

# Differential Features of COPD in China

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## ABSTRACT

Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow limitation, is a public health problem worldwide. It is a major chronic disease in China, which has the largest population of elderly and smokers in the world, as well as the largest number of COPD patients. The occurrence of COPD is linked to multiple risk factors, including smoking, use of biomass fuel, and air pollution. COPD has a major negative effect on the quality of life, including limitations on the work ability. It increases mortality and leads to a significant use of health-care resources. Much progress has already been made in the prevention and treatment of COPD in China, but early diagnosis using spirometry should become more widespread, and general COPD knowledge among clinicians needs to be improved. This review summarizes the clinical characteristics of COPD in China, as well as current concepts for COPD diagnosis and treatment, and future actions to improve disease management in the country. (BRN Rev. 2017;3:74-85)

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease involving persistent airflow limitation and chronic airway inflammation. It places a heavy burden on patients and family members, healthcare professionals and society, especially in developing countries<sup>1-3</sup>. COPD has a major negative effect on the quality of life, including limitations on the work ability. It increases mortality and leads to a significant use of health-care resources. Based on projections through 2020, COPD is projected to move from the sixth to the third most frequent cause of mortality worldwide, and to rise from the fourth to the third most frequent cause of morbidity<sup>4</sup>.

As one of the largest developing countries in the world, China is subject to great pressure in concerning COPD. Census data from 2010 indicate a population of 1.33 billion, accounting for nearly 20% of the entire world's population; approximately 568 million people, 42% of the Chinese population, is at least 40 years old<sup>5</sup>. Since COPD incidence increases exponentially beyond this age threshold, China faces a particularly heavy burden from COPD, especially since many COPD risk factors are also prevalent in this country, such as cigarette smoking, air pollution, and use of biomass fuel. Additional factors contributing to the long-term COPD burden are late diagnosis of COPD and substandard treatment.

Although the diagnosis, evaluation, and treatment of COPD have advanced in China in recent decades, many challenges remain<sup>6</sup>. This review summarizes the clinical characteristics of Chinese COPD patients, the progress in clinical care so far, and the challenges for the future.

## COPD RISK FACTORS IN CHINA

The Chinese population is exposed to numerous COPD risk factors. Smoking is the most common risk factor for COPD worldwide, and 2010 data suggest approximately 300 million current smokers in China (Fig. 1)<sup>7,8</sup>. In fact, China is regarded as the largest consumer of tobacco in the world<sup>9</sup>. Passive smoking is also a major problem: among non-smokers aged 15 years and older, approximately 556 million (72.4%) are exposed to second-hand smoke, with 292 million (52.5%) exposed on a daily basis<sup>10</sup>. A study of 500,000 adults aged 30-79 years from 10 regions across mainland China over the period 2004-2008 showed that 7.2% of men who smoked regularly had airflow limitation, compared to only 5.4% of never-smokers. In this study, the amount of smoking was significantly associated with the risk of airflow limitation, defined as a pre-bronchodilator ratio of forced expiratory volume in one second over forced vital capacity ( $FEV_1/FVC$ ) below 0.7 and/or below the lower limit of normal for the specific population<sup>11</sup>. In addition, the risk of COPD was associated with self-reported exposure to second-hand smoke at home and work (adjusted odds ratio: 1.48; 95% CI: 1.18-1.85)<sup>12</sup>.

Approximately 60% of Chinese families use biomass fuel and 31% use coal for cooking or heating in rural areas, making these factors significant contributors to the risk of COPD in China<sup>13</sup>, particularly in the rural southern part of the country<sup>14</sup>. Risk is also exacerbated by air pollution, dust, physical and chemical contamination, respiratory tract infection, tuberculosis, and poor socioeconomic status, all of which are prevalent in

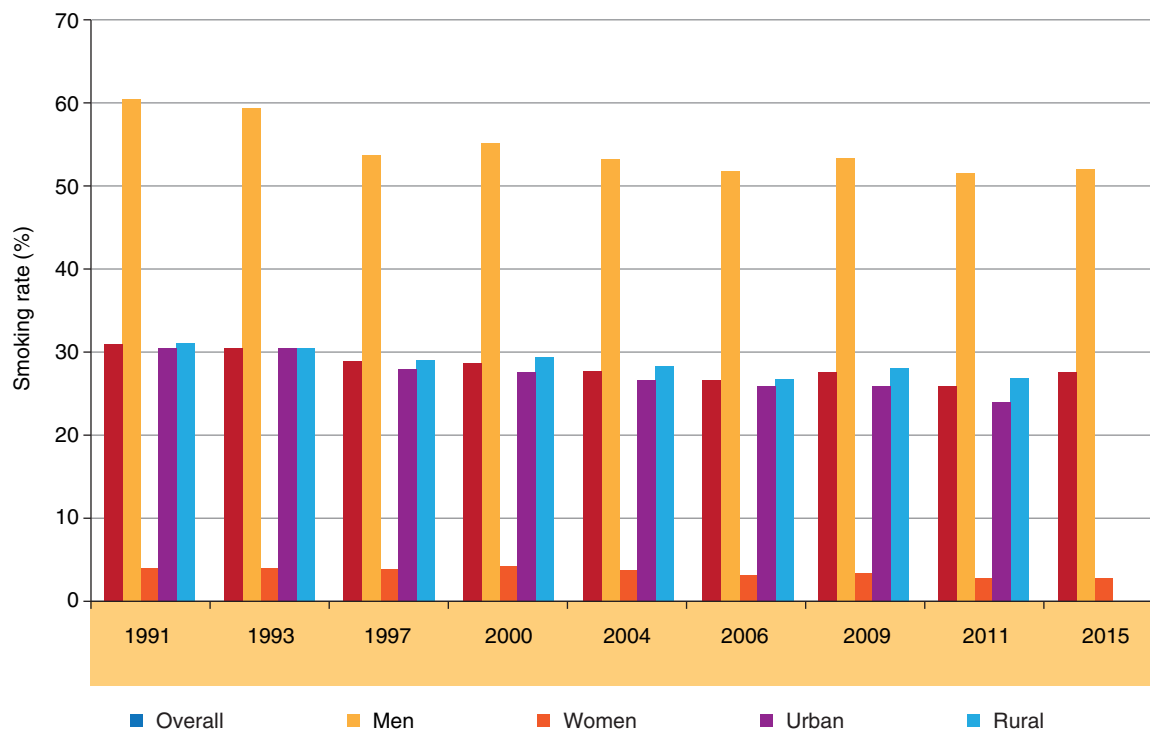


FIGURE 1. Rate of smoking in China, 1991 to 2015. Trends are shown for men and women living in urban or rural areas.

China<sup>15</sup>. Managing or even reducing such risk factors poses an enormous challenge for the country.

## COPD INCIDENCE IN CHINA

With so many COPD risk factors present in China, it is not surprising that incidence of the disease is high. Incidence across 12 Asian countries, including China, is 6.3%, considerably higher than the 3.8% based on data from the World Health Organization (WHO) for the same region<sup>16</sup>. In the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO) study, performed in five major Latin American cities: São Paulo (Brazil), Santiago

(Chile), Mexico City (Mexico), Montevideo (Uruguay), and Caracas (Venezuela), the incidence of COPD ranged from 7.8% to 19.7%<sup>17</sup>. In the Burden of Obstructive Lung Disease (BOLD) study which was carried out in 12 cities, the mean COPD incidence was 17.3%<sup>18</sup>. A systematic review has indicated worldwide COPD prevalence of 7.6% based on 37 studies, and worldwide prevalence of spirometry-confirmed COPD of 8.9% based on 26 studies<sup>19</sup>. This review also highlighted notable regional differences in the incidence.

Similarly, classical studies of COPD incidence in China, involving over than 1,000 subjects<sup>20-47</sup>, have revealed variations in incidence across provinces and cities (Table 1).

TABLE 1. Summary of main epidemiologic studies on COPD incidence in China and worldwide

Author (Ref)	Year	Location	Number	Age	Sampling method	COPD diagnosis method	COPD incidence (%)
Ruan et al. <sup>35</sup>	2000	Jiangsu	16,813	≥ 35	C	Self-report	3.5
Yao et al. <sup>20</sup>	2005	Beijing	1,624	≥ 40	M	Lung function tests	9.1
Liu et al. <sup>24</sup>	2005	Guangdong	3,286	≥ 40	M	Lung function tests	9.4
Wang et al. <sup>25</sup>	2005	Guangdong	1,498	≥ 40	C	Lung function tests	12.0
Xu et al. <sup>34</sup>	2005	Jiangsu	29,319	≥ 35	M	Self-report	5.9
Ma et al. <sup>41</sup>	2005	Shanghai	1,214	≥ 60	S	Lung function tests	12.1
Qiu et al. <sup>45</sup>	2005	Yunnan	5,791	≥ 15	M	Lung function tests	2.0
Weng et al. <sup>47</sup>	2005	Zhejiang	1,209	≥ 60	C	Lung function tests	6.5
Weng et al. <sup>26</sup>	2006	Guangdong	1,100	≥ 40	C	Lung function tests	12.6
Zhong et al. <sup>21</sup>	2007	Beijing, Tianjing, Liaoning, Shanghai,Guodong, Shanxi,Chongqin	20,245	≥ 40	M	Lung function tests	8.2
Jiang et al. <sup>33</sup>	2007	Hubei	1,883	≥ 40	M	Lung function tests	9.9
Shan et al. <sup>42</sup>	2007	Tianjin	3,008	≥ 40	C	Lung function tests	9.6
Chen et al. <sup>27</sup>	2008	Guangdong	1,368	≥ 40	C	Lung function tests	7.0
Li et al. <sup>22</sup>	2009	Chongqin	1,518	≥ 40	M	Lung function tests	12.8
Yu et al. <sup>32</sup>	2009	Hebei	1,948	≥ 40	M	Lung function tests	10.7
Cai et al. <sup>44</sup>	2009	Yunnan	6,006	≥ 45	M	Self-report	6.7
Weng et al. <sup>23</sup>	2011	Chongqin	2,024	≥ 40	M	Lung function tests	7.9
Fu et al. <sup>30</sup>	2011	Hunan	1,000	≥ 40	C	Lung function tests	9.1
Li et al. <sup>39</sup>	2011	Shandong	4,047	≥ 40	M	Lung function tests	8.6
Wang et al. <sup>40</sup>	2011	Shandong	2,055	≥ 40	M	Lung function tests	7.6
Wang et al. <sup>46</sup>	2011	Zhejiang	1,467	≥ 55	C	Lung function tests	16.3
Cai et al. <sup>28</sup>	2012	Guangdong	1,019	≥ 40	C	Lung function tests	10.2
Tang et al. <sup>29</sup>	2012	Helongjiang	1,509	≥ 40	C	Lung function tests	11.3
Hong et al. <sup>31</sup>	2012	Hunan	8,269	≥ 15	C	Lung function tests	5.1
Hou et al. <sup>36</sup>	2012	Liaoning	2,194	≥ 35	C	Lung function tests	5.1
Qiu et al. <sup>38</sup>	2013	Ningxia	4,626	≥ 40	M	Lung function tests	8.9
Zhu et al. <sup>43</sup>	2014	Xinjiang	2,874	≥ 35	C	Lung function tests	7.5
Liu et al. <sup>37</sup>	2015	Liaoning	5,420		C	Lung function tests	17.5
Menezes et al. <sup>17</sup>	2005	São Paulo, Santiago, Mexico City, Montevideo, Caracas.	5,571	≥ 40	M	Lung function tests	14.3
Buist et al. <sup>18</sup>	2007	Guangzhou, Adana, Salzburg, Cape Town, Reykjavik, Hannover, Krakow, Bergen, Vancouver, Lexington, Manila, Sydney	8,775	≥ 40	M	Lung function tests	17.3

C: cluster random sampling; COPD: chronic obstructive pulmonary disease; M: multi-stage cluster random sampling.

One particularly large, population-based, cross-sectional survey of COPD involving 20,245 respondents from Beijing, Tianjin, Liaoning, Shanghai, Guodong, Shanxi, and Chongqing found overall prevalence of spirometry-confirmed COPD to be 8.2% overall, 12.4% in men and 5.1% in women (corresponding to nearly 43 million people) for the period 2002-04<sup>21</sup>. COPD incidence in that study varied across the areas and was linked to specific occupations. For example, a cross-sectional study of greenhouse farmers in Northeast China found an overall COPD prevalence of 17.5%<sup>37</sup>.

A recent meta-analysis of 30 studies covering 18 Chinese provinces and cities for the period 1990-2014 indicated a COPD incidence of 9.9% overall, 13.0% of men and 5.8% of women aged 40 or older. The incidence increased with age group, from 3.2% among those aged 40-49 years to 20.3% among those aged 70 or older. Over the last 20 years, COPD prevalence has gradually increased among those aged 40 or older<sup>48</sup>. Thus, as the Chinese population ages, more and more will be diagnosed with COPD in the coming years. Indeed, nationwide Chinese data presented at the 2016 Annual Conference of the European Respiratory Society (ERS) suggest that COPD incidence is more than 14% among those older than 40 and 8% among those older than 20<sup>49</sup>. This means that China has the world's highest incidence of COPD. Dealing with this epidemic poses enormous challenges for the country.

## COPD-RELATED MORTALITY IN CHINA

In 2010, an estimated 328 million people worldwide had COPD, being the third leading cause

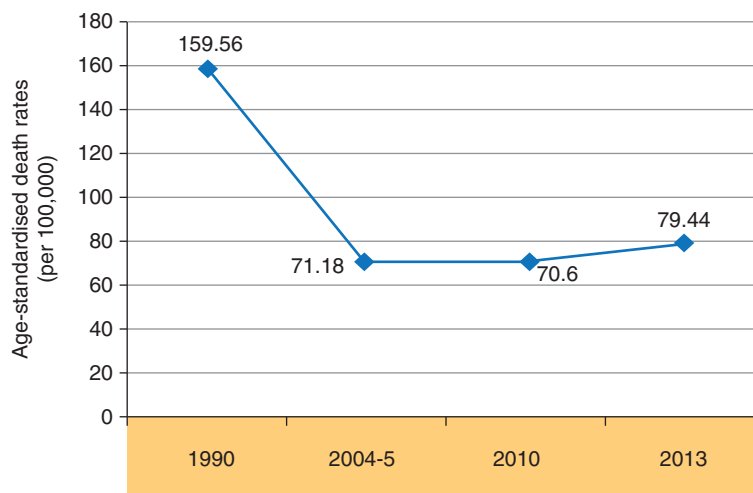
of death. Although age-standardized rates of COPD-related death have decreased by 43.3% in the past two decades, falling from 77.4 per 100,000 in 1990 to 43.8 per 100,000 in 2010<sup>50</sup>, COPD-related mortality remains high in China (Fig. 2). In 2004-2005, the crude death rate in the country was 82.32 per 100,000 and the standardized death rate was 71.18 per 100,000. COPD is the third-leading cause of mortality in China, accounting for 934,000 deaths in 2010 and 910,809 deaths in 2013, corresponding to one COPD-related death approximately every 2 minutes<sup>51,52</sup>.

COPD accounts for as many as 81% of deaths in China related to respiratory disease<sup>53</sup>. The burden of COPD-related deaths may be heavier in western rural areas than in other rural areas<sup>54</sup>: the crude rate of COPD-related deaths in western rural areas is as high as 122.04 per 100,000. COPD-related mortality is much higher in China than elsewhere in the Asia-Pacific region, where it is reported to be 64-92 per 100,000 men and 21-35 per 100,000 women<sup>55</sup>.

## COPD BURDEN IN CHINA

COPD places a high economic burden on countries. Direct costs in the European Union are 38.6 billion euros, accounting for 56% of the costs of all respiratory diseases. In the United States, direct costs are \$29.5 billion and indirect costs are \$20.4 billion<sup>56,57</sup>. In China, the costs associated with COPD are even higher and they pose a severe burden on patients and their families.

A cross-sectional survey in 2006 based on interviews with 723 COPD outpatients in the large cities of Beijing, Shanghai, Guangzhou,



**FIGURE 2.** Age-standardized rate of chronic obstructive pulmonary disease (COPD)-related deaths (per 100,000) in China. Data were taken from references 47, 49-50. When data were conflicting, only the most recent data were used.

Chengdu, Xi'an, and Shenyang found the average annual direct medical expenses to be \$1,732.24 per patient. Indirect costs, for example, for nutritional support, transportation, and end-of-life care were approximately \$231.6 per patient, accounting for 40% of an average family's total income (\$4,849.8)<sup>58</sup>.

COPD costs correlate strongly with disease severity, and a major contributor to these costs is hospitalization<sup>59</sup>. A survey based on 83 third-tier hospitals in 17 provinces and cities of China revealed that for 97.5% of patients, the cost of a monthly supply of medicines was greater than their monthly wage; the average annual economic burden of disease was 20107.56 Renmibi (RMB) per patient<sup>60</sup>. In general, the affordability of COPD drugs is quite low in third-tier hospitals, with annual medication costs for inpatients rising as high as 628440.6 RMB per patient<sup>59,61</sup>. This highlights the need to make COPD drugs more

affordable and to protect patients from economic risk associated with their disease.

COPD burden tends to be underestimated because of premature mortality of patients and the loss of work productivity of patients and family members. COPD seriously affects the quality of life of COPD patients, largely due to disease-related changes in dyspnoea, comorbidities and loss of body mass index<sup>62</sup>. Overall disease burden in terms of disability-adjusted life years (DALYs) is predicted to double over the next 2.5 decades. By then, COPD is expected to move from position 13 to position 7 in terms of DALYs. In 2010, COPD was the fifth major cause of years lived with disability in China<sup>63</sup>. In this same year in China, COPD-related DALYs were 16,598 million person-years; years of life lost due to premature mortality, 12,946 million person-years; and, years lived with disability, 3,652 million person-years<sup>64</sup>. This burden affects patients



**TABLE 2.** Percentage of chronic obstructive pulmonary disease (COPD) patients received spirometry examination before diagnosis

Study	Number of COPD patients	Number of patients with spirometry performed before diagnosis	Percentage
Zhong et al. <sup>21</sup>	1,668	108	6.50
Weng et al. <sup>23</sup>	160	39	24.38
Liu et al. <sup>24</sup>	310	26	8.39
Cai et al. <sup>28</sup>	105	9	8.57
Lin et al. <sup>66</sup>	283	33	11.66
Lv et al. <sup>67</sup>	145	10	6.90
Tang et al. <sup>68</sup>	102	24	23.53

and family members alike: 36% of COPD patients reported losing an average of 17 working days over the preceding 12 months because of their disease, and 17% of patients' family members reported losing an average of 14 working days due to taking care of patients<sup>58</sup>.

Decreased quality of life related with COPD may be associated with higher medical costs. A cross-sectional survey of 678 COPD patients found poorer quality of life to be significantly associated with higher direct medical costs. This may be important for healthcare policymakers to take into account<sup>65</sup>.

## LOW RATE OF SPIROMETRY-BASED COPD DIAGNOSIS

COPD diagnosis occurs too late for many patients in China, and treatment is often insufficient. Spirometry is the gold standard to detect airflow limitation and diagnose COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>1</sup>, but it is not often used in China to diagnose the disease

(Table 2)<sup>21,23,24,28,66-68</sup>. This can lead to a disturbingly high rate of misdiagnosis: one study of 185 patients diagnosed with "COPD" without performing lung function tests showed that only 75 truly had COPD based on spirometry, while another 47 had a normal lung function based on this GOLD standard<sup>69</sup>. A survey in Beijing involving 708 subjects revealed that only 8.33% of the COPD patients received spirometry examination in rural areas<sup>70</sup>. A large population-based survey found that only 6.5% of COPD patients were tested with spirometry<sup>21</sup>. A China Kadoorie Biobank report of 512,891 adults from 10 regions across China found that only 11.2% of diagnoses of airflow limitation made in the period 2004-08 were correct, based on spirometry findings<sup>71</sup>. The proportion of cases of airflow limitation that went undiagnosed was greater among women, younger individuals, those with lower household income, those with fewer chronic respiratory symptoms, and current regular smokers<sup>71</sup>.

The use of spirometry may significantly improve timely diagnosis of COPD, but clinicians in the country often do not regard it as critical for accurate diagnosis. A cross-sectional

survey of COPD knowledge among physicians at tertiary hospitals in northern China revealed that only 59.0% recognized the importance of spirometry for COPD diagnosis<sup>72</sup>. A survey of physicians at basic hospital in Nanjing found them to prefer chest X-ray to lung function tests as the first choice for COPD diagnosis<sup>73</sup>. Of course, failure to use spirometry to diagnose COPD can reflect not only a lack of knowledge but also a lack of equipment and funding, especially in primary care settings.

Another challenge to the timely diagnosis of COPD in China is the fact that many Chinese patients are asymptomatic. In one study of 25,627 subjects, 1,668 were diagnosed with COPD, of whom 589 (35.3%) were asymptomatic<sup>74</sup>. And in the PLATINO study performed in São Paulo, the undiagnosed group of COPD patients had a lower proportion of subjects with respiratory symptoms than the previously diagnosed patients<sup>75</sup>. Both the PLATINO and BOLD studies highlight that spirometry can help in the diagnosis of COPD at a stage when treatment will lead to better outcomes and improved quality of life<sup>76</sup>. Without spirometry examination, clinicians may tend to over-diagnose COPD based only on clinical symptoms, and to under-diagnose it in asymptomatic individuals.

## LOW RATE OF STANDARDIZED COPD TREATMENT

Physicians' knowledge on COPD can strongly influence treatment efficacy, and awareness of COPD treatment standards in China is inconsistent. A survey among 372 physicians found that COPD knowledge was not satisfactory at district and community hospitals<sup>77</sup>. While such

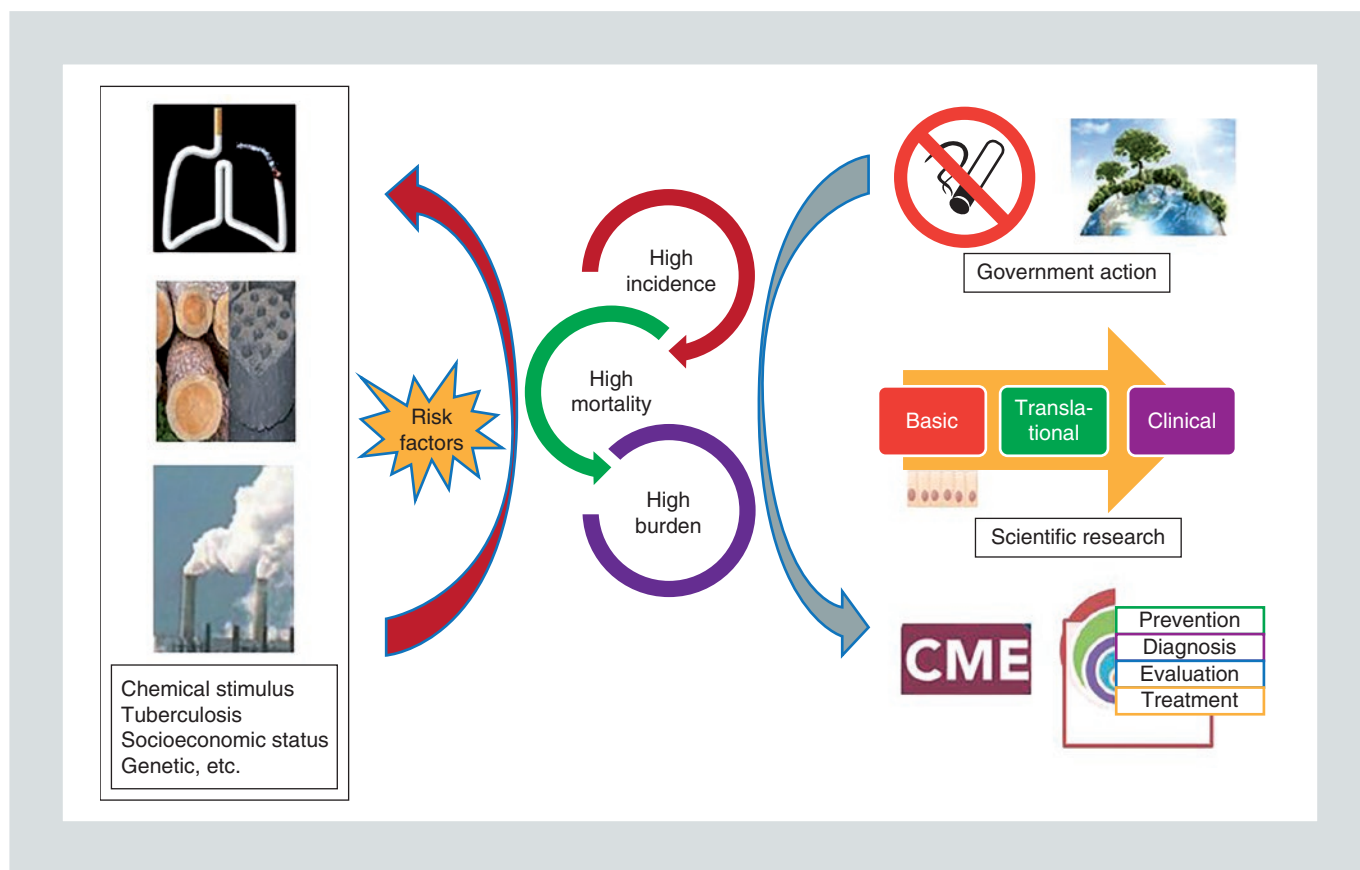
knowledge levels have improved among physicians in large cities, knowledge of long-term COPD interventions such as pharmacotherapy remains unsatisfactory<sup>78</sup>. A survey among 700 COPD patients treated in China found that 61% received mucoactive drugs as first-line pharmacotherapy for COPD<sup>79</sup>, even though GOLD standards recommend bronchodilators such as  $\beta$ 2-agonists, anticholinergic agents, and aminophylline as COPD drugs. In fact, patients with moderate or severe COPD are prescribed mucoactive drugs in as many as 87% of newly diagnosed cases, and in as many as 80% of follow-up patients<sup>78</sup>. Even when Chinese physicians prescribe bronchodilators, more than 50% choose short-acting bronchodilators<sup>79</sup>. Moreover, even though mucoactive therapy is considered of great importance in China to treat patients with COPD<sup>80</sup>, this questionable recommendation principle is not always followed in clinical practice.

A similar gap between international standards and Chinese practice occurs in the management of patients with stable COPD. Although GOLD standards recommend maintenance therapy for such patients, as many as 15% of physicians at basic hospitals think that no active treatment is necessary<sup>73</sup>. That said, the five most common interventions in northeast China are smoke cessation, antibiotic use, inhaled corticosteroids, long-acting anti-cholinergics and oxygen<sup>72</sup>. There is a long way to go before COPD patients can benefit from standard treatment in China.

## PROSPECTS FOR COPD IN CHINA

China has already made substantial progress in improving diagnosis and treatment of





**FIGURE 3.** Challenges and recommendations for diagnosing and treating chronic obstructive pulmonary disease (COPD) in China. CME: continuing medical education.

COPD, and the latest national plan on the Prevention and Treatment of Chronic Diseases pledges to bring the incidence of COPD in those older than 40 below 8%<sup>81</sup>. The Chinese government has taken steps to reduce many COPD risk factors. For example, advertising laws have been revised to prohibit cigarette advertising, and the tax on tobacco has been increased. In 18 major cities, China has set up local tobacco control laws to forbid smoking in public places, especially hospitals and schools<sup>82</sup>. Guidelines to help individuals quit smoking have been published<sup>83</sup>. A prospective cohort study spanning 9 years has provided strong evidence that cooking with clean fuels such as biogas rather than biomass and improving kitchen ventilation (by providing support and

instruction for improving biomass stoves or installing exhaust fans) are associated with a smaller decline in FEV<sub>1</sub> and lower risk of COPD<sup>84</sup>.

Both the Chinese government and clinical professionals are stepping up to increase COPD knowledge among physicians and to encourage the use of spirometry for early diagnosis of the disease. The Chinese National Health and Family Planning Commission issued a “China Health Knowledge Dissemination and Incentive Plan” focusing on COPD management (COPD 2012-2013). The People’s Medical Publishing House has organized a training program to increase the knowledge of 5,000-6,000 physicians in primary hospitals

about COPD prevention, diagnosis, and treatment<sup>85</sup>. COPD has been included in “specific clinics” in most Chinese provinces, and Local Social Security Bureaus in urban and rural areas cover some of the fees related to COPD drugs and exams.

Efforts to expand research and clinical translation of new knowledge and treatment for COPD and other diseases are funded through the National Ministry of Science and Technology of China, which has launched several grant programs such as “Precision Medicine” and “Major Chronic Non-infectious Diseases”. COPD-related projects alone received more than 60 million RMB of funding in 2016<sup>86</sup>. These projects cover COPD pathogenesis, phenotypes, treatment, and management of acute exacerbations. Figure 3 summarizes the current challenges and actions for COPD in China.

These recent developments speak of the overall commitment of the Chinese government, researchers and clinicians to improve COPD diagnosis and treatment around the country. While many challenges stand in the way, China is poised to make impressive headway in COPD patient care in the years to come.

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## CONFLICT OF INTEREST

Professor Fuqiang Wen and Dr. Yongchun Shen have nothing to disclose.

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