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Early View

Original research article

Prevalence and burden of chronic cough in China: a national cross-sectional study

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Prevalence and burden of chronic cough in China: a national cross-sectional study

Authors:

Kewu Huang, Xiaoying Gu, Ting Yang, Jianying Xu, Lan Yang, Jianping Zhao, Xiangyan Zhang, Chunxue Bai, Jian Kang, Pixin Ran, Huahao Shen, Fuqiang Wen, Yahong Chen, Tieying Sun, Guangliang Shan, Yingxiang Lin, Sinan Wu, Ruiying Wang, Zhihong Shi, Yongjian Xu, Xianwei Ye, Yuanlin Song, Qiuyue Wang, Yumin Zhou, Wen Li, Liren Ding, Chun Wan, Wanzhen Yao, Yanfei Guo, Fei Xiao, Yong Lu, Xiaoxia Peng, Dan Xiao, Xiaoning Bu, Hong Zhang, Xiaolei Zhang, Li An, Shu Zhang, Zhixin Cao, Qingyuan Zhan, Yuanhua Yang, Lirong Liang, Huaping Dai, Bin Cao, Jiang He, Kian Fan Chung, Chen Wang[†], for the China Pulmonary Health (CPH) Study Group.

Author affiliations:

Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Department of Pulmonary and Critical Care Medicine (Prof K Huang MD, Y Lin MD, Y Lu MD, X Bu MD, H Zhang MD, L An MD, S Zhang MD, Z Cao MD, Prof Y Yang MD), Department of Epidemiology (L Liang MD), Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China;
Beijing Institute of Respiratory Medicine, Beijing, China (Prof K Huang MD, Y Lin MD, Y Lu MD, X Bu MD, H Zhang MD, L An MD, S Zhang MD, Z Cao MD, Prof Y Yang MD, L Liang PhD, W Wang MD);
National Center for Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, Beijing, China (X Gu PhD, T Yang MD, S Wu MD, Prof D Xiao MD, Xiaolei Zhang MD, Prof Q Zhan MD, Prof H Dai MD, Prof B Cao MD, Prof C Wang MD);
Department of Pulmonary and Critical Care Medicine (T Yang MD, Xiaolei Zhang MD, Prof Q Zhan MD, Prof H Dai MD, Prof B Cao MD, Prof C Wang MD), Tobacco Medicine and Tobacco Cessation Center (Prof D Xiao MD), and Institute of Clinical Medical Sciences (X Gu PhD, S Wu MD,), Center of Respiratory Medicine, China-

Japan Friendship Hospital, Beijing, China;
Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China (X Gu PhD, T Yang MD, S Wu MD, Prof D Xiao MD, Xiaolei Zhang MD, Prof Q Zhan MD, Prof H Dai MD, Prof B Cao MD, Prof C Wang MD);
Department of Respiratory Medicine, Capital Medical University, Beijing, China (T Yang MD, Prof Q Zhan MD, Prof B Cao MD, Prof H Dai MD, Prof Chen Wang MD);
Department of Pulmonary and Critical Care Medicine, Shanxi Bethune Hospital, Taiyuan, Shanxi, China (Prof J Xu MD, R Wang MD);
Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, China (Prof L Yang MD, Prof Z Shi MD);
Department of Pulmonary and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China (Prof J Zhao MD, Prof Y Xu MD);
Department of Pulmonary and Critical Care Medicine, Guizhou Provincial People's Hospital, Guiyang, Guizhou Province, China (Prof Xiangyan Zhang MD, Prof X Ye MD);
Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China (Prof C Bai MD, Prof Y Song MD);
Department of Pulmonary and Critical Care Medicine, The First Hospital of China Medical University, Shenyang, Liaoning Province, China (Prof J Kang MD, Prof Q Wang MD);
State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Diseases, Guangzhou Institute of Respiratory Diseases, The First Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong Province, China (Prof P Ran MD, Prof Y Zhou MD);
Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, Zhejiang Province, China (Prof H Shen MD, Prof W Li MD, Prof L Ding MD);
State Key Laboratory of Biotherapy of China and Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China (Prof F Wen MD, C Wan MD);
Department of Respiratory and Critical Care Medicine, Peking University Third Hospital, Beijing, China (Prof Y Chen MD, Prof W Yao MD);

Department of Respiratory and Critical Care Medicine, Beijing Hospital, Beijing, China; (Prof T Sun MD, Y Guo MD);
National Center of Gerontology, Beijing Hospital, Beijing, China (Prof T Sun MD, Y Guo MD, Prof F Xiao PhD);
Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences; School of Basic Medicine, Peking Union Medical College, Beijing, China (Prof G Shan MD);
WHO Collaborating Center for Tobacco Cessation and Respiratory Diseases Prevention, Beijing, China (Prof D Xiao MD, Prof Chen Wang MD);
Center for Clinical Epidemiology and Evidence-based Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China (X Peng MD);
Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA (Prof J He MD);
National Heart & Lung Institute, Imperial College London & Royal Brompton & Harefield NHS Trust, London, UK (Prof KF Chung MD);
Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (Prof Chen Wang MD)
†Corresponding author

Corresponding Author:

Prof Chen Wang
National Center for Respiratory Medicine, Beijing, China
Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China
National Clinical Research Center for Respiratory Diseases, Beijing, China
Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
Department of Respiratory Medicine, Capital Medical University, Beijing, China
WHO Collaboration Center for Tobacco Cessation and Respiratory Diseases Prevention, Beijing, China
Phone: (86-10)65105565
Fax: (86-10)65105567
Email: wangchen@pumc.edu.cn or cyh-birm@263.net.

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Take home message (234 characters)

In the general adult population in China, chronic cough is prevalent and associated with a poorer health status, especially in individuals aged 50 years or older, and those with the diagnosis of COPD, or with small airway dysfunction.

Word counts: Abstract: 249; Text: 3967

Abstract

Background: Chronic cough is a common complaint but there is no population-based data on its burden in China.

Objectives: We determined the prevalence of chronic cough and its impact on health status in adults stratified by sex, age and the diagnosis of chronic obstructive pulmonary disease (COPD) or the presence of small airway dysfunction (SAD).

Methods: A representative sample of 57,779 Chinese adults aged 20 years or older was recruited and pulmonary function test was measured. Chronic cough was defined as cough lasting for more than 3 months in each year. Quality of life was assessed by the 12-item Short Form Health Survey (SF-12) and self-reported history of hospital visits was recorded.

Results: Chronic cough was found in 3.6% (95% CI 3.1-4.1) of Chinese adults, 2.4% (95% CI 1.9-3.1) of those aged 20-49 age old, and 6.0% (95% CI 5.3-6.8) of those aged 50 years or older. Individuals with chronic cough had an impaired physical component summary (PCS) score of the SF-12 (P<0.0001), more emergency visits (P=0.0042) and hospital admissions (P=0.0002). Furthermore, the impact of chronic cough on PCS score was more significant in those aged 50 years or older, or with COPD (P=0.0018 or 0.0002, respectively), with the impact on hospital admission being more significant in those with COPD or with SAD (P=0.0026 or 0.0065, respectively).

Conclusions: Chronic cough is prevalent in China and is associated with a poorer health status, especially in individuals aged 50 years or older and those with the diagnosis of COPD or SAD.

Key words: chronic cough; prevalence; risk factor; quality of life

Introduction

Chronic cough is a common complaint in the clinic, and can be a major manifestation of many lung diseases including asthma and chronic obstructive pulmonary disease (COPD)[1-3]. Although cough for more than 8 weeks is recommended as the cut-off duration of chronic cough by clinical guidelines[4], many studies have utilized the 3-month cut-off duration based on the Medical Research Council definition of chronic bronchitis[5]. Using the definition of chronic cough present over at least 3-month duration every year, the prevalence of chronic cough has been reported to vary quite widely both in studies conducted among general population (2.6-11.7%)[6-8]and among COPD patients (14.4-74.1%)[9, 10]. The reported risk factors for chronic cough have included tobacco smoke, air pollution and occupational exposures[11, 12]. Despite more than 1.3 billion population in China, which occupied the largest population in the world[13], there is no data on the prevalence and risk factor of chronic cough in a representative population of adults in China.

Previous studies have also reported that chronic cough was associated with impaired lung function, quality of life, more disease severity in the general population[11, 14], or subjects with COPD[3, 15]. However, there have been no direct comparison of the impact of chronic cough on health status in different populations, such as between men and women, younger and older, with or without COPD, and the presence or absence of small airway dysfunction (SAD).

To address these issues, we used data from the national cross-sectional China Pulmonary Health (CPH) study, where chronic cough was defined as cough for ≥3 months in each year in order to estimate the prevalence of chronic cough. Additionally, we identified the risk factors and assessed the impact of chronic cough on health status stratified by sex, age and the diagnosis of COPD or SAD.

Methods

Study Design and Population

The CPH study was conducted between June 2012 and May 2015, which enrolled a nationally representative sample of 57779 Chinese adults aged 20 years or older. The study design and the questionnaires used have been previously described[16]. Briefly, we used a multi-stage stratified cluster sampling procedure, which considered geographical region, degree of urbanization, economic development status, and sex and age distribution. In stage one, we selected ten provinces, autonomous regions, and municipalities (only regions below 1500 meters of altitude were included), which represented the socioeconomic statuses and lifestyles of six major geographical regions in China. We randomly selected a large city, a midsize city, an economically developed county, and an underdeveloped county from each province or autonomous region in stage two. We randomly selected two urban districts from every city and two rural townships from every county in stage three. We further randomly selected two urban residential communities or rural village communities (about 1000–2000 households) from the urban districts or rural townships, respectively in stage four. Finally, we randomly selected individuals aged 20 years or older from the selected communities stratified by sex and age distribution based on the 2010 China census data[17]. We selected only one participant from every household, without replacement. Temporary residents (living in their current residence less than one year); those who were physically incapable of taking a spirometry test; those admitted to hospital for any cardiac condition in the past 3 months, or with treated tuberculosis; or women who were pregnant or breastfeeding were excluded.

Trained interviewers administered the questionnaire in Chinese to obtain information regarding demographic characteristics, medical history, parental history of respiratory disease, and risk factors. The study protocol was approved by the ethics committees of the Capital Medical University (Beijing, China) and all other participating institutes. Written informed consent was obtained from all participants.

Procedures

Chronic cough was defined as an affirmative response to both questions: Do you often cough when you don't have a cold? Does your cough last more than 3 months each year? The use of 3 months' cutoff duration in cough was derived from the definition of chronic bronchitis[5], and this definition has been commonly used in epidemiological investigations of chronic cough[1]. COPD was defined as a post-bronchodilator (BD) forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.70[18]. SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: maximal mid-expiratory flow (MMEF), forced expiratory flow (FEF) at 50% of the FVC (FEF50%), and FEF75% after bronchodilator inhalation[19, 20]. We obtained information on cigarette smoking, history of childhood pneumonia or bronchitis, and history of chronic bronchitis, as previously described[16]. We defined allergic rhinitis as having 2 or more of the following symptoms for >1 hr on most days according to the Allergic Rhinitis and Its impact on Asthma questionnaire[21], 1. watery rhinorrhea; 2. sneezing, especially paroxysmal; 3. nasal obstruction; 4. nasal pruritis. Additionally, we defined biomass use as using woody fuels or animal waste for cooking or heating during the past 6 months or longer. We defined occupational exposure as exposure to dust, allergens, noxious gases (e.g mining, forging, chemical

industry, cement, greenhouse planting) for more than 3 months. We derived exposure to ambient particulate matter with a diameter less than 2·5 μm ($PM_{2·5}$) from the regional satellite-retrieved aerosol optical depth model[22]. We measured the health status of all participants using the physical component summary (PCS) score and the mental component summary (MCS) score of the 12-item Short Form Health Survey (SF-12)[23].

Trained and certified technicians carried out pulmonary function tests on all participants using a MasterScreen Pneumo PC spirometer (CareFusion, Yorba Linda, CA, USA). We did daily calibration with a 3 L syringe. Participants were required to do up to eight forced expiratory maneuvers until FVC and FEV_1 were reproducible within 150 mL. We administered a bronchodilator (salbutamol 400 μg) by inhalation through a 500 mL spacer and repeated spirometry 20 min later, using the same criteria. Test results were stored in the spirometer and downloaded them daily to a central computer system. All the spirometric data were reviewed centrally by an expert panel on the basis of the criteria of the American Thoracic Society and European Respiratory Society[24], and reference values for spirometry[25]. Poor-quality data were excluded.

Statistical analysis

All calculations were weighted to represent the general adult population aged 20 years or older in China[17]. A technique appropriate for this complex survey design, the Taylor series linearization method, was used to calculate standard errors (SEs)[26]. We used all participants for whom the variables of interest were available, and we did not impute missing data.

We assessed the significance of differences using t-test for continuous variables and by χ^2 test for categorical variables. The comparisons were performed according to

chronic cough status, sex, and other characteristics including age (20-49 years, ≥50 years), COPD and SAD. The comparisons were weighted with taking into account of the multistage cluster sampling design. We examined the association between risk factors and chronic cough by multivariable adjusted logistic regression analyses. The associations of chronic cough with continuous outcomes (including FEV_1/FVC, FEV_1%pred, MMEF%pred, FEF 50%pred, FEF 75%pred, PCS, and MCS) and categorical outcomes (including FEV_1/FVC<70%, SAD, positive bronchodilator reversibility, emergency, and hospital admission) were estimated with multivariable adjusted linear regression and logistic regression models, respectively. The variables adjusted included age, sex, urbanization, body mass index, cigarette smoking, biomass, annual mean $PM_{2.5}$, education, occupational exposure, visible mold spots in the current residence, history of pneumonia or bronchitis during childhood, parental history of respiratory diseases, and allergic rhinitis. The above logistic or linear regression analyses were weighted, taking into account of the multistage cluster sampling design.

Subgroup analyses were also performed for the association of chronic cough with PCS, MCS, and emergency or hospital admission due to acute exacerbation of respiratory symptoms in the preceding 12 months according to sex, age (20-49 years and ≥50 years), diagnosis of COPD, and the presence of SAD. Furthermore, the interaction terms between chronic cough and the subgroup variables were added into the above regression model in order to explore any potential interactions.

All statistical analyses were performed with SUDAAN (Version 11.0; Research Triangle Institute, Research Triangle Park, NC) and SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

The final analysis included 50, 991 subjects (21, 446 men and 29, 545 women) who completed the questionnaire survey and provided reliable pulmonary function tests before and after a bronchodilator. A total of 1985 people with chronic cough were identified from the 50,991 participants. The demographics and risk factors by diagnosis of chronic cough are summarized in Table 1.

The prevalence of chronic cough was 3.6% (95% CI 3.1-4.1) among the general Chinese population aged 20 years or older (Table 2). The prevalence of chronic cough among the different regions is shown in Figure 1. Men had a higher prevalence (4.6%, 95% CI 3.9-5.4) than women (2.6%, 95% CI 2.1-3.3) (P=0.0005) across the whole age-group. The prevalence of chronic cough increased with age, being 2.4% (95% CI 1.9-3.1) among individuals aged 20-49 years and 6.0% (95% CI 5.3-6.8) among those aged 50 years or older (P <0.0001). We also observed that the prevalence of chronic cough was higher in the individuals with SAD than in those without SAD (4.4% vs 2.8%, P=0.0039). However, the prevalence of chronic cough was not significantly different between those with COPD and those without COPD (6.0% vs 3.2%, P=0.0845) (Table 2). Not surprisingly, smokers had a higher prevalence (5.9%, 95% CI 4.9-7.0) than never-smokers (2.5%, 95% CI 2.0-3.0) (P<0.0001) (Table E1). With respect of the concomitant symptoms accompanying chronic cough, phlegm was the most common concomitant symptom, present in 67.5% of those with chronic cough, and only 404 (22.6%) subjects with chronic cough had neither phlegm nor dyspnea and wheeze. (Table E2).

Multivariable adjusted analyses in the entire population showed that age, cigarette smoking, occupational exposure, history of pneumonia or bronchitis during childhood, and allergic rhinitis were consistently associated with the prevalence of chronic cough

(P<0.01 for all). However, biomass use and exposure to high concentrations of $PM_{2.5}$ (≥75 μg/m^3) were not associated with the prevalence of chronic cough (Table 3). When considering only never-smokers, similar results were observed (Table E3).

People with chronic cough had lower lung function after bronchodilator inhalation, including FEV_1/FVC, FEV_1%pred (P<0.0001, P=0.0155, respectively) than those without chronic cough (Table 4). Compared with people without chronic cough, those with chronic cough had an impaired physical health state (mean PCS scores of 48.7 vs 52.6 points, P < 0.0001) as measured by PCS scores based on the SF-12 questionnaire. Furthermore, among people with chronic cough, 3.5% and 5.5% reported at least one emergency room visit or hospital admission in the past 12 months due to an exacerbation of respiratory symptoms, respectively, which were significantly higher than those without chronic cough of 0.5% for emergency room visit and 0.4% for hospital admission (P =0.0042 and 0.0002, respectively). The impact of chronic cough on lung function before bronchodilator inhalation and medication use is shown in Table E4. To test the impact of chronic cough solely on lung function, health status and medication use, we have also performed a sensitivity analysis in 404 patients solely presenting with chronic cough, and observed the similar adverse impact of chronic cough solely on FEV_1/FVC (Table E5).

After adjusting for confounding factors, such as age, sex, smoking status, biomass or $PM_{2.5}$ exposure, chronic cough was associated with reduced spirometry parameters after bronchodilator inhalation, including FEV_1/FVC, MMEF%pred, FEF50%pred and FEF75%pred (P<0.05 for all) (Table 5). The similar impact on spirometry parameters before bronchodilator inhalation was showed in Table E6.

Finally, subgroup analysis showed that the association of chronic cough with PCS scores or hospital admission was independent on sex, age, the diagnosis of COPD and

the presence of SAD. Furthermore, interaction analysis showed that the impact of chronic cough on PCS score were significantly stronger among people aged 50 years old, or with COPD than those aged 20-49 years old, without COPD (P=0.0018 and P=0.0002 respectively). Similarly, the impact of chronic cough on hospital admission was significantly stronger among those with COPD, or SAD than those without COPD, or SAD (P=0.0026 and P=0.0065, respectively) (Figure 2).

Discussion

The main findings of the present analysis from the CPH database are: 1) chronic cough was prevalent in general adult population in China; 2) age, cigarette smoking, occupational exposure, history of pneumonia or bronchitis during childhood and allergic rhinitis were the main risk factors associated with the prevalence of chronic cough; 3) the impact of chronic cough on quality of life or medication utilization were more significant in those aged ≥ 50 years, and in those with COPD or SAD.

Our present study from a large comprehensive survey in a nationally-representative sample of Chinese adults indicated that the prevalence of chronic cough was 3.6% in Chinese adults aged 20 years or older, and increased with age from 2.4% in individuals aged 20-49 years to 6.0% in those aged 50 years or older. Consistent with other previous epidemiological studies, we used 3 months as the cutoff duration for chronic cough which has been widely used in the epidemiologic survey of chronic cough in general population[27-29].

The prevalence of 3.6% in the present study is very similar to the value of 3.48% among adults aged 40 years or older based on the same criterion reported by Won et al from the Korean National Health and Nutrition Examination survey of 2010-2016[29], and was also similar to the 4% prevalence reported in adults aged 20 and older in Denmark using an 8-week or more duration of chronic cough[30]. The prevalence of 3.6% in the present study was higher than the value of 1.7% among the general population aged 40 years or older reported by Omori et al in Japan, in which chronic cough was defined as having both cough and phlegm for at least 3 months of the year and for at least 2 consecutive years, or as receiving any treatment for chronic bronchitis at the time of recruitment[31]. However, the prevalence of 3.6% in the present study was far lower than the estimation of 7.9% of prevalence in the global

general adults using the 3 months cut-off definition reported from a systematic review and meta-analysis by Song[1] and the 16% of prevalence in Northern Europe from the Respiratory Health in Northern Europe (RHINE) III cohort using the definition of chronic cough lacking a specified timeframe, but described as protracted and troublesome[32]. Existing chronic cough prevalence data vary widely which might be due to differences in survey method, sample populations, definition, and ethnicity.

By contrast, a recent meta-analysis of several Chinese studies showed that the prevalence of chronic cough was 6.22% (95% CI 5.03–7.41%) in Chinese adults[33]. 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 be representative of the real prevalence of chronic cough in China.

Most previous reports from clinics showed that prevalence of chronic cough was greater in women[34, 35]. However, we observed that men had a higher prevalence than women in the representative general adults. The higher prevalence of chronic cough in men might be partly due to higher smoking rate in men with 47.2% than in women with 2.7%[36]. In addition, the other possible explanation is that women have a heightened cough reflex sensitivity, resulting in more hospital visits for their cough[37].

For the prevalence of chronic cough, we did not find a statistically significant difference between participant with and without COPD (6.0% vs 3.2%, *P*=0.0845), although the multivariable adjusted analysis (Table 5) showed that the risk of COPD was 59% higher among participants with chronic cough compared with those without chronic cough (OR 1.59; 95% CI, 1.13-2.23). The present results also support our previous findings that asymptomatic patients with COPD was common in China,

especially in those with a mild degree of airflow limitation, such as patients at GOLD I or II stage[16]. A similar result was also reported from general population in the Danish population where only 10% of COPD people diagnosed by spirometry from the general population had chronic cough defined as cough lasting for more than 8 weeks[3]. These results demonstrate that chronic cough may not be a common symptom of early COPD and imply that screening of the early COPD in the community based on the self-reported chronic cough may not be appropriate, at least in Chinese general population.

The identified risk factors associated with chronic cough in this study have been reported previously, including age, smoking, occupational exposure, history of pneumonia or bronchitis during childhood and allergic rhinitis[30, 38-40]. We found that ever-smokers had double to triple risk of chronic cough compared with never-smokers. Likewise, occupational exposure also increased the risk of chronic cough by 40%. Therefore, smoking cessation and avoiding occupational exposure should be mandatory in the management of patients with chronic cough. In accordance with previous studies reporting an inconsistent association of ambient air pollution with chronic cough[12, 41], we did not observe an impact of air pollution on the prevalence of chronic cough. This lack of association of air pollution with chronic cough may be due to the use of only one measure of $PM_{2.5}$ level averaged over a year within the geographic region of the participant, when the degree of personal exposure to $PM_{2.5}$ and other constituents of air pollution may also be more important in underlying the cough response.

In the present study, people with allergic rhinitis had nearly three times the risk for chronic cough compared with people who had no allergic rhinitis, which is supported by the report that upper airway inflammation is one of the most commonly identified

cause of chronic cough[42]. In addition, a multicenter survey to identify causes of chronic cough in Chinese adults showed that cough variant asthma (32.6%) and upper airway cough syndrome (18.6%) were the two top-ranked causes of chronic cough[43]. We also showed that 21.0% people with chronic cough reported concomitant recurrent wheezing (Table E2). Therefore, in some cases, chronic cough in individuals with allergic rhinitis or concomitant recurrent wheezing may represent undiagnosed asthma, and these individuals will most likely benefit from treatment with inhaled corticosteroids.

Although a previous study from a small hospital-based asthma cohort reported that cough frequency was not associated with lung function[44], our present study from a large general population showed that chronic cough was associated with an adverse impact on the lung function, consistent with previous findings in COPD patients[3] and from the general population[11]. These inconsistent results might be due to different scale of cough (e.g. cough frequency vs. cough duration) and a different small population recruited.

Our study showed that chronic cough associated with an adverse impact on PCS score by the SF-12 questionnaire and healthcare resource use. Furthermore, the impact of chronic cough on PCS score was independent of age, sex, the diagnosis of COPD and the presence of SAD. Our results are similar to that conducted in an elderly population from a small community in Korea showing that chronic cough was associated with an adverse impact on PCS and also on MCS of the SF-36 questionnaire[45].

A previous study has reported that women have a heightened cough reflex sensitivity, and experience a greater impact on health-related quality of life, resulting in more women seeking medical attention for their cough[37]. However, we did not

observe that chronic cough had a greater impact on PCS score in women than in men, even though women with chronic cough had more night-time sleep disturbance compared with men with chronic cough (Table E2). This is similar to a previous report of no significant difference in overall quality of life between men and women, although embarrassment, frustration and sleep disturbance were more common in women[46].

We observed that the prevalence of chronic cough increased with age and that chronic cough was more prevalent in subjects aged 50 years and above, similar to results from the Copenhagen General Population Study in Denmark, or the Rotterdam Study in Netherlands[30, 38]. The impact of chronic cough on quality of life in the elderly is complex. On the one hand, the elderly have more concomitant symptoms accompanying chronic cough, such as sputum production, wheezing, dyspnea and urinary incontinence as we and others have reported[47], which contribute to making chronic cough having a notably large impact on quality of life in the elderly[29]. On the other hand, a reduced cough reflex may also be a significant problem in the elderly, that may be associated with a greater risk of aspiration pneumonia[48]. In the present study, the interaction analysis showed that the impact of chronic chough on PCS scores was significantly stronger among people above aged 50 years old. This "double-sidedness" of cough in the elderly indicates the need for a more comprehensive but balanced clinical approach in this age group.

Consistent with previous findings[3], our present study further showed that comorbid chronic cough in individuals with COPD was associated with a more severe disease in terms of poorer quality of life and more healthcare utilizations than those without COPD. These findings accords well with the fact that individuals with COPD

and chronic cough have more accompanying respiratory symptoms, such as phlegm and wheezing.

SAD is considered as a precursor of COPD and asthma and is common in the general population[20, 49, 50]. In our previous analysis of the same population, the presence of COPD or asthma was associated with about a two-fold higher odds-ratio for SAD[20]. We now observe that individuals with chronic cough were also associated with SAD. Furthermore, we found that those with SAD had more hospital admission than those without SAD as we have observed in those with COPD. These finding imply that individuals with SAD and chronic cough represent a more vulnerable group compared with those without SAD and they should be paid more attention in the clinic.

We assessed the impact of overall chronic cough on health status stratified by sex, age and the diagnosis of COPD or SAD, but not stratified by the diagnosis of asthma, because the sex, age and the diagnosis of COPD or SAD defined by spirometry are objective indicators, while asthma determined by the epidemiological definition is not.

To our knowledge, our study is the first nationally-representative survey reporting the prevalence, risk factors of chronic cough in China, and investigates its impact on health status, healthcare resource use in adults according to age, sex and the diagnosis of COPD or the presence of SAD. However, there are some limitations. First, chronic cough was defined by period prevalence, not by point prevalence, which is prone to recall bias. The definition was also dependent on the duration of cough, which has limited value in disease burden and risk factors. Second, similar to other large-scale population-based survey, we did not exclude lung parenchymal diseases by chest radiograph or computed tomography and neither did we pursue the clinical cause(s) of chronic cough. Third, we assessed the impact of chronic cough overall on health

status in the present study, without considering the synergistic effects of other concomitant symptoms accompanying chronic cough, such as phlegm, dyspnea, and wheeze. We recognize that besides cough symptom, other respiratory symptoms such as dyspnea, wheezing, and sputum would also affect worse clinical outcome in subjects with COPD or SAD. Thus, whether the impact of chronic cough on health status was independent of cough itself need to be further investigated in future.

Conclusion

Our finding in this representative general population is that chronic cough is common, increases with age, and is associated with poorer health status. Furthermore, the impact of chronic of cough on health status is more significant in individuals aged 50 yrs old or older, and those with COPD, or with SAD. It is important now to determine the long-term outcomes of in these various subgroups of chronic cough.

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TABLE 1 Demographics and risk factors by diagnosis of chronic cough in the general Chinese adult population

Variables	No chronic cough (n=49006)	Chronic cough (n=1985)	*P*-value
Men	20255 (50.0%)	1191 (64.0%)	0.0031
Age, years	43.5 (0.8)	52.0 (1.5)	<0.0001
Urban residents	31637 (51.6%)	1242 (52.1%)	0.9135
Education level			0.0359
Primary school or less	12090 (22.2%)	665 (33.0%)	
Middle and high school	28113 (52.5%)	1057 (46.8%)	
College and higher	8803 (25.3%)	263 (20.2%)	
Cigarette smoking			0.0001
Never smoker	35466 (69.4%)	963 (45.9%)	
Ever smoker*	13540 (30.6%)	1022 (54.1%)	
Passive smoking at home#	17130 (47.8%)	470 (52.9%)	0.2546
Biomass use	12967 (25.8%)	661 (32.4%)	0.0747
Annual mean $PM_{2.5}$ exposure, $\mu g/m^3$	70.7 (2.9)	72.3 (3.6)	0.3203
Occupational exposure	11608 (24.5%)	719 (37.3%)	0.0017
Visible mold spots in the current residence			0.2377
Rarely	36152 (69.1%)	1319 (62.3%)	
Sometimes	10098 (24.2%)	487 (28.7%)	
Often	2265 (6.7%)	170 (9.0%)	
History of pneumonia or bronchitis during childhood	2227 (4.9%)	217 (11.3%)	0.0033
Parental history of respiratory diseases	8070 (16.5%)	539 (24.4%)	0.0006
Body mass index, kg/m^2	23.6 (0.1)	23.9 (0.2)	0.1855
Allergic rhinitis	4676 (10.6%)	407 (25.0%)	0.0006

Values are weighted and shown as number (%) or mean (SE). Abbreviations: $PM_{2.5}$, particulate matter with a diameter less than 2.5 μm.

P-value are weighted, taking into account of the multistage cluster sampling design and based on χ^2 test for categorical variables or Student's t test for continuous variables.

* Ever smoker was defined as having smoked equal to or more than 100 cigarettes in the lifetime.

Demographics of passive smoking at home were shown for never smokers.

TABLE 2 Age-specific and age-standardized prevalence of chronic cough in the general adult population

Variables	Total	Men	Women	*P*-value
Total	3.6% (3.1-4.1)	4.6% (3.9-5.4)	2.6% (2.1-3.3)	0.0005
Age, years				
20-49	2.4% (1.9-3.1)	3.0% (2.2-4.2)	1.7% (1.1-2.7)	0.0433
≥50	6.0% (5.3-6.8)	7.7% (6.7-8.8)	4.3% (3.6-5.0)	<0.0001
***P*-value for difference**	<0.0001	<0.0001	<0.0001	
COPD*				
No	3.2% (2.7-3.7)	4.1% (3.4-5.0)	2.3% (1.8-3.0)	0.0006
Yes	6.0% (3.5-10.0)	5.2% (4.0-6.7)	6.9% (2.5-18.1)	0.5777
***P*-value for difference**	0.0845	0.1155	0.1846	
SAD#				
No	2.8%（2.3-3.5）	3.7% (3.0-4.5)	2.0%（1.5-2.8）	0.0010
Yes	4.4%（3.7-5.2）	5.4% (4.2-6.9)	3.2%（2.4-4.2）	0.0101
***P*-value for difference**	0.0039	0.0229	0.0233	

Values are represented as percentage (%) (95% confidence interval, CI). Abbreviations: COPD, chronic obstructive pulmonary disease; SAD, small airway dysfunction.

P-value for difference is for the comparison of binary variables. All the calculations of *P*-value are weighted, taken into account the multistage cluster sampling design and based on χ^2 test.

* COPD was defined as the individuals with post-bronchodilator FEV_1/FVC less than 70%.

SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: maximal mid-expiratory flow, forced expiratory flow (FEF) 50%, and FEF 75% after bronchodilator inhalation.

TABLE 3 Multiple adjusted odds ratios of chronic cough in the general Chinese adult population

Variables	OR (95% CI)	*P*-value
Men	0.93 (0.63-1.37)	0.7045
Age (10 years)	1.43 (1.26-1.61)	<0.0001
Rural resident	0.84 (0.59-1.19)	0.3094
Smoking status		
Never smoker	1.00 (Reference)	
Ever smoker*	2.61 (2.10-3.25)	<0.0001
Biomass use	1.04 (0.86-1.26)	0.6621
Annual mean $PM_{2.5}$, $\mu g/m^3$		
<50	1.00 (Reference)	-
50-75	0.96 (0.59-1.57)	0.8784
≥75	1.05 (0.62-1.79)	0.8471
Education level		
Primary school and lower	1.00 (Reference)	-
Middle and high school	0.80 (0.61-1.05)	0.1083
College and higher	0.97 (0.68-1.39)	0.8770
Occupational exposure	1.41 (1.10-1.80)	0.0086
Visible mold spots in the current residence		
Rarely	1.00 (Reference)	-
Sometimes	1.31 (0.91-1.90)	0.1414
Often	1.19 (0.73-1.93)	0.4652
History of pneumonia or bronchitis during childhood	2.23 (1.49-3.34)	0.0006
Parental history of respiratory diseases	1.23 (0.95-1.59)	0.1165
Body mass index, kg/m^2		
<18.5	1.45 (0.97-2.16)	0.0662
18.5-24.9	1.00 (Reference)	-
≥25	1.23 (0.94-1.61)	0.1197
Allergic rhinitis	2.84 (1.98-4.09)	<0.0001

The variables listed in the table are all included in the model. Abbreviations: OR, odds ratio; 95% CI: 95% confidence interval; $PM_{2.5}$, particulate matter with a diameter less than 2.5 μm.
The logistic regression analyses are weighted, taking into account of the multistage cluster sampling design.
*Ever smoker was defined as having smoked equal to or more than 100 cigarettes in the lifetime.

TABLE 4 Clinical characteristics and use of healthcare resources by diagnosis of chronic cough

Variables	No chronic cough (n=49006)	Chronic cough (n=1985)	*P*-value
Lung function*			
FEV_1/FVC, %	82.0 (0.4)	75.2 (1.2)	<0.0001
FEV_1 %pred	99.8 (0.9)	94.5 (2.5)	0.0155
FEV_1/FVC<70%	4420 (8.1%)	488 (22.8%)	0.0010
MMEF%pred	76.0 (1.0)	62.6 (2.8)	<0.0001
FEF 50%pred	88.4 (1.0)	74.4 (3.4)	<0.0001
FEF 75%pred	77.2 (1.3)	62.7 (2.6)	<0.0001
SAD#	15991 (28.3%)	988 (48.0%)	0.0017
Positive bronchodilator reversibility†	3059 (6.1%)	222 (13.0%)	0.0315
Short form (SF)-12 scores			
PCS scores	52.6 (0.2)	48.7 (0.6)	<0.0001
MCS scores	54.1 (0.3)	53.1 (0.6)	0.0656
Comorbidities			
Hypertention	3846 (6.4%)	309 (13.1%)	0.0116
Coronary heart disease	698 (1.9%)	87 (3.2%)	0.3501
Diabetes	1203 (2.6%)	96 (3.9%)	0.2589
Acute exacerbation of respiratory symptoms in the last 12 months			
Emergency	174 (0.5%)	89 (3.5%)	0.0042
Hospital admission	167 (0.4%)	119 (5.5%)	0.0002

Values are weighted and shown as number (%) or mean (SE). Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; capacity PCS, physical component summary; MCS, mental component summary; SAD, small airway dysfunction.

All the calculations of *P*-value are weighted, taking into account the multistage cluster sampling design and based on χ^2 test for categorical variables or Student's t test for continuous variables.

*The parameters were measured at 20 min after inhalation of 400μg of salbutamol.

#SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: maximal mid-expiratory flow, forced expiratory flow (FEF) 50%, and FEF 75% after bronchodilator inhalation.

†A positive bronchodilator reversibility test was defined as an increase in post-bronchodilator forced expiratory volume in 1 s of more than 12% and more than 200 ml from baseline, 20 min after inhalation of 400μg of salbutamol.

TABLE 5 Associations of chronic cough with lung function after bronchodilator inhalation

Variables	OR or β (95% CI)	*P* value
FEV_1/FVC	-3.30 (-4.93, -1.66)	0.0005
FEV_1 %pred	-4.42 (-8.89, 0.05)	0.0522
FEV_1/FVC<70%	1.59 (1.13, 2.23)	0.0106
MMEF%pred	-5.73 (-9.06, -2.40)	0.0020
FEF 50%pred	-7.64 (-12.16, -3.11)	0.0023
FEF 75%pred	-6.51 (-10.29, -2.74)	0.0019
SAD*	1.47 (1.14, 1.89)	0.0049
Positive bronchodilator reversibility#	1.87 (1.01, 3.47)	0.0472

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEF50%, forced expiratory flow at 50% of the FVC; FEF75%, forced expiratory flow at 50% of the FVC; SAD, small airway dysfunction.

Adjusted for age, sex, urbanization, body mass index, cigarette smoking, biomass, annual mean $PM_{2.5}$, education, occupational exposure, visible mold spots in the current residence, history of pneumonia or bronchitis during childhood, parental history of respiratory diseases, parental history of respiratory diseases, and allergic rhinitis. The logistic or linear regression analyses are weighted, taking into account of the multistage cluster sampling design.

*SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: MMEF, FEF50%, and FEF 75% after bronchodilator inhalation.

#A positive bronchodilator reversibility test was defined as an increase in post-bronchodilator forced expiratory volume in 1 s of more than 12% and more than 200 ml from baseline, 20 min after inhalation of 400μg of salbutamol.

Figure legends

FIGURE 1 The prevalence of chronic cough in the different regions

FIGURE 2 Association of chronic cough with quality of life and the respiratory exacerbations

Abbreviations: COPD, chronic obstructive pulmonary disease; SAD, small airway dysfunction.

A: PCS score; **B:** MCS score; **C:** Emergency; **D:** Hospital admission

Adjusted for age, sex, urbanization, body mass index, cigarette smoking, biomass, annual mean $PM_{2.5}$, education, occupational exposure, visible mold spots in the current residence, history of pneumonia or bronchitis during childhood, parental history of respiratory diseases, and allergic rhinitis. The subgroup variables were not adjusted in the corresponding subgroup analysis for themselves, except that age was still adjusted as continuous variable for the subgroup analysis conducted among those aged 20-49 and ≥50 years old.

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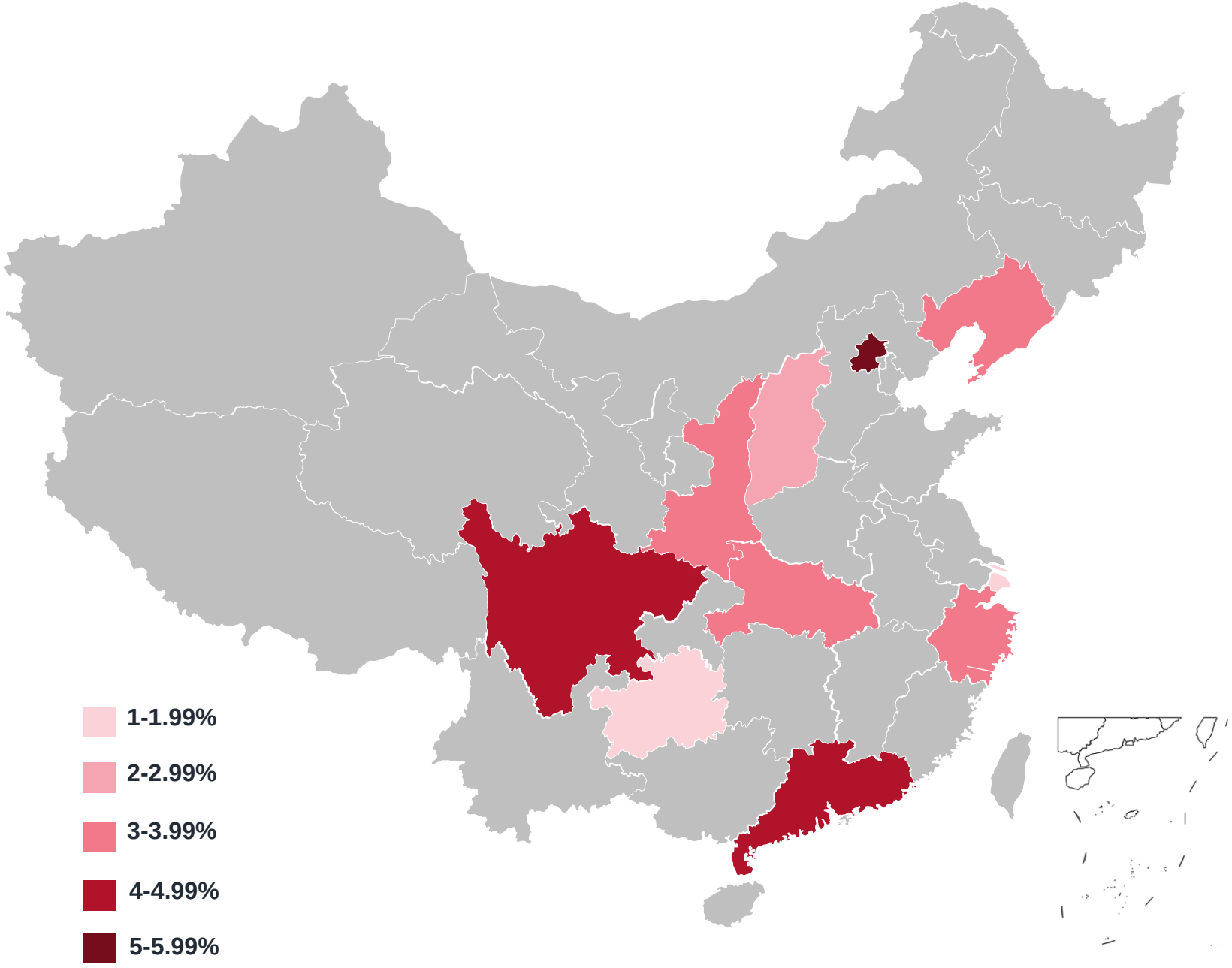
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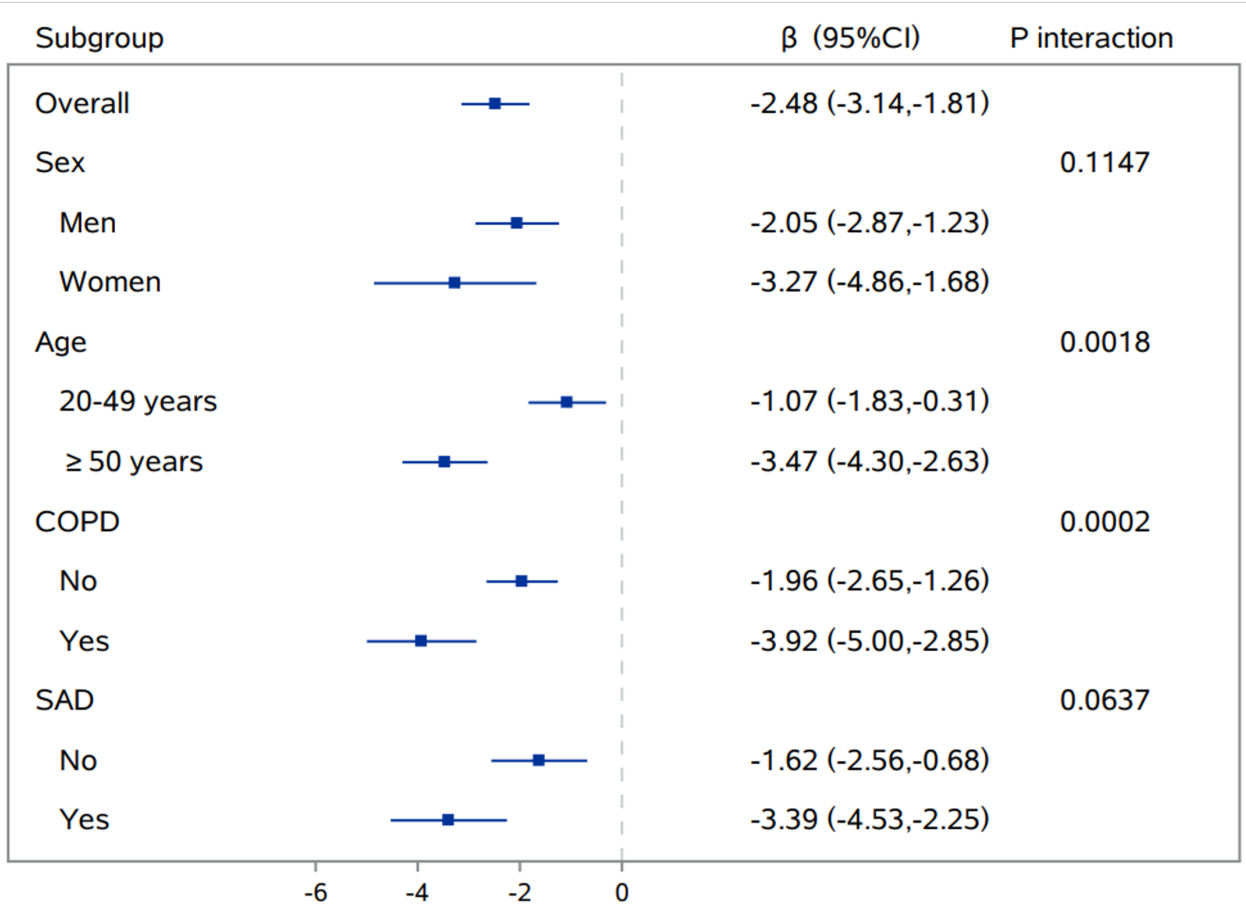
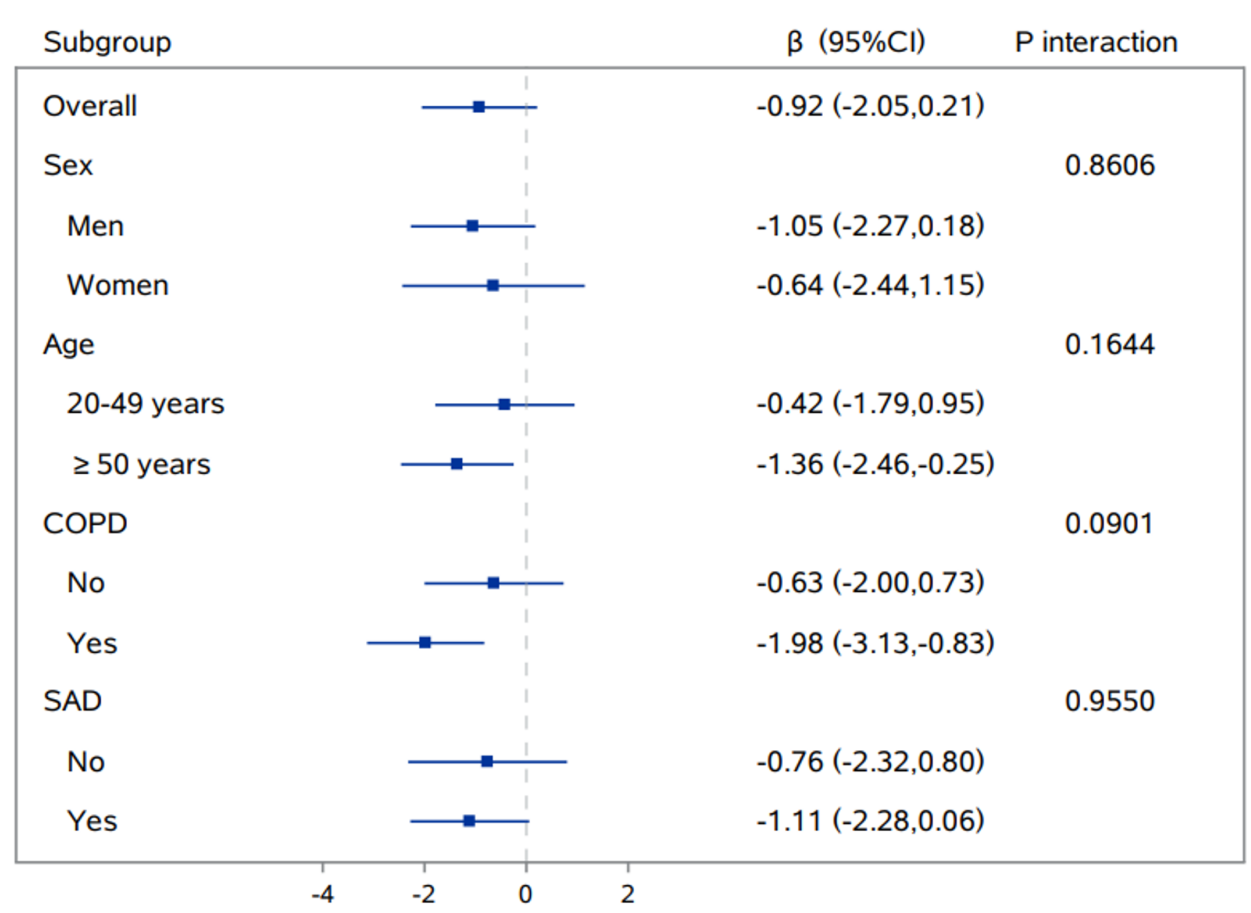
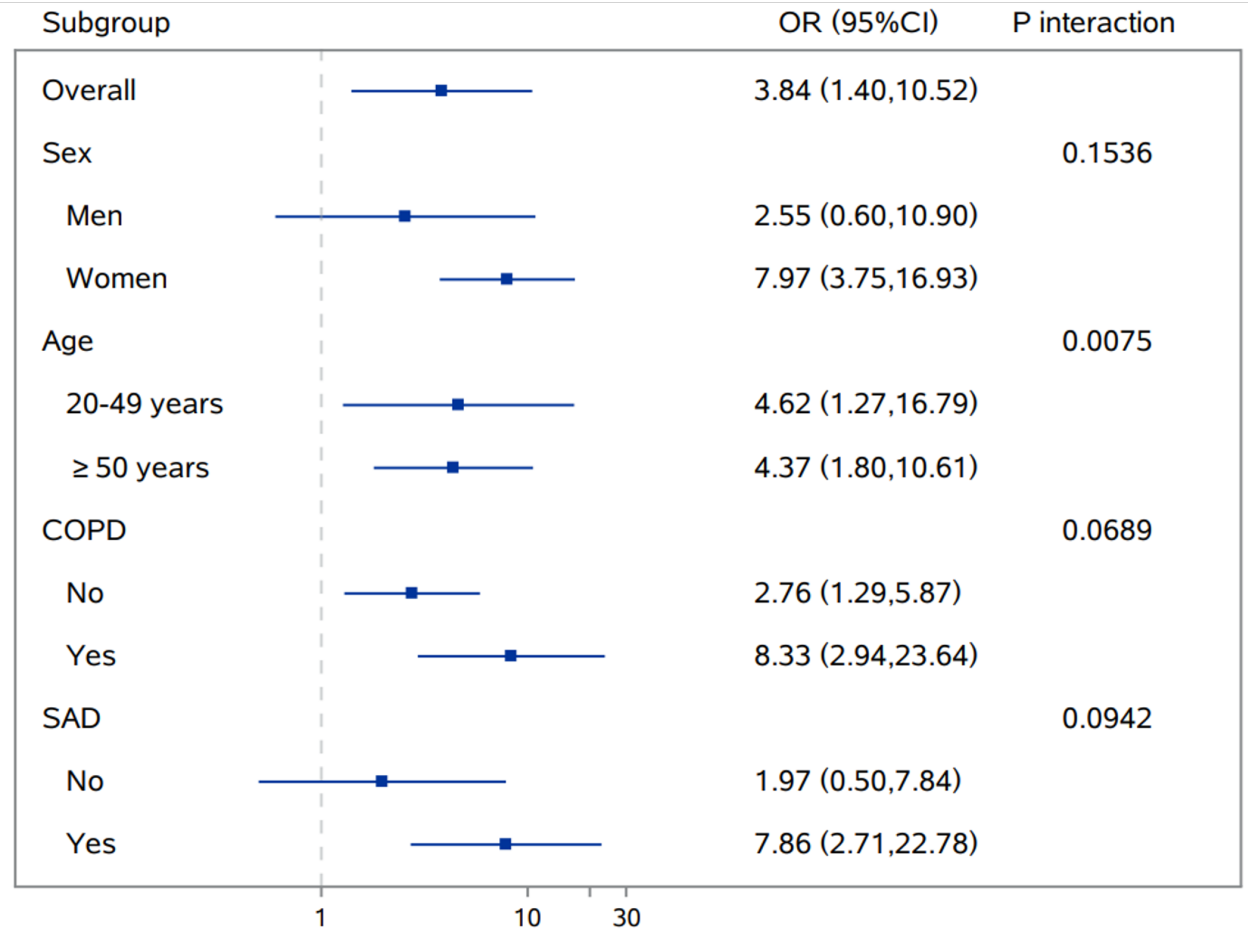
(A) PCS score



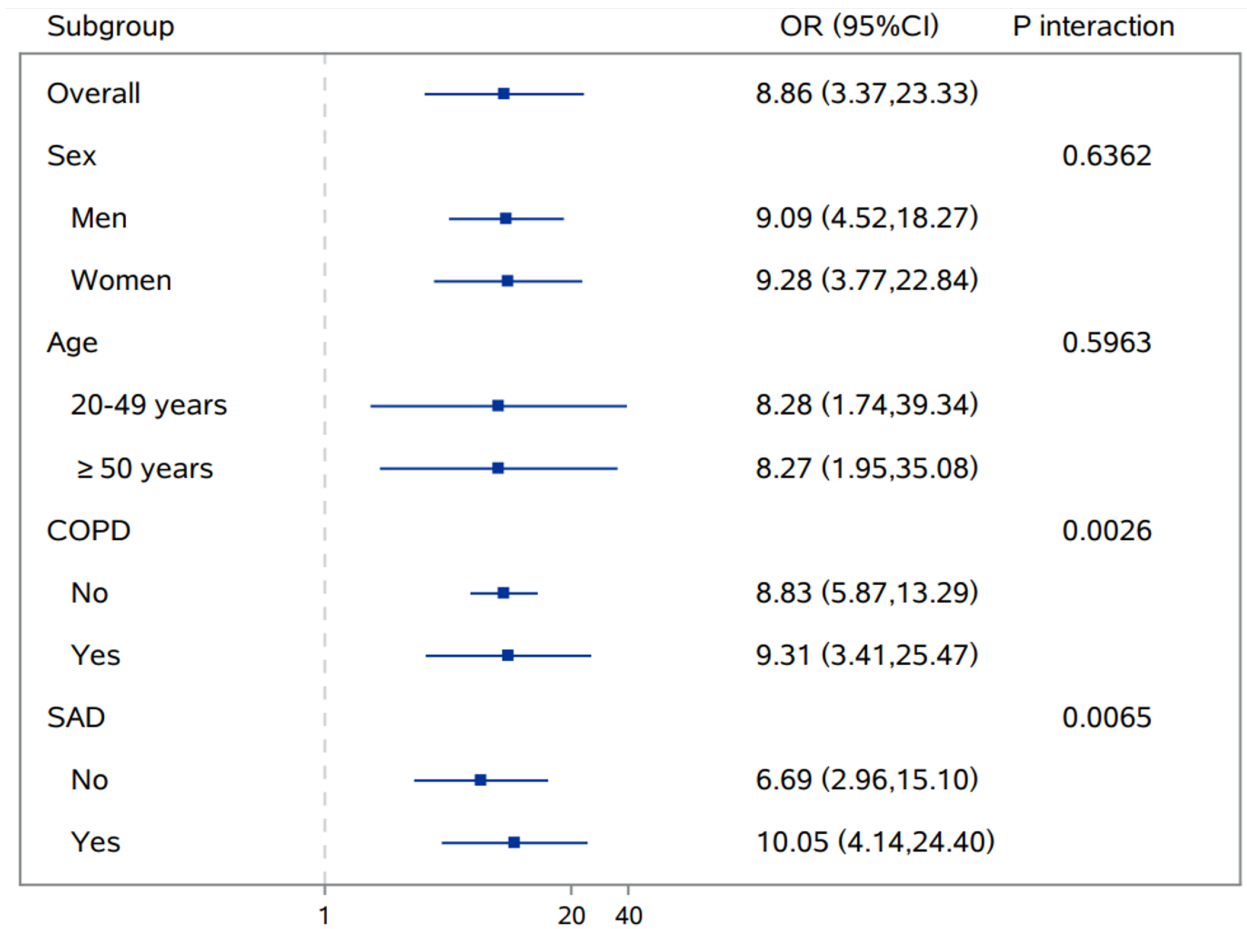
(B) MCS score



(C) Emergency



(D) Hospital admission



Supplementary Appendix

Supplement to:

Prevalence and burden of chronic cough in China: a national cross-sectional study

Table E1 Age-specific and age-standardized prevalence of chronic cough in the general adult population stratified by smoking status

Variables	Never smoker	Ever smoker*	*P*-value
Total	2.5% (2.0-3.0)	5.9% (4.9-7.0)	<0.0001
Sex			
Men	2.3% (1.7-3.0)	6.0% (5.0-7.3)	<0.0001
Women	2.5% (2.0-3.2)	3.1% (2.1-4.7)	0.4125
***P*-value for difference**	0.5127	0.0035	
Age, years			
20-49	1.6% (1.1-2.4)	4.1% (3.0-5.8)	0.0022
≥50	4.1% (3.6-4.7)	9.4% (8.2-10.7)	<0.0001
***P*-value for difference**	<0.0001	<0.0001	
COPD#			
No	2.2% (1.8-2.8)	5.4% (4.5-6.6)	<0.0001
Yes	4.6% (1.8-10.9)	6.4% (4.8-8.4)	0.3193
***P*-value for difference**	0.2483	0.2867	
SAD§			
No	2.0% (1.5-2.7)	4.7% (3.6-6.2)	0.0003
Yes	2.9% (2.3-3.7)	6.6% (5.1-8.6)	0.0006
***P*-value for difference**	0.0396	0.1120	

Values are represented as percentage (%) (95% confidence interval, CI). Abbreviations: COPD, chronic obstructive pulmonary disease; SAD, small airway dysfunction.

P-value for difference is for the comparison of binary variables. All the calculations of P-value are weighted, taken into account the multistage cluster sampling design and based on χ^2 test.

* Ever-smoker was defined as having smoked equal to or more than 100 cigarettes in the lifetime.

#COPD was defined as the individuals with post-bronchodilator FEV_1/FVC less than 70%.

§SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: maximal mid-expiratory flow, forced expiratory flow (FEF) 50%, and FEF 75% after bronchodilator inhalation.

TABLE E2 The distribution of concomitant symptoms in population with chronic cough stratified by sex, age, COPD or SAD

Concomitant symptoms	ALL	Sex			Age			COPD*			SAD#		
		Men	Women	*P* value	20-49 yrs	≥50 yrs	*P* value	No	Yes	*P* value	No	Yes	*P* value
Phlegm	1380 (67.5%)	919 (75.8%)	461 (52.8%)	0.0102	413 (58.7%)	967 (74.6%)	0.0122	984 (63.6%)	396 (80.8%)	0.0045	617 (58.4%)	738 (76.9%)	0.0009
Wheezing	487 (21.0%)	272 (18.2%)	215 (25.9%)	0.0542	100 (13.0%)	387 (27.3%)	0.0115	263 (14.0%)	224 (44.4%)	0.0066	140 (12.6%)	333 (29.5%)	0.0070
Dyspnea	547 (24.6%)	298 (21.1%)	249 (30.5%)	0.1471	119 (18.0%)	428 (29.6%)	0.0432	319 (18.5%)	228 (43.9%)	0.0006	188 (18.2%)	343 (30.2%)	0.0081
Nighttime sleep disturbance	827 (40.8%)	405 (33.9%)	422 (53.0%)	0.0051	226 (37.9%)	601 (43.1%)	0.3461	611 (41.1%)	216 (40.0%)	0.8556	376 (41.4%)	433 (38.9%)	0.6669

Values are weighted and shown as number (%). Abbreviations: COPD, chronic obstructive pulmonary disease; SAD, small airway dysfunction.
P-value is weighted, taking into account of the multistage cluster sampling design and based on χ^2 test.
*COPD was defined as post-bronchodilator $FEV_1/FVC<70\%$.
#SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: maximal mid-expiratory flow, forced expiratory flow (FEF) 50%, and FEF 75% after bronchodilator inhalation.

TABLE E3 Multiple adjusted odds ratios of chronic cough in the never-smokers

Variables	OR (95% CI)	*P*-value
Men	0.86 (0.51-1.44)	0.5416
Age (10 years)	1.51 (1.34-1.70)	<0.0001
Rural resident	0.85 (0.56-1.29)	0.4351
No. of ever smokers living in the home		
0	1.00 (Reference)	-
1	1.43 (0.96-2.14)	0.0771
≥2	1.04 (0.60-1.83)	0.8774
Biomass use	1.17 (0.78-1.77)	0.4289
Annual mean $PM_{2.5}$, μg/m^3		
<50	1.00 (Reference)	-
50-75	1.12 (0.68-1.86)	0.6419
≥75	1.05 (0.61-1.80)	0.8519
Education level		
Primary school and lower	1.00 (Reference)	-
Middle and high school	0.70 (0.55-0.90)	0.0070
College and higher	1.24 (0.60-2.56)	0.5329
Occupational exposure	0.99 (0.71-1.39)	0.9488
Visible mold spots in the current residence		
Rarely	1.00 (Reference)	-
Sometimes	0.94 (0.69-1.27)	0.6581
Often	1.19 (0.65-2.19)	0.5575
History of pneumonia or bronchitis during childhood	2.09 (1.32-3.30)	0.0033
Parental history of respiratory diseases	1.15 (0.78-1.72)	0.4571
Body mass index, kg/m^2		
<18.5	1.65 (1.02-2.69)	0.0427
18.5-24.9	1.00 (Reference)	-
≥25	1.08 (0.77-1.51)	0.6411
Allergic rhinitis	3.85 (2.34-6.34)	<0.0001

The variables listed in the table are all included in the model. Abbreviations: OR, odds ratio; 95% CI: 95% confidence interval; $PM_{2.5}$, particulate matter with a diameter less than 2.5 μm.
The logistic regression analyses were weighted, taking into account of the multistage cluster sampling design.

TABLE E4 The comparison of lung function before bronchodilator inhalation and medication use between people with chronic cough and those without chronic cough

Variables	No chronic cough (n=49006)	Chronic cough (n=1985)	*P*-value
Lung function			
FEV_1/FVC, %	79.7 (0.4)	73.0 (1.3)	<0.0001
FEV_1 %pred	96.9 (0.8)	89.7 (2.1)	0.0005
SAD*	22464 (41.4%)	1196 (62.6%)	0.0011
Medication use			
Inhaled corticosteroid			0.1478
	242 (1.5%)	70 (6.2%)	
Inhaled bronchodilator			0.1232
	237 (1.8%)	88 (7.0%)	
Aminophylline			0.1236
	172 (5.9%)	98 (10.6%)	
Systemic corticosteroid			0.5301
	112 (4.7%)	60 (5.8%)	
Antibiotics			0.0650
	478 (20.2%)	234 (32.6%)	
Expectorants			0.0610
	181 (7.4%)	117 (28.4%)	
Anti-allergic agent			0.2994
	120 (4.3%)	39 (13.3%)	

Values are weighted and shown as number (%) or mean (SE). Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; SAD, small airway dysfunction.
All the calculations of *P*-value are weighted, taking into account of the multistage cluster sampling design and based on χ^2 test for categorical variables or Student's t test for continuous variables.
*SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: maximal mid-expiratory flow, forced expiratory flow (FEF) 50%, and FEF 75% before bronchodilator inhalation.

TABLE E5 Clinical characteristics and use of healthcare resources by diagnosis of solely chronic cough

Variables	Neither chronic cough nor phlegm, dyspnea and wheeze (n=38589)	Solely chronic cough (n=404)	*P*-value
Lung function*			
FEV_1/FVC, %	82.5 (0.4)	79.6 (1.2)	0.0144
FEV_1 %pred	100 (0.8)	104 (4.6)	0.3513
FEV_1/FVC<70%	2920 (6.5%)	39 (9.1%)	0.2747
MMEF%pred	77.3 (1.1)	72.5 (2.7)	0.0920
FEF 50%pred	89.5 (1.2)	85.6 (3.4)	0.2445
FEF 75%pred	78.3 (1.5)	73.8 (2.9)	0.1271
SAD#	11869 (26.4%)	143 (31.8%)	0.0847
Positive bronchodilator reversibility†	2192 (5.5%)	26 (16.9%)	0.3296
Short form (SF)-12 scores			
PCS scores	53.2 (0.2)	52.2 (0.5)	0.0689
MCS scores	54.5 (0.3)	54.7 (0.8)	0.8041
Comorbidities			
Hypertention	2450 (4.7%)	54 (10.7%)	0.1103
Coronary heart disease	327 (1.2%)	8 (2.1%)	0.4544
Diabetes	799 (1.9%)	15 (1.7%)	0.8398
Acute exacerbation of respiratory symptoms in the last 12 months			
Emergency	22 (0.1%)	12 (4.7%)	0.1328
Hospital admission	22 (0.0%)	7 (1.0%)	0.1337

Values are weighted and shown as number (%) or mean (SE). Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; capacity PCS, physical component summary; MCS, mental component summary; SAD, small airway dysfunction.

All the calculations of P-value are weighted, taking into account the multistage cluster sampling design and based on χ^2 test for categorical variables or Student's t test for continuous variables.

*The parameters were measured at 20 min after inhalation of 400μg of salbutamol.

#SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: maximal mid-expiratory flow, forced expiratory flow (FEF) 50%, and FEF 75% after bronchodilator inhalation.

†A positive bronchodilator reversibility test was defined as an increase in post-bronchodilator forced expiratory volume in 1 s of more than 12% and more than 200 ml from baseline, 20 min after inhalation of 400μg of salbutamol.

TABLE E6 Associations of chronic cough with lung function before bronchodilator inhalation

Parameters	OR or β (95% CI)	*P* value
FEV_1/FVC	-3.44 (-5.24, -1.64)	0.0008
FEV_1 %pred	-6.24 (-10.04, -2.44)	0.0029
FEV_1/FVC<70%	1.64 (1.26, 2.13)	0.0009
MMEF% pred	-6.07 (-10.09, -2.04)	0.0053
FEF 50% pred	-8.43 (-13.33, -3.53)	0.0020
FEF 75% pred	-6.32 (-10.02, -2.62)	0.0021
SAD*	1.64 (1.17, 2.28)	0.0059

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEF 50%, forced expiratory flow at 50% of the FVC; FEF 75%, forced expiratory flow at 50% of the FVC; SAD, small airway dysfunction.

Adjusted for age, sex, urbanization, body mass index, cigarette smoking, biomass, annual mean $PM_{2.5}$, education, occupational exposure, visible mold spots in the current residence, history of pneumonia or bronchitis during childhood, parental history of respiratory diseases, parental history of respiratory diseases, and allergic rhinitis. The logistic or linear regression analyses are weighted, taking into account of the multistage cluster sampling design.

*SAD was diagnosed on the basis of at least two of the following three indicators of lung function being less than 65% of predicted: MMEF, FEF 50%, and FEF 75% before bronchodilator inhalation.