cough, with or without phlegm. The effect of smoking cessation on lessening chronic cough was unclear, so future studies will be useful to confirm and further promote smoking abstinence. It is important to note that the evidence included in our review comes mostly from high income countries. The roles of diet, breastfeeding, snoring, obesity, COPD without bronchitis, GORD, and air pollution in adult chronic cough, although generally assumed, would benefit from further clarification. Ideally, future studies would use both the chronic bronchitis definition (cough with phlegm for ≥ 3months/2 years) as well as the chronic cough

definition from recent guidelines (cough ≥ 8 weeks) to be able to effectively undertake meta-analysis and tease out the complexities in this evolving body of evidence.

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Human Ethics Approval Declaration: Not applicable. This systematic review and meta-analysis has been registered in PROSPERO: CRD42020161973 at www.crd.york.ac.uk/prospero/

CONFLICT OF INTEREST

M.J. Abramson holds investigator-initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He also received a speaker's fee from GSK. S.C. Dharmage has received research funds from GSK's competitively awarded Investigator Sponsored Studies program for unrelated research. Other authors have no conflicts of interest to declare.

Author contributions:

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Table 1. Characteristics of included studies (N=26)

Study [NOS]	Study design [a][Sample size]		Risk factor [tool]	Chronic cough [tool]	Main objectives of the study
Krzyzanowski, 1990 [NOS=7]	Cracow cohort Poland BS: 1968	1st FUP: 19732nd FUP:1981 Age 19-60yrs [N=2730, M=1132]	Occupational exposure to dust, variable temperature	CC: cough ≥3 mo for 2 yrs; CB: cough with phlegm ≥3 mo for 2 yrs' Incident case as reported at 1st or 2nd FUP [IA-Q]	Incidence rates of chronic respiratory symptoms and related occupational factors
Krzyzanowski, 1992 [NOS=7]		FUP: 1981. Age 19-70 yrs .[N=3082, M=1264]	Smoking		Relationships of the change of respiratory symptoms to age, gender, and smoking, compared in two cohorts.
	Tucson cohort USA BS: 1972	FUP: 1985 Age 19-70 yrs [N=1452, M=613]			
Silva, 2004 [NOS=7]		Age ≥ 20 yrs; 12 follow-ups until 1993 [N=3099, M=1405]	Asthma Smoking Atopy (skin prick test)	CB: cough with phlegm ≥3 months for 2 yrs [P-Q]	Association between doctor diagnosed asthma and subsequent development of COPD
Eagan, 2002 [NOS=7]	Norway Age 15-70 yrs. BS: 1985 FUP:1996-1997	[N=2819, M=1352]	Smoking	CC: cough ≥3 months for 1 yr [P-Q]	Incidence rates for respiratory symptoms and asthma and their associations with sex, age, smoking and educational level
Eagan, 2004 [NOS=7]			Education as indicator for SES		
Skorge, 2009 [NOS=7]		[N=2312, males =1123, females=1189	Occupational exposure to dust, gas or fumes		Occupational exposure on incident adult asthma and respiratory symptoms
Guerra, 2005 [NOS=6]	Pisa cohort Italy	Age ≥15 yrs. BS: 1985-1988; FUP:1991-1992 [N=1670, M=592]	Rhinitis. Asthma Smoking. Occupation	CC: cough ≥3 months for 2 yrs. [IA-Q]	1. Identify risk factors for cough 2. Rhinitis as independent risk factor for occasional and chronic cough
Maio, 2019 [NOS=7]		Age ≥20 yrs BS:1991-1992; FUP:2009-2011[N=970, M=426]	Smoking Occupation Vehicular traffic exposure	Usual cough apart from common colds [IA-Q]	Cumulative incidence of respiratory symptoms related to smoking occupation, environment
Hu, 2016 [NOS=5]	China. Retrospective study. Age ≥ 35 yrs in 2009 long term (≥ 3 yrs) residents [N= 1003, M=312]		Air pollution (home-road distance)	CC: cough ≥ 8 wks in the past year. [Questionnaire]	Home-road distance and lung functions, airway inflammation markers, prevalence of respiratory symptoms and diseases
Ellison-Loschmann, 2007 [NOS=7]	BS: 1991-1993; FUP: 1998-2002; 2010-12. Age 20-44 yrs ;	ECRHS 13 countries ‡. [N= 6455, M=3412]	SES	CB: cough with phlegm ≥3 mo last year[IA-Q]	Prevalence and incidence of asthma and CB, in relation to SES
Lytras, 2018 [NOS=8]		ECRHS 15 countries ‡ [N = 8794, M = 4168]	Smoking Occupational exposure	CC: cough ≥3 mo/yr;	Effect of occupational exposures on CB incidence
Butler, 2004 [NOS=8]	Singapore Age 45-74 yrs. BS: 1993-1998	FUP: 1999-2002 [N = 49140, M = 20786]	Diet (isoflavones, fruit, energy, vitamins, soy)	CC: cough ≥3 mo for 2 yrs; CB: CC and phlegm [IA-Q]	Fruits, vegetables, decrease risk of developing cough and phlegm
LeVan, 2006 [NOS=7]		FUP: 1999-2004 [N=45104, M =18319,]	Occupational exposure to dust, vapour, smoke		Occupational risk for asthma, cough and phlegm
Baik, 2008 [NOS=8]	South Korea, Age 40-69 yrs; BS: 2001; FUP: 2003-2005 [N=4270, M=2220]		Snoring [IA-Q]	CB: cough with phlegm ≥3 mo for 2 [IA-Q]	Effect of snoring on the development of chronic bronchitis

(Continued)

Study [NOS]	**Study design & population* [Sample size]**	**Risk factor(s) [measurement]**	**Chronic cough [measurement]**	**Main objectives of the study**
Holm, 2014 [NOS=7]	Sweden; Age 20-60 yrs. BS:1993; FUP: 2003 [N=11148, M=5230]	Smoking. Asthma. Atopy (hay fever, atopic dermatitis) [P-Q].	CB: cough with phlegm ≥3 mo for 2 yrs [P-Q]. Onset-age asked in 2003 to confirm incident cases	Incidence rate of CB in relation to smoking, age, sex, atopy and asthma
Brutsche, 2006 [NOS=7]	Switzerland. Age 18-60 years. BS: 1991; FUP:2001. [N=4855, M=2573]	Bronchial hyperresponsiveness to methacholine.	CC: cough ≥3 mo for 2 yrs; CB: CC+ phlegm [IA-Q]	BHR as risk factors of asthma COPD, respiratory symptoms
Schikowski, 2010 [NOS=6]	Germany. Females only; Age = 45 BS: 1985-1994; FUP: 2006; [N= 2116]	Smoking. Air pollution (PM_{10}, NO_2) [local monitor station data based on home address]	CC: frequent cough without phlegm production. CB: self-reported & physician diagnosed. CC with phlegm [PQ]	Whether air pollution reduction attenuate prevalence of respiratory symptoms
Chhabra, 2001 [NOS=6]	India. Age ≥18 yrs in 1999 and resided in the area for ≥10yrs. [N=4141, M=2344]	Smoking. Retrospective air pollution data SES [IAQ]	CC: cough ≥3 mo for 2 yrs [IAQ]	Role of ambient air pollution in chronic respiratory morbidity
Mirabelli, 2012 [NOS=8]	US. Age 45-64 yrs; BS: 1980. FUP: 1983. [N=8967, M=3949]	Occupation [IA-Q]	CC: cough ≥ 4-6 times/day, ≥ 4 days/wk. [IA-Q]	Incidence of CC, wheezing, lung function and occupational risks
Xu, 1997 [NOS=7]	Netherland. Age 15-45 yrs BS: 1965-1969; FUP: every 3 yrs until 1990. [N= 2684, M =1482]	Airway responsiveness (histamine threshold test)	CC: cough ≥3 mo per year. CB: cough with phlegm ≥ 3 ws for 3 yrs [IA-Q]	Increased airway responsiveness and remission of chronic respiratory symptoms
Kagamimo, 1996 [NOS=6]	Japan. 3 cohorts during 1972-1990. Age 6-14 years. [N= 1796, M =1003]	Skin prick test.	Persistent cough : usually cough in winter. [P-Q] §	Predictive value of SPT at childhood for future respiratory symptoms
Hedlund, 2006 .[NOS=7]	Sweden. Age 45, 50, 65 yrs. BS: 1985-1986; FUP:1996. [N=,4754 M=2341]	SES. Smoking. Family history of asthma. [P-Q]	CB: cough with phlegm ≥3 mo for 2	SES, incidence of asthma and respiratory symptoms
Terho, 1995 [NOS=7]	Finland. Twin study. Age ≥ 18 yrs. BS: 1975. FUP: 1981. [N=17134, M=9221]	Smoking. Farmers allergic rhinitis or allergic dermatitis)	CB: cough with phlegm ≥3 mo/yr. [P-Q]yrs. [P-Q]	atopy, smoking, and living in farm environment on the development of CB
Arinze, 2020 [NOS=8]	Nether lands. Age ≥ 45 yrs — BS: 2009-2014; FUP: 2009-2016 [N=7141, M=2984]	Smoking. BMI. ACE inhibitor. COPD, GORD Asthma, OAD; CRS	CC: daily cough ≥3 mo for 2 yrs [IA-Q] Unexplained CC defined as CC without identifiable risk factors. [IA-Q]	Period prevalence, incidence and risk factors of CC
Arinze, 2021 [NOS=8]	BS: 2002-2008; FUP: 2006-2014 [N=9824, M=4549]	Chronic pain, Clinically relevant depressive symptoms		Bi-directional associations between chronic cough and chronic pain
Wang, 2021 [NOS=7]	Sweden. From birth to 24 years old. BS: 1994-1996 [N=2519, M=1156]	Early life exposure and environment from 2 months to 16 yrs. [Parents P-Q]	CB: usually cough and bring up mucus waking up in the morning during winter. [P-Q]	Prevalence of CB and early-life risk factors including environmental exposures.

M: males; F: females; NOS: Newcastle-Ottawa Scale scores; CC: chronic cough; CB: chronic bronchitis; BS: baseline study; FUP: follow-up study; P-Q: postal questionnaires; IA-Q: interviewer administrated questionnaire; BMI: body mass index ACE inhibitor: angiotensin converting enzyme inhibitor; mo: month(s); yr(s): year(s); wk: week(s).

* Combined rows indicated multiple published articles from the same cohort or multiple cohorts reported by the same article.

‡ The countries in the ECRHS study are Australia, Belgium, Denmark, Estonia, France, Germany, Iceland, Italy, Norway, New Zealand, Spain, Sweden, Switzerland, UK and the USA; Estonia and France were excluded from the occupational analysis due to no incident CB cases reported during follow-up

§ Baseline questionnaires were filled by parents and confirmed by interviewing the children.

Figure Legends

Figure 1. List of potential risk factors for chronic cough assessed in eligible studies.

Studies were grouped by risk factors, regardless of their measurements and definitions. The size of the bubbles and numbers in the brackets represent numbers of studies. Hollow bubbles or dots represent factors only assessed by one study but were put under the 'consistent finding' column for readability. 'Inconsistent finings' refers only to directions of associations, represented by colours of bubbles.

VGDF: vapor, gas, dust and fumes; COPD: chronic obstructive pulmonary disease; OAD: obstructive airway disease including asthma, COPD and asthma-COPD overlap; GORD: gastro-oesophageal reflux disease; CRS: chronic rhinosinusitis.

* Obesity defined as BMI $\geq 30 kg/m^2$.

Figure 2. Associations between asthmatic features and chronic cough.

CB: chronic bronchitis. Fixed-effect models were used. Odds ratio (in normal scale) of doctor diagnosed asthma and chronic cough were presented unless otherwise stated in Notes as "asthma measure, cough measure (effect estimate)". Estimates from "results not pooled" were only shown for comparison without been meta-analysed.

Figure 3. Associations between smoking and chronic cough by different smoking status.

All reference groups are never smoking; past smoking defied as quit smoking before baseline (ex-smoking at baseline); remitted smoking defined as quit until follow-up (ex-smoking at baseline and at follow-up); fixed-effect models were used.

Figure 4. Associations between socio-economic status (SES) and chronic cough.

Fixed-effect models were used. SES was categorised into low/middle/high levels by ordinal income level (Chhabra, 2001); highest attained education levels (Eagan, 2004); and education-year tertiles (Ellison-Loschmann, 2007). Model 1 adjusted for age and gender only; Model 2 adjusted for age, gender, smoking, occupational exposures, and allergic diseases.