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The Pearl River runs through Guangzhou in China, where high levels of smog increase the incidence of COPD.

## PUBLIC HEALTH

# Where there's smoke

*Air pollution and smoking have made COPD a major problem in China, now compounded by outdated diagnostics and treatments — and experts say it's bound to get worse.*

BY VIRGINIA HUGHES

A visitor to China may well notice the country's smog problem as the plane descends. Smog levels in large cities such as Beijing and Shanghai frequently dwarf those of other metropolitan centres. Then there's the cigarette smoke. China, the world's most populous country, claims about one-third of the world's smokers — at least 300 million people — who collectively puff 1.7 trillion cigarettes a year. In rural areas, cigarette smoke permeates buses, shops and even doctors' offices.

Beyond cigarette smoke and outdoor air pollution, hundreds of millions of Chinese people breathe unclean air while working in factories and on industrial-scale farms or while cooking at wood-burning stoves inside their homes.

These airborne toxicants — many of which are by-products of China's economic boom — are risk factors for chronic obstructive pulmonary disease (COPD), an incurable respiratory disorder that can cause severe breathing

difficulties. And they have public-health officials worldwide worried about a coming epidemic. "We're just seeing the tip of the iceberg on COPD in China," says Don Sin, a respiratory medicine specialist at the University of British Columbia in Vancouver, Canada, who researches COPD. "In 30 years, [the number of cases] is going to explode."

A large-scale study in China put the prevalence of COPD in 2004 at roughly 8% in people who are 40 or older<sup>1</sup>, in line with rates in the United Kingdom and the United States. But because China has seen soaring rates of industrialization and tobacco use over the past few decades, and because COPD symptoms aren't typically noticed until after age 50, public-health experts say the future is bleak. According to Sin, projections based on current trends and World Health Organization estimates show that by 2030, COPD will kill 3 million Chinese people a

year — a million more than die annually now.

## SMOKE SIGNALS

Since the late 1970s, disposable income has been on the rise in China and so has the Chinese tobacco industry, which has ramped up production and advertising. (However, recent laws have banned cigarette advertisements on television, the radio and in newspapers.) Cigarettes are cheap: as little as 30 US cents per pack, says Sin.

Because of a strong cultural stigma, only about one in fifty Chinese women smoke. But more than half of all men, and about two-thirds of middle-aged men, do. Smoking is popular among men in the city and the country, among those of all educational levels. And a survey of doctors in six Chinese cities, published in 2007, found that 41% of male doctors smoke, and about 15% have smoked in front of their patients<sup>2</sup>.

Smoking-cessation programmes exist, but their impact is minimal. Chunxue Bai, director of the Respiratory Research Institute at Fudan University, in Shanghai, says he has launched

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smoking-cessation clinics at 58 hospitals across China. But the clinic at his own hospital sees only about 300 people a year.

Despite the known link between smoking and COPD, most Chinese smokers do not fully appreciate the harm caused by smoking or are unconcerned. “They have some knowledge, but it doesn’t go deep enough to change their behaviour,” says Frank Hu, a nutrition specialist and epidemiologist at the Harvard School of Public Health in Boston, Massachusetts, who grew up in China.

China’s high smoking rates explain only part of its COPD problem though, because non-smokers are also at risk. For example, even though few women smoke, women still have high rates of COPD.

One explanation is that women — 82.5%, according to one study<sup>3</sup> — are exposed to second-hand cigarette smoke. Two large studies in China have pointed to a link between this ‘passive smoking’ and COPD. The first of these studies, published in 2007, relied on the Guangzhou Biobank Cohort Study, a collection of blood samples and extensive medical data from more than 20,000 people over age 50 from Guangzhou, the largest city in southern China. In this group, the longer the duration of exposure to second-hand smoke, the higher the likelihood of COPD. The authors of this study also estimated that, of the 240 million people in China who were 50 years or older at the time of the study, 1.9 million non-smokers would die because of second-hand smoke<sup>4</sup>.

Similarly, the second study, published in May 2012 by Hu and his colleagues, followed 910 non-smoking Chinese women for 17 years. They found that women who were exposed to second-hand smoke were 2.3 times more likely to die from COPD than those who were not exposed, with cumulative exposure increasing the risk<sup>5</sup>.

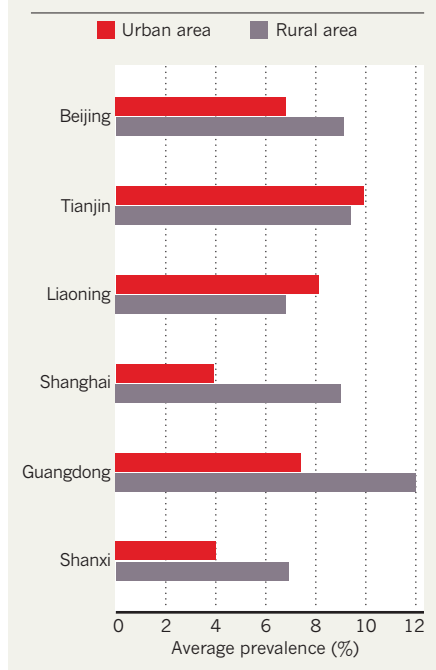
But these data are controversial. Studies of second-hand smoke in Western countries have shown a suggestive but not definitive link to COPD. Three other studies in China also did not find an association between second-hand smoke and COPD. And COPD rates are up to three times higher for non-smoking Chinese women who live in rural areas than for non-smoking Chinese women who live in cities, even though their levels of second-hand smoke exposure are similar.

“There’s no question that second-hand smoke is bad, but the [estimate] for how much COPD it causes in China is still not known,” says David Christiani, an environmental geneticist at the Harvard School of Public Health. “It’s much more than just a simple linear connection.”

Christiani became interested in the non-smoking causes of COPD in the late 1970s, when US health officials were pushing for regulations to limit workers’ exposure to cotton dust in textile factories. The process of turning fluffy cotton flowers into strong thread throws off particles of plant matter, pesticides and

## COPD IN CHINA: WHERE IT’S WORST

In four of six provinces included in one study<sup>1</sup>, the disease was more common in the countryside, which has its own risk factors — such as home cook stoves that throw off toxins and poor healthcare.



bacterial endotoxin, and textile workers had high levels of respiratory disease. But, at the time, the US cotton industry suggested that workers’ lung problems stemmed from cigarette smoking rather than conditions at the mills. “Most workers were smokers, so it was very hard to tease these things apart,” Christiani says.

Thanks to a serendipitous partnership with a university in Shanghai, Christiani realized that China offered a natural experiment to settle the debate. In Chinese factories, men and women work side by side; however, whereas most of the men smoke, hardly any of the women do.

For the past 30 years, Christiani has followed hundreds of people working at two cotton mills and one silk mill in Shanghai. His research has shown that even in non-smokers, breathing cotton dust causes significant airway blockage.

Although China has passed some labour laws to limit exposure to cotton dust, they’re often not enforced. And many other industries pose similar threats or worse ones. Coal mining, welding, construction, grain processing and animal breeding produce their own airborne toxicants — including silica crystals, asbestos and faecal matter — all of which can contribute to COPD.

The impact of these occupational hazards is evident even in the layout of Chinese hospitals, notes Peymané Adab, an epidemiologist at the University of Birmingham in the UK and an investigator on the Guangzhou Biobank Cohort Study. “There are specific wards for

people who have been exposed to certain dusts or people with lung disease related to a particular toxin,” she says.

Another key factor is indoor air pollution. More than 70% of all Chinese households, and 90% of rural ones, use stoves that run on wood, crop residues, coal or animal dung. Burning these fuels releases particulate matter, as well as fumes laced with carbon monoxide, formaldehyde and free radicals. In 2007, China’s Ministry of Environmental Protection set emissions standards for pollutants inside the home, but studies that measure air quality in rural homes have found levels exceeding the standards many times over. And exposure to biomass smoke increases COPD risk by 2.4 times, according to a 2010 meta-analysis of 15 studies<sup>6</sup>. “Women being the predominant cooks for families, they would be exposed to more of that,” says Sin. That might partly explain why the COPD rates in non-smoking Chinese women are higher in rural areas than in cities — the dangerous types of stove are more common in the countryside.

Sin points to a slew of other factors too. About 1.5 million people in China have tuberculosis, and many areas of China have high rates of childhood pneumonia and malnutrition. All three factors increase the risk of COPD later in life.

## DEVICES WANTED

As recently as a decade ago, COPD research in China was scant. Although awareness has grown considerably in the past few years, scientists still have trouble gauging the full extent of the disease.

COPD prevalence ranges widely from region to region, from 5.5% in the province of Shanxi to 13.7% in the city of Chongqing, according to the large prevalence survey of 2004<sup>1</sup>. Other studies have found even greater discrepancies (see ‘COPD in China: Where it’s worst’).

One reason for this variability is inconsistency in the methods of diagnosis. Spirometry, in which the patient blows as hard as possible for as long as possible into a machine that measures lung capacity, is the global gold standard. But spirometers are rarely used in China, especially outside the big cities. Even though these machines are relatively inexpensive for specialized medical equipment — several thousand dollars apiece — many doctors, especially in the countryside, do not use them. The large COPD prevalence study found that less than 7% of participants diagnosed with COPD had previously been tested by spirometry<sup>1</sup>.

Instead, Chinese doctors tend to rely on subjective descriptions of symptoms to make the call, which can lead to misdiagnosis as asthma or a non-chronic form of bronchitis. “People go to see their doctor complaining of shortness of breath, and responses would be, ‘You’re getting old’ or ‘You have bronchitis, take some antibiotics,’” Sin says.

Even for individuals who receive a bona fide COPD diagnosis, medical care and drug treatments can be lacking. In Western countries,



One study found that fewer than 7% of COPD patients in China had been tested by spirometry.

common treatments for COPD include several kinds of inhalants, such as corticosteroids and  $\beta$ -agonists, that open up the airways in the lungs and provide immediate relief from symptoms. In the later stages of the disease, many patients use portable oxygen tanks. But these options are far too expensive for most Chinese patients.

In China, the most common COPD treatments are two inexpensive tablets. One, called carbocisteine, helps break up mucus and phlegm in the respiratory tract and has antioxidant properties that may slow the progression of COPD (see 'A radical treatment', page S4). The other, called theophylline, is a decades-old bronchodilator, or respiratory muscle relaxant, and anti-inflammatory. Theophylline is structurally similar to caffeine and is known for its erratic absorption and harsh side effects, including nausea, headache and life-threatening changes to heart rhythms.

Chinese researchers are focused on rigorously testing the effectiveness of their small drug arsenal. Studies of Western patients have found little benefit to adding carbocisteine or theophylline to other, reportedly more effective, treatments. But, in China, where most patients use nothing else, research has shown that the two drugs can help. For example, a 2008 report found that in Chinese patients with COPD, carbocisteine treatment for one year reduced the number of exacerbations, or sustained disease flare-ups, better than a placebo<sup>7</sup>. The same was found for theophylline given in a slow-release formulation at doses low enough to prevent severe side effects<sup>8</sup>.

Both drugs are much cheaper than inhalants. In 2008, the average annual cost of carbocisteine therapy in China was 650 renminbi (about US\$90 at the time) for each patient, compared with 4,320 renminbi (\$580) for treatment with the standard combination of

inhaled medications used in Western countries. Yet even the cheap drugs present an economic burden for most families, who shoulder the bulk of their healthcare costs without insurance or government assistance. One study found that the total cost for a patient with COPD in China was US\$1,732 a year — a tremendous amount, given that the average urban Chinese household pulled in only \$3,000 per capita in 2010, according to an analysis of government statistics by the China Market Research Group.

Beyond cost, the difference in quality of life is enormous. The inhalers used in Western countries slow down lung deterioration and give patients years of additional mobility. They are also better at preventing exacerbations, which cause intense anxiety and often take weeks to recover from. These flare-ups often mean time off from work, making treatment costs even harder to bear.

#### HAZY FUTURE

For now, inhalers are available only to wealthy Chinese citizens. But, as China's economy continues to grow, so too will its middle class — and its market for more expensive drugs.

Pharmaceutical giants have taken notice. A spokesperson for Novartis, headquartered in Basel, Switzerland, says the company recently approached a regulatory agency in China about one of its inhalers, a once-a-day bronchodilator. Jinping Zheng, deputy director of the Guangzhou Institute of Respiratory Disease, says that London-based AstraZeneca is investigating COPD in China. And he says that four years ago, GlaxoSmithKline (GSK), also headquartered in London, launched

COPD Academy, a programme that has reached more than 20,000 general practitioners across China. A third of the programme focuses on a COPD drug called Seretide, a combined anti-inflammatory and bronchodilator that is marketed by GSK. The other two-thirds — developed with the help of the top 18 respiratory experts in China, according to GSK — aims to deliver unbiased education on the basics of COPD diagnosis.

There has also been some regulatory movement on the antismoking front. In the past few years, major cities in China have banned smoking in hospitals, restaurants, public transport and other indoor public places, and a similar nationwide ban was instituted in 2011. These laws are difficult to enforce, however, and many smokers blatantly ignore them.

Smoking regulations promoted by prominent doctors and China's Ministry of Health have a powerful enemy in the Chinese tobacco companies, which are controlled by the government at the local and national levels. "The tobacco companies are much stronger [than the health department] because they have the money," says Tai Hing Lam, director of the School of Public Health at the University of Hong Kong. "That's why the progress has not been as good as we would like." Lam and other experts say that China's COPD problem will not be curbed until the public makes demands for more-sweeping political changes from its government.

There is a precedent. It happened in the summer of 2008, when the Olympic Games were held in Beijing, and China shut down dozens of nearby factories and ordered half of all private cars off the road. The Beijing government also passed smoking bans in schools, hospitals and government offices, and required non-smoking sections in hotels and restaurants. Air pollution dropped quickly.

But as soon as the festivities were over, business continued as usual, and many of the smoking bans were lifted.

All China needs is a wake-up call to realize the significant human and economic burden of COPD, according to Christiani. "Once China starts recognizing the problem as something that needs to be tackled, it can make some significant strides." But for millions of older Chinese people, any hope of avoiding COPD risks has gone up in smoke. ■

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