

The FACES of INNOVATION

Meeting the Challenge of chronic respiratory diseases





Introduction

Data released by the World Health Organization (WHO) in 2016 showed that the number of deaths due to the world's four major noncommunicable diseases, including cardiovascular diseases, cancer, diabetes and chronic respiratory diseases, accounted for about 79% of the global noncommunicable disease total deaths¹ (Figure 1). Based on the 2015 report on Chinese Nutrition and Chronic Disease issued by the prior National Health and Family Planning Commission, the mortality rate of chronic respiratory diseases in China was 68/100,000, which had become the third cause of death among major chronic diseases in China.

Due to the aging of population, smoking and second-hand smoke, air pollution, use of biofuels, and large differences in drug accessibility in different regions (Figure 2), the management status of chronic respiratory disease in China is very challenging. At present, chronic respiratory diseases represented by chronic obstructive pulmonary disease (COPD) and asthma are showing a trend of increasing incidence, but the management, diagnosis and treatment status is not satisfactory. The standard treatment rate of COPD and control rate of asthma are low, mainly manifested by low public awareness; disease prevention, screening and long-term management system not fully established; clinical diagnosis and treatment not standardized; poor awareness and ability of disease diagnosis and treatment by grassroots doctors; basic medical equipment such as pulmonary function testers and atomizing inhalation devices not widely used; and the poor accessibility of therapeutic drugs.

Figure 1 Percentage of deaths due to four chronic diseases among global noncommunicable disease total deaths

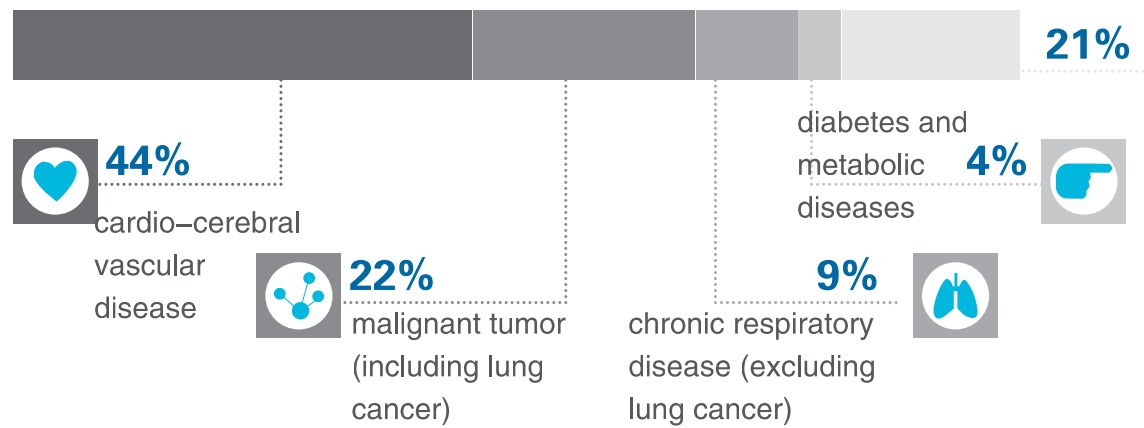


Figure 2 Risk factors for chronic respiratory diseases

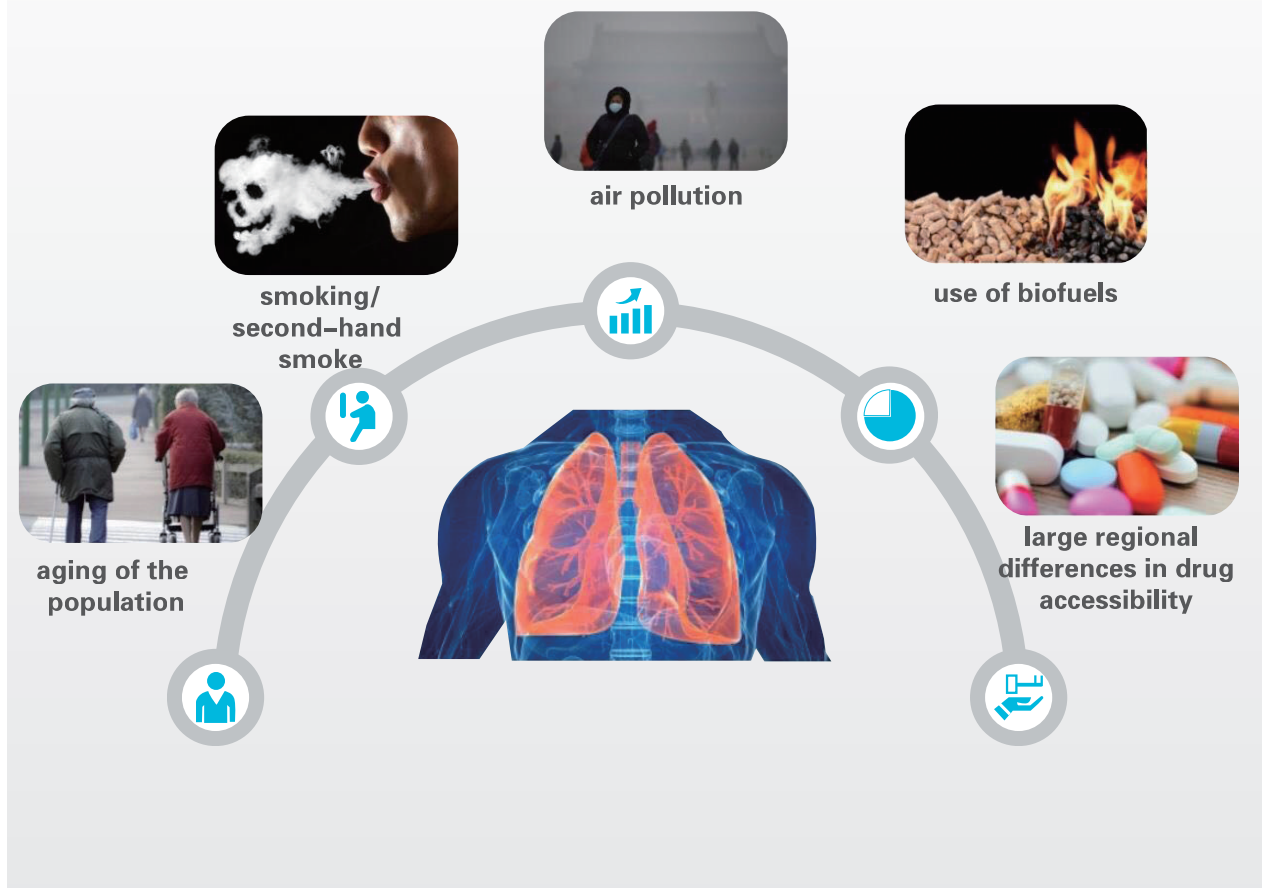


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Part 1 COPD epidemiology and challenges

1.1 Global COPD disease burden: prevalence, morbidity, mortality and trends

The global disease burden data for COPD and asthma in 2015 showed³ that 174.5 million people had COPD , including 104.7 million male and 69.7 million female(note: the number of people with COPD in the world may be underestimated), accounting for 2.6% of the global disease burden. From 1990 to 2015, the prevalence of COPD increased by 44.2%, and the age-standardized prevalence rate decreased by 14.7%.

In 1990, COPD was the sixth leading cause of death in the world⁴, causing about 2.8 million deaths; in 2015, COPD was the fourth leading cause of death (causing about 3.2 million deaths, an increase of 11.6% compared with 1990)⁵, ranking after ischemic heart disease, stroke and lower respiratory tract infections. COPD is expected to be the third leading cause of death (approximately 4.57 million deaths) by 2030, after ischemic heart disease and stroke⁵.

1.2 China's COPD disease burden: prevalence, morbidity, mortality and trends

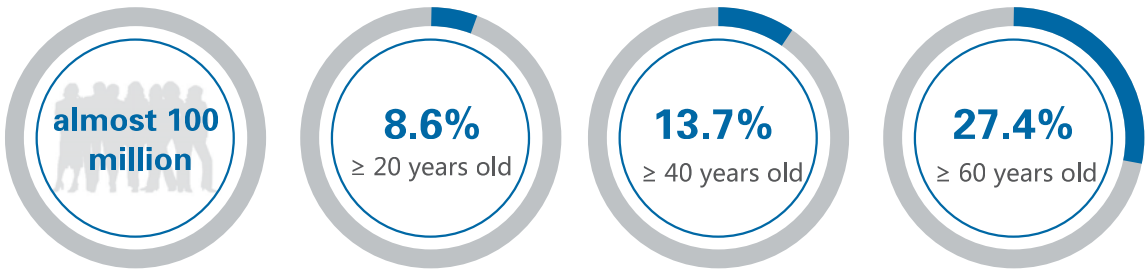


Figure 3 The number of COPD patients in China is about 100 million constituting a huge disease burden.

1.2.1 Prevalence of COPD in China

According to the Chinese Adult Pulmonary Health Study led by Chinese Academy of Medical Sciences & Peking Union Medical College Academician Wang Chen, the prevalence of COPD in China was 8.6% among people aged 20 and over, 13.7% among people aged 40 and over, and 27.4% among people aged 60 and over⁶. The burden of COPD disease has been comparable to that of hypertension and diabetes (Figure 3), and the prevalence of COPD has increased significantly with age (Figure 4). Another nationwide cross-sectional study showed that the prevalence of COPD in people aged 40 years and over in different regions of China ranged from 10.2% to 20.2% between 2014 and 2015, suggesting that COPD has become a major public health problem⁷.

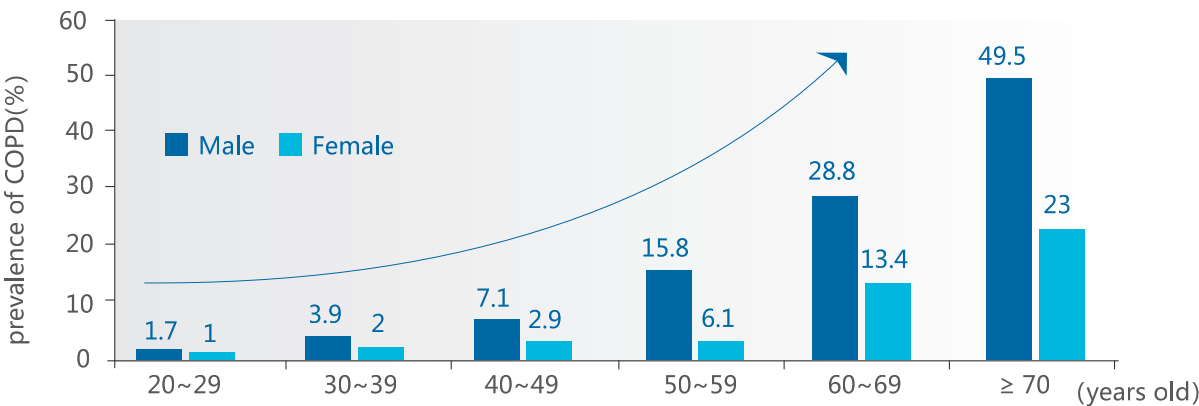


Figure 4 The prevalence of COPD in China increases significantly with age

1.2.2 Changes in incidences of COPD in China

From 1990 to 2013, the number of both male and female COPD patients increased year by year (Figure 5); the number of COPD cases increased sharply from 32.4 million in 1990 to 54.8 million in 2013⁸. According to the Chinese Adult Pulmonary Health Study in 2018, the number of COPD patients in China was 99.9 million, the number of male patients was 68.4 million, and the number of female patients was 31.5 million⁶.

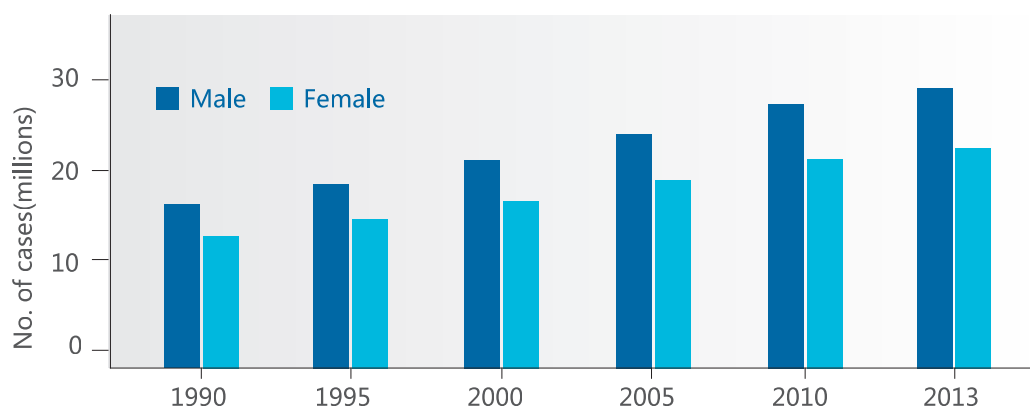


Figure 5 Incidences of COPD in different sex groups in China from 1990 to 2013

1.2.3 Changes in COPD mortality trend in China

In 2013, the number of deaths due to COPD in China was 910,809, accounting for 31.1% of the global death toll from COPD. From 1990 to 2013, China's COPD age-standardized mortality rate was higher in male than in female, but both male and female mortality rates were decreasing year by year⁸ (Figure 6).

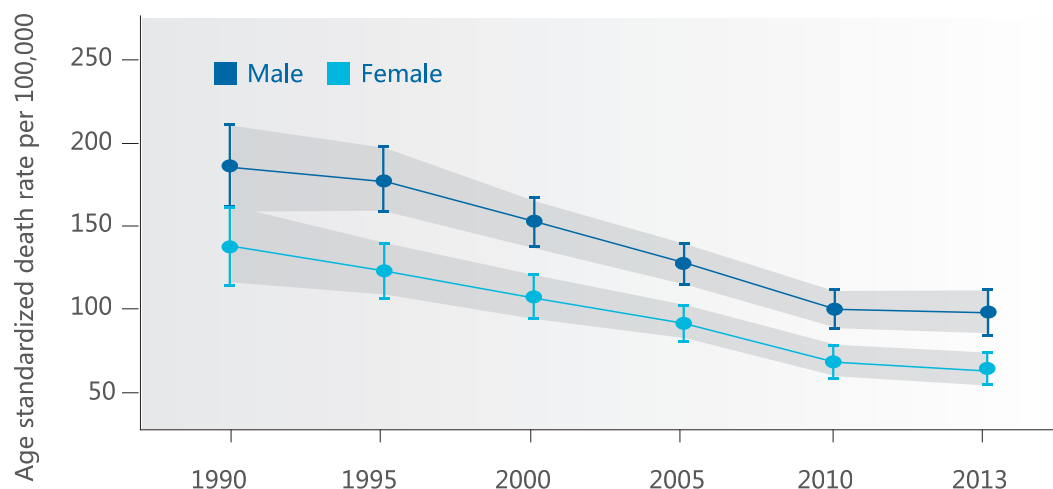


Figure 6 Age-standardized COPD mortality in different sex groups in China from 1990 to 2013

1.2.4 China's COPD age standardized mortality rate

From 1990 to 2013, the age-standardized mortality of COPD in all provinces of China showed a downward trend⁸, with the largest declines in Heilongjiang Province (70.2%) and Jilin Province (70.0%) , and the smallest decline (26.8%) in Guizhou Province (Figure 7). In 2013, the highest male mortality rate in China was in Guizhou Province (196.0/100,000), the lowest was in Tianjin (34.0/100,000); the highest female data was in Gansu Province (141.1/100,000), and the lowest was in Beijing City (23.7/100,000)⁸ (Figure 8).

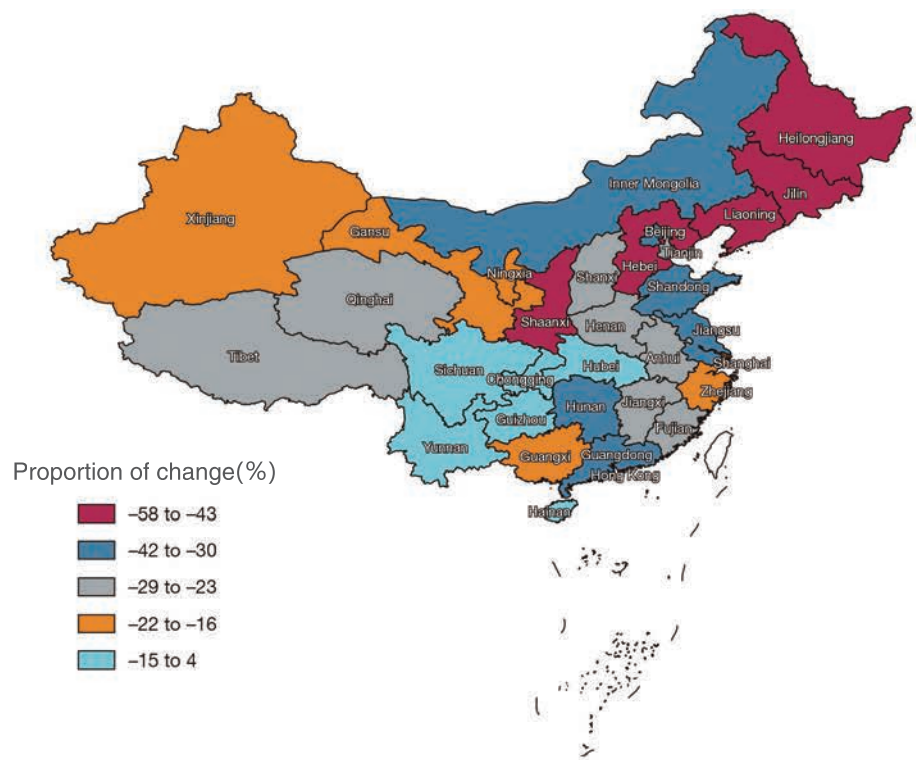


Figure 7 Proportion of age-standardized COPD mortality in provinces and cities in China from 1990 to 2013 (/100,000)

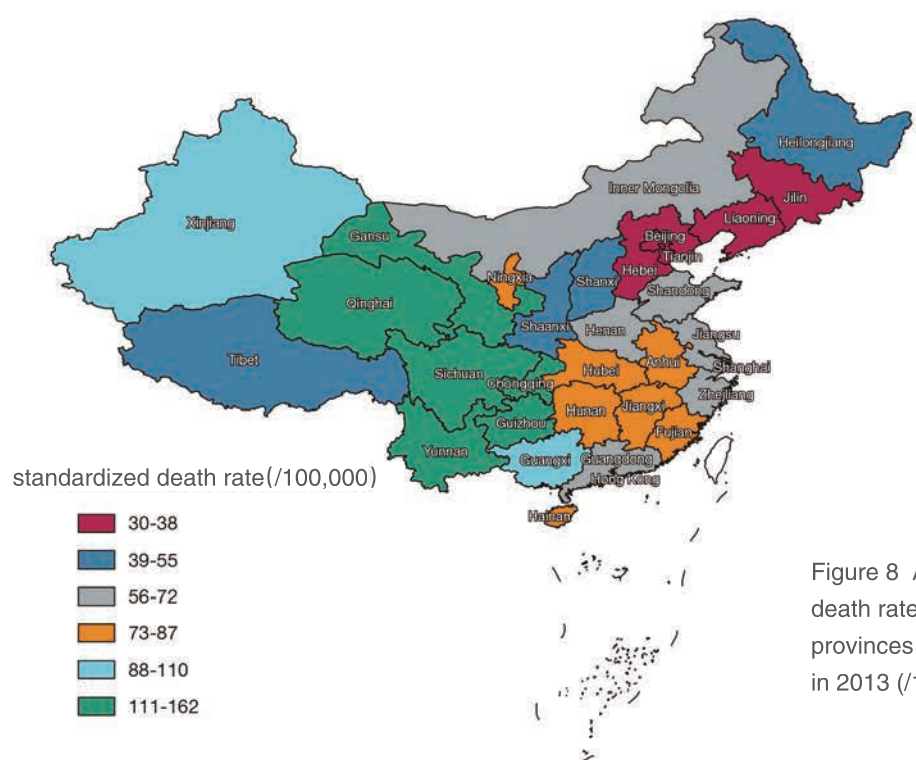


Figure 8 Age-standardized death rate of COPD in various provinces and cities in China in 2013 (/100,000)

1.3 COPD imposes a heavy financial burden on Chinese patients and society

The economic burden analysis of patients with COPD in tertiary referral hospitals in China showed⁹ that with reference to the classification criteria proposed by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD)¹⁰, 6.9% of patients in Group A had a medicine cost lower than average daily wages, and in other groups (B, C and D groups) only 1.6% to 2.3% of patients had a medicine cost lower than average daily wages (Table 1). Overall, more than a quarter of the monthly income of COPD patients was used to purchase medicines, which exerted a heavy economic burden.

Patients with COPD at an extremely high economic risk accounted for 24.4% to 24.8%. The average number of hospitalizations per patient was 0.56, the average length of hospital stay was 10.38 days, and the average hospitalization cost was RMB 6390.24 per year. The direct economic burden of diseases including outpatients and inpatients was RMB 12,552.38, and the average work loss was RMB 613.86 per year (Table 2).

Table 1 Economic affordability of therapeutic drugs for patients in different GOLD groups

Patient groups	Patient ratio	Treatment cycle cost (RMB)	Treatment cycle cost / average daily wage	Proportion of patients who can afford medicines
A	11.30%	424.42	6.67	6.90%
B	22.80%	480.84	8.44	2.30%
C	8.30%	493.32	8.33	1.60%
D	57.70%	509.88	8.98	1.90%

Table 2 Annual total disease economic burden for patients with COPD in different GOLD groups (RMB)

Patient group	Direct economic burden	Indirect economic burden	Total economic burden
A	6636.67	3980.98	10617.65
B	8324.80	6747.34	15072.14
C	12471.33	4003.70	16475.03
D	15402.86	9181.36	24584.22

1.4 Awareness, treatment and control rates of COPD in China

1.4.1 Patients with COPD have a lower level of disease-related knowledge

A national multicenter survey on treatment status and self-cognition in patients with COPD showed¹¹ that 59.1% of patients considered that the goal of COPD treatment was to alleviate symptoms; 72.0% of patients followed the doctor's advice to take medicines; more than 80% of patients did not know whether medications of anticholinergic drugs, β_2 receptor agonists, inhaled corticosteroids (ICS), long-acting β_2 agonists (LABA), and theophylline had any adverse effects; 37.4% of patients were concerned about ICS adverse effects; 42.2% of patients often took antibiotics; 60.1% of patients did not have oxygen supply equipment at home; 70.5% of patients had not received respiratory rehabilitation training; 77.4% of patients believed that COPD requires long-term regular treatment; 79.6% of patients thought that efficacy (good effect, fast onset and long duration) ranked first among ideal drugs.

1.4.2 COPD is inadequately diagnosed and undertreated

The survey showed¹² that only 35.1% of patients with COPD had previously been diagnosed with COPD, suggesting that COPD was inadequately diagnosed (Figure 9). 82% of doctors believed that most patients with COPD had better treatment compliance, but in fact about 50% of patients would reduce medications on their own, especially when symptoms were relieved¹³ (Figure 10).

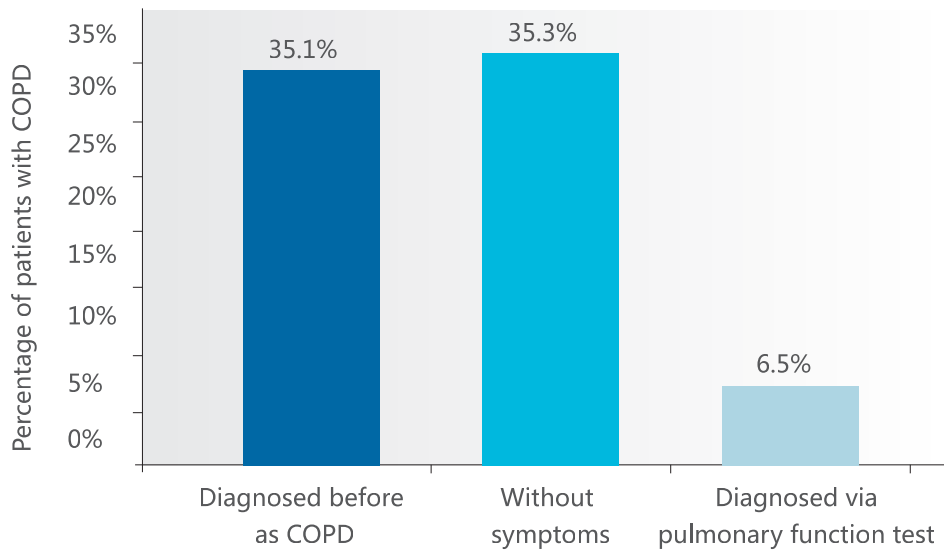


Figure 9 COPD is inadequately diagnosed

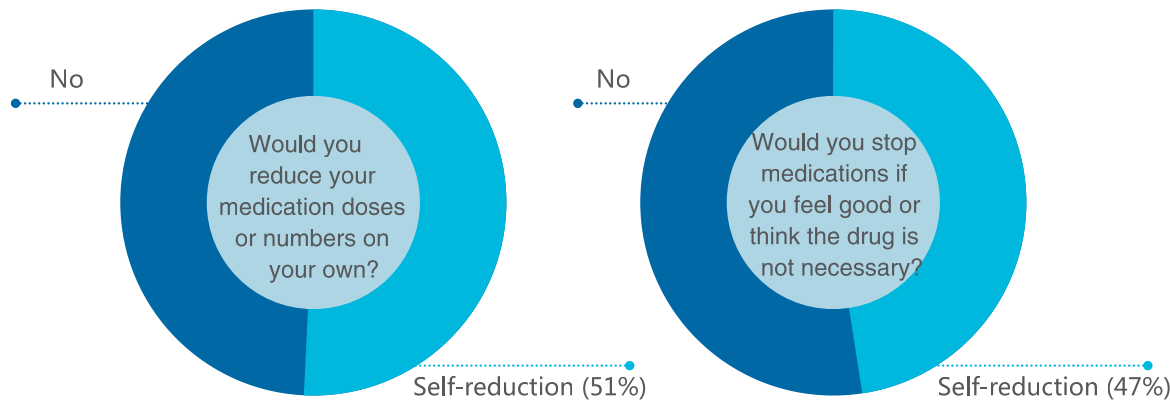


Figure 10 Poor compliance in Chinese COPD patients

456 patients with COPD were followed up every 3 months while patients were routinely treated for one year in a study¹⁴. The dyspnea scores at the time of enrollment and at 1 year of follow-up, as well as the number of acute exacerbations within 1 year of follow-up were recorded. The results of the analysis showed that the number of acute exacerbations and dyspnea scores in the good compliance group were lower than those in the poor compliance group within 1 year of follow-up ($P < 0.05$). The compliance differences may affect the frequency and clinical symptoms of the patients with acute exacerbations (Figure 11).

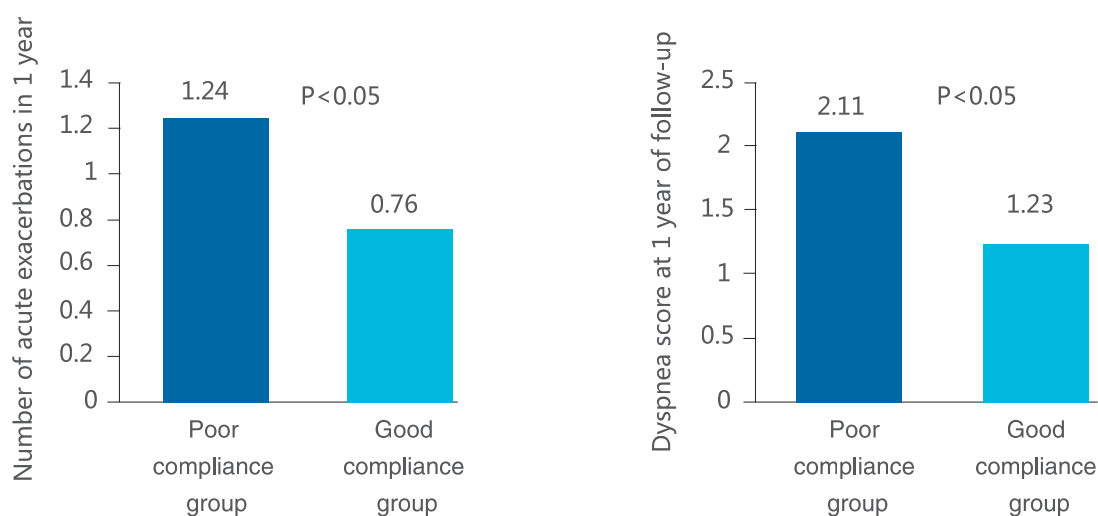


Figure 11 Comparison of the number of acute exacerbations and dyspnea scores in groups with good and poor compliances

1.4.3 Status of non-standard treatment of COPD in China

As a significant number of physicians in our country have low awareness of COPD diagnosis and treatment, their treatment options and recommendations are often contrary to the standardized prevention and treatment of the GOLD guidelines. According to the survey, only 20% of primary care physicians are fully aware of the drug treatment options for COPD. According to the 2019 GOLD guidelines, bronchodilators are still the basis for the stable treatment of COPD; long-acting anticholinergic drugs (LAMA) are preferred monotherapy for patients of all groups; LAMA prevention for acute exacerbation is superior to LABA and LAMA/ LABA combination as the recommended regimen for patients in B~D groups. A survey of approximately 700 patients with stable COPD in China found that the most frequently prescribed were expectorants, followed by β_2 agonists and anticholinergic drugs; more than half of the patients who took bronchodilators used a short-acting or intermediate-acting drug. In addition to the above problems, the irregular treatments commonly observed in clinical practices include merely focusing on the treatment of acute exacerbations of COPD while neglecting the management of stable phase of COPD; focusing on the reduction of symptoms and short-term effects while neglecting the long-term treatment and the goal of controlling future risks; and reducing treatment levels at will as well as premature drug discontinuation¹⁵.

1.4.4 Common errors in using inhalation devices

Up to 90% of patients with COPD in China have problems with correct inhalation techniques, especially when using a fixed-pressure aerosol device, which may increase the risk of acute exacerbations¹⁶.

Part 2 Asthma epidemiology and challenges

2.1 Global asthma disease burden: prevalence, mortality and trends

The 2018 Global Initiative for Asthma (GINA) shows that the global prevalence of asthma is 1% to 18%¹⁷; the average prevalence rate in countries with high prevalence is 15% to 18%, and the average prevalence rate in countries with low prevalence rates is 7%¹⁸; and the prevalence of asthma in most countries or regions is on the rise¹⁹ (Figure 12). According to the global disease burden of COPD and asthma in 2015³, a total of 358.2 million people suffered from asthma, including 168 million males and 190.2 million females. A total of 400,000 people worldwide died of asthma, down by 26.7% from 1990, and the age-standardized death rate dropped by 58.8 %. Analysis of data from the WHO mortality database from 1993 to 2012 in 46 countries showed that the global decline in asthma mortality may have stalled²⁰ (Figure 13).

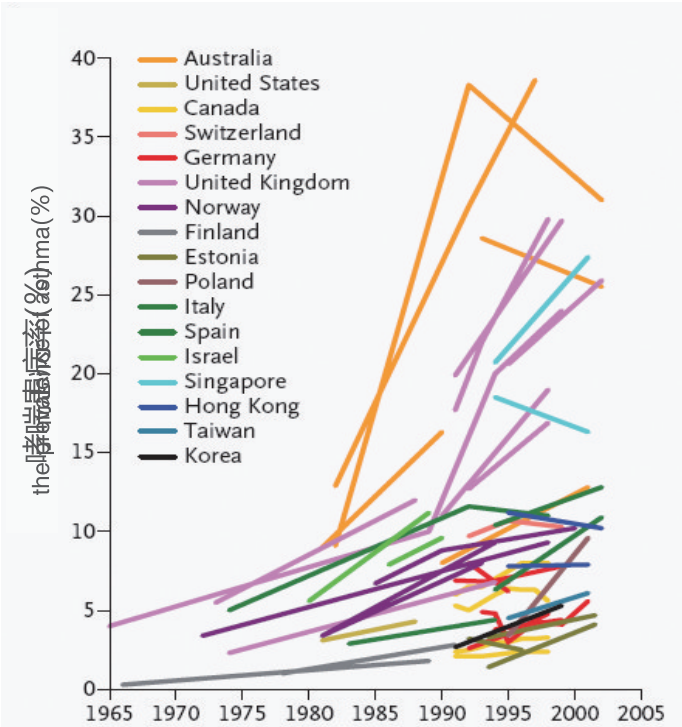


Figure 12 Changes in the prevalence of asthma in different countries (children and young people)

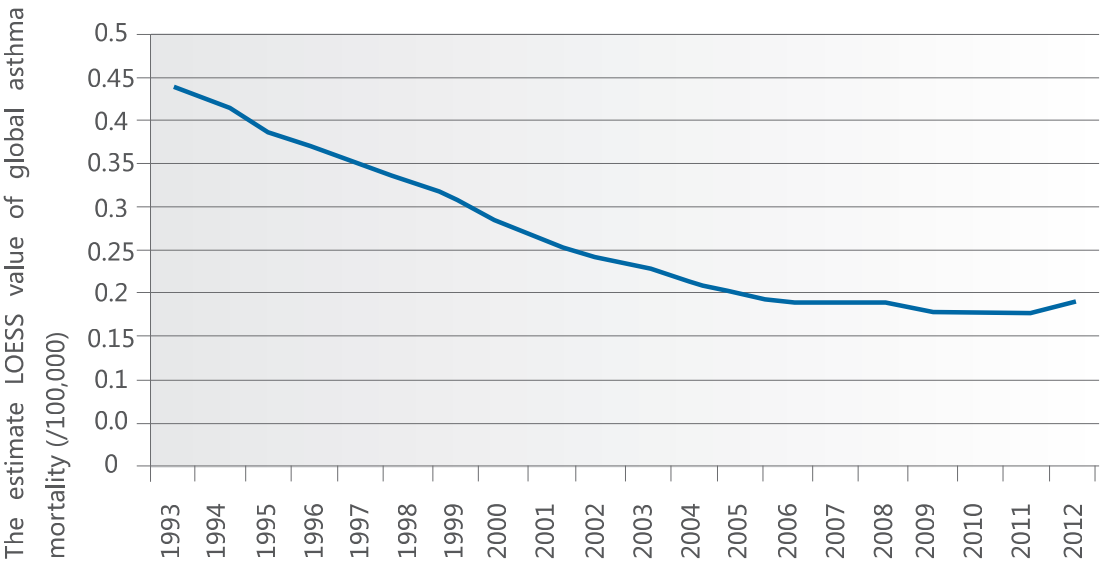


Figure 13 International trends of asthma mortality from 1993 to 2012

2.2 China's asthma disease burden: prevalence, mortality and trends

It is estimated that there are about 30 million²¹ asthma patients in China and the mortality rate is 36.7/100,000, much higher than that of developed countries. From 1990 to 2010, the prevalence of asthma in children aged 0-14 years in China showed an upward trend²²⁻²³ (Figure 14). A summary of previous survey reports showed that the prevalence of adult asthma in different regions was 0.38% to 3.38%²⁴ (Figure 15).

In 2010, the prevalence of asthma in people aged 14 and over was surveyed in 8 provinces and cities in China. The prevalence rates in Beijing, Shanghai, Guangdong and Liaoning were higher in 2010 than that from 1998 to 2000 in the same region, respectively, with an increase of 14.5%~190.2%²¹ (Figure 16). The prevalence of asthma in China has increased year by year, and asthma control should not be delayed.

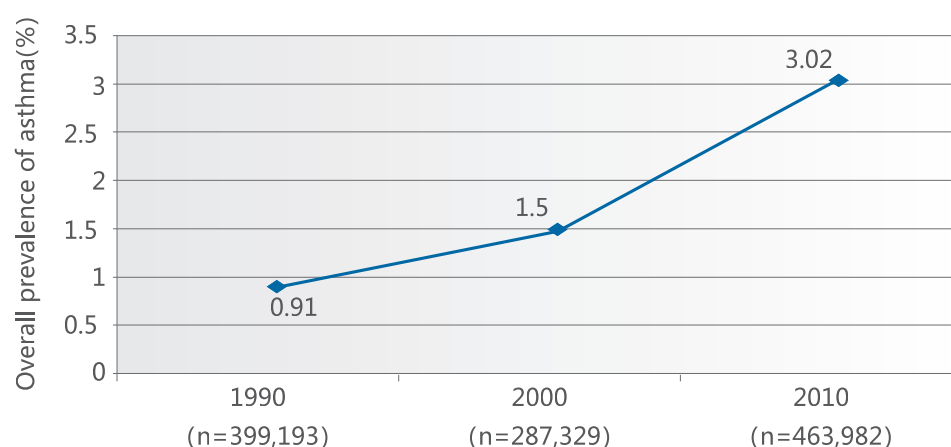


Figure 14: Prevalence of asthma in children aged 0–14 years in China (1990–2010)

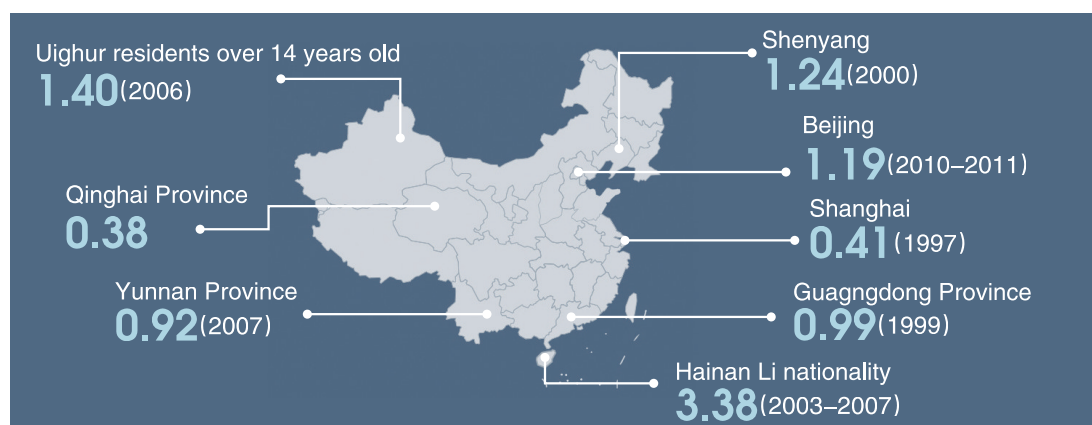


Figure 15 Prevalence of adult asthma in regional China(%)

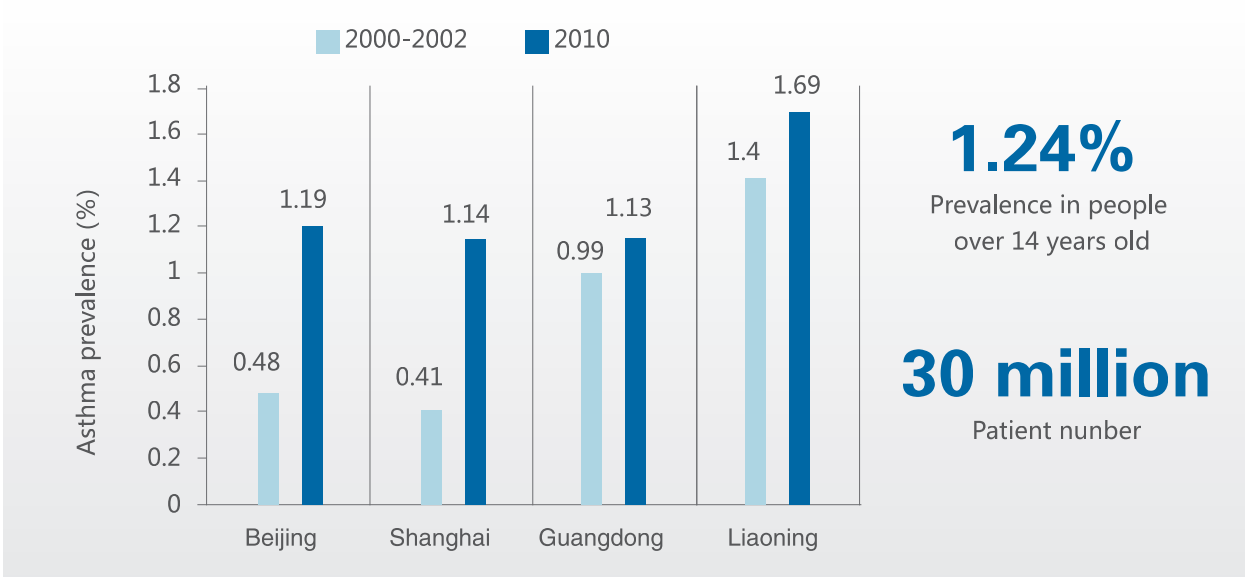


Figure 16 10-year changes in asthma prevalence in people over 14 years old in different regions

2.3 Risk factors associated with acute asthma attacks

2.3.1 Risk factors for acute asthma attacks

A retrospective survey of the cost and related conditions of hospitalized patients with acute asthma in urban areas²⁵ revealed the influencing factors for acute asthma attacks: comparing with the mild and moderate episode group, the ratio of patients that are over 60 years old, male, with a disease duration more than 10 years, a history of smoking and hospitalization or emergency visit for acute asthma attacks within a year is significant higher. (Figure 17)

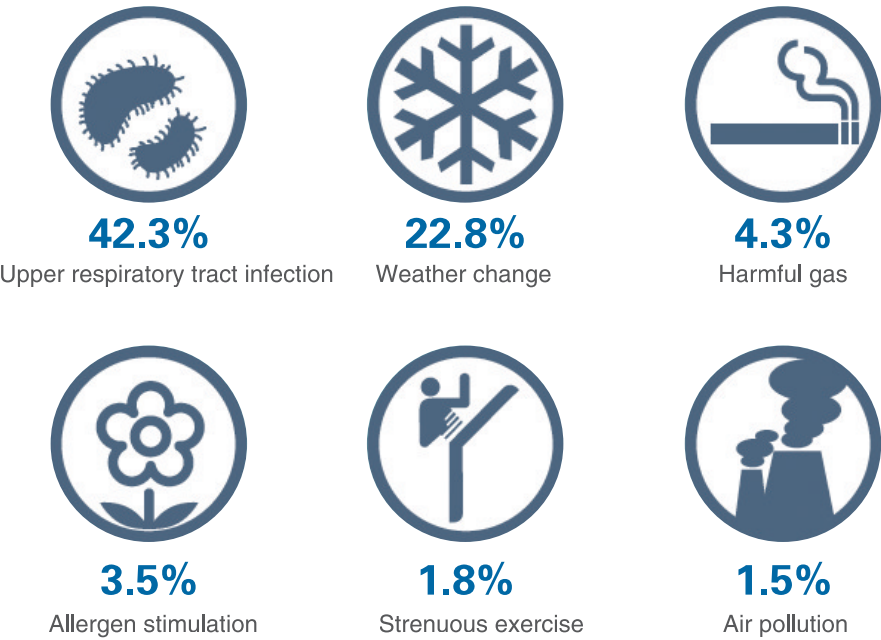


Figure 17 Risk factors for acute asthma attacks

2.3.2 Acute asthma hospitalization peaks in March and September, higher in the north than the south

According to the monthly analysis²⁴ of the proportion of hospitalized patients with acute asthma onset accounted for all hospitalized patients during the same period, the highest proportion was found in March, it gradually decreased from April to June, began to rise month by month from July and reached the second peak in September and decreased again afterwards monthly. The proportion of patients with acute asthma attacks in northern cities is higher than those in southern cities.

2.4 Asthma imposes a heavy financial burden on Chinese patients and society

The National Asthma Research Collaborative Group conducted a multi-center retrospective survey²⁵ among 3,240 patients, 1369 males (42.3%) and 1871 females (57.7%), admitted to 29 Level A Tertiary hospitals in 29 provinces, autonomous regions, and municipalities from 2013 to 2014(Figure 18). The results of the study showed that women who were hospitalized for acute asthma attacks accounted for the majority of patients, and there was a high proportion of patients with irregular medications. The cost of a single hospitalization for patients with acute asthma attacks is several folds higher than the cost of maintenance treatment for asthma patients throughout the year.

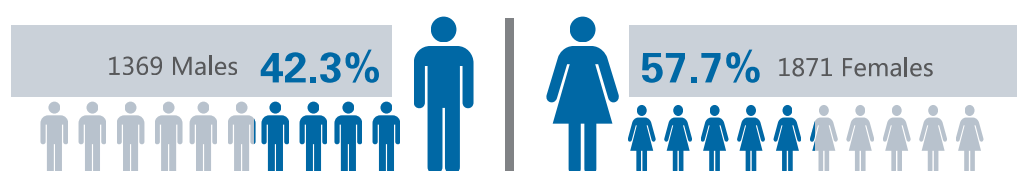


Figure 18 Population and gender distribution of the Survey on the Status of Asthma Control and Disease Awareness

Studies have shown that the average hospitalization cost for all patients is RMB 11,051, of which 52.1% is for medicines, 27.6% for auxiliary inspections, and 9.6% for treatment. Among drug costs, asthma treatment drugs accounted for only 22.7%, while antibacterial drugs accounted for 44.0%(Figure 19).

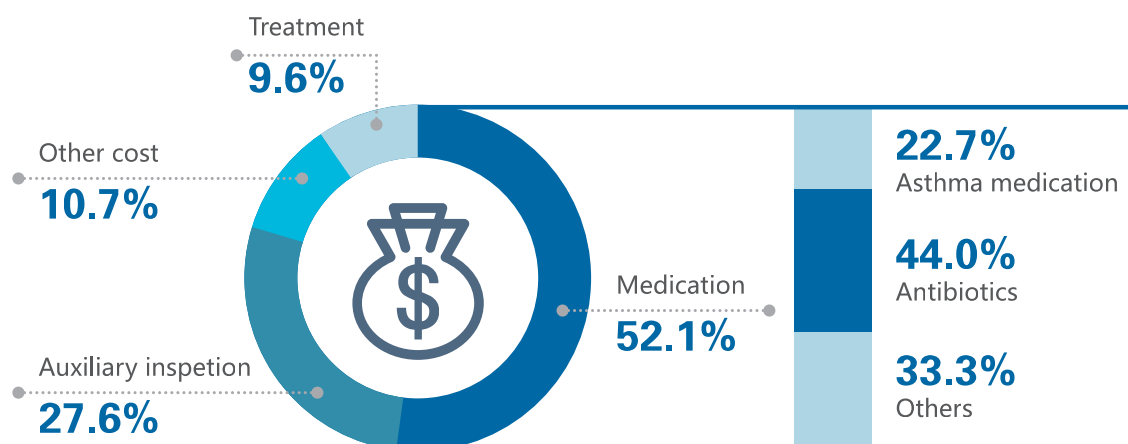


Figure 19 Single hospitalization costs for patients with acute asthma attacks are significantly higher than annual maintenance costs

The average cost of mechanical ventilation patients was RMB 26,740, which was 2.42 times that of non-mechanical ventilation. It is estimated that the cost of a medium-dose ICS combined with LABA for one year is about RMB 3,000. The cost of an acute episode of hospitalization far exceeds the cost of maintenance treatment. Therefore, the promotion of standardized asthma treatment which can reduce the number of acute attacks will reduce the economic burden of asthma patients.

2.5.2 The overall management level of asthma in China is not satisfactory, but the level of asthma management in some cities has improved

10.1% of patients have used a peak flow meter, 62.1% of patients had pulmonary function tests, and 57.4% of patients chose ICS combined with LABA for daily regular control. 43.3% of patients had an asthma treatment (follow-up) action plan developed by a specialist. Only 13.2% of patients participated in the asthma prevention knowledge lecture held by the hospital.

The 2008 Asthma Control Survey in ten cities included 1,362 asthma patients in this study, of which 17.9% used peak flow meters, 66.6% of patients had pulmonary function tests, 63.1 % of patients chose ICS in combination with LABA as managing medicine for regular daily use, and 50.4% of patients had an asthma treatment (follow-up) action plan developed by a specialist. 11.9% of the patients participated in the asthma prevention knowledge lecture held by the hospital(Figure 21).

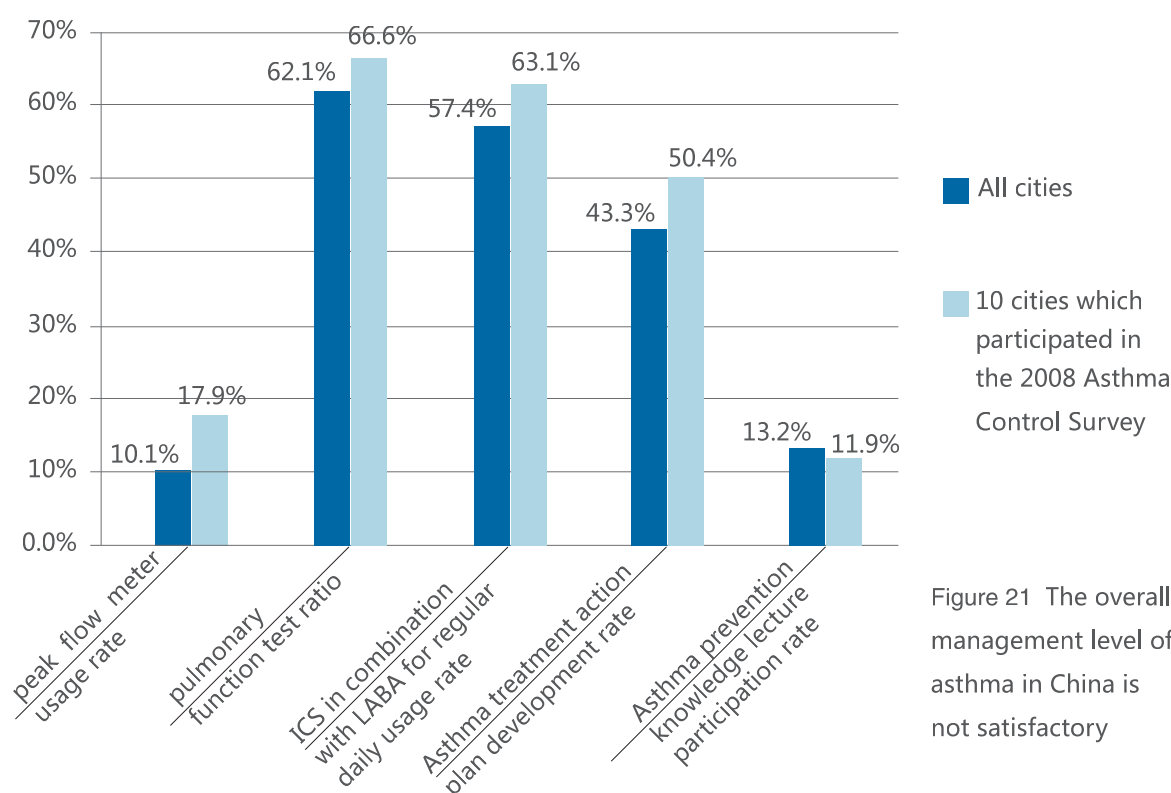


Figure 21 The overall management level of asthma in China is not satisfactory

The above data suggest that the overall management level of asthma in China is still not ideal. There are differences in cities with different socioeconomic development levels. However, in some cities, the improvement of asthma management level can be seen. The use of asthma action plan and peak flow meter should be vigorously promoted.

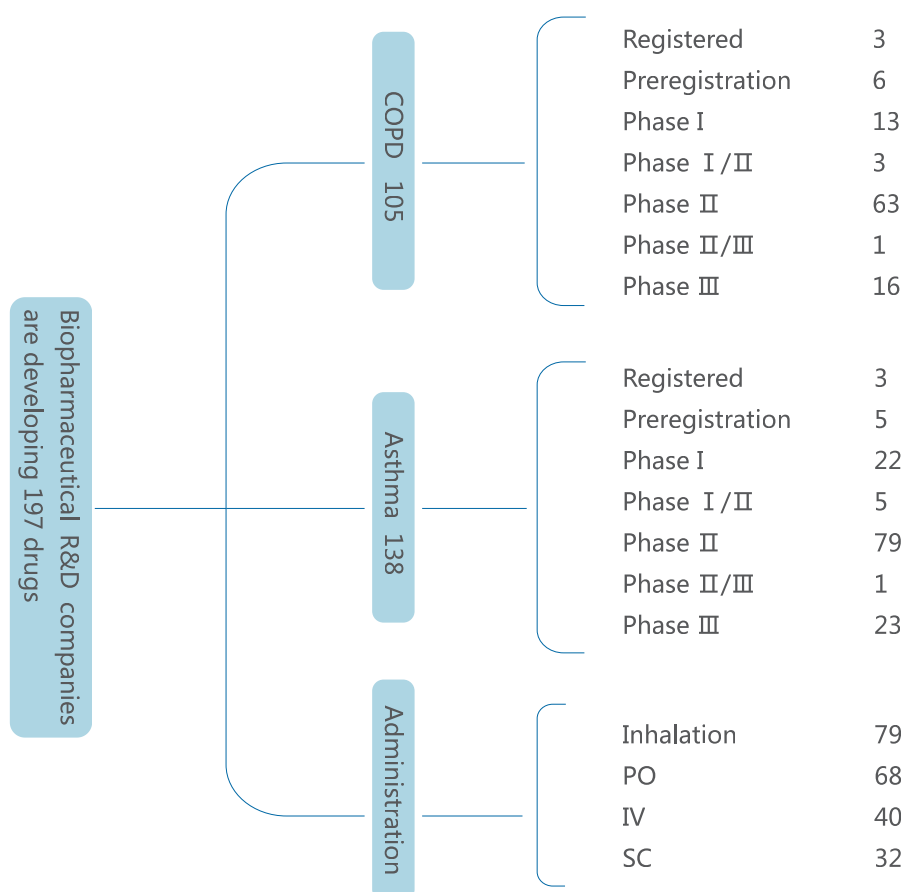
2.5.3 Most asthma attacks have clear signs or symptoms. Asthma attacks have a significant impact on the life of patients, and the proportion of patients who can self-manage is low

Studies have shown that 83.0% of asthma patients have experienced asthma attacks, 78.1% of asthma patients would restrict or stop exercises and daily activities when symptoms worsened. 82.5% of asthma patients had clear signs or symptoms when they last experienced asthma attacks. The three most frequent symptoms were: cough (60.5%), chest tightness (58.8%), and shortness of breath (54.8%). The median time from symptom occurring to the onset of asthma was 2 hours, with an average of 90 hours.

When asthma symptoms worsened, only 4.4% of patients had confidence in asthma control. 23.3% of asthma patients with asthma symptoms worsening or obstructing daily life used asthma medication. In terms of drug use, 45.8% of asthma patients selected to receive a combination of fumarate and glucocorticoid inhalers, and 23.9% of asthma patients selected short-acting β_2 agonist inhalers.

Part 4 The current status of global development of COPD and asthma treatment drugs

According to the latest data from the world of IQVIA, there are 197 drugs under development worldwide for COPD and asthma, among which are 105 COPD drugs and 138 asthma drugs. All these drugs are in the clinical trial phase, pre-registration or registration phase.



The report on the Epidemic Situation and Prevention Strategy for Chronic Respiratory Diseases²⁶ in China published in 2018 pointed out that the lack of research and development of new drugs related to chronic respiratory diseases and the lag of production are the problems faced by the prevention and control of Chinese chronic respiratory diseases. Although a variety of new bronchodilators and other therapeutic drugs for chronic respiratory diseases have emerged internationally, but overall the cure rate of chronic respiratory diseases such as COPD and asthma is still low.

October 2017, the Organization Department of the CPC Central Committee and the General Office of the State Council issued the "Opinions on deepening the reform of the review and approval system to encourage the Innovation of drugs and medical Devices", encouraging the development of new drugs and innovative medical devices, and giving priority to review and approval. The National Drug Administration (NMPA) has issued a series of supporting policies to optimize the review and approval procedures. The pace of the approval of new drugs into China has been greatly accelerated. The latest data from IQVIA shows that 14 COPD/asthma drugs were approved worldwide from 2011 to 2018, and five of them have been approved by NMPA. It is hoped that the advent of more and more innovative drugs will provide better choices for the control of COPD/asthma.

5.1.1 Improve the accessibility to effective treatment for patients with COPD

5.1.4 Increase research funding for chronic respiratory diseases

5.1.5 The road to COPD development: individualized medicine is the trend

– 15 –

5.1.6 Pay attention to the early prevention of COPD and carry out extensive awareness and education programs

COPD is preventable and controllable. In 2017, the results of the world's first large-scale clinical trial of Tie-COPD, led by Guangzhou Institute of Respiratory Diseases Academician Zhong Nanshan, were published in the New England Journal of Medicine. The study showed that the use of tiotropium in the treatment of early COPD patients can effectively improve lung function, improve the quality of life, reduce acute exacerbations, and delay the progression of the lung function decline²⁹. Therefore, Academician Zhong Nanshan pointed out that the results of this study are of great significance for the diagnosis and treatment of early COPD. It indicates that in patients with early or no symptoms of early COPD, the use of the long-acting bronchodilator tiotropium can bring significant clinical benefit. This provides a very valuable inspiration for the treatment of early COPD. We need to change the concept of COPD diagnosis and treatment, and make early diagnosis and treatment of COPD, just like early treatment of hypertension and diabetes, so as to save the lung function of COPD patients as early as possible and to delay the progression of the disease.

5.2 Four strategies to achieve asthma control

5.2.1 GINA 2018 still recommends managing asthma based on control levels

GINA 2018 still recommends the management of asthma based on control levels, and symptom control assessment and future risk assessment should be performed for each asthma patient¹⁷. The guidelines state that once asthma diagnosis is established, lung function is the most effective indicator for assessing future risks. Pulmonary function assessment should be performed at the time of diagnosis or initiation of treatment; the individual's best forced expiratory volume in one second (FEV₁) should be assessed 3 to 6 months after treatment, and thereafter. GINA 2018 clearly recommends ICS/LABA as the drug of choice for the treatment of moderate to severe asthma.

5.2.2 In view of the current situation of asthma prevention and control in China, we should strengthen the long-term standardized management of asthma

In view of the current status of asthma prevention and control in China, we should strengthen the long-term standardized management of asthma²⁸.①Determine the danger of acute asthma attacks, focusing on high-risk groups of acute attacks; ②Use ICS/LABA for maintenance control which can reduce severe asthma attack risk by 56% compared with low-dose ICS monotherapy; ③Follow the GINA guidelines which strictly stipulate that degraded treatment could be adapted only after asthma has been controlled for more than 3 months and lung function is stable, but ICS discontinuation is not recommended; ④Strengthen asthma patients' self-management, which will play an important role in achieving overall control of asthma.

5.2.3 To achieve the overall control objective of asthma, a variety of factors need to be considered in drug treatment strategies

At the group level, it is necessary to pay attention to factors such as the effectiveness, safety, accessibility and potency/price ratio of drugs. At the individual level, it is necessary to consider the patient's clinical phenotype, preferences, mastery of inhalation techniques, medication compliance, economic ability, etc. Besides, the use of novel research and development drugs also provides a better choice for asthma control.³⁰

5.2.4 To point out that asthma is a heterogeneous disease

"Guidelines for the Prevention and Treatment of Bronchial Asthma (2016 Edition)"²¹ pointed out that asthma is a heterogeneous disease that may not presents same clinical courses and treatment responses. Identifying specific phenotypic characteristics will not only contributes to the prognosis assessment of asthma but also facilitates the choice of individualized treatment strategies.

