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Beyond the lungs—a new view of COPD

Despite being the fifth leading cause of death in high-income countries, and the sixth in low-income and middle-income nations, chronic obstructive pulmonary disease (COPD) has not received the attention it deserves. It is underdiagnosed, undertreated, and underfunded and neglected by the public, pharmaceutical industry, and physicians alike when compared with other major killers, such as cardiovascular disease and stroke. This neglect is sadly due in part to the perception that COPD is a self-inflicted smokers’ disease that affects only elderly people and has no effective treatment. Thankfully, these misconceptions about COPD are rapidly being challenged. As this week’s issue of The Lancet—which focuses on the condition to coincide with this year’s European Respiratory Society meeting in Stockholm, Sweden (Sept 15–19)—shows, COPD can affect never-smokers, be caused by factors other than cigarette smoke, and susceptibility to the disease could be established in utero.

Over 15% of COPD occurs in people who have never smoked. Although smoking is the most important risk factor for COPD in high-income and middle-income countries, in low-income nations exposure to indoor air pollution, such as the fumes from biomass fuels for cooking and heating, causes most COPD cases. The BOLD study in this week’s issue, which estimates the worldwide prevalence of COPD, illustrates the importance of risk factors other than smoking. The investigators found that the prevalence of COPD among individuals aged 40 years and older who had never smoked was similar to that for those who had ever smoked and had 0–10 pack-years of cigarette smoking exposure. Several study sites had exposure to potential risk factors for COPD other than smoking, including occupational hazards—irritants, fumes, and vapours—and tuberculosis.

Second-hand smoke is another risk for people who have never smoked. As Peng Yin and colleagues show, passive smoking in workplaces and homes could be responsible for 1·9 million (95% CI 0·9–2·8 million) excess deaths from COPD among never-smokers in China. The results from Yin and colleagues’ study should urgently inform tobacco-control policy in China, where, according to this week’s World Report, economic arguments about the country’s billion-dollar tobacco industry are currently triumphing over health concerns. However, the human and economic ramifications of smoking and passive smoking in terms of health-care costs, lost years of work and productivity, and premature deaths should be the Chinese Government’s greater concern.

COPD is not just a “smokers’ disease”. Nor is it solely an affliction in old age, since 5–10% of non-smoking young adults show signs of COPD. Future preventive interventions might be applicable in pregnancy or infancy. As Debra Stern and colleagues show, poor airway function shortly after birth is a risk factor for airway obstruction in early adult life—a strong predictor of COPD.

What of the view that little can be done for patients? Currently, the condition cannot be reversed by the mainstay therapies—bronchodilators and anti-inflammatories—but medications can provide patients with symptomatic relief and improve quality of life. One of the problems in the search for new drugs for COPD has been that large clinical trials have excluded patients who have comorbidities commonly associated with the condition, such as ischaemic heart disease and diabetes. Such exclusion means that the results from large trials have little relevance to real-life patients.

This lack of attention to COPD comorbidities makes the suggestion put forward by the authors of this week’s Viewpoint all the more compelling. Leonardo Fabbri and Klaus Rabe argue that COPD and all its comorbidities should come under a new umbrella term—chronic systemic inflammatory syndrome—because the systemic effects of smoking contribute to several other conditions, including cardiovascular disease, some cancers, and increased blood pressure.

We support this call for a new view of the disease. The non-pulmonary conditions associated with COPD need to be recognised as part of the diagnosis rather than as separate medical conditions, especially since patients are more likely to die from these conditions than COPD. Such a shift in thinking could bring us closer to the goal that has so far been elusive—treatments that can reduce mortality associated with COPD. That this year’s European Respiratory Society meeting has a session devoted to COPD comorbidities is a promising start. Only with a view of COPD that goes beyond the lungs can the research community deliver what many clinicians want and patients need—a holistic approach to the management of this disabling condition. ■ The Lancet
WHO fails to address health security

Global public-health security cannot be achieved without international cooperation between all countries, especially those where new and emerging threats are most likely. Infectious diseases, both new and old, pose substantial threats, given the tendency for pathogens to disrespect borders, rapidly spread, mutate, and develop resistance. But there are other, sometimes less predictable, threats to public-health security such as accidental or deliberate release of chemical or biological agents, or radionuclear materials; natural disasters; and conflict.

This year’s World Health Report from WHO purports “to provide guidance and inspiration...to secure the highest level of global public health security”. The report outlines how the revised International Health Regulations (2005), which came into force in June, 2007, can be used to control risks to security. With respect to containing infectious disease threats, the report is useful. Sections on lessons learnt from chemical, nuclear, or biological events are included. But the response to conflict is woefully inadequate in that the sole focus is on the infectious disease consequences of conflict. The humanitarian disasters that result from armed conflict, of which the mortality and morbidity in Iraq are good examples, are a serious omission from the 2007 report. Failure to discuss the wider effects of conflict on global security are even more puzzling given March’s bold and brave theme issue of the Bulletin of the World Health Organization devoted to health and foreign policy. It seems that not until the World Health Report 2008 will humanitarian action in times of crisis be discussed.

WHO claims that the World Health Report 2007 “marks a turning point in the history of public health, and signals what could be one of the biggest advances in health security in half a century”. We disagree. The World Health Report 2007 is a missed opportunity and adds little to what WHO has achieved with the International Health Regulations. The clear and present danger of infectious disease epidemics is undisputed. What is needed is leadership from WHO on how health should shape foreign policy and how global public health security can be achieved in its entirety. ■

USAID hunts for terrorists...under the duvet

The United States Agency for International Development (USAID) had its genesis in the noble ideals that underpinned the Marshall Plan for the reconstruction of Europe after World War II. Since its founding in 1961, USAID has provided humanitarian, economic, and development assistance, in more than 100 developing countries. Because it exists in part to support the foreign policy interests of the USA, tensions in its missions are inherent, making the agency something of a permanent political football, despite a large contingency of dedicated employees.

Recently, the agency announced that it was implementing a Partner Vetting System, in which all organisations applying for USAID funding would be required to submit detailed personal information on every one of its employees, and possibly on the recipients of aid. Some of the required information includes name, date and place of birth, social security or other government-issued identification information, telephone numbers, email addresses, nationality, citizenship, and profession.

The ostensible reason? To ensure that no USAID funds are being used to support terrorists or terrorist activities. The information would be supplied directly by the people involved, apparently in the belief that terrorists will voluntarily supply truthful identifying information to the US Government.

Aid groups have protested that the programme imposes undue burdens and will adversely affect their work. President of DKT International, Philip D Harvey, said the proposal reflects the paranoia of an administration that “sees a terrorist under every bedcover”.

Is there any evidence that such vetting is effective? Just as one example, the intelligence available on the terrorists who carried out the 9/11 attacks suggests that reams of data do not result in effective analysis and plans. To its credit, USAID has said its proposal might be modified, as well it should be. The partner vetting plan, as proposed, is a piece of unworkable nonsense. The money spent on the plan would be far better put towards the real, often admirable, work of USAID. ■

For more on the International Health Regulations see Lancet 2007; 369: 1763
COPD: a chronic and overlooked pulmonary disease

Chronic obstructive pulmonary disease (COPD) imposes an important societal burden worldwide. The WHO Global Burden of Disease Project states that more than 2·5 million people die of the disease every year, which is about the same number as for HIV/AIDS. COPD is the tenth leading disease burden, expressed in disability-adjusted life-years (DALYs), and causes about 2% of the burden of disease worldwide. Overall, COPD was estimated to have resulted in more than 26 million DALYs in 2000. Estimated prevalence rates for people older than 30 years vary between 0·6% and 4% in men and 0·2% and 3·2% in women, but the general perception is that these estimates are not accurate. Further quantification of the burden of COPD is, therefore, crucial for public-health planning.

One quantitative summary of COPD prevalence provided the first high-quality estimates in the important subgroups of age, smoking status, and sex. The data suggested that the prevalence of physiologically defined COPD in adults older than 40 years was 9–10%. However, the authors concluded that high-quality estimates were still absent for key regions outside Europe and North America, and that different methods of measurement hindered the ability to make meaningful comparisons between various studies.

In today’s Lancet, A Sonia Buist and colleagues report worldwide data for COPD prevalence that were obtained as part of the Burden of Lung Disease (BOLD) initiative. BOLD was designed to provide a means to obtain high-quality country-specific data for the prevalence and social burden of COPD under strictly standardised methods. The method was developed in conjunction with The Latin-American Project for Investigation of Pulmonary Obstruction (PLATINO), undertaken in five Latin American countries. Both initiatives have embraced systematic quality criteria for spirometry as an essential component of the programme, and systematically tested before and after bronchodilator use, as recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

The prevalence of COPD reported by Buist and colleagues is much greater than that reported before: GOLD stage I or higher disease (FEV\textsubscript{1}/FVC<0·7 and predicted FEV\textsubscript{1}<80%) was 10·1% (SE 4·8) overall: 11·8% (7·9) for men and 8·5% (5·8) for women. Much the same data were reported in the PLATINO study; the prevalence of COPD ranged from 7·8% to almost 20%, with a consistent pattern of higher prevalence in men, older people, and those with less education, lower body-mass index, and an increased exposure to smoking. The prevalence of disease of GOLD stage II or higher in the PLATINO study varied between 2·6% and 7·1%. A higher percentage of people who had never smoked and who had a substantially lower smoking exposure were reported to have COPD in the PLATINO study than in the BOLD report. However, both studies used high-quality estimates to confirm that COPD is a much greater health problem than was previously recognised.

In addition to smoking, the BOLD study confirms that age is a strong contributing factor to COPD prevalence and possibly to disease severity. The overall pooled adjusted odds ratio for stage II or higher COPD per 10-year age-increment was 1·94. The prevalence of stage II or higher COPD exceeded 20% in four sites for...
men and in two sites for women in individuals aged 60–69 years; these numbers increased to nine and seven sites, respectively, for individuals aged 70 years or older. In the PLATINO study, the prevalence of COPD ranged from 18.4% to 32.1% in those aged 60 years or older. It would be intriguing to integrate these observations into longitudinal follow-up studies to analyse if this higher prevalence is just a result of the progressive nature of the disease or if other factors, such as inflammation, contribute to an accelerated decline with ageing. When the ageing of the world’s population and the comorbidities that accompany the multicomponent nature of COPD are considered, it becomes clear that health systems should prioritise this health issue by implementing an integrated approach, as formulated by WHO.6

The BOLD and PLATINO studies show that physiologically defined COPD occurs in non-smokers as well as smokers. More research focused on non-smokers and sex differences is necessary if we are to improve our understanding of the pathogenesis and heterogeneity of COPD. Continual assessments in other BOLD sites and future studies applying the strictly standardised BOLD method will undoubtedly strengthen our understanding of the size of the burden of COPD. Even so, with quantitative data already available, it is already clear that COPD is a major disease worldwide. Recognition of this fact obligates us to make efforts to increase public awareness and efforts towards the adoption of an integrated approach aimed at reducing or stabilising the present and future burden of disease generated by COPD.

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Role of passive smoking on COPD risk in non-smokers

In today’s Lancet, Peng Yin and colleagues publish an important article on the association between passive smoking and the risk of chronic obstructive pulmonary disease (COPD) in China.1 The results are particularly relevant in view of the increasing epidemic of active and passive smoking in China, as in other low-income and middle-income countries.2 COPD rates are also high in that region, as shown in the BOLD study’s3 finding that 7.2% of Chinese adults aged 40 years or older have this serious condition.

Yin and colleagues’ cross-sectional analysis included almost 15,400 people who have never smoked, of whom 6497 (42%) had valid prebronchodilator spirometric data. Although this rate is fairly low, only those lung-function results that met rigorous standards were included in the analysis. Passive smoking at home and at the workplace was measured in terms of density and duration of exposure, and COPD was defined according to the stages of severity proposed by the Global Initiative for Chronic Obstructive Lung Disease.4 Individuals who were highly exposed to passive smoking (more than 40 h per week for more than 5 years) were 48% more likely to present with...
COPD than were unexposed individuals. Passive smoking was also associated with respiratory symptoms.

Yin and colleagues’ study has several strengths. First, the sample size was larger than in most studies on this topic. Second, the exclusion of current and former smokers—confirmed by urinary cotinine measurements—avoids potential confounding by active smoking. Third, the use of spirometry was a major strength, because most large-scale surveys rely solely on questionnaires. Possible limitations include the cross-sectional nature of the data, the sex imbalance in the sample (almost 90% of participants were women), and the fairly poor quality of the spirometries, as recognised by the authors.

The main contribution by Yin and co-workers is to help our understanding of the burden of COPD in non-smokers—a finding reported in multicentre studies.1-3 This study adds fuel to the controversy, showing that passive smoking might also have a role. Previous studies show that exposure to other pollutants, such as biomass and coal smoke and dust, might also account for COPD in non-smokers.4 These results suggest that future anti-smoking policies should, in addition to targeting active smoking, also consider addressing passive smoking.

Yin and colleagues estimate that, if the association is causal, 1.9 million excess deaths from COPD would be attributable to passive smoking in the Chinese population. Their findings, added to what is already known about the harmful effects of passive smoking, suggest that urgent strategies to reduce this exposure are needed.

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See Articles page 758

Early lung development and COPD

To state that disturbed early development paves the way for later illness and accelerated senescence seems a truism. For pulmonary disease, this has been postulated for 30 years.1 Yet evidence to support this hypothesis is sparse. As recently as 2002, a major workshop on future directions in chronic obstructive pulmonary disease (COPD) failed to include early lung development in its future research agenda.2 Why has so little research been done?

The overwhelming evidence that cigarette smoking is the single biggest avoidable risk factor for adult lung diseases, both lung cancer and COPD, has dominated the research agenda for 50 years. Yet only a minority of smokers develop COPD, suggesting that it is the interaction between environmental exposures (such as tobacco smoke, air pollutants) and host factors (genetics, early lung growth, race, sex) that determines an individual smoker’s susceptibility to COPD.3 Although the role of genetics has been emphasised,4,5 other host factors have been relatively neglected.

A limiting factor in this research is the huge logistical difficulty of studying the effect of exposures in fetal life or infancy on a disorder that only becomes apparent 50–60 years later. The journey from the uterus to senescence is long and eventful, with study participants surviving generations of researchers. Therefore, research must rely on intermediate endpoints, biological events lying on the causal pathway between exposures and outcome. One such intermediate measure is lung function in early adulthood, which strongly predicts development of COPD.5,5 Joining together these links in the chain, the evidence for the importance of events in early life as precursors of COPD is strengthened.

One such link is the report by Debra Stern and colleagues in today’s Lancet.4 In a small but carefully nurtured cohort, the authors convincingly show that those individuals who had the lowest forced expiratory flows by the “squeeze” chest-compression technique (figure) as infants had poorer airway function than other participants by age 22 years. The association was not explained by...
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current wheeze, atopy, or smoking, and persisted after bronchodilatation. These results are supported by data from other groups that show remarkable tracking of airway function from birth to middle childhood\(^7,8\) and from childhood to adulthood,\(^9,10\) although no study has so far reached old age. The age of 22 years is important, because by then the lung has achieved maximum growth. Those with the poorest airway function at 22 years are likely to retain their low position in the lung function population and hence be the first to reach the threshold for diagnosis of COPD (FEV\(_1\)/FVC<0·7).\(^5\)

Stern and colleagues’ report throws up several questions. First, what is the nature of the impairment in neonatal and young-adult lung function? The assumption is that, in both age-groups, airway function (airway calibre or the elastic properties of the airway wall) is impaired. However, reduced pulmonary elastic recoil might also contribute to reduced flows. Therefore, the effect of airspace development (alveolar or acinar) must also be considered. Abnormalities in this hidden region of the developing lung can influence forced flows and may contribute to the development of COPD, which includes airspace disease (emphysema) and airway abnormalities. Alveolar development occurs during the final 3 months of fetal life and the first 2–3 postnatal years, and is a prime target for many environmental exposures and pulmonary disorders at these ages. Until recently, there has been no direct technique to study airspace development. New non-invasive methods that use the diffusion properties of stable noble gas isotopes such as helium-3, which can be detected by magnetic resonance, promise to provide a sensitive window on the acinus,\(^11,12\) allowing the contribution of peripheral lung development to COPD to be studied.

Second, what are the fetal causes of impaired lung growth? Maternal cigarette smoking is the best recognised cause, with independent effects persisting into adult life.\(^12\) Stern and colleagues’ study might be too small to show this effect. More work is needed to identify other causes, both environmental (such as nutritional deficiency) and genetic. Such work would mean the collection of large prospective cohorts of newborn babies and doing lung-function tests in infants before postnatal exposures dominate. The ethical climate is changing and steadily moving against this sort of research, which makes Stern’s study so important.

Finally, Stern and colleagues found that only 9–14% of the variability in spirometric lung function at age 22 years was explained by neonatal forced expiratory flows, leaving much room for other childhood exposures in the COPD pathway. Lower respiratory illness in young children, which Stern and others have shown to be strongly associated with neonatal airway function, might be an additional risk factor. Could preschool viral wheeze (formerly, wheezy bronchitis) be a marker of later COPD? Chronic childhood asthma may contribute to adverse airway remodelling that tracks into adulthood.\(^9\) Outdoor air pollution affects growth in airway function.\(^14\) Worldwide, indoor air pollution from biomass cooking might be a greater environmental threat, but because it occurs in developing countries and exposure is mainly among women and young children, this topic has been largely ignored.

As COPD is set globally to become the third most important cause of death, now is the time to add research into its earliest origins to the agenda.

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Cochlear implantation: one or two?

Since the 1980s more than 120 000 patients have received cochlear implants worldwide.¹ Such devices allow adults and children with severe-to-profound hearing loss to improve their perception of sound and speech, with significant benefits for communication. In patients with severe-to-profound sensorineural hearing loss, the hair cells within the cochlea cannot convert acoustic energy into electrical impulses, and the brain fails to receive useful information. However, most of these patients still have residual auditory nerve cells and the cochlear implant, which is placed into the inner ear, stimulates the auditory nerve directly, circumventing the non-functioning inner ear.

Since the introduction of cochlear implantation in clinical practice, unilateral cochlear implantation has been shown to be an effective method of auditory rehabilitation for patients with bilateral severe-to-profound hearing loss. Although unilateral use of cochlear implants is successful in providing good understanding of speech in a quiet environment, many implant recipients still have difficulty in understanding speech in a noisy environment. Recent research has shown that bilateral cochlear implantation can improve speech perception, especially in noisy environments.² Four The benefit in perception is mainly a result of the “head-shadow effect”. The physical presence of the head allows the listener to selectively attend to the ear with the most favourable auditory signal and thus maximises speech recognition in noisy conditions.⁴ Five Children who receive two implants early in life seem able to separate speech signals from background noise more effectively than older recipients. In young children, the central auditory system might be able to learn to process the differences between the signals reaching the two ears to form a better central representation of the auditory input.⁴ Five The central auditory system also benefits from duplicate representations of the same signal from both ears.⁴ Five

A recent study further supports the growing evidence for the benefit of improved sound localisation with bilateral implantation. Arlene Neuman and colleagues⁶ found that identification accuracy for sound direction was significantly better with two implants than with one. These researchers studied adults in a large classroom with an array of nine loudspeakers. Sound localisation accuracy was significantly better with the use of two implants than with one. We will see more patients who are deaf receiving bilateral cochlear implantation, which can provide better speech perception in quiet and noisy environments and better sound localisation.

Another important advance in cochlear implantation is the development of implants that preserve the residual hearing of patients to allow combined electric-acoustic stimulation. Previously, cochlear implantation was reserved for patients with little or no usable acoustic hearing anywhere in the frequency range. However, many patients who could benefit from cochlear implantation still have some residual hearing in the low-frequency range, which is processed by the upper turns of the cochlea. Implantation with standard-length cochlear implants will usually destroy the residual hearing. This loss can be due to intracochlear trauma from the size and the design of the cochlear implant and the surgical technique used. A shorter hybrid 10 mm cochlear implant was designed to be minimally invasive and to enter only the lower basal turn of the cochlea where the high-frequency auditory neurons are located.⁷ Preservation of some hearing in 95% of

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patients has been reported in a multicentre FDA clinical trial of the new hybrid 10 mm implant.7 Furthermore, some residual hearing can also be preserved in up to 70% of patients implanted with the standard full-length cochlear implant using an atraumatic “soft” surgical technique.8,9 However, continued progression of hearing loss after surgery remains a major unresolved issue.

Irrespective of the implant design, recipients with preserved low-frequency residual acoustic hearing may benefit from combined electric and acoustic stimulation in the same ear. The benefits of preserved residual low-frequency acoustic hearing include improved word understanding in the presence of background noise and the preservation of musical perception.7,10 These benefits are largely due to the ability of patients to distinguish fine differences in pitch as a result of preserved residual low-frequency acoustic hearing.11-14 As selection criteria for cochlear implantation continue to expand, it will become increasingly important to preserve residual low-frequency hearing to improve the perception of speech in noisy environments and to provide patients with a better musical appreciation.

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Prevention of cardiovascular disease in developing countries

Cardiovascular disease is the main cause of disability and premature death worldwide,1 and is projected to remain the leading cause of death. An estimated 17·5 million people died from this disease in 2005, representing 30% of all global deaths. Of these deaths, 7·6 million were because of coronary heart disease and 5·7 million because of stroke. If appropriate action is not taken, by 2015 an estimated 20 million people will die from cardiovascular disease, mainly from heart disease and stroke.1 Hence, this disease greatly contributes to the rising costs of health care in the world. It is a major public-health challenge, especially for low-income and middle-income countries, where 80% of these deaths occur and where there are competing health priorities and few resources for health care. WHO has released cardiovascular risk prediction charts for all WHO regions that will help low-income and middle-income
countries to manage the burden of cardiovascular disease effectively by targeting limited health-care resources at people who are at high risk of cardiovascular disease.

High blood pressure, glucose, and cholesterol, as well as high body-mass index, can be manifestations of unhealthy behaviours and major risk factors that determine cardiovascular risk. For successful prevention and control of cardiovascular disease the present distribution of risk factors within the population should be reduced. A combination of population-based strategies and strategies that focus on individuals are essential to achieve this objective.1,3

The underlying abnormality in coronary heart disease and cerebrovascular disease is atherosclerosis, which develops over many years, and it is usually advanced by the time symptoms become manifest. Acute life-threatening events such as heart attacks and strokes occur in middle age as well as in later stages of life. These events frequently happen suddenly and are often fatal. Modification of risk factors reduces mortality and morbidity in people with diagnosed or undiagnosed cardiovascular disease. Health systems in low-income and middle-income countries are unable to use resource-intensive risk-prediction interventions, especially in primary health care. In 2001, WHO released a cardiovascular risk management package containing simple algorithms for management of cardiovascular risk with hypertension as entry point, which has been subsequently validated in primary health care in low-income and middle-income countries.4,5 Apart from this strategy, to the best of our knowledge, there have been no cardiovascular risk prediction systems until now that are not only applicable worldwide but are also specifically applicable for different populations in low-income countries.

The cardiovascular risk prediction charts,6 developed in collaboration with the International Society of Hypertension (ISH), enable the risk of heart attacks and strokes to be predicted, even in settings that do not have sophisticated technology (figure). Collaborations between WHO and ISH are in progress to validate this approach against other methods, such as those that rely on the Framingham Heart Study risk prediction equations.8

Several forms of treatment can prevent coronary, cerebral, and peripheral vascular events. Decisions about whether to start specific preventive action, and with what degree of intensity, should be guided by estimation of the risk of any such vascular event. The risk prediction charts allow treatment to be targeted according to simple predictions of absolute cardiovascular risk for the populations of different WHO-defined regions. Recommendations are made for the management of major cardiovascular risk factors through changes in behaviour related to diet, physical activity, tobacco use, and drug treatments. The guidelines provide a framework for the development of national guidance on prevention of cardiovascular disease that consider political, economic, social, and medical circumstances.5 Population-wide strategies, such as tobacco control and promotion of a healthy diet and physical activity, need to be implemented by reduction of dietary salt through voluntary agreements with food industry, mass education, and other appropriate measures. These strategies are cost effective in all countries.7

A shift from management of single risk factors to total cardiovascular risk prediction and management will

![Figure: A sample of a WHO/ISH risk prediction chart (South East Asia subregion D) for use in settings in which blood cholesterol can be measured](image)

10-year risk of a fatal or non-fatal cardiovascular event by sex, age, systolic blood pressure, total blood cholesterol, and smoking status for people without diabetes mellitus. SBP=systolic blood pressure.8
enable restricted health-care resources to be targeted to individuals who are most in need and most likely to benefit. Hence, taking the absolute-risk approach for prevention of cardiovascular disease through the new WHO/ISH cardiovascular risk-prediction charts and the WHO guidelines for primary prevention of cardiovascular disease is an important step forward for cost-effective management of the burden of cardiovascular disease in low-income and middle-income countries.

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The African private sector steps in to fill the drug gap

In April, 2007, Canada’s Access to Medicines Regime (CAMR) was reviewed.1 The goal was to assess the contribution the system has made to the AIDS crisis. In 2005, the legislation designed to improve access through the export of generic drugs from Canada came into force. Despite lofty aspirations, CAMR has yet to see a single pill exported to countries in need. Citing cumbersome hurdles, Canadian manufacturers have been slow to get behind the effort.2 Only one company, Apotex Inc, has made any serious attempt to engage with CAMR, by producing a triple-fixed-dose pill.3 However, as of May, 2007, efforts to get the drug to those who need it seem to have been fruitless, with neither a voluntary nor a compulsory licence for export on the horizon.2

Meanwhile, over the past year in Ghana, DanAdams, a Ghanaian generic manufacturer, has been quietly producing antiretroviral drugs for distribution throughout the country. The Government of Ghana has placed several orders for first-line antiretrovirals from the manufacturer. DanAdams has developed the same generic triple-fixed dose as Apotex and is awaiting approval from Ghana’s regulatory authority. If DanAdams could afford the bioequivalence tests to obtain WHO approval, it could be supplying even more of the country’s drug needs at prices on a par with or lower than those from India. Monies from the Global Fund to Fight AIDS, Tuberculosis and Malaria can only be used to purchase from companies with WHO prequalification4 or approval from one of the qualifying national regulators (almost exclusively from developed nations).4 Although quality assurances are important for antiretrovirals, obtaining WHO approval is expensive and daunting for burgeoning manufacturers. By linking Fund money to WHO approval, a monopoly has been created, ensuring that only well established manufacturers, such as Apotex and DanAdams, can benefit.

as those in the USA, Canada, Europe, and India, will be able to supply most of the world’s antiretrovirals. Unless something changes, manufacturers in developing countries will be left out from the potential financial boon in antiretrovirals created by the Fund and WHO.

Despite problems with counterfeit drugs in west Africa, African manufacturers should not be thought incapable of producing antiretrovirals of sufficient quality. In view of the success of DanAdams and the failure of CAMR, the time has come to reassess how developed countries can best support the drive for enhanced access to treatment. Could Africa, like Brazil and India before it, develop a drug industry to supply its needs? Rather than flooding the African market with Canadian generics, countries like Canada, and manufacturers such as Apotex, could instead invest in enhancing manufacturing capacity abroad, fulfilling international obligations to provide technical assistance.5

The benefits to countries like Ghana in development of manufacturing capacity are multifaceted, including job creation, enhanced response time to drug shortages, a better understanding of demand and capacity, greater focus on neglected disease,6 and the added benefit of putting Africa’s already limited financial resources back into the continent.

Consistent with the goals of the region, DanAdams eventually hopes to expand supply beyond Ghana. Since 2001, the West African Health Organisation has been examining the possibility of regional procurement and distribution of antiretrovirals.7 One of the ways regional procurement could become a reality is by use of the rarely discussed, and never before invoked, section 6(i) of the World Trade Organization decision of Aug 30, 2003.2 Under this provision, developing countries that belong to a Regional Trade Agreement and share a public-health concern can benefit from exceptions that would otherwise constrain their ability to export generics. The resulting economies of scale could open the west African market to the reach of generic manufacturers.

Corporate Canada and elected representatives have made sweeping promises to address the continuing lack of access to medicines in the developing world. If a Ghanaian company has taken the lead to produce much needed antiretrovirals, perhaps we should turn our minds to other ways Canada can assist. The provision of technical assistance to those committed to making access to medicines a reality is one possibility.

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Clinical update: childhood convulsive status epilepticus

Convulsive status epilepticus is the most common neurological emergency in childhood and is associated with substantial morbidity and mortality. For research purposes, the condition is defined as a tonic-clonic seizure, or a series of seizures lasting at least 30 min, between which full consciousness is not regained. However, after the initial phase, the seizures can become unilateral clonic and eventually non-convulsive. The 30-min period is too long to wait before starting treatment, and definitions with 5 min and 10 min have been proposed.

The incidence of a first episode of convulsive status epilepticus in childhood is 17–23 per 100,000 children per year, which extrapolates to 1500–2000 lifetime first episodes in England and Wales annually. This incidence is highest in children younger than the age of 1 year. About 50% of children are developmentally and neurologically normal before the first episode, but are at risk of adverse outcomes, which can be related to convulsive status epilepticus itself or to any underlying acute cause. Diagnostic assessment of causes and predictors of adverse outcomes are therefore required.

In 2006, the American Academy of Neurology published guidelines for the diagnostic assessment of childhood convulsive status epilepticus. The Academy applied a four-tiered classification to establish the validity of a study, on the basis of yield of established diagnostic and screening tests. Recommendations were made on the basis of evidence about the usefulness of several tests, including blood culture and lumbar puncture, antiepileptic drug concentrations, toxicology screening, metabolic and genetic testing, electroencephalography (EEG), and neuroimaging.

Convulsive status epilepticus in childhood is often associated with fever, and, therefore, advice on appropriate use of investigations to diagnose a serious infection (eg, meningitis or encephalitis) should be provided. The Academy says that there is insufficient evidence to either support or refute the use of blood culture or lumbar puncture after convulsive status epilepticus, despite 12–15% of children with fever-associated convulsive status epilepticus having a CNS infection compared with about 1.5% of children with fever-associated short seizures, and the high mortality for missed meningitis in this context. An acceptable approach is to start appropriate antibiotics and antivirals without lumbar puncture in children with focal neurological signs and those who remain deeply unconscious. However, lumbar puncture provides useful diagnostic and therapeutic information and should be done as soon as it is considered safe to do so.

About 20% (3–63%) of children with epilepsy who have convulsive status epilepticus have low concentrations of anticonvulsant drugs. However, this group forms a small proportion of childhood convulsive status epilepticus, and, therefore, even if low concentrations of anticonvulsants are a factor, ensuring adequate treatment with drugs is unlikely to have a major effect on the incidence of convulsive status epilepticus. Nevertheless, the individual child should receive appropriate doses of anticonvulsants, according to blood concentrations, to achieve the key endpoint of epilepsy control. If drug concentrations are low, the drugs might need switching. The effect of the rate of withdrawal of apparently ineffective or effective anticonvulsants on the risk of convulsive status epilepticus needs further investigation.

Ingestion of toxins underlies at least 3.6% of cases of convulsive status epilepticus in children, and can need specific treatment. Tricyclic antidepressants were most commonly associated with the condition in a series of paediatric intoxications. Therefore, toxic ingestion should be considered when no cause is identified. Urine toxicological screening alone focuses on drugs of abuse and might miss prescribed drugs (eg, theophylline).

Inborn errors of metabolism are identified in about 4% of children with convulsive status epilepticus, although individual diagnoses are rare. Even electrolyte imbalance, such as hyponatraemia, is uncommon. In children in whom no cause is apparent, metabolic disorders should be considered, and, if a specific diagnosis is suggested on clinical assessment, appropriate investigations should be done. Measurement of glucose, urea and electrolytes, calcium, magnesium, and blood gases is recommended.

There are at least two situations in which EEG should be considered after convulsive status epilepticus. The first is when generalised convulsive status epilepticus needs to be distinguished from a focal presentation, which could have prognostic and therapeutic (medical
and surgical) implications. The second is when pseudostatus epilepticus needs to be diagnosed. There are few data on the prevalence of non-convulsive seizures or non-convulsive status epilepticus after convulsive status epilepticus has been controlled in children. Non-convulsive status epilepticus is common in neonates after asphyxia and stroke, and in comatose adults, and seems to predict death and poor outcome. Defining the natural history of non-convulsive status epilepticus across causes and in settings where life support is often withdrawn is difficult. EEG is becoming widespread in unconscious children or those needing intensive care after convulsive status epilepticus to establish whether clinically recognised seizures have stopped, or to distinguish subtle seizures from movement disorders secondary to drug withdrawal. Routine or continuous EEG with videorecording seems to diagnose non-convulsive seizures or non-convulsive status epilepticus in at least a third of patients presenting with convulsive status epilepticus in paediatric intensive-care. Ongoing electrical-seizure activity can be under-recognised in these patients, who are usually sedated and sometimes paralysed for ventilation.

Status epilepticus is a predictor of poor outcome in some encephalopathies (eg, encephalitis), yet there has been little research on whether treatment has any benefit in convulsive status epilepticus or the non-convulsive seizures/status epilepticus that often follows, or on whether prognosis is determined by the presence of an encephalopathy. For children in a coma, it might be important to exclude non-convulsive seizures, even if no clinical seizures are recorded, and EEG should be used to assess whether a burst-suppression pattern has been achieved with anticonvulsants. However, continuous EEG is labour-intensive and expensive, treatment protocols have not been defined, non-convulsive seizures do not seem to predict death in children compared with neonates, and there are few data on any association with neurological outcome in patients presenting with convulsive status epilepticus, in whom prognosis is usually good, or those in a coma with acute symptomatic convulsive status epilepticus. Future research might look at the reliability of one-channel or two-channel EEG monitoring for diagnosing non-convulsive seizures, because the technical issues have largely been resolved and outcome might be predicted in the paediatric intensive-care unit.

There is insufficient evidence for routine neuroimaging with CT or MRI after convulsive status epilepticus. At least 8% of children with convulsive status epilepticus will have an imaging abnormality, more commonly in patients presenting with coma. Abnormalities identified on neuroimaging include many with therapeutic and prognostic implications, such as venous sinus thrombosis (table). Neuroimaging should be done when convulsive status epilepticus is unexplained, the patient remains unconscious, or new focal neurological signs become apparent.

Thus there is little evidence for the current practices of investigating children with convulsive status epilepticus. Physicians should be aware of the limitations of the Academy guidance and be prepared to modify practice as more data become available.

When recommending aggressive treatment for any disorder, the adverse outcomes of that disorder need to be characterised. Although poor outcome might have been over-reported in studies of poor methodological quality, epilepsy, cognitive and behavioural impairments, and occasionally death do occur. The major predictor of adverse outcome is the cause of the convulsive status epilepticus, which often needs neuroimaging for confirmation and prognosis. Mortality directly attributable to convulsive status epilepticus (as with febrile status epilepticus) is 0–2%, compared with 12.5–16% in children with acute symptomatic convulsive status epilepticus. New neurological impairment is identified in more than 20% of children with acute symptomatic convulsive status epilepticus and in fewer

<table>
<thead>
<tr>
<th>Cause</th>
<th>Neuroimaging technique</th>
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<tbody>
<tr>
<td>Vascular disorders5,12</td>
<td>CT or MRI, MRA, MRV</td>
</tr>
<tr>
<td>Haemorrhage1</td>
<td></td>
</tr>
<tr>
<td>Focal infarction2</td>
<td>MRI, MRA, MRV</td>
</tr>
<tr>
<td>Venous sinus thrombosis4</td>
<td>MRI, MRV, CT, CTV</td>
</tr>
<tr>
<td>Reversible posterior leucoencephalopathy6</td>
<td>MRI with DWI</td>
</tr>
<tr>
<td>Focal changes compatible with encephalitis5</td>
<td>MRI with FLAIR and DWI</td>
</tr>
<tr>
<td>Cerebral oedema2</td>
<td>CT, MRI with DWI</td>
</tr>
<tr>
<td>White-matter abnormality3</td>
<td>CT, MRI with DWI and DTI</td>
</tr>
<tr>
<td>Hydrocephalus3</td>
<td>CT, MRI, MRV</td>
</tr>
<tr>
<td>Cortical dysplasia2</td>
<td>MRI with FLAIR, DTI, “unfolding” quantitation</td>
</tr>
<tr>
<td>Hippocampal oedema/atrophy/sclerosis15</td>
<td>Coronal MRI with T2-relaxation or hippocampal volume quantitation</td>
</tr>
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MRA=magnetic resonance angiography. MRV=magnetic resonance venography. CTV=computed tomography venography. DWI=diffusion-weighted imaging. DTI=diffusion tensor imaging. FLAIR=fluid-attenuated inversion recovery.
than 10% of children with a prolonged febrile seizure or idiopathic convulsive status epilepticus. As a factor of study quality, estimates of the proportion of children developing epilepsy after convulsive status epilepticus are imprecise, ranging from 13% to 74%. Further studies to identify predictors of subsequent epilepsy, perhaps including environmental exposures during the characteristic lag phase as well as neuroimaging, are needed. Evidence that convulsive status epilepticus is associated with brain injury, adverse outcomes, or epileptogenesis in any given aetiological group is not robust. This question remains important in view of the therapeutic implications of neuroprotection and antiepileptogenesis and of data showing brain injury in animal models and human beings.

Emergency treatment of seizures is most effective if started early—ie, if the seizure has not spontaneously stopped after 5 min—and this means starting treatment in the community. Prehospital treatment with rectal diazepam is long established in Europe, but, in view of the negative social implications, buccal midazolam is increasingly being used. If seizures last more than 30 min they are likely to be refractory to benzodiazepines, and rapid use of second-line treatments (eg, phenobarbital, phenytoin, sodium valproate, midazolam, propofol, thiopental, and lidocaine) is needed. Respiratory and cardiac depression, secondary to the status epilepticus itself and to any drugs given, is common at this stage, and these patients are usually managed with ventilation in developed countries. Trials of pyridoxine, biotin, and folinic acid are worthwhile in intractable status and in developed countries. Trials of pyridoxine, biotin, and folinic acid are worthwhile in intractable status, but uncertainty remains about important aspects of investigation, outcome, and treatment, especially for patients with acute symptoms. Future research should focus on accurate diagnosis of underlying abnormalities in intractable status by use of neuroimaging, and on predicting and improving outcome.
President Thabo Mbeki’s dismissal of the respected deputy health minister Nozizwe Madlala-Routledge—one of the driving forces behind the country’s new 5-year HIV/AIDS strategy—and newspaper allegations of theft and alcoholism against Health Minister Manto Tshabalala-Msimang have produced a crisis of confidence in a ministry long dogged by controversy.

It has also led to fears for the HIV/AIDS National Strategic Plan (NSP), which was launched in April with the goal of extending treatment and care to 80% of those in need by 2011 and halving the number of HIV infections. The Treatment Action Campaign (TAC) says that there has been little concrete action and the targets for this year are unlikely to be met.

“We are seeing alarming signs of a return to the rhetoric and confrontation of the past over HIV”, warned the Southern African HIV Clinicians Society.

Faced with a tidal wave of international and national criticism, the government closed ranks to protect Tshabalala-Msimang, instead turning its ire on journalists for “the distasteful media coverage”.

“I’m not stepping down because I don’t understand why I should step down unless, as the president has said, you give him reasons for what it is that I have done”, a defiant Tshabalala-Msimang said at an Aug 23 media conference. “Have I neglected the duties assigned to me?”

Helen Zille, leader of the Democratic Alliance opposition party, quickly sent Mbeki a long list of reasons, including the minister’s controversial stance on HIV/AIDS, the failure to tackle the country’s tuberculosis epidemic, the department’s poor financial management record, and the staff crisis in public sector hospitals.

Zille said delays and bureaucracy meant that South Africa now took four times longer than the international average to approve new medicines and that it was still awaiting regulations allowing nurses to prescribe medications, including antiretrovirals (ARVs).

The TAC published a copy of a letter it sent to President Mbeki last September with detailed grounds for dismissal of the health minister. It said it had received no reply and threatened possible court action if the president did not provide, by a Sept 7 deadline, his reasons for retaining Tshabalala-Msimang.

South Africa’s Sunday Times newspaper alleged that she was dismissed from her post as medical superintendent at a Botswana clinic in 1976 for theft. It went on to state that under Botswana law she was declared a prohibited immigrant for the next 10 years. Tshabalala-Msimang’s spokesman denied the allegations, dismissing the report as “false, speculative, and bizarre”.

The Sunday Times also alleged that Tshabalala-Msimang had a liver transplant in April because of years of excessive drinking. It went on to claim that doctors were pressurised into agreeing to the transplant even though she did not fulfil the criteria.

However, her physician stated that the reason for the transplant was because Tshabalala-Msimang had been diagnosed with autoimmune hepatitis. In addition, Johannesburg’s Donald Gordon Medical Centre denied that the 66-year-old minister jumped the queue and said it acted according to the internationally accepted Model for End-Stage Liver Disease system, whereby the sickest person gets priority.

The minister, who returned to work in June, sued the Sunday Times to recover medical records pertaining to her 2005 stay in a Cape Town clinic for shoulder surgery. The newspaper reported that during her stay she consumed alcohol and was abusive toward staff. The minister responded that the report was “false” and “malicious” and that “many allegations and insinuations are so bizarre, scandalous, speculative, and incredible that [she] does not wish to dignify them with a response”.

Tshabalala-Msimang has said that she is not stepping down from her post
Amid outrage over the breach of patient-doctor confidentiality, the Cape Town Medi-Clinic joined in the legal action against the theft of the records, which disappeared from the clinic. Tshabalala-Msimang also sought to ensure in the court hearing that all records and any references to her hospitalisation, treatment, and medical status was deleted from reporters’ notebooks and personal laptop computers. As The Lancet went to press, no ruling had been made by the court.

The newspaper denied theft. It said its reports were a legitimate part of a debate on whether the minister was fit to hold office and did not breach confidentiality.

President Mbeki’s office said there was no immediate reason to investigate the allegations of alcohol abuse or a theft conviction. Mbeki’s close ties with the minister date back decades when the two were in exile from the apartheid regime. Critics say the fact that her husband is treasurer of the ruling African National Congress has also helped shield her, as well as the fact that Mbeki harbours denialist tendencies on HIV/AIDS.

Tshabalala-Msimang is widely dubbed Dr Beetroot or Dr Garlic because of her promotion of certain foods for people with AIDS and her open mistrust of ARVs (she went out of her way at a recent news conference to warn that the price of next generation drugs may soar by 500%).

Her theories, long ridiculed by the international medical establishment, were also refuted in a 300-page report by the Academy of Science of South Africa.

“The panel has concluded that no food, no component made from food, and no food supplement has been identified in any credible study as an effective alternative to appropriate medication”, said professor Barry Mendelow, one of the authors.

Madlala-Routledge was nearly dismissed 2 years ago when she spoke out in favour of ARVs rather than nutrition in parliament.

Mbeki sacked the deputy minister after she took her son and an adviser on an unauthorised trip to an International AIDS Vaccine Initiative meeting in Spain. She said she was unaware that Mbeki had refused his approval and returned home as soon as she found out. Mbeki also accused her of not acting as part of a team.

In addition to her differences with her boss over HIV/AIDS, Madlala-Routledge also infuriated the country’s leadership by declaring that infant mortality at some public sector hospitals was a “national emergency”. Nokuzola Ntshona, a senior doctor at the Frere hospital at the centre of the scandal, was suspended for a breach of conduct after she also went public with her concerns.

The dismissal prompted shock and anger. The South African Medical Association, Rural Doctors Association of Southern Africa, and the former UN special envoy on HIV/AIDS in Africa, Stephen Lewis, were among those who voiced their unequivocal support.

The HIV Clinicians Society said Madlala-Routledge played a “fundamental role in bringing civil society and professionals together”.

“Our country desperately needs trusted and brave leadership in the area of HIV. The deputy minister gave us hope that this was possible”, it said.

The Society and TAC asked for urgent clarification why the mother-to-child HIV prevention programme (PMTCT) was still at only 30% coverage after 5 years, and questioned the delay in upgrading single-dose nevirapine for PMTCT to the dual therapy recommended by WHO.

It said that fewer than 20% of adults requiring antiretrovirals were receiving them, after more than 3 years of publicly available antiretroviral therapy (ART). An estimated 250 000-280 000 people are receiving ART in the public sector, although reliable figures are hard to come by because of lack of monitoring and evaluation.

TAC said if the government was serious about achieving the NSP targets, it would mean bringing an additional 120 000 adults and 17 000 children on treatment by the end of the year. It said 70% of all pregnant women should — according to the targets — be tested for HIV, and 25 000 pregnant women should receive a comprehensive package of AIDS care including ART.

Fatima Hassan of the AIDS Law Project told The Lancet there was no way the government would reach its target of 1·6 million people on treatment by 2011 at the current rate.

Specifically, she said that the health department was slowing the accreditation of new ART dispensing facilities by insisting on central control rather than giving responsibility to individual provinces. Nor had there been any moves to allow nurses to administer ART as provided for in the plan, Hassan said.

Mark Heywood, a civil society activist nominated to be vice-chairman of the revitalised South African National AIDS Council, said the mood was one of uncertainty over the future direction of the council.

“There is frustration because people are thinking that things are not happening at the speed at which they are meant to be. The government keeps saying there is no threat to the NSP. But it’s not just a case of saying it, it’s all about demonstrating it.”

Clare Kapp
Economic concerns hamper tobacco control in China

As a 12-year-old tennis player mulled over his loss at the All-China National Junior championships in Hebei, one of the umpires wandered over to give him a little friendly advice. “You need to take up smoking. It will make you strong”, he said flexing his biceps. “I always smoke before a match, it makes me play much better.”

Wherever you go in China, be it a hospital, factory, school, office, or shopping mall, it will be filled with cigarette smoke. China accounts for about a third of the world’s smokers, an estimated 360 million people, and one in four tobacco-related deaths (1 million per year). And China’s men top the smoking league table, with close to two thirds smoking.

“We need to get out the message about how harmful smoking is, especially second-hand smoking”, says Henk Bekedam who has just finished a stint as WHO representative in China. “The first step is to make tobacco more expensive for consumers. It is a very effective measure.”

That message is not making much impact at central government level, where the decisions about tobacco control are taken. The Chinese government earns about 240 billion yuan (US$30 billion) from the profits and taxes related to tobacco production and large sections are resistant to curbing smoking rates by hitting consumers with retail tobacco taxes.

Additionally, none of the taxation revenues currently being collected are linked to health, even though smoking now imposes a massive disease burden on the country. A study using 1998 mortality data put the number of premature deaths from smoking at 514,000. The direct hospital service cost of managing this burden was estimated as 22.9 billion yuan or 6% of China’s total medical costs.

With cramped housing, overcrowding, and poor ventilation the norm in most of China, second-hand smoking rates are very high too. It has been estimated that at least 50% of China’s non-smokers are regularly exposed to second-hand smoke.

Chinese women have much lower smoking rates than men, hovering around the 3-4% mark, but this does not protect them from second-hand smoke. A study of over 72,000 non-smoking women in Shanghai found that women whose husbands smoked had an almost 40% increased risk of dying from lung cancer and heart disease, whether or not they were smokers themselves.

Bekedam says the situation in China reminds him of the Europe he grew up in before smoking bans, anti-tobacco campaigns, and the recognition of the dangers of second-hand smoking. “It is a state where it is normal to smoke.”

China’s approach to smoking resembles that of Europe in the 1970s, does that mean China’s smoking patterns will follow those seen in Europe over the past quarter century? Bekedam does not think so, particularly because cultural norms are keeping female smoking rates low. “For women to smoke is, culturally, somehow not good. But this will be challenged with globalisation.”

As yet there is still little appreciation of the dangers that parents who smoke pose to their children. Although the smoking prevalence seems to be fairly stable, the average age at first smoking seems to be dropping. According to national surveys of smoking prevalence, in 1984, the average age at which people said they took up smoking was 22.4 years but this had fallen to 19.7 years by 2002.

Along with having the world’s greatest number of smokers, China is world’s largest cultivator of tobacco, producing about 2.66 million tons of tobacco leaf, or a third of global tobacco leaf production, per year. Most of the home grown tobacco leaf (95%) is grown for domestic consumption and rates of tobacco leaf production are tightly controlled. It is this fact that is limiting the government’s commitment to serious
tobacco-control measures. At present the government’s business-oriented ministries dominate tobacco-control policy. In fact, senior Chinese officials in trade roles argue against tobacco control as damaging to China’s national economic interests and as potentially socially divisive and destabilising.

This fear of a revolt by the poor, who are increasingly being dispossessed of land, jobs, and rights of all kinds, is a very real one in Beijing. Ministers have argued that curbing smoking rates in China will hurt the poor by taking away one of their few affordable pleasures and by affecting the income of the 5 million small-scale farmers who grow tobacco leaves and are already among the poorest groups in the country.

“The cost of cigarettes is low, in keeping with widespread thinking that smoking is the poor man’s pleasure...Many officials still believe that tax increases reduce revenue, and that tobacco control will harm the economy”, says Judith Mackay, director of the Hong Kong-based Consultancy on Smoking and Health.

However, others argue that the small farmers—who do make up the bulk of tobacco growers—are not benefiting from growing tobacco anyway. Although tobacco leaf is an agricultural product, China’s Ministry of Agriculture has no role in its production, pricing, or marketing. The government’s State Tobacco Monopoly (STMA) Association tightly controls tobacco leaf production by setting a tobacco leaf production quota. It also pays farmers a fixed price and controls all domestic cigarette manufacturing and marketing.

The small farmers growing tobacco usually have less than 1 hectare of land that they plant with other crops, such as vegetables, grain, and fruit. Along with having to accept the fixed price imposed by the STMA, the small farmers have to pay state taxes on tobacco leaves. The other crops their land can support may be more profitable, but because there is a government imposed tobacco quota, and the provincial governments earn good taxation revenues from tobacco leaf production, the small farmers are obliged to keep growing it, whether they want to or not.

Even if tobacco growing were a highly profitable activity for small farmers, those who believe that China should try to curb tobacco consumption by imposing a retail tax on cigarettes argue that it would not have any impact on farmer’s incomes. Teh-wei Hu—a professor of health economics at the University of California, Berkeley, USA—has analysed the economics of tobacco control in China and found that “on average, a 10% tax increase [which will be passed on to smokers in retail prices] would reduce cigarette consumption by 1.5%, equivalent to 1.02 packs per person, or a total reduction of 1017 million packs a year”.

“Because the percentage of reduction in cigarette consumption is less than the percentage increase in price, the Chinese government’s revenue would, in fact, increase by $3.6 billion (30 billion yuan). Therefore the Chinese government’s concern about losing government revenue due to tax increase is unfounded.”

Although there is a lot of resistance to using taxation and other effective means of curbing smoking, such as workplace bans, at central government level, there are some positive signs of commitment to a more effective tobacco-control policy. In 2003, China signed the Framework Convention on Tobacco Control (FCTC) and eventually ratified it 2 years later. Under the FCTC, the country is obliged to take firm action on a range of tobacco control issues, including advertising (now freely permitted) and indoor air quality.

China’s Ministry of Health has announced that it will ban smoking in hospitals, schools, kindergartens, and other places used by children. And in June, the Ministry of Health submitted draft legislation to the State Council banning smoking on public transport, such as taxis, buses, trains, planes, and in waiting rooms. As yet, this legislation is in the “consultation” phase, and its existence will not mean anything unless it is effectively enforced. There are already a large number of regulations banning smoking in different places in China, but they are rarely enforced.

The Ministry of Health has also announced that they are committed to having a smoke-free Olympic Games in Beijing in 2008. But so far the only concrete measure they have promised is that the hospitals catering to the Olympic Games will be smoke-free by the end of this year.

Bekedam says that until the central leadership decides to make tobacco control a serious part of their agenda, little will change in China. Of a recent meeting convened to discuss progress on the issue, Bekedam said “plenty of ministries are involved and they all very kindly submitted reports. But the spillage of urgency was missing”.

“They are trying to look at it seriously, but there is a big difference in the approach to avian influenza and tobacco control. With avian influenza, where the leaders are really supporting it, action is taken. With tobacco control, they are just going through the motions.”

Margaret Harris Chen
The most remarkable thing about this book, I think, is that it was written at all. It is a weighty tome, tipping the scales at a little under 3 kg. The authorship can fairly be called stellar—the best minds of their generation in pulmonary medicine. And all 892 pages to examine our collected knowledge of a single disease entity: chronic obstructive pulmonary disease (COPD). How did COPD gain the respect that would support such an effort? I have been focusing almost exclusively on COPD for a little more than 20 years, but there aren’t too many like me. During the 1980s and early 1990s, I remember this COPD research as a lonely pursuit. The “big lung” organisations were loath to touch it. I distinctly recall attending a strategic planning meeting held by the American Lung Association and almost being hooted out of the room when I suggested that COPD should be included among the top three focus priorities (asthma, air pollution, and tuberculosis were the preferred choices). Pharmaceutical companies were also largely indifferent, allowing drugs designed for asthmatics to be adopted by COPD patients without much examination. Physicians, too, shared this lack of interest—feeling, I suspect, that smokers deserved their fate and that, besides, there wasn’t much that could be done for these elderly, yellow-fingered people. Part of the change has been one of perception. Instead of blaming COPD patients for their dirty little habit, we recognise the true addictive nature of cigarettes and put the blame where it belongs: on the tobacco companies."

"Instead of blaming COPD patients for their dirty little habit, we recognise the true addictive nature of cigarettes and put the blame where it belongs: on the tobacco companies."

Research into COPD has literally exploded. An only slightly scientific quantitative assessment of this is shown in the figure below. It plots the yearly citations identified as related to COPD on a PubMed search from 1987 to 2006. Note the steep increase: 613% over the 20-year period with a marked acceleration in the present decade. Compare this with asthma, which presently has about twice the citations, but has increased by only 172% in the same period. Looked at one way, *Chronic Obstructive Pulmonary Disease: A Practical Guide to Management* is a report card on the progress all this research has brought us. The initial sections of the book on physiology draw strongly on ideas developed by the previous generation of physiologists, although supplemented with recent refinements. Physiology still has plenty to teach us about how to manage COPD. Lung mechanics, gas exchange, and muscle physiology yield important insights into the problems COPD patients face and suggest helpful strategies for symptom relief. But in section 3 we arrive at the heart of the recent research focus. Cell and molecular biology has revolutionised the way we think about this disease (as is the case for many other diseases); in particular, lung and associated systemic inflammation has been identified as a major mediator of damage not only in chronic
bronchitis, but in emphysema as well. The hope has been that, if we understand the genesis and consequences of inflammation, the road to better therapies will be cleared. There are 12 chapters that cover the breadth of cell and molecular biology topics of relevance to COPD and a substantial number of additional chapters on pathogenesis that have a strong emphasis on cell biology.

The remarkable thing, of course, is that despite funnelling public funds for COPD research preferentially into cell and molecular biology pursuits for the past 20 years, these efforts have yielded no therapies we can offer to our patients. What do we have to offer? Our current mainstays are bronchodilators, mainly using refined versions of drugs that have been around for a long, long time. For hypoxic and hypercapnic respiratory failure, we use supplemental oxygen and mechanical ventilatory support, respectively. Pulmonary rehabilitation is proving to be a highly effective (although currently poorly available) therapy; recent developments have served to cement its physiological base. Smoking cessation programmes now have the benefit of rational adjunctive pharmacological aids. Surgery is a viable option for only a minority of patients.

What of the future? Both by public funding of research and through the efforts of the pharmaceutical industry, a number of avenues are being explored: chronic antibiotics, antioxidants, anti-inflammatory agents, mucolytics, alveolar growth factors, and protease inhibitors. The payoff potential is big; COPD is a major killer, a major source of misery, and a major consumer of health-care dollars. All of this for a disease that would be rare, were it not for cigarette smoking. It would be nice to think that, after we win our battle against the tobacco interests, this book will be regarded by future generations as an interesting artifact. But, sadly, I wouldn’t bet on this happening any time soon; I’m afraid this excellent volume will find use for a number of editions.

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In brief

**Book** *The story of fenoterol*

*Vintage Papers from The Lancet*, which was published a couple of years ago, is a wonderful anthology of some of the most influential articles that *The Lancet* published between 1823 and 2005. Selecting these articles was a challenging task for the editor, Ruth Richardson. However, one paper that Richardson did not include, but perhaps might have done, describes how fenoterol, a β agonist, was responsible for the increased mortality seen in young people with asthma in New Zealand during the 1980s (*Lancet* 1989; 333: 917–22). One of the authors of that study, Neil Pearce, has written a compelling book that describes the real-life events behind the identification of fenoterol as the causative agent behind the epidemic. Like all good thrillers, it contains a healthy dose of intrigue, conspiracy, deception, and perseverance in the face of adversity.

For 10 years, starting in 1977, fenoterol had at least a 30% market share of β agonists in New Zealand, but was not marketed to the same degree in other countries and was not licensed at all in the USA. At around the same time, New Zealand’s asthma mortality started to rise, reaching a death rate of 3.5 per 100 000 at the peak of the epidemic from 1977 to 1980, around three times the rate seen in other developed countries. But it took more than 10 years for epidemiologists to prove that the two were linked and it is this process that Pearce describes so expertly in his book.

Pearce tells how New Zealand’s official body, the Asthma Task Force, dragged its heels over the epidemic. He also describes the tactics that Boehringer Ingelheim, the makers of the drug, used to convince doctors that Pearce and his team’s study was methodologically unsound and that the drug was safe. Even *The Lancet* comes out badly—according to Pearce, the editors at the time almost caved in to heavy industry pressure, in the form of commissioned peer-review comments, and threatened to withdraw the paper, after acceptance, but before publication.

Pearce wrote the first draft of the book soon after the controversy ended, in 1993, but he decided to wait 15 years before re-editing it because the original version was “too serious, too technical—and too angry”. Perhaps that was the right decision. But it seems a shame that such a wonderfully informative and well-written book was in limbo for so long. *Adverse Reactions: The Fenoterol Story* should be considered essential reading for anyone interested in epidemiology. It also shows what can be achieved when a researcher with a real talent for writing takes it upon himself to describe his controversial work. There must be many hundreds of other stories out there, as yet unwritten, that deserve to be committed to paper so that others can learn from such collective mistakes.

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Profile

A Sonia Buist: expanding our knowledge of COPD

Chronic obstructive pulmonary disease (COPD) doesn’t get much sympathy, or a lot of research funding, says A Sonia Buist, one of the world’s leading experts on this increasingly burdensome but still poorly understood condition. In the developed world, Buist points out, COPD is almost exclusively a smoker’s problem, and hence considered to be “self-inflicted”. Little research has been done on risk factors beyond smoking, and there is no drug to stop progression of the disease. “There are lots of important and unanswered questions”, says Buist, a professor of medicine, physiology, pharmacology, public health, and preventive medicine at Oregon Health and Science University in Portland, USA.

Ever since she decided to go into pulmonary medicine during her residency, inspired by the “tremendous international respiratory group” at the University of Colorado in Denver, Buist has been seeking answers to these questions. Her investigation of the worldwide prevalence of COPD, the BOLD Initiative in this week’s Lancet, “may well end up being her most important scientific contribution”, says her long-time colleague Philip C Hopewell, a professor of medicine at the University of California, San Francisco. Hopewell also points to Buist’s determined efforts to launch the Methods in Epidemiological, Clinical and Operations Research (MECOR) programme. Since 1994, more than 300 scientists, chiefly in Latin America, have learned to do respiratory epidemiology through the course, with many publishing original research in top-tier journals. The first MECOR course in Africa begins this month, in Malawi, and courses are planned next year for Turkey and India. “The idea is that you are training people to do basic epidemiological and clinical research to quantify the burden of disease in their environment and to come up with interventions that are appropriate to their environment”, Buist explains. “The solutions to health problems in Africa or Latin America or elsewhere have to come from their own environment, and they have to come from their data.”

Buist dates her interest in international work to her childhood in India, where her father served as a policeman during the days of the British Raj. The family returned to the UK in 1945, settling in the small Scottish town of Dollar, where Buist and her two brothers attended Dollar Academy. After graduating from medical school at St Andrews, Buist moved with her then-husband to the University of Colorado, where she completed her residency. She spent a year in Montreal studying COPD and airflow obstruction and went on to Oregon for two pulmonary fellowships, where she developed and evaluated tests of small-airway function. In 1973, Buist received her first research grant from the National Institutes of Health (NIH), and has been funded by the NIH ever since.

Buist was on-hand for the eruption of Mount St Helens in nearby Washington State in 1980. As the only person in the region with expertise in epidemiology and pulmonary medicine, she took on the job of investigating the health effects of the eruption. “It was very exciting because at the time there was so much anxiety in the community about the health effects of the volcanic ash”, Buist recalls. “Businesses were not locating here, people were actually leaving here because of the anxiety.” But by comparing loggers who worked in volcanic ash-coated forests with those employed in areas free of volcanic debris, Buist and her colleagues were able to show that breathing the volcanic ash produced only transient health effects. “She was terrific”, says Thomas R Martin, who was a pulmonary fellow in training at the time and joined Buist’s research team. “She became one of my role models because she was so knowledgeable, thoughtful, and she was tremendous at getting things done.”

Buist’s other interests include how asthma may affect COPD later in life, as well as how occupational exposures can contribute to the disease, especially in the developing world, where regulation of such exposures is lax or non-existent. She also recently investigated patient-guided decision making in asthma. So far, her 600-patient study has shown that, by engaging patients with poorly controlled asthma in making decisions about their care, outcomes and adherence are better than with usual care, or management by guidelines. “It makes physicians a little uncomfortable that they may be departing from the guidelines”, she explains, but “for that patient it may be the right thing.”

Buist’s sense of humour and “whimsy” has been as inspiring as her scientific achievements, her colleagues say. “She’s been a tremendous role model for me in how to develop professionally and how to try to have a sense of balance and a sense of having fun at the same time”, says Martin. Buist has written two books on hiking in Oregon’s Mount Hood, launching her own company—Lolits (Little Old Ladies in Tennis Shoes) Press—to publish them.

“For somebody with a background in clinical science she has a very wide vision”, says Peter M Calverley, a professor of respiratory medicine at the University of Liverpool in the UK, who has collaborated with Buist for many years. “It’s that breadth of vision that perhaps sets her apart from others.”

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Obituary

Sornchai Looareesuwan
Prominent malaria researcher, physician, and administrator. Born on March 26, 1949, in Kongkhaen, northeastern Thailand, he died in Bangkok, Thailand, on July 22, 2007, of metastatic hepatoma, aged 58 years.

Any historian who wanted to understand the fight against malaria in the late 20th century could do much worse than read the published works of Sornchai Looareesuwan, a charismatic and prolific researcher whose 490 scientific articles closely mirror the struggle to develop effective treatments for this global scourge.

Sornchai began his career in malaria research in 1979, when he joined the team of David Warrell, who had arrived in Bangkok to establish the Wellcome Mahidol University, Oxford Tropical Medicine Programme. “He was a very bright, very enthusiastic, and well trained young clinician”, remembers Warrell, now emeritus professor of tropical medicine at the University of Oxford, Oxford, UK.

Between 1979 and 1986, Sornchai’s indefatigable energy and resourcefulness were central to the success of the programme’s ambitious goal of establishing randomised controlled trials in Thailand’s provincial hospitals. Their early successes, which included helping elucidate the pathogenesis of severe, cerebral malaria, were followed by a long list of publications that evaluated malaria therapy, including the issues of malaria in pregnancy, and cerebral blood flow in infected patients.

Warrell and Sornchai also shared an interest in venomous snakes, and their publications on snakebites in regional Thailand also helped clarify the species that most often envenomed human beings. On one occasion, Warrell remembers some local men bringing them a 9-foot long king cobra. “I said we didn’t want it because it wasn’t in very good shape and I didn’t want people risking their lives for our project”, he recalls. “But that was a tactical error. They took offence and released this snake into the middle of town.” As Warrell recalls, Sornchai “went down to the town and located the snake and organised its capture. That impressed me enormously.”

Sornchai had trained in Bangkok at the famous Siriraj Hospital Medical School and joined the Faculty of Tropical Medicine, at Mahidol University, in 1979, immediately after finishing his residency. Malaria was his primary research focus from that moment on. “He was an astonishing man. The magnitude of his work in the chemotherapy and chemoprophylaxis of malaria is incredible”, says Stephen Hoffman, founder of malaria vaccine firm Sanaria, who first met Sornchai in the 1980s. “He just went from one drug to another.” He was, for example, a pioneer investigator of the artemisinin derivatives, as well as of atovaquone-proguanil, a combination sold as Malarone—now the best-known antimalarial prophylactic drug for western travellers. His successful research career sprang from a combination of intelligence, dedication to his patients, and “the capacity to work from morning to night”, says Hoffman. “That’s a pretty potent mixture.”

During the 1990s, Sornchai took on an increasingly important administrative role at Mahidol University, which culminated in his being appointed dean of the faculty of tropical medicine in 1996. His strategy for coping with the challenges of leading a sometimes-fractious faculty involved arriving early and spending time each morning meditating, Hoffman remembers. No doubt the smile that was often on his face, and the laugh on his lips contributed to his successful management of the department.

Sornchai held concurrent positions as Director of Emerging and Re-emerging Diseases Research Programme and Head of the Division of Clinical Care Research Unit in Tropical Diseases at Mahidol. He was the Secretary General, Coordinator, and Director of the SEAMEO Regional Tropical Medicine and Public Health Network and a past President of the International Federation for Tropical Medicine. His decorations in Thailand included Companion (Fourth Class) of the Most Admirable Order of the Direkgunabhorn and Knight Grand Cordon (Special Class) of the Most Exalted Order of the White Elephant. An honorary Fellow of the UK’s Royal College of Physicians, Sornchai was a valued member of the editorial boards of this journal and The Lancet Infectious Diseases. Sornchai is survived by his wife, Vaewta Sornchai, and their children Panita and Panu.

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Prevention of venous thromboembolism after acute ischaemic stroke

David Sherman and colleagues (April 21, p 1347) report that enoxaparin 40 mg subcutaneously once daily is preferable to unfractionated heparin 5000 IU subcutaneously every 12 h for prevention of venous thromboembolism in patients with acute ischaemic stroke in view of its better clinical benefit-to-risk ratio and convenience of administration.

The systematic review of published randomised trials mentioned in the Discussion showed that unfractionated heparin 5000 IU twice daily reduced the relative risk of venous thromboembolism compared with placebo, but that it was less effective than unfractionated heparin 5000 IU three times daily. When comparing enoxaparin with unfractionated heparin, similar efficacy in preventing venous thromboembolism in non-surgical patients has been seen only when enoxaparin 40 mg once daily was compared with unfractionated heparin 5000 IU three times daily. One study did show that enoxaparin once daily was as effective as unfractionated heparin 5000 IU twice daily at preventing venous thromboembolism; however, enoxaparin was used at a dose (20 mg once daily) which the MEDENOX Study showed to be ineffective for preventing venous thromboembolism in acutely ill patients.

In light of these points, it is noteworthy that there are data to suggest better efficacy with unfractionated heparin given on a three times daily basis, but no data to show that unfractionated heparin twice daily is as effective as either enoxaparin 40 mg once daily or unfractionated heparin 5000 IU three times daily.

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In the Introduction section of their paper, David Sherman and colleagues state that “[low-molecular-weight] heparin and unfractionated heparin are... recommended in guidelines from expert consensus groups”. This is not completely true: some authorities and guidelines do not recommend routine use of heparin for prevention of deep-vein thrombosis (DVT) in patients with ischaemic stroke, although it is usually suggested for high-risk patients.

Sherman and colleagues randomised 1762 patients, but only analysed 1335 (a 24% loss). How many patients did not have doppler scans or venography because of deterioration (perhaps due to haemorrhagic complications)? It is rather likely that the trial was underpowered for picking up some important differences, especially in the rate of haemorrhages.

The mean age of the included patients was low compared with that of patients routinely seen in clinical practice (only a quarter were older than 75 years). Older patients can have a higher risk of haemorrhagic transformation, but also more severe strokes and a higher risk of DVT.

In the Discussion, Sherman and colleagues refer to numbers needed to treat for benefit and harm (13 vs 173). The “benefit” actually refers to avoidance of asymptomatic DVT (which is mostly irrelevant) whereas the “harm” refers to events that clinicians thought important—eg, haemorrhages. To justify use of low-molecular-weight heparin (which is also more expensive) on this basis seems wrong.

We are told that the 3-month functional outcome of the patients was measured, but it was not reported. In the Cochrane review, a reduction of DVT was seen with heparin, but there was no net effect on death and disability because of the increase in haemorrhages. Can Sherman and colleagues tell us something about outcome in terms of death and disability?

Finally, we would like to quote a sentence from the Discussion: “The occurrence of any bleeding was about two-fold higher for patients with a [NIHSS] score of 14 or more than for those with a score less than 14.” These severe strokes are exactly the ones for which we might wish to prescribe heparin.

We declare that we have no conflict of interest.

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Correspondence

David Sherman and colleagues’ suggest that, for patients with acute ischaemic stroke, enoxaparin is preferable to unfractionated heparin for prevention of venous thromboembolism. Some points merit critical analysis.

The numbers needed to treat to avoid one pulmonary embolism or one symptomatic venous thromboembolism were similar in the enoxaparin and unfractionated heparin groups, and there was no significant difference between them.

In Sherman and colleagues’ table 2, the statistical analysis should have been done for the intention-to-treat population and not the on-treatment population.

Sherman and colleagues’ table 1 shows that 50 more patients in the enoxaparin group were using aspirin or clopidogrel than in the unfractionated heparin group. The PEP trial¹ showed that aspirin alone was associated with a reduction in pulmonary embolism of 43% and in symptomatic deep-vein thrombosis of 29%.

In our opinion, especially because of the high costs of enoxaparin, the most cost-effective way of reducing venous thromboembolism in clinical situations is still unfractionated subcutaneous heparin.

We declare that we have no conflict of interest.

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Author’s reply

Marcelo Melero and colleagues discuss the relative efficacy and safety of twice-daily and three-times daily unfractionated heparin in acutely ill patients. Since publishing our study, a meta-analysis of studies in hospital inpatients has been published.¹ This report shows that, compared with unfractionated heparin three times daily, a twice-daily regimen results in fewer major bleeding episodes; three-times daily reduces the risk of clinical venous thromboembolism events.

We agree with Stefano Ricci and colleagues that some guidelines do not specify that heparin should be used for prophylaxis in patients with acute ischaemic stroke. However, on the basis of guidelines from internationally recognised organisations which do recommend such prophylaxis, our study focused on comparing enoxaparin 40 mg once daily with a commonly used regimen of unfractionated heparin.

In studies that use venography to detect venous thromboembolism, a 24% dropout rate is regarded as acceptable and is consistent with that seen in other major studies.² Of 126 and 105 patients who did not undergo venography or ultrasonography in the enoxaparin and unfractionated groups, respectively, one patient in each group had a major haemorrhage and was considered in the safety analysis.

Our study showed a similar net clinical benefit of enoxaparin over unfractionated heparin in patients older than 75 years as in the complete population; the prevalence of venous thromboembolism was 16·4% versus 21·3%, respectively (number needed to treat [NNT]=21), and the prevalence of major extracranial and clinically significant intracranial haemorrhage was 3·0% versus 1·7%, respectively (number needed to harm [NNH]=77).

Ricci and colleagues comment that an endpoint of asymptomatic deep-vein thrombosis is “mostly irrelevant”. However, the relation between asymptomatic and symptomatic venous thromboembolism is well established.³ Furthermore, a subanalysis of the PREVENT study⁴ showed a clear relation between the prevalence of asymptomatic deep-vein thrombosis and an increased risk of death. Although we did not observe differences in mortality rates between groups because the study was not powered to do so, we are looking further at long-term treatment effects which will be reported in a subsequent paper.

There was a net clinical benefit for enoxaparin versus unfractionated heparin in patients with an NIHSS score of less than 14 (prevalence of venous thromboembolism 8·3% vs 14·0% [NNT=18]; major extracranial haemorrhage and clinically significant intracranial haemorrhage 0·8% vs 0·3% [NNH=218]) and for patients with a score of 14 or more (prevalence of venous thromboembolism 16·3% vs 29·7% [NNT=8]; major extracranial haemorrhage and clinically significant intracranial haemorrhage 2·6% vs 1·6% [NNH=102]).

We agree with Herlon Martins and colleagues that comparing the prevalences of pulmonary emboli and symptomatic venous thromboemboli did not show significant differences between groups. A very large study population would be required to test this hypothesis.

As Martins and colleagues mention, our analysis was not restricted to treated patients only, but to patients who had an evaluable venogram or ultrasonography scan. This approach to

⁵ Sherman DG, Albers GW, Bladin C, et al., on behalf of the PREVAIL Investigators.
efficacy analysis is consistent with that used in other major studies of venous thromboembolism prophylaxis. 5

Martins and colleagues comment on a difference in the numbers of patients receiving aspirin or clopidogrel between groups. In total, 815 patients (92%) received antiplatelet agents in the enoxaparin group versus 791 (90%) in the unfractionated heparin group. This difference was not significant and is unlikely to have had an effect on outcomes.

Finally, we disagree with Martins and colleagues about the relative cost-effectiveness of prophylaxis with enoxaparin versus unfractionated heparin. A cost-effectiveness analysis, 5 which took into account hospital resource use as well as drug expense, suggested that enoxaparin is a cost-saving approach compared with low-dose unfractionated heparin. We are currently doing these analyses on PREVAIL data.

I have received honoraria from Sanofi-Aventis for speaker bureau and consultancy.

David G Sherman, on behalf of the PREVAIL Investigators

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1 King CS, Holley AB, Jackson JL, et al. Twice daily unfractionated heparin. A cost-effectiveness analysis, 5 enoxaparin versus unfractionated and colleagues about the relative effect on outcomes. This difference was not (90%) in the unfractionated heparin group versus 791 (92%) received antiplatelet agents receiving aspirin or clopidogrel a difference in the numbers of patients thromboembolism prophylaxis. 2

For postmenopausal women, the production of oestrogen is solely intracellular in the peripheral tissues and thus dependent entirely on the production of dehydroepiandrosterone, dehydroepiandrosterone sulphate, androstenedione, and other adrenal prohormones, and any ovarian dehydroepiandrosterone, androstenedione, and testosterone if ovaries remain. Moreover, the major production of androgen is also intracellular in middle-aged and older women from these same prohormones.

Unfortunately, neither clinical experience nor published studies confirm that “female sex hormone substitution can return libido” when the substitution in question is as listed in Schneider and colleagues’ table 5, namely larger or smaller amounts of oestrogen (20–35 µg ethinyl oestradiol or 0·625–1·250 mg equine oestrogens or equivalent transdermal oestradiol). Scientific study of the replacement of dehydroepiandrosterone in primary or secondary hypoadrenal states is limited. In many countries dehydroepiandrosterone is either unobtainable or unobtainable or non-regulated. Thus I would have welcomed the clinical experience of Schneider and colleagues in addressing this very difficulty entity of women being unable to become sexually aroused because of lack of intracrine-produced sex hormones.

I have been a temporary consultant to Pfizer and to Solvay. My clinical practice occasionally necessitates provision of medicolegal reports without prejudice.

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Female sexual dysfunction in hypopituitarism

I was disappointed that the Seminar on hypopituitarism by Harald Schneider and colleagues (April 28, p 1461) did not discuss the lack of production of adrenal cortical hormones other than cortisol.

For postmenopausal women, the production of oestrogen is solely intracellular in the peripheral tissues and thus dependent entirely on the production of dehydroepiandrosterone, dehydroepiandrosterone sulphate, androstenedione, and other adrenal prohormones, and any ovarian dehydroepiandrosterone, androstenedione, and testosterone if ovaries remain. Moreover, the major production of androgen is also intracellular in middle-aged and older women from these same prohormones.

Unfortunately, neither clinical experience nor published studies confirm that “female sex hormone substitution can return libido” when the substitution in question is as listed in Schneider and colleagues’ table 5, namely larger or smaller amounts of oestrogen (20–35 µg ethinyl oestradiol or 0·625–1·250 mg equine oestrogens or equivalent transdermal oestradiol). Scientific study of the replacement of dehydroepiandrosterone in primary or secondary hypoadrenal states is limited. In many countries dehydroepiandrosterone is either unobtainable or non-regulated. Thus I would have welcomed the clinical experience of Schneider and colleagues in addressing this very difficulty entity of women being unable to become sexually aroused because of lack of intracrine-produced sex hormones.

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Authors’ reply

We do not recommend continuation of female sex hormone replacement in women with hypopituitarism after the age of menopause, unless symptoms of sex hormone deficits persist that cannot be treated by alternative therapies. The Women’s Health Initiative and Million Women Study have shown that the risks of postmenopausal sex hormone replacement outweigh their benefits.

We agree with Rosemary Basson that there is little evidence on the effects of oestrogens on sexual function in premenopausal women with hypopituitarism. However, randomised, controlled studies of oestrogen therapy in postmenopausal women have shown beneficial effects on sexual desire, arousal, and satisfaction. 1

We also agree that data on dehydroepiandrosterone replacement are inconclusive. In women with hypopituitarism, no clear effects on parameters of sexual function could be shown, 1 3 and in women with primary hypoadrenalism, either positive or no effects were found. 1 4 We did not address the question of dehydroepiandrosterone replacement or other potential therapies since there is too little evidence to give clear-cut recommendations.

We declare that we have no conflict of interest.

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Heparin in sepsis treatment

Simon Nadel and colleagues, in their randomised trial on drotrecogin alfa in children with severe sepsis (March 10, p 836), 1 do not mention heparin. Treatment with heparins was a consistent confounder in three large trials of anticoagulant proteins for sepsis. 2-4 Non-randomised heparin administration was associated with better outcome. 1 We would like to ask Nadel and colleagues to present the outcome in the subgroups receiving heparin versus those not.

We declare that we have no conflict of interest.

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Authors’ reply

Christoph Pechlaner and Michael Joannidis raise an important question about heparin being a potential confounder in our trial of activated drotrecogin alfa in children with severe sepsis. In our trial, 62% of the patients in the drotrecogin alfa and placebo arms were receiving heparin at baseline. Differences in 28-day mortality between those receiving and not receiving heparin are shown in the table. The Breslow-Day test for subgroup interaction in the baseline heparin versus no heparin groups was 0·56, indicating that there was no statistical difference between the two groups with respect to treatment group mortality rates.

There is probable selection bias regarding baseline heparin use, in view of the higher mortality in patients without baseline heparin, which probably represents children with higher bleeding potential and thus higher risk of death.

SN and BG have been paid consultants of Eli Lilly and have participated in previous trials by Eli Lilly and Co. MDW is an employee and stockholder of Eli Lilly and Co.

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Table: 28-day mortality among children who received and did not receive heparin at baseline

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<th>Baseline heparin</th>
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<tr>
<td>Drotrecogin alfa (n=150)</td>
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<td>Placebo (n=144)</td>
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<td>28-day mortality</td>
<td>22 (14·7%)</td>
<td>19 (13·2%)</td>
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<td>19 (12·1%)</td>
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Table: 28-day mortality among children who received and did not receive heparin at baseline

Whipple’s disease and sarcoidosis

Larisa Dzirlo and colleagues (May 26, p 1832) report a case that they interpret as an example of how Whipple’s disease can mimic sarcoidosis. Whipple’s disease can cause extraintestinal disease that clinically can be confused with other diseases including sarcoidosis, but it is not true that Whipple’s disease can cause histological sarcoid-like granulomas. 2 The correct interpretation of this patient’s problems is that he indeed had sarcoidosis and subsequently also developed Whipple’s disease.

The lipogranulomatous reaction of Whipple’s disease is histologically very different from the well formed, highly epithelioid-cell “true” granulomas characteristic of sarcoidosis. 3 Additionally, it seems unlikely that the patient would have remained well during the 5 years that he was treated with steroids for sarcoidosis if he actually had Whipple’s disease. 1 The patient probably would have died.

Finally, the initial biopsy specimens suggesting sarcoidosis were retrospectively searched specifically for Whipple’s bacteria and they were not found. My colleagues who are infectious disease pathology experts assure me that, when they examine tissues affected by Whipple’s disease, they can find the infectious agent with relative ease, with “ordinary” histological stains, and irrespective of the organ or tissue (Wear DJ, personal communication).

The two factors just mentioned are also present in other articles that purport to show sarcoid-like manifestations of Whipple’s disease and which also include histological findings strongly suggestive of sarcoidosis. 1 The characteristic delay of several years, during which patients improve on steroid treatment, before “relapse” and final diagnosis of Whipple’s disease is important in trying to explain such cases. The abnormal, dysregulated immune
variables that have been found in sarcoidosis could predispose patients to the development of Whipple's disease. Also, the steroid therapy might slightly increase the chance of Whipple's disease developing. I declare that I have no conflict of interest.

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Authors' reply

We appreciate the comments made by Dennis Heffner, although we cannot agree with his arguments or his conclusion. Many studies have shown clearly that sarcoid-like granulomas can be found in some patients with Whipple's disease. This sarcoid-like inflammation has been described in various organs including lymphatic tissue, gastrointestinal tract, bone marrow, kidneys, synovial tissue, liver, and lungs. Especially in extraintestinal Whipple's disease, the density of Tropheryma whipplei is often so low that routine histological stains for microbes, including periodic acid Schiff (PAS), are negative. The authors of one review concluded that, in patients with Whipple's disease, non-caseous granulomas can be found in many organs including the lung, and, most importantly, that these granulomas are PAS-negative in 40% of cases. It is important that pathologists and clinicians are aware of this fact because in this situation a diagnosis of Whipple's disease has to be established (or excluded) by PCR or electron microscopy. Even if Heffner should believe that all the positive PCR results obtained from PAS-negative tissue in patients with Whipple's disease are false-positives, he should be convinced by investigators who show T whipplei by electron microscopy in PAS-negative sarcoid-like granulomas. In summary, there is overwhelming evidence that sarcoid-like inflammation in Whipple's disease, even if PAS-negative, cannot generally be interpreted as coexisting sarcoidosis as suggested by Heffner, but is clearly caused by T whipplei, at least in a subgroup of patients.

In the case reported by us, three lines of evidence support the conclusion that the patient already had Whipple's disease at the time of initial presentation (1998). First, and most importantly, PCR examination of paraffin material from biopsies taken from mediastinal lymph nodes in 1998 were positive for T whipplei. PCR examination was done in an international reference laboratory for Whipple's disease with extensive experience in this field. Second, as described by others, treatment with corticosteroids only led to a short-term improvement of pulmonary symptoms. During further follow-up, immunosuppressive therapy led to a progressive deterioration of pulmonary function (slow deterioration from 1998-2003; rapid deterioration beginning November, 2003), which seems to be typical of Whipple's disease. Third, initiation of antibiotic treatment led to a striking improvement of pulmonary function: the patient stopped his long-term oxygen therapy and resumed his jogging training.

Sarcoidosis is an inflammatory disease of unknown cause. It has been repeatedly suggested that it could be caused by a yet-undefined infection. On the basis of our findings and those of others, we strongly recommend prospective studies to test the hypothesis that a subgroup of cases of presumed sarcoidosis could be caused by T whipplei.

We declare that we have no conflict of interest.

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Medical interventions, social science, and resource-poor countries

We are gratified to note the call by John Imrie and colleagues (July 7, p 10) for high-quality social and behavioural research to complement the scaling-up of biomedical HIV interventions. They correctly identify the desperate need to make emerging innovations in prevention culturally acceptable and effective on individual and community levels.

The importance of incorporating social research in this approach is starkly evident in our own context of Papua New Guinea— a culturally diverse society where there exist 850 languages; the challenges cannot be underestimated. In the midst of the emerging HIV epidemic in Papua New Guinea (so geographically close to this year’s International AIDS Society conference in Sydney, Australia), institutions struggle to support, source, and maintain social researchers who can fulfil this call for social and behavioural investigation. Indeed baseline research on HIV...
interventions on which to reference new strategies still remain to be done. These challenges become evident if one considers the undertaking of innovative investigations into the cultural consequences of pre-exposure and postexposure prophylaxis in a country where attitudes to antiretroviral therapies in general have yet to be explored.

As international researchers explore ways to better incorporate social research into their plans for biomedical prevention and treatment, we invite them to also consider the challenges faced by resource-poor countries in supporting and conducting social and behavioural research. With such consideration, the innovative biomedical aspirations can become a meaningful reality today, allowing the 10% of funding cited in the Sydney declaration to be used to its full potential.

We declare that we have no conflict of interest.

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AusAID Australian Government, Port Moresby, Papua New Guinea (EK); National Research Institute of Papua New Guinea, Port Moresby, Papua New Guinea (TW); Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea (PS); and National AIDS Council Secretariat of Papua New Guinea, Port Moresby, Papua New Guinea (JP)


High-dose vitamin A

Momodou Darboe and colleagues (June 23, p 2088)1 show that the new International Vitamin A Consultative Group (IVACG) early supplementation with high-dose vitamin A was no more beneficial in Gambian mothers and infants than the standard WHO protocol, and that possible adverse effects on the gut mucosa might occur. Darboe and colleagues encourage further investigations with half the WHO dose that achieved better outcomes in terms of mortality than did the full dose recorded in the trial from Guinea-Bissau.2 We report pharmacokinetic and toxicological evidence that reinforces such claims. Although in Darboe and colleagues’ study vitamin A status, measured by plasma retinol concentrations, improved during supplementation, it was similar in the high IVACG and standard WHO groups. This finding is in perfect agreement with the observation that single-dose supplements, repeated-dose supplements, and high vitamin A intake do not alter retinol bioavailability; conversely, such intakes are associated with greatly increased exposure to toxic metabolites of vitamin A such as retinyl palmitate, 13-cis-retinoic acid, and 13-cis-4-oxo-retinoic acid.3 The well known phototoxicity and photomutagenicity of these compounds, which is linked to the generation of reactive oxygen species,4 could be of concern, particularly in geographic areas with intense sunlight such as The Gambia. Osseous side-effects have also been shown in children and adults treated with 13-cis-retinoic acid.5 We declare that we have no conflict of interest.

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Guidelines on guidelines

I have recently received guidelines from my local network on the management of lipids in those with or at risk of cardiovascular disease. I have added these to the pile of such guidelines on my desk, which consists of those from the hospital trust, the local Primary Care Trust, the Joint British Societies, the European Society of Cardiology, and the US National Cholesterol Education Program. Within the UK, lipid guidelines have also been generated by the Scottish Intercollegiate Guidelines Network and the National Institute for Health and Clinical Excellence.

This profusion of guidelines from multiple sources illustrates well the current obsession with guidelines, particularly from multiple tiers of bureaucracy, at the expense of service delivery. Unless something is done to curb this fixation, we will need a set of guidelines on the management of guidelines.

I declare that I have no conflict of interest.

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International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study

A Sonia Buist, Mary Ann McBurnie, William M Vollmer, Suzanne Gillespie, Peter Burney, David M Mannino, Ana M B Menezes, Sean D Sullivan, Todd A Lee, Kevin B Weiss, Robert L Jensen, Guy B Marks, Amund Gulsvik, Ewa Nizankowska-Mogilnicka, on behalf of the BOLD Collaborative Research Group

Summary

Background Chronic obstructive pulmonary disease (COPD) is a growing cause of morbidity and mortality worldwide, and accurate estimates of the prevalence of this disease are needed to anticipate the future burden of COPD, target key risk factors, and plan for providing COPD-related health services. We aimed to measure the prevalence of COPD and its risk factors and investigate variation across countries by age, sex, and smoking status.

Methods Participants from 12 sites (n=9425) completed postbronchodilator spirometry testing plus questionnaires about respiratory symptoms, health status, and exposure to COPD risk factors. COPD prevalence estimates based on the Global Initiative for Chronic Obstructive Lung Disease staging criteria were adjusted for the target population. Logistic regression was used to estimate adjusted odds ratios (ORs) for COPD associated with 10-year age increments and 10-pack-year (defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years that the participant smoked) increments. Meta-analyses provided pooled estimates for these risk factors.

Findings The prevalence of stage II or higher COPD was 10·1% (SE 4·8) overall, 11·8% (7·9) for men, and 8·5% (5·8) for women. The ORs for 10-year age increments were much the same across sites and for women and men. The overall pooled estimate was 1·94 (95% CI 1·80–2·10) per 10-year increment. Site-specific pack-year ORs varied significantly in women (pooled OR=1·28, 95% CI 1·15–1·42, p=0·012), but not in men (1·16, 1·12–1·21, p=0·743).

Interpretation This worldwide study showed higher levels and more advanced staging of spirometrically confirmed COPD than have typically been reported. However, although age and smoking are strong contributors to COPD, they do not fully explain variations in disease prevalence—other factors also seem to be important. Although smoking cessation is becoming an increasingly urgent objective for an ageing worldwide population, a better understanding of other factors that contribute to COPD is crucial to assist local public-health officials in developing the best possible primary and secondary prevention policies for their regions.

Introduction Chronic obstructive pulmonary disease (COPD) is an important and growing cause of morbidity and mortality worldwide.1 2 3 The WHO Global Burden of Disease Project1–3 estimated that COPD was the fifth leading cause of death worldwide in 2001 and will be the third leading cause by 2020. The growing burden of COPD is partly due to the ageing of the world’s population and partly to the continued use of tobacco, which is the most important risk factor for this disease.2 4

WHO estimates of the burden of COPD are based on the little data available for both COPD and present patterns of cigarette smoking. Available information about COPD has not been obtained by consistent methods, and evidence suggests that rates of disease are generally under-estimated.4 5 Accurate estimates of the prevalence of COPD and its risk factors would help guide future projections of the worldwide burden of this disease and assist public-health officials in planning to meet the growing demand for services that rising COPD rates will create.

The Burden Of Obstructive Lung Disease (BOLD) Initiative4 developed standardised methods for estimating COPD prevalence and for obtaining information about risk factors. These methods can be used in countries at all levels of development and were developed in conjunction with The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO),7 which was undertaken in five Latin American countries.

Our aim was to measure the worldwide prevalence of COPD and its risk factors in adults aged 40 years and older and to investigate variation in prevalence across countries by age, sex, and smoking status.

Methods

Study design and participants A description of the design and rationale for the BOLD initiative has been published elsewhere.4 Participants were recruited with use of population-based sampling plans. Questionnaires were used to obtain information about respiratory symptoms, health status, exposure to risk factors, and economic data for the burden of COPD. Prebronchodilator and postbronchodilator spirometry testing was also done for all participants. Data were entered into a secure web platform maintained by the BOLD Operations Center, which provided centralised training, standardised materials, data management, quality control, and data analysis.

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As of Dec 31, 2006, 12 sites had completed data collection and are included in this report. Table 1 shows locations of the clinical centres for these sites. (Data from one site have been published separately,8 but are included in this analysis for completeness and as part of our cross-site comparisons). Participating sites agreed to recruit a population-based sample of at least 600 adults (300 men and 300 women) who were not institutionalised, were aged 40 years and older, and who were living in a well-defined administrative area in which the total population exceeded 150 000. These target populations, as well as the sampling plans, were approved in advance by the Operations Center. Every site had to obtain approval from its local ethical committee and written informed consent from every participant. Table 1 provides a summary of the sampling designs used by all sites. Further details about every site’s target population are included in the webappendix.

The minimum sample size requirement was designed to provide an acceptable degree of precision for estimates of prevalence at any specific site assuming simple random sampling and to allow for the reduced precision that might result from alternative sampling designs. For example, with a sample size of 600 participants, an estimated prevalence of 15%, and a gender-stratified simple random sampling design, a 95% CI for each sex would be 15% (11–19%), whereas the comparable CI for the sample as a whole (assuming equal prevalences for men and women) would be about 15% (12–18%).

Questionnaire data were obtained by face-to-face interviews with trained and certified staff in the participant’s native language. A core questionnaire based on standardised instruments6 was completed for all individuals and included questions about respiratory health and symptoms, smoking history, quality of life, respiratory-related health care use, and limitation of activities. The questions about cigarette smoking, in particular, derive from the 1978 American Thoracic Society (ATS)—the Division of Lung Disease’s Epidemiology Standardization Project.9 Translation of questionnaires into the sites’ local languages followed Mapi Institute (Lyon, France) guidelines.10 Lung function data were obtained at all BOLD sites with use of the ndd EasyOne Spirometer (ndd Medical Technologies, Andover, MA, USA), which is a hand-held, battery-operated device chosen for its level of accuracy and portability.11 Lung function was measured before and 15 min after 200 µg of salbutamol was given. All spirograms were reviewed by the BOLD Pulmonary Function Reading Center (PFRC) and assigned a quality score based on acceptability and reproducibility criteria from the ATS and European Respiratory Society (ERS).12 Spirometry technicians were certified before the start of data collection and received regular feedback about the quality of their performance.

As part of the quality control review process, all volume-time and flow-volume graphs were simultaneously displayed and examined by staff at the PFRC. Data for forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were deemed usable and included in this analysis if they fully met ATS acceptability criteria and were reproducible to within 200 mL.

With the rare exception of participants for whom spirometry was contraindicated (eg, chest or abdominal surgery, heart attack or admission for a heart disorder, detached retina or eye surgery, last trimester of pregnancy, or severe lung disease), all participants were asked to perform a postbronchodilator spirometry test with use of the same spirometer.

Table 1: Summary of sampling designs by site

<table>
<thead>
<tr>
<th>Sampling design</th>
<th>Strata</th>
<th>Number of clusters</th>
<th>Number of respondents*</th>
<th>Response rate†</th>
<th>Cooperation rate‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guangzhou, China</td>
<td>Stratified random sample</td>
<td>Sex</td>
<td>1</td>
<td>602</td>
<td>87%</td>
</tr>
<tr>
<td>Adana, Turkey</td>
<td>Stratified cluster sample</td>
<td>Urban versus rural</td>
<td>45</td>
<td>875</td>
<td>82%</td>
</tr>
<tr>
<td>Salzburg, Austria</td>
<td>Stratified random sample</td>
<td>Sex</td>
<td>1</td>
<td>1349</td>
<td>65%</td>
</tr>
<tr>
<td>Cape Town, South Africa</td>
<td>Cluster samples§</td>
<td>None</td>
<td>852</td>
<td>896</td>
<td>63%</td>
</tr>
<tr>
<td>Reykjavìk, Iceland</td>
<td>Simple random sample</td>
<td>None</td>
<td>1</td>
<td>758</td>
<td>81%</td>
</tr>
<tr>
<td>Hannover, Germany</td>
<td>Stratified random sample</td>
<td>Administrative area and sex</td>
<td>1</td>
<td>733</td>
<td>59%</td>
</tr>
<tr>
<td>Krakow, Poland</td>
<td>Stratified random sample</td>
<td>Administrative area and sex</td>
<td>1</td>
<td>603</td>
<td>78%</td>
</tr>
<tr>
<td>Bergen, Norway</td>
<td>Stratified random sample§</td>
<td>Previous responders and non-responders</td>
<td>1</td>
<td>707</td>
<td>68%</td>
</tr>
<tr>
<td>Vancouver, Canada</td>
<td>Random-digit dialling</td>
<td>None</td>
<td>1</td>
<td>856</td>
<td>26%</td>
</tr>
<tr>
<td>Lexington, USA</td>
<td>Random-digit dialling</td>
<td>None</td>
<td>1</td>
<td>563</td>
<td>14%</td>
</tr>
<tr>
<td>Manila, Philippines</td>
<td>Cluster sample</td>
<td>Administrative districts</td>
<td>95</td>
<td>918</td>
<td>58%</td>
</tr>
<tr>
<td>Sydney, Australia</td>
<td>Stratified random sample</td>
<td>Sex</td>
<td>1</td>
<td>585</td>
<td>25%</td>
</tr>
</tbody>
</table>

Sites are ordered in chronological order of completion. *Participants with core questionnaire and any postbronchodilator spirometry. The total number of respondents was 9425. †Denominator includes people of unknown eligibility status who could not be contacted. Only known ineligible participants were excluded. ‡Denominator includes only participants who were contacted and eligible. §The sample was derived from a previously studied population-based sample.

See Online for webappendix.
pregnancy, resting pulse rate greater than 120, or positive for or taking drugs for tuberculosis), sites attempted to collect prebronchodilator and postbronchodilator spirometry for all participants.

**Definition of COPD**

BOLD uses the Global Initiative for Chronic Obstructive Lung Disease (GOLD) lung function criteria for defining and staging COPD. The GOLD definition is consistent with ATS and ERS standards. BOLD follows standard practice in the published work, and bases the COPD diagnosis strictly on the lung function criteria without requiring documented exposure to a known causative agent.

Because of the low frequency of occurrence of stage IV COPD in these population-based samples, stages III and IV are combined in this paper. BOLD uses the prediction equations for white men and women derived from the third US National Health and Nutrition Examination Survey to compute percentage predicted FEV1 (FEV1%).

**Statistical analysis**

Participants at every site were assigned an analysis weight, which was computed as the product of a pure sampling weight times adjustment factors. Where applicable, weighting class adjustments were used to directly adjust for non-response within age-sex specific strata. When this adjustment was not possible, we used adjustment stratification to ensure that the age-sex distribution of the weighted sample matched that of the target population. Both adjustments were used in sites with sampling protocols that were especially difficult.

Response rates (table 1) were defined as the number of responders (those who completed the core questionnaire and postbronchodilator spirometry), divided by the total number of individuals contacted, less those known to be ineligible. Cooperation rates were defined as the number of responders divided by the total number of responders plus active refusers. Standard methods were used to adjust these rates for multistage sampling designs and, for random-digit-dialling sites, to estimate the proportion of

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**Table 2: Estimated population demographics and risk factors of sites**

<table>
<thead>
<tr>
<th></th>
<th>Guangzhou, China</th>
<th>Adana, Turkey</th>
<th>Salzburg, Austria</th>
<th>Cape Town, South Africa</th>
<th>Reykjavik, Iceland</th>
<th>Hannover, Germany</th>
<th>Krakow, Poland</th>
<th>Bergen, Norway</th>
<th>Vancouver, Canada</th>
<th>Lexington, USA</th>
<th>Manila, Philippines</th>
<th>Sydney, Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>321 (52%)</td>
<td>450 (50%)</td>
<td>643 (45%)</td>
<td>564 (62%)</td>
<td>355 (47%)</td>
<td>346 (49%)</td>
<td>301 (50%)</td>
<td>359 (51%)</td>
<td>493 (58%)</td>
<td>537 (58%)</td>
<td>533 (58%)</td>
<td>294 (50%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.9 (0.6)</td>
<td>53.9 (0.6)</td>
<td>60.1 (0.6)</td>
<td>54.2 (0.5)</td>
<td>57.7 (0.7)</td>
<td>57.3 (0.7)</td>
<td>58.0 (0.10)</td>
<td>59.3 (0.7)</td>
<td>57.5 (0.65)</td>
<td>57.5 (0.8)</td>
<td>53.4 (0.6)</td>
<td>59.9 (0.8)</td>
</tr>
<tr>
<td>Number of pack years*</td>
<td>17.3 (3.0)</td>
<td>16.4 (2.1)</td>
<td>20.3 (1.3)</td>
<td>15.1 (0.9)</td>
<td>16.5 (1.0)</td>
<td>20.4 (1.5)</td>
<td>18.9 (2.2)</td>
<td>17.3 (1.1)</td>
<td>18.5 (1.1)</td>
<td>35.5 (2.1)</td>
<td>9.3 (0.9)</td>
<td>22.7 (2.0)</td>
</tr>
<tr>
<td>Number of years in dusty job</td>
<td>18.4 (1.1)</td>
<td>23.3 (1.8)</td>
<td>19.8 (1.4)</td>
<td>12.9 (0.7)</td>
<td>8.1 (1.1)</td>
<td>13.0 (1.7)</td>
<td>22.2 (1.6)</td>
<td>14.3 (1.0)</td>
<td>11.3 (1.1)</td>
<td>13.2 (1.4)</td>
<td>11.2 (1.2)</td>
<td>14.6 (1.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 (0.2)</td>
<td>26.2 (0.2)</td>
<td>26.3 (0.2)</td>
<td>27.5 (0.3)</td>
<td>26.5 (0.3)</td>
<td>28.0 (0.3)</td>
<td>26.2 (0.3)</td>
<td>26.3 (0.3)</td>
<td>30.8 (0.4)</td>
<td>24.9 (0.3)</td>
<td>27.8 (0.4)</td>
<td>22.7 (0.0)</td>
</tr>
<tr>
<td>Number of years in education</td>
<td>27.7 (0.2)</td>
<td>58.1 (0.2)</td>
<td>9.7 (0.9)</td>
<td>8.1 (0.4)</td>
<td>12.5 (0.2)</td>
<td>10.3 (0.1)</td>
<td>10.1 (0.2)</td>
<td>12.2 (0.2)</td>
<td>15.1 (0.2)</td>
<td>12.6 (0.2)</td>
<td>9.3 (0.2)</td>
<td>29.8 (0.1)</td>
</tr>
<tr>
<td>Number of pack years*</td>
<td>4.8 (1.2)</td>
<td>19.8 (2.1)</td>
<td>19.3 (2.1)</td>
<td>40.6 (2.3)</td>
<td>20.8 (2.3)</td>
<td>21.4 (2.5)</td>
<td>21.9 (2.2)</td>
<td>27.3 (2.5)</td>
<td>11.6 (1.5)</td>
<td>25.5 (2.6)</td>
<td>19.0 (2.1)</td>
<td>13.9 (2.0)</td>
</tr>
<tr>
<td>Number of years in dusty job</td>
<td>32.8 (2.7)</td>
<td>40.0 (3.3)</td>
<td>18.2 (3.6)</td>
<td>38.8 (2.1)</td>
<td>19.8 (2.1)</td>
<td>14.3 (2.0)</td>
<td>28.2 (2.6)</td>
<td>28.7 (2.5)</td>
<td>23.7 (1.9)</td>
<td>31.4 (2.8)</td>
<td>37.7 (2.1)</td>
<td>20.0 (2.3)</td>
</tr>
</tbody>
</table>

Data are number (%), mean (SE), or % (SE). BMI=body-mass index. TB=tuberculosis. *Among ever-smokers. †Among those with a year or more in a dusty job.
individuals with uncertain eligibility who were likely to have been eligible. Data describing population demographics include all responders. For estimation of COPD prevalences, however, the population is restricted to responders who had usable spirometry. We did not report prevalence estimates if there were fewer than 20 participants in a specific category.

The term pack-years was defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years that the participant smoked. This variable was winsorised by setting all pack-year estimates greater than 200 to 200.

Stata survey analysis facilities (version 9.2 [Stata Corp, College Station, TX, USA]) were used to obtain point estimates and standard errors that show the sampling designs used at every site. For sites that used multistage cluster sampling, only the highest level of clustering was modelled. The adjusted Wald test was used to test hypotheses comparing prevalences and risk factors across subgroups. Logistic regression models incorporating cluster, strata, and weighting information were generated for every site to estimate odds ratios (and 95% CIs) of COPD for 10-year intervals of pack-years and for 10-year age increments. Models were adjusted for age, years of education, and smoking status (current, former, never). Random effects meta-analysis models were used to estimate pooled prevalence estimates and odds ratios, and to assess heterogeneity across sites and sex with use of the I² measure.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

At the 12 study sites, 9425 study participants completed core questionnaires and postbronchodilator spirometry
The prevalence of COPD that was GOLD stage I or higher (postbronchodilator FEV₁/FVC <0·7) varied significantly across sites (p<0·0001) and was generally greater in men than in women (table 3). These variations tended to track the differences in smoking prevalence between sexes. Much the same sex-related differences were seen for GOLD stage II or higher disease.

Generally, the prevalence of COPD that is GOLD stage II or higher increased steadily with age for men and women in every site (table 4); disease that was GOLD stage II or higher was usually less than 5% in individuals aged 40–49 years. For those aged 70 years

The age of male participants ranged from 52–58 years for male participants and 53–60 years for female participants (table 2). Patterns of cigarette smoking varied widely across sites and between men and women. Sex-related differences in smoking patterns (especially in the ever-smoked group) were recorded for almost all sites, and mean pack-years were consistently higher for men than for women.

The prevalence of COPD that was GOLD stage I or higher (postbronchodilator FEV₁/FVC <0·7) varied significantly across sites (p<0·0001) and was generally greater in men than in women (table 3). These variations tended to track the differences in smoking prevalence between sexes. Much the same sex-related differences were seen for GOLD stage II or higher disease.

The prevalence of stage II or higher COPD was 10·1% (SE 4·8) overall, 11·8% (7·9) for men, and 8·5% (5·8) for women. Figure 1 shows the prevalence of stage II and higher disease for men and women at every site. Within each sex, the sites are ordered by decreasing prevalence of ever smoking. Despite a slight trend in male participants, this crude ecological analysis suggests that factors other than smoking also affect prevalence of COPD.

Generally, the prevalence of COPD that is GOLD stage II or higher increased steadily with age for men and women in every site (table 4); disease that was GOLD stage II or higher was usually less than 5% in individuals aged 40–49 years. For those aged 70 years

<table>
<thead>
<tr>
<th>Smoking exposure in pack-years</th>
<th>Never smoker</th>
<th>0–10</th>
<th>10–20</th>
<th>20+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4·5% (3·1)</td>
<td>5·9% (3·2)</td>
<td>4·6% (3·1)</td>
<td>3·1% (3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>4·5% (3·1)</td>
<td>5·9% (3·2)</td>
<td>4·6% (3·1)</td>
<td>3·1% (3)</td>
</tr>
<tr>
<td>50–59</td>
<td>5·3% (3·2)</td>
<td>3·1% (3)</td>
<td>5·4% (1·8)</td>
<td>4·3% (2)</td>
</tr>
<tr>
<td>60–69</td>
<td>25·9% (8·4)</td>
<td>18·9% (9·2)</td>
<td>22·3% (3·8)</td>
<td>28·2% (4·9)</td>
</tr>
<tr>
<td>70+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking exposure in pack-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>4·5% (3·1)</td>
<td>5·9% (3·2)</td>
<td>4·6% (3·1)</td>
<td>3·1% (3)</td>
</tr>
<tr>
<td>0–10</td>
<td>4·0% (2·8)</td>
<td>11·6% (5)</td>
<td>8·2% (3·0)</td>
<td>30·8% (5·3)</td>
</tr>
<tr>
<td>10–20</td>
<td>15·8% (3·4)</td>
<td>21·2% (2·6)</td>
<td>18·6% (2·6)</td>
<td>33·9% (5·1)</td>
</tr>
<tr>
<td>20+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking exposure in pack-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>4·5% (3·1)</td>
<td>5·9% (3·2)</td>
<td>4·6% (3·1)</td>
<td>3·1% (3)</td>
</tr>
<tr>
<td>0–10</td>
<td>0</td>
<td>9·4% (3·9)</td>
<td>7·8% (3·1)</td>
<td>16·2% (3·9)</td>
</tr>
<tr>
<td>10–20</td>
<td>4·0% (2·8)</td>
<td>11·6% (5)</td>
<td>8·2% (3·0)</td>
<td>30·8% (5·3)</td>
</tr>
<tr>
<td>20+</td>
<td>15·8% (3·4)</td>
<td>21·2% (2·6)</td>
<td>18·6% (2·6)</td>
<td>33·9% (5·1)</td>
</tr>
</tbody>
</table>

Data are % (SE). *Due to small number (<20), prevalence estimates are not reported for these cells. †Stage II or higher defined as FEV₁/FVC <0·7 and FEV₁% <80%.
and older, the prevalence was 19–47% for men and 6–33% for women. However, the relation between COPD that was GOLD stage II or higher and pack-years was less clear, partly because of confounding by age. Generally, the prevalence increased with increasing pack-years, and the prevalence among participants who had never smoked tended to be similar to that for those who had ever smoked and who had 0–10 pack-years of cigarette smoking exposure.

Figure 2 shows odds ratios (ORs) by sex and site for stage II or more COPD associated with an increase of 10 pack-years in ever-smokers, by sex and site. All models except that for men from Lexington were adjusted for age, years of education, and smoking status (current, former, never). The model for men from Lexington was adjusted only for years of education. These OR estimates for men tended to be greater than those typically reported in previous studies,1 but are generally similar to those reported in the PLATINO Study.7 PLATINO, which used similar methods to our study, reported crude rates of stage I or higher COPD between 7.8% (95% CI 5.9–9.7) and 19.7% (17.2–22.2) in samples from five Latin American countries. An absence of standardisation in previous studies has hindered cross-site comparisons. Our study implemented rigorous methods to achieve the maximum accuracy and completeness of the surveys and to obtain high-quality postbronchodilator spirometry.6 These methods ensured that the data were as comparable as possible across countries.

The GOLD classification of COPD severity,1 which is based on postbronchodilator spirometry, has been widely used since it was introduced in 2002. Whether GOLD stage I should be regarded as early COPD is debated,21,22 because the fixed FEV₁/FVC ratio falls with age in healthy individuals, resulting in substantial overdiagnosis in groups aged older than 50 years.23,24 This issue needs longitudinal follow-up of populations in good health to those with clinically significant disease.25,26 From a public-health perspective, the social and economic burden of COPD is modest in stage I and thereafter rises steadily with increasing severity of disease.20-28

A recent, careful meta-analysis1 of surveys investigating prevalence of COPD reported a pooled prevalence estimate for people aged 40 years and older of 10.0% (95% CI 8.4–11.8) and showed the following distribution of COPD stages: stage I 6.6% (4.2–10.3), stage II 4.3% (3.7–5.0), and stage III/IV 1.2% (0.8–1.8) (Halbert R, UCLA School of Public Health, CA, USA, personal communication). Our estimates of the overall prevalence and staging of COPD are consistently higher than these figures, which accord with claims that COPD
has generally been underestimated in the past.\cite{1,4} In view of the acknowledged bias in prevalence of stage I disease with increasing age,\cite{23,24} we have shown that the prevalence of stage II and higher disease also was increased in our sites, six of which had a combined stage II or more prevalence greater than 10% (four sites for women and seven for men). In three sites (Cape Town, Manila, and Lexington), the prevalence of stage II disease was more than twice that of stage I, suggesting a much higher than usual burden of clinically significant COPD in these populations.

The high burden of COPD that we found might be the result of our choice of sites or our methods, or an indication of the changing nature of COPD worldwide, but in any case it needs attention for future health-care planning. The substantial differences in prevalences of COPD that we observed between sites question the relevance of a single, pooled estimate of COPD prevalence; the prevalence of this disease will depend on the prevalence of COPD risk factors in the population being studied as well as the age distribution.

We restricted our population samples to individuals aged 40 years and older because COPD develops over several decades of exposure to inhaled particulates. We imposed no upper age limit since age itself is an important risk factor for this disease.\cite{23,24} This notion is confirmed by our finding that the overall pooled adjusted OR estimate for stage II and higher COPD per 10-year age increment was almost two. The individual sites’ adjusted ORs and lower 95% CIs were generally greater than one. For individuals aged 70 years or older, the prevalence of COPD that was stage II or higher exceeded 20% in nine sites for men and seven sites for women, which is a striking finding in view of projections for the ageing of the world’s population.\cite{1,4}

We attempted to obtain information about several potential risk factors for COPD, including smoking,\cite{1,2} occupational exposures to dust,\cite{10} indoor exposure to biomass fuels used for home heating and cooking,\cite{11,12} tuberculosis,\cite{13} and socioeconomic status.\cite{1} Although we reported crude exposure data for most of these risk factors, we focussed on the association of COPD with smoking, age, sex, and cigarette smoking. Differences in smoking patterns between men and women helped to explain much of the observed sex-related differences in prevalence of COPD. Nonetheless, several sites had high amounts of exposure to other risk factors that probably contributed to the variation in prevalence that we observed. For example, Cape Town, which had by far the highest prevalence of stage II or greater COPD, had very high reported levels of prior tuberculosis and occupational exposures in addition to high smoking rates. Adana, Krakow, Lexington, and Manila, which along with Cape Town had the highest reported occupational exposures in men, also had high prevalences of stage II or greater COPD in men. Future work will explore the effect of these and other risk factors in more detail.

**Table 3: Odds ratios of stage II or more COPD for a 10-year increase in age, by sex and site**

<table>
<thead>
<tr>
<th>Women</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannover</td>
<td>1.05 (0.97–1.13)</td>
</tr>
<tr>
<td>Guangzhou</td>
<td>1.07 (0.96–1.19)</td>
</tr>
<tr>
<td>Vancouver</td>
<td>1.82 (1.08–3.05)</td>
</tr>
<tr>
<td>Bergen</td>
<td>1.89 (0.99–3.63)</td>
</tr>
<tr>
<td>Reykjavik</td>
<td>1.85 (1.01–3.39)</td>
</tr>
<tr>
<td>Adana</td>
<td>1.96 (1.03–3.73)</td>
</tr>
<tr>
<td>Salzburg</td>
<td>1.83 (0.99–3.40)</td>
</tr>
<tr>
<td>Sydney</td>
<td>1.98 (1.00–3.96)</td>
</tr>
<tr>
<td>Krakow</td>
<td>1.99 (1.00–3.98)</td>
</tr>
<tr>
<td>Manila</td>
<td>2.01 (1.01–4.01)</td>
</tr>
<tr>
<td>Lexington</td>
<td>2.03 (1.04–4.00)</td>
</tr>
<tr>
<td>Cape Town</td>
<td>2.05 (1.04–4.02)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>2.07 (1.05–4.09)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Men</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hannover</td>
<td>1.05 (0.96–1.15)</td>
</tr>
<tr>
<td>Guangzhou</td>
<td>1.07 (0.96–1.19)</td>
</tr>
<tr>
<td>Vancouver</td>
<td>1.82 (1.08–3.05)</td>
</tr>
<tr>
<td>Bergen</td>
<td>1.89 (0.99–3.63)</td>
</tr>
<tr>
<td>Reykjavik</td>
<td>1.85 (1.01–3.39)</td>
</tr>
<tr>
<td>Adana</td>
<td>1.96 (1.03–3.73)</td>
</tr>
<tr>
<td>Salzburg</td>
<td>1.83 (0.99–3.40)</td>
</tr>
<tr>
<td>Sydney</td>
<td>1.98 (1.00–3.96)</td>
</tr>
<tr>
<td>Krakow</td>
<td>1.99 (1.00–3.98)</td>
</tr>
<tr>
<td>Manila</td>
<td>2.01 (1.01–4.01)</td>
</tr>
<tr>
<td>Lexington</td>
<td>2.03 (1.04–4.00)</td>
</tr>
<tr>
<td>Cape Town</td>
<td>2.05 (1.04–4.02)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>2.07 (1.05–4.09)</td>
</tr>
</tbody>
</table>

The fairly high prevalence of stage II or more COPD in individuals who had never smoked and the increased risk in women raise important questions about the role of other exposures, and possibly of a greater genetic susceptibility in women. At present, COPD in those who have never smoked is poorly understood.\cite{1} In some people, the high prevalence of disease might indicate long-standing asthma with remodelling in the small airways, whereas in others it could suggest other unidentified exposures. Whether women are at greater risk for COPD than men, if they are equally exposed to smoking and other particulates, remains controversial.\cite{2,10}

We used the GOLD criterion of a fixed postbronchodilator ratio of FEV1/FVC less than 0.7 as the primary indicator of irreversible airflow obstruction, despite its shortcomings,\cite{23,24} because it allows comparison across countries without the need for reference values and is a widely used standard that can be readily compared with other published findings. Other definitions, such as those for GOLD stage II and higher COPD, typically need the use of prediction equations to account for the age-related decrease in lung function in healthy individuals. Widely accepted reference equations for spirometric variables are available from the US.  

![Figure 3: Odds ratios of stage II or more COPD for a 10-year increase in age, by sex and site](image-url)
NHANES III Study and from large cross-sectional surveys in some other countries, but they are not available for many parts of the world. Even if they were available, whether country-specific or race-specific reference equations are appropriate to use in the context of cross-cultural comparisons is unclear, since such use might mask true differences related to exposure between countries or between racial groups within countries. Specifically, some investigators have noted that lung function is partly determined by factors associated with deprivation in early life, and these factors are probably as important in determining normal values of local lung function as are any genetic differences between populations. We used the NHANES III reference equations because NHANES is a large, high-quality, population-based survey. We used only the NHANES Caucasian equations for these reasons. Recognising that this issue may still be controversial, we also have developed reference equations using all the sites’ healthy participants who have never smoked, and plan to assess the effect of using these reference equations, and other prediction equations, in place of the NHANES equations for future work.

Our study also has limitations. First, the BOLD protocol calls for sample sizes of at least 300 men and 300 women in every site, although sites were encouraged to recruit more individuals if they could. The minimum sample size was purposely kept small to make the surveys as affordable as possible while providing acceptable confidence limits for overall and sex-based comparisons. This strategy allows more countries to participate and permits cross-site comparisons with a sufficiently large pooled sample. The weakness of this strategy is that the absolute number of patients with COPD within any particular site is generally small, thus limiting power for specific types of within-site analyses, such as detailed subgroup analyses or analyses designed to characterise the effect or patterns of care for patients with COPD.

A second limitation is that the lower than desirable response rates at some sites could have introduced the potential for response bias. Our analysis weights were designed to show both the sampling design and non-response at every site by adjustment of prevalence estimates to the target populations; however, the representativeness of responders cannot be assessed. When sites’ meta-analysis weights were adjusted by their response rates, the overall and sex-specific pooled OR estimates were similar. Also, unlike PLATINO, our study did not require that sites use entire cities as their target population, which was a practical decision driven largely by logistics and the widely different sampling frames that our sites had access to. Additionally, unlike PLATINO, we had no centralised funding for local site operations. Every site obtained its own funding, and largely by logistics and the widely different sampling frames that our sites had access to. Also, unlike PLATINO, we had no centralised funding for local site operations. Every site obtained its own funding, and budgetary constraints sometimes restricted the type of sampling that was feasible. Nonetheless, the protocol requirement that every target population represents a well-defined administrative area of at least 150,000 individuals was designed to keep to a minimum the likelihood that any specific population’s prevalence would be overly affected by a single, unique exposure. Caution should therefore be exercised when extrapolating any individual site’s data to a broader population.

Contributors
This paper was written by the BOLD Collaborative Research Group Writing Committee. ASB, WMV, PB, DMM, AMBM, AMN, SG acquired data or actively participated in data management activities. MAM and WVM directed the statistical analysis. ASB, WMV, SG, MAM, PB, and RLJ drafted the report, and all co-authors revised the manuscript. ASB obtained funding for the study.

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Conflict of interest statement

ASB, WVM, MAM, SG, TAL, SDS, KW, DMM, and RJL received funding for the BOLD study operations center and/or research from unrestricted educational grants from GlaxoSmithKline, Pfizer, Boehringer Ingelheim, AstraZeneca, ALTANA, Novartis, Merck, Chiesi, Schering-Plough, and Sepracor. Several co-authors have served on advisory boards for GlaxoSmithKline (ASB, SDS, DMM), ALTANA (ASB, Merck), Schering-Plough (ASB, WVM, SDS), Novartis (ASB, SDS, DMM), Pfizer (ASB, SDS, DMM), Sepracor (ASB, DMM), Ortho Biotech (DMM), and Astra-Zeneca (SDS, DMM). Several authors have participated in COPD workshops funded by AstraZeneca (ASB, SDS), GlaxoSmithKline (ASB, WVM, TAL, SDS), and Merck (WVM). RJL has served on oversight committees for Pfizer and Eli Lilly. DMM serves on Speakers Bureaus for Dey, GlaxoSmithKline, Pfizer, and Boehringer-Ingelheim. GM received funding for the BOLD Sydney site from Air Liquide Healthcare P/L, AstraZeneca P/L, Boehringer Ingelheim P/L, GlaxoSmithKline Australia P/L, Pfizer Australia P/L, ENM received funding for the BOLD Krakow site from GlaxoSmithKline Pharmaceuticals, Polpharma, Ivax Pharma Poland, AstraZeneca Pharma Poland, ZF ALTANA Pharma, Pliva Kraków, Adamed, Novartis Poland, Linde Gaz Polska, Lek Polska, Tarchomińskie Zakłady Farmaceutyczne Polfa, Starostwo Proszowice, Skrzydlewski, Sotwin, and Agroplon. All other authors declare that they have no conflict of interest.

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Exposure to passive smoking is associated with an increased prevalence of COPD and respiratory symptoms. If this association is causal, we estimate that 1·9 million excess deaths from COPD among never smokers could be attributable to passive smoking in the current population in China. Our findings provide strong evidence for urgent measures against passive smoking in China.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality worldwide, and is estimated to be the third most common cause of death by 2020. Active smoking is well established as the predominant risk factor. However, less than a quarter of all smokers develop COPD and more than 15% of COPD occurs in never smokers, suggesting that other factors also play a part.

China has one of the largest populations of tobacco consumers worldwide, with smoking rates as high as 70% among men during the 1990s. Also, the proportion of never smokers who develop COPD in China is much higher than that in most other countries. Compared with women in Europe, the USA, and Canada, Chinese women have a higher risk of respiratory disease, although their smoking rates are lower.

The prevalence of passive smoking exposure is high in China and there is not much legislation to restrict exposure in the workplace and public areas. However, there is little information on the effects of passive smoking on lung function in Chinese populations. In this study, we analysed baseline data from 15 379 never smokers among 20 430 participants in the Guangzhou Biobank Cohort Study to examine the relation between passive smoking, self-reported respiratory symptoms, and COPD, based on spirometry.

Methods

Participants

The Guangzhou Biobank Cohort Study is a continuing prospective study among older individuals (50 years and older) that aims to examine environmental and genetic determinants of several chronic diseases in a southern Chinese population. Details of recruitment and description of phase 1 participants are reported elsewhere. Briefly, a community social and welfare association was chosen as a sampling frame. This association, with around 100,000 members, has branches throughout Guangzhou and its membership is open to anyone over the age of 50 years for a nominal fee. People were randomly recruited from the association’s membership list. We only included those who were ambulatory and not receiving treatment for life threatening diseases, such as cancer. However, a cultural unwillingness of Chinese men to give blood due to the belief of an associated loss of so-called life energy has...
resulted in fewer men than women recruits. The participants received a full medical check-up including lung function assessment. A detailed questionnaire was given by interview to assess a range of measures including smoking, passive smoking and occupational exposures, and personal disease history. This report is based on data from 20430 participants, including 10413 from phase I (September, 2003, to November, 2004) and 10017 from phase II of recruitment (April, 2005, to May, 2006).

The study received ethics approval from the Medical Ethics Committee of the Guangzhou Medical Association. All participants gave written, informed consent before participating in the study.

Procedures
The questionnaire included a detailed assessment of passive smoking exposure both at home and at work. Two separate self-reported measures were used. The first measure was based on density, and defined as the presence of none, one, or more smokers living in the same household as the participant recorded separately for childhood and adulthood exposure, or co-workers smoking nearby while indoors. The second measure was based on duration of exposure in adulthood (since age 18 years). Participants were asked to report the number of hours per week of usual exposure to passive smoking at home and at work, and the number of years of such exposure for each. We calculated total hours of adulthood exposure at home and work separately and combined, based on 52 weeks per year. The level of exposure was categorised into low (less than 2 years of 40 h a week), medium (2–5 years of 40 h a week), and high (more than 5 years of 40 h a week). We used 40 h as the typical number of working hours in a week, but repeated the analyses using different cutoffs (30 h or 50 h per week) for level of exposure, to assess the robustness of our findings.

The Medical Research Council respiratory questionnaire was used to assess respiratory symptoms and the following definitions were used: cough or phlegm (usually having cough or phlegm first thing in the morning or either during the day or at night); shortness of breath (troubled by shortness of breath when hurrying on level ground or walking up a slight hill); or any symptoms (having any one of the symptoms defined above).

Spirometry was done with a pneumotachograph (Chestgraph H1-701, Chest M1 Inc, Tokyo, Japan) in phase I and a turbine flowmeter (Cosmed microQuark, Rome, Italy) in phase II. The test was done in a standing position without nose clips. At least three manoeuvres were done and the best measure of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC were recorded. Predicted values for lung function were derived using the equations of Ip and colleagues.22 To classify tests for reliability and validity, a numerical quality-check algorithm was developed according to European Respiratory Society recommendations using criteria used in the BRONCUS trial.23 The remaining results were assessed by visual inspection of flow-volume and volume-time curves by two authors (PY, KHL). In those patients with no reported physician-diagnosed asthma, we defined COPD as FEV1/FVC of less than 0·70, according to GOLD guidelines,24 but without the use of a bronchodilator. We repeated the analyses in men and women separately, on the basis of data from phase I and then II, and using the 5th percentile of the lower limit of normal as the basis for cutoff in defining COPD.

| Table 1: Baseline characteristics of never smoking participants (N=15379) |
|------------------|------------------|------------------|
| **N (%)**       | **Sex**          | **Age (years)**  |
|                 | Men 1777 (11·6)  | 50–59 6717 (43·7)|
|                 | Women 13602 (88·4)| 60–69 6607 (42·9) |
|                 |                  | >70 2055 (13·4)  |
| **Education**   |                  |                  |
|                 | <Primary school 1768 (11·5) | 50–59 6717 (43·7) |
|                 | Primary school 5405 (35·2) | 60–69 6607 (42·9) |
|                 | Middle school 6922 (45·0) | >70 2055 (13·4)  |
|                 | >Middle school 1277 (8·3) |                  |
| **Occupational dust exposure**   |                  |                  |
|                 | Yes 6447 (40·3) |                  |
|                 | No 9113 (59·7)  |                  |
| **Indoor air pollution exposure** |                  |                  |
|                 | Yes 5134 (33·4) |                  |
|                 | No 10245 (66·6)  |                  |
| **Passive smoking exposure**     |                  |                  |
| **Childhood home exposure**      |                  |                  |
|                 | Yes 8283 (54·1)  |                  |
|                 | None 7029 (45·9)  |                  |
| **Adulthood home exposure**      |                  |                  |
|                 | Yes 8846 (57·7)  |                  |
|                 | None 6487 (42·3)  |                  |
| **Work exposure**                |                  |                  |
|                 | Yes 6848 (44·7)  |                  |
|                 | None 8465 (55·3)  |                  |
| **COPD status**                 |                  |                  |
| No COPD           | 6068 (93·4)      |                  |
| COPD GOLD I       | 140 (2·2)        |                  |
| COPD GOLD II      | 222 (3·4)        |                  |
| COPD GOLD III     | 55 (0·8)         |                  |
| COPD GOLD IV      | 12 (0·2)         |                  |

*Based on 6497 participants with valid spirometry data and no self-reported asthma. GOLD I=FEV1/FVC <0·70 and FEV1 ≥80% predicted. GOLD II=FEV1/FVC <0·70 and 50%≤FEV1<80% predicted. GOLD III=FEV1/FVC<0·70 and 30%≤FEV1<50% predicted. GOLD IV=FEV1/FVC<0·70 and FEV1<30% predicted.
A detailed smoking history was obtained and used to classify individuals as never smokers and ever smokers, if they had ever smoked each day. We measured urinary cotinine levels in the phase I participants, by gas chromatograph mass spectrometry, to validate smoking status. We also obtained a detailed occupational history, including exposure to dust and to indoor pollutants (household biomass fuels). Reported educational level was used as proxy for socioeconomic status. Interviewers who obtained data for passive smoking and other exposures, symptoms, and medical history were blinded to the spirometry findings, as were the participants at the time of interview.

Statistical analysis
For all analyses of the relation between passive smoking exposure and respiratory symptoms or COPD, we used only never smokers. Logistic regression models were done to assess the association between passive smoking exposure (measured as density and duration of exposure at home or work and density of exposure during childhood) and respiratory symptoms and COPD. The models were adjusted for age, sex, educational level, and exposure to occupational dust and indoor air pollutants. Odds ratios and 95% CI were computed. The models assessing the relation between passive smoking exposure and COPD included participants with valid spirometry (n=6497). The models assessing the relation between passive smoking exposure and respiratory symptoms included all never smokers (n=15379). We calculated a p value for trend to assess any dose-response relation for each measurement of passive smoking exposure. We tested for interaction between passive smoking exposure and sex in relation to COPD prevalence.

Role of the funding source
The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
The baseline characteristics of the participants are shown in table 1. The mean age was 61.7 years (range 50–93). There were only 18 people (0.3%) who said they had never smoked who had urinary cotinine levels above 50 ng/mL. Of the 20430 participants, 15379 (75.3%) were never smokers. Spirometry data were available for 14790 (96.1%). Application of the quality algorithm for spirometry measures and visual inspection resulted in rejection of data from 8145 participants. Of the remainder, 148 (2.2%) reported physician-diagnosed asthma and were excluded from analysis. Therefore, 6497 never smokers with spirometry data were available for use in the analysis for this report.
(figure). Participants who had never smoked and whose spirometry data were included were similar to those excluded in terms of age, sex, educational level, occupational exposure, reporting of respiratory symptoms, and passive smoking exposures (table 2).

The prevalence of COPD defined by spirometry was higher among smokers (n=342, 16·7%) compared with never smokers (n=429, 6·6%; odds ratio 2·85, 95% CI 2·44–3·31), and in men (n=354, 15·1%) compared with women (n=417, 6·7%; 2·48; 2·13–2·88).

Among never smokers, 98 (5·5%) men and 1667 (12·3%) women had never worked indoors. Among men and women combined, 13·7% reported high levels (more than 5 years of 40 h a week) of exposure to passive smoking at work and 14·5% at home. There were significant but weak associations between exposure to dust and indoor pollutants and risk of COPD. We therefore adjusted for these factors in subsequent analyses.

The relation between the categories of passive smoking exposure and COPD is shown in table 3. There was no significant relation between risk of COPD and passive smoking exposure assessed by density of exposure during childhood or adulthood. However, using the duration of exposure, there was a significantly increased risk with increasing levels of adulthood exposure both at home and at work.

After adjustment for potential confounding factors, COPD prevalence among never smokers was significantly greater with high-level exposure to passive smoking at home (OR 1·60, 95% CI 1·23–2·10) and at work (1·50, 1·14–1·97) than those who had low-level exposure. When home and work exposures were combined, there was also a significantly increased risk of COPD with high exposure (1·48, 1·18–1·85 for longest duration of total adulthood exposure).

All measurements of passive smoking exposure, including childhood exposure, were significantly associated with reporting of any respiratory symptom (table 4). Adult passive smoking exposure was significantly associated with shortness of breath. Work, but not home, exposure was found to be associated with cough. No significant associations were seen between any exposure and phlegm.

We recorded no significant interaction between passive smoking exposure and sex (data not shown). We repeated the analyses on participants from phase I and II separately, since different spirometers were used in each phase. The direction of results for both phases was the same as the combined analysis, although the results were generally less significant because of smaller numbers of participants (and the association between duration of work exposure and COPD was not significant in phase I participants). When the lower limit of normal was used to define COPD, the proportion of those classified as having COPD reduced, but the direction and magnitude of results remained similar. When different cutoffs were used for categorising levels of passive smoking exposure, the direction of results remained the same. The magnitude of effect differed according to whether fewer or more people were included in the high-exposure category. Repeating the analyses on symptoms and passive smoking exposure separately for those with valid and invalid spirometry results showed that the direction of results was the same for both, and the magnitude of effect almost identical (results not shown).

### Discussion

In this study, older adults who were exposed to passive smoking at work and at home, particularly higher level exposure, were associated with higher prevalence of COPD than those not exposed. Passive smoking exposure was also associated with respiratory symptoms. These results were particularly seen when exposure assessment

<table>
<thead>
<tr>
<th>Childhood home exposure</th>
<th>N (%) without COPD</th>
<th>N (%) with COPD</th>
<th>Crude odds ratio (95% CI)</th>
<th>*Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of smokers living in the same household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2680 (92·3)</td>
<td>225 (7·7)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2534 (94·2)</td>
<td>157 (5·8)</td>
<td>0·74 (0·60–0·91)</td>
<td>0·89 (0·72–1·10)</td>
</tr>
<tr>
<td>≥2</td>
<td>829 (94·6)</td>
<td>47 (5·4)</td>
<td>0·68 (0·49–0·93)</td>
<td>0·81 (0·58–1·12)</td>
</tr>
<tr>
<td>p</td>
<td>0·002</td>
<td>0·14</td>
<td></td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Adulthood home exposure</th>
<th>N (%) without COPD</th>
<th>N (%) with COPD</th>
<th>Crude odds ratio (95% CI)</th>
<th>*Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of smokers living in the same household</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2567 (92·9)</td>
<td>195 (7·1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>3011 (93·7)</td>
<td>201 (6·3)</td>
<td>0·88 (0·72–1·08)</td>
<td>0·96 (0·77–1·20)</td>
</tr>
<tr>
<td>≥2</td>
<td>490 (93·7)</td>
<td>33 (6·3)</td>
<td>0·89 (0·61–1·30)</td>
<td>0·92 (0·62–1·36)</td>
</tr>
<tr>
<td>p</td>
<td>0·26</td>
<td>0·63</td>
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<td></td>
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<table>
<thead>
<tr>
<th>Adulthood hours of exposure at home</th>
<th>N (%) without COPD</th>
<th>N (%) with COPD</th>
<th>Crude odds ratio (95% CI)</th>
<th>*Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years of 40 h per week</td>
<td>4129 (93·8)</td>
<td>273 (6·2)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2–5 years of 40 h per week</td>
<td>1082 (93·7)</td>
<td>73 (6·3)</td>
<td>1·02 (0·78–1·33)</td>
<td>1·11 (0·84–1·47)</td>
</tr>
<tr>
<td>&gt;5 years of 40 h per week</td>
<td>857 (91·2)</td>
<td>81 (8·8)</td>
<td>1·17 (1·13–2·10)</td>
<td>1·10 (1·23–2·10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Work exposure</th>
<th>N (%) without COPD</th>
<th>N (%) with COPD</th>
<th>Crude odds ratio (95% CI)</th>
<th>*Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of smokers exposed to indoors at work</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3328 (93·3)</td>
<td>240 (6·7)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>251 (94·4)</td>
<td>15 (5·6)</td>
<td>0·83 (0·48–1·42)</td>
<td>0·88 (0·51–1·52)</td>
</tr>
<tr>
<td>≥2</td>
<td>2465 (93·5)</td>
<td>172 (6·5)</td>
<td>0·97 (0·79–1·19)</td>
<td>0·97 (0·78–1·20)</td>
</tr>
<tr>
<td>p</td>
<td>0·73</td>
<td>0·76</td>
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</table>

<table>
<thead>
<tr>
<th>Hours of exposure at work</th>
<th>N (%) without COPD</th>
<th>N (%) with COPD</th>
<th>Crude odds ratio (95% CI)</th>
<th>*Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years of 40 h per week</td>
<td>4501 (94·0)</td>
<td>286 (6·0)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2–5 years of 40 h per week</td>
<td>757 (92·1)</td>
<td>65 (7·9)</td>
<td>1·35 (1·02–1·79)</td>
<td>1·35 (1·01–1·80)</td>
</tr>
<tr>
<td>&gt;5 years of 40 h per week</td>
<td>810 (91·2)</td>
<td>78 (8·8)</td>
<td>1·52 (1·17–1·97)</td>
<td>1·50 (1·14–1·97)</td>
</tr>
<tr>
<td>p</td>
<td>0·001</td>
<td>0·002</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Total hours of adulthood home and work exposure</th>
<th>N (%) without COPD</th>
<th>N (%) with COPD</th>
<th>Crude odds ratio (95% CI)</th>
<th>*Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years of 40 h per week</td>
<td>2999 (94·0)</td>
<td>191 (6·0)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2–5 years of 40 h per week</td>
<td>3409 (94·5)</td>
<td>82 (5·5)</td>
<td>0·91 (0·70–1·19)</td>
<td>0·95 (0·72–1·24)</td>
</tr>
<tr>
<td>&gt;5 years of 40 h per week</td>
<td>1660 (91·4)</td>
<td>156 (8·6)</td>
<td>1·48 (1·18–1·84)</td>
<td>1·48 (1·18–1·85)</td>
</tr>
<tr>
<td>p</td>
<td>0·001</td>
<td>0·001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, educational level, occupational dust exposure, and indoor air pollution.
was based on duration of exposure rather than density (as measured by numbers of smokers they were exposed to).

Our study has several strengths. The study population included in the analysis, with almost 6500 individuals, represents one of the largest studies addressing the relation between objectively assessed COPD and passive smoking exposure among never smokers. We were able to examine this group separately without the major confounding factor of active smoking, and self-report of smoking status was verified by urinary cotinine measures. We also had several measures of self-reported passive smoking exposure. Repeating analyses with different definitions of COPD and various cutoffs for passive smoking exposure all yielded similar results, with a significant association between passive smoking exposure and COPD.

One limitation of our study is the cross-sectional nature. Temporal associations cannot be inferred, and those with impaired lung function might have altered their exposure pattern. The study population might not be representative of the population of Guangzhou, since our participants were drawn from an association concerned with health and welfare, although it was open to all older residents in the city for a low yearly fee. Our exclusion criteria also meant that the participants represent a relatively healthy population of survivors compared with the general population, and those with the most severe COPD did not participate. Bias arising from differential recall of passive smoking in participants with COPD or respiratory symptoms could also generate a spurious association. In this connection, one important advantage of our study is that it is based on a large cohort.
study with many objectives. In fact, COPD was not explicitly mentioned to participants at any stage. Furthermore, during interviews, questions on smoking and passive smoking were asked early on, after which participants were asked a large number of questions concerning sociodemographic and other lifestyle factors before they came to the section on symptoms. Also, respiratory symptoms were only a subset in the symptomatology section. The risk was further reduced by blinding the participants and the interviewers to spirometry findings. Also, few participants had a physician diagnosis of COPD. Finally, a survey in China showed that only about a third of respondents believed that passive smoking is harmful to health.25 The combination of these features makes recall bias an unlikely explanation for the observed association between passive smoking and COPD.

The overall quality of spirometry was fairly poor, resulting in a large proportion of tests having to be discarded, which indicates the difficulty in doing lung function tests in large-scale studies, where a vast number of measurements are taken. However, by using a comprehensive and stringent quality check, we included only those data which were valid and reliable. Furthermore, baseline characteristics of those with valid and invalid spirometry were similar. Also the relation between exposure and respiratory symptoms were the same in both groups. Thus exclusion of those with invalid spirometry is unlikely to have resulted in any bias.

Our results of increased risk of COPD with high levels of adulthood exposure to passive smoking concur with some previous studies,8,11 including a study showing excess mortality from COPD among those with passive smoking exposure in Hong Kong.26 However, previous studies have shown mixed results,8,11,13,16 and most have examined lung function rather than COPD as the outcome. One study that examined the risk of physician-diagnosed COPD, verified by spirometry in a small sample, reported that only those with long duration of passive smoking exposure (42 years or more at work and 23 years or more at home) were at increased risk (odds ratio 1·68; 95% CI 1·19–2·38, and 1·60; 1·20–2·14, respectively).27 Some studies have shown that the relation between passive smoking exposure and poorer lung function is confined to those with increased susceptibility (bronchial hyper-responsiveness or asthma).14,15,18 We specifically excluded those patients with physician-diagnosed asthma from this analysis. We noted that only duration of exposure, but not the number of smokers around the individual, was associated with COPD. This finding might mean that duration of exposure is a more accurate indicator of true total exposure.

Our finding of a dose-response relation between passive smoking exposure at work and home and any respiratory symptoms is consistent with several other studies,11,16 although we did not find any association with phlegm. The magnitude of excess risk is generally lower than in previously reported studies, being between 13 (for any symptom in relation to work exposure) and 31% (for breathlessness in relation to home exposure).

Although there was a decrease in odds ratios for COPD with childhood passive smoking exposure in the unadjusted analysis, this effect disappeared after adjustment for age and other factors. The lack of association between childhood passive smoking exposure and COPD is in keeping with reports from a longitudinal study, when the analysis was confined to never smokers.28 However, another large cross-sectional study which included smokers showed some association between parental smoking in childhood and respiratory symptoms and impaired lung function in adulthood.29

The prevalence of COPD among never smokers, particularly women, in this population is high, in keeping with other studies from China.30 The prevalence of physician-diagnosed asthma, although lower than in most European and North American populations, is also in keeping with previous Chinese studies.31

In summary, passive smoking exposure in adulthood both at home and at work is related to COPD and respiratory symptoms in this southern Chinese population. However, the magnitude of increased risk is fairly small and the high prevalence of disease among never smokers in this population cannot be wholly explained by this exposure. Therefore other risk factors still need to be explored and identified.

Over 60% of adults in China are never smokers.32 This population is exposed to high levels of passive smoking, since there is little restriction on smoking in indoor places. In our study population, more than half of never smokers reported exposure to passive smoking in their workplace and at home, with 28% reporting high levels of total adult exposure (more than 5 years with 40 h exposure per week). Of all deaths in China, around 11-6% among never smokers are attributable to COPD.4 If our risk estimates are correct, and assuming that current mortality and passive smoking exposure patterns continue, of the 240 million people aged over 50 years alive today in China, high exposure to passive smoking would result in about 1·9 million (95% CI 0·9–2·8 million) excess deaths from COPD among never smokers. This finding has serious implications for population health, health services, and the economy, and lends further support to strong measures to ban smoking in public places and workplaces, and to increase availability of smoking cessation services in this region.

Contributors

All authors contributed to the study design, development of study instruments, and took part in the interpretation of findings and contributed to the final manuscript. PY undertook data cleaning checking and coding, did the analysis for the study, and wrote the first draft. CQJ, KKC, and THL originally designed the idea of the cohort study, and have been responsible for obtaining funding. CQJ oversaw data collection and facilities for participant recruitment, and has contributed to the final manuscript. KKC contributed to the design of the study, the decisions on the strategy for analysis, paper writing, and the amendment of the final manuscript. MRM developed the quality
check algorithm, checked the spirometry data, and contributed to the final manuscript. GNT contributed to data checking, writing the methods section, and approving the final manuscript. THL contributed to amendment of the manuscript and suggestions for data analysis.

WSZ and KHL have contributed to data cleaning and checking, and have contributed to the final manuscript. PA conceived the idea for this paper, designed the study, contributed to the strategy for analysis, supervised and checked the analysis, and wrote the final draft.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
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References
Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study

Debra A Stern, Wayne J Morgan, Anne L Wright, Stefano Guerra, Fernando D Martinez

Summary

Background Together with smoking, the lung function attained in early adulthood is one of the strongest predictors of chronic obstructive pulmonary disease. We aimed to investigate whether lung function in early adulthood is, in turn, affected by airway function measured shortly after birth.

Methods Non-selected infants were enrolled at birth in the Tucson Children's Respiratory Study between 1980 and 1984. We measured maximal expiratory flows at functional residual capacity ($V_{\text{max,FRC}}$) in 169 of these infants by the chest compression technique at a mean of 2.3 months (SD 1.9). We also obtained measurements of lung function for 123 of these participants at least once at ages 11, 16, and 22 years. Indices were forced expiratory volume in 1 s (FEV$_1$), forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC (FEF$_{25-75}$), both before and after treatment with a bronchodilator (180 μg of albuterol).

Findings Participants who had infant $V_{\text{max,FRC}}$ in the lowest quartile also had lower values for the FEV$_1$/FVC ratio ($−5.2\%, p<0.0001$), FEF$_{25-75}$ ($−663 \text{ mL/s, } p<0.0001$), and FEV$_1$ ($−233 \text{ mL, } p=0.001$) up to age 22, after adjustment for height, weight, age, and sex, than those in the upper three quartiles combined. The magnitude and significance of this effect did not change after additional adjustment for wheeze, smoking, atopy, or parental asthma.

Interpretation Poor airway function shortly after birth should be recognised as a risk factor for airflow obstruction in young adults. Prevention of chronic obstructive pulmonary disease might need to start in fetal life.

Introduction

30 years ago, Burrows and coworkers made the seminal observation that adults with a history of paediatric respiratory illness had lower levels of lung function and were more likely to develop obstructive lung disease than those without such a history. One plausible interpretation of this finding is that respiratory infections can damage the lung and predispose to obstructive lung disease. However, events before any respiratory illness could also possibly predispose individuals both to these early illnesses and to subsequent chronic impairment of lung function. Our findings and those of others supported this contention, by showing that children who presented with illnesses of the lower respiratory tract during their first years of life had lower maximal expiratory flows than others shortly after birth and before any such illnesses developed. These results suggest the hypothesis that chronic obstructive pulmonary disease has origins in fetal life, and specifically in the factors that determine intrauterine growth of lungs and airways.

Longitudinal studies have suggested that a substantial proportion of deficits in lung function that present during the third decade of life, and especially those in individuals who have a diagnosis of asthma, persist into late adulthood and predispose for the development of chronic obstructive pulmonary disease. We aimed to assess to what degree these deficits in lung function are already present in the early postneonatal period.

Methods

Participants We enrolled 1246 healthy infants at birth, between 1980 and 1984, in the Tucson Children's Respiratory Study, a longitudinal non-selected cohort study. We developed a chest-compression technique, for assessment of pulmonary function in infancy, as the last 376 infants were enrolled in the study. Of these 376 eligible infants, 20 could not be contacted within the testing time, 111 did not have the consent of their parents, 27 had a lower respiratory infection, 35 did not fall asleep, seven were older than 6 months, six changed health-care providers, and we did not have length information for one. We tested the remaining 169 infants shortly after birth, at a mean of 2.3 (SD 1.9) months. Details of the selection and exclusion criteria have been reported previously. We obtained informed consent from participants or their parents each time lung function was measured. The study was approved by the institutional review board of the University of Arizona.

Procedures We obtained partial expiratory flow-volume curves by the chest-compression technique and recorded the maximal expiratory flow at functional residual capacity ($V_{\text{max,FRC}}$) for 169 infants. We did follow-up spirometry for 123 of these individuals at three ages: 109 at a mean of 10.9 (SD 0.4) years, 87 at a mean of 16.8 (0.5) years, and 83 at a mean of 21.7 (0.6) years. At age 11 years, follow-up spirometry was done with a custom-built, pneumotachometer-based system, running software on a portable

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computer," and at ages 16 and 22 with a portable Schiller Spirovit SP-1 (Schiller AG, Baar, Switzerland). We calibrated these systems with a Jones flow-volume calibrator (Model FVC-3000; Jones Medical Instrumentation Company, Oakbrook, IL, USA). No children had used a bronchodilator within 6 h of testing. After we took baseline measurements, a fixed dose of two puffs of albuterol (180 µg) was administered from a metered-dose inhaler and aerochamber-holding device (Monaghan Medical Corp, Plattsburgh, NY, USA), and we did postbronchodilator spirometry after 15 min. Spirometry indices included the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and forced expiratory flow between 25% and 75% of the FVC (FEF25–75). We calculated the response to bronchodilation for all spirometric indices as at ages 11, 16, and 22, as follows:

\[
\frac{\text{postbronchodilation measurement-prebronchodilation measurement}}{\text{postbronchodilation measurement-prebronchodilation measurement}} \times 100
\]

We did methacholine challenge tests at age 11, and defined bronchial hyper-responsiveness as values for methacholine-dose response below the tenth percentile for a healthy reference subgroup (who had negative skin tests, and neither had wheeze, nor had been diagnosed with asthma), as previously reported. Study nurses recorded height, weight, and age at the time of testing.

At enrolment, parents completed a questionnaire about their ethnicity, history of physician-diagnosed asthma, years of education, age, and smoking. We also gathered information about pregnancy and delivery for each participating infant. We noted any lower respiratory illnesses that had been confirmed by a physician from the participating infant. We assessed follow-up spirometry longitudinally by age (11, 16, and 22 years). We did skin-prick tests with six local airborne allergens (Hollister-Stier Laboratories, Everett, WA, USA), and an airborne allergen (Hollister-Stier Laboratories, Everett, WA, USA) at 6 years. We did skin-prick tests with six local airborne allergens (Hollister-Stier Laboratories, Everett, WA, USA)

### Statistical Analysis

Airway function measured in infancy (Vmax\text{FRC}) was logarithmically transformed (base e), adjusted for infant length, and standardised to the average length of the infants at 2 months of age (57·4 cm) as previously reported. We used length-adjusted infant Vmax\text{FRC} as a time-independent covariate (natural logarithm of mL/sec) or as a categorical predictive variable (grouped into quartiles). Follow-up spirometry indices at ages 11, 16, and 22 years (FVC, FEV1, FEF25–75, and the FEV1/FVC ratio) were normally distributed. For separate analyses at each survey, the follow-up spirometry indices were adjusted for concurrent height, weight, and sex, and the standardised residuals used as the outcome measure. We used Pearson correlation to assess the relation between normally distributed continuous variables. \( R^2 \), calculated as the square of the Pearson correlation coefficient, was used to estimate the proportion of variability explained by infant airway function.

We assessed follow-up spirometry longitudinally by use of a random-effects model, with age, height, and weight as time-dependent covariates, and gender and infant Vmax\text{FRC} as time-independent covariates (webpanel). We also assessed other covariates that were associated with participants (ethnicity, early lower respiratory illnesses, wheeze, active smoking, and atopy) and with their parents (history of physician-diagnosed asthma, years of education, age, and smoking history). Potential confounders and covariates were entered separately in the basic random-effects model. Covariates related to any of the follow-up spirometry indices with
Results
The 123 participants included in our study had more educated mothers (p=0.02) and more fathers with asthma (p=0.01) than the other 1123 children enrolled in the Children’s Respiratory Study (table 1). Other than that, the baseline characteristics of the two groups did not differ.

Length-adjusted infant VmaxFRC did not seem to be associated with potential confounders such as birthweight or type of delivery, or parental ethnicity, asthma, smoking, age, or level of education (webtable 1). These results did not change when the analyses were stratified by sex (data not shown). However, male participants had lower infant VmaxFRC than did female participants (p=0.003).

Unadjusted baseline spirometry indices for male and female participants at ages 11, 16, and 22 years are shown in webtable 2. VmaxFRC in infants, adjusted for body length, was correlated with FEV1/FVC ratio and FEF25–75, adjusted for height, weight, and sex, at ages 11, 16, and 22 years (table 2 and webfigure). Infant airway function accounted for between 9% and 14% of the variability in subsequent adjusted FEV1/FVC ratio and FEF25–75 at ages 11, 16, and 22 years. No association was noted between length-adjusted infant VmaxFRC and adjusted FVC and FEV1, at any separate survey (p=0.05). Infant VmaxFRC was less closely correlated with postbronchodilator FEV1/FVC ratio and FEF25–75 than with postbronchodilator measures of airway function, but correlation coefficients remained significant at ages 11, 16, and 22 years (table 2). Length-adjusted VmaxFRC was associated with subsequent FEV1/FVC ratio and FEF25–75 in both male and female participants at ages 11, 16, and 22 years, although with small fluctuations in statistical significance at different ages (webtable 3).

A longitudinal random-effects model was used to assess the relation between length-adjusted infant VmaxFRC and subsequent lung function. Infant VmaxFRC was directly associated with subsequent prebronchodilator FEV1/FVC ratio (p=0.001) and FEF25–75 (p=0.001) up to the age of 22 years, after adjustment for age, height, weight, and sex (table 3). In the longitudinal model, infant VmaxFRC was directly associated with FEV1...
(p=0.009), but there was no association with FVC. Only wheeze and atopy, tested in the models as time-dependent covariates, and active smoking by the participant at ages 16 or 22 years or both, met the cutoff for inclusion in the random-effects models (p<0.1); maternal smoking at enrolment was also retained. When the models shown in table 3 were repeated to include wheeze, atopy, and smoking, the magnitude and significance of the relation between infant VmaxFRC and subsequent lung function did not change (webtable 4). The associations between infant lung function and postbronchodilator FEV/FVC ratio and FEF25–75 were similar to those calculated by use of prebronchodilator values, although the association between infant lung function and postbronchodilator FEV1 did not reach statistical significance (table 3 and webtable 5).

The relation between infant VmaxFRC and subsequent lung function was assessed separately in male and female participants by stratifying the longitudinal models by gender. Length-adjusted VmaxFRC was directly associated with subsequent prebronchodilator FEV1/FVC ratio and FEF25–75 in both male and female participants (webtable 3), but not with FEV1 or FVC after adjustment for height, weight, and age. The associations between infant lung function and postbronchodilator FEV1/FVC ratio and FEF25–75 did not differ widely by sex of participant (webtable 3).

The relation between infant VmaxFRC and subsequent lung function was further assessed by grouping infant VmaxFRC into quartiles. The figure shows the use of random-effects models to plot the predicted values for FEV1, FEV1/FVC ratio and FEF25–75 for male participants by quartiles of length-adjusted infant VmaxFRC. Participants in the lowest quartile for infant VmaxFRC had persistently diminished values for FEV1/FVC ratio (−5.2% [95% CI: −7.4 to −3.0], p<0.0001), FEF25–75 (−666 mL/s [−955 to −378], p<0.0001) and FEV1 (−234 mL [−377 to −91], p=0.001) up to age 22 years compared with the upper three quartiles combined (after adjustment for height, weight, age, and sex). Moreover, age did not interact with infant VmaxFRC. Similar results were obtained for the lowest quartile for infant VmaxFRC and adjusted post-bronchodilator FEV1/FVC ratio (−3.6% [−5.4 to −1.9], p<0.0001), FEF25–75 (−602 mL/s [−881 to −322], p<0.0001) and FEV1 (−176 mL [−311,−42], p=0.1) through age 22 years compared with the upper three quartiles.

Infant VmaxFRC was inversely related to bronchodilator response for FEV1/FVC ratio at 11 and 22 years, and FEV1 at 22 years (webtable 6). When assessed with the random-effects model, infants with VmaxFRC in the lowest quartile had greater responses to bronchodilation for FEV1/FVC ratio (1.18% [95% CI 0.4, 1.9], p=0.002), FEF25–75 (3.37% [0.9, 5.8], p=0.006) and FEV1 (1.38% [0.4, 2.4], p=0.006) through age 22 years compared with the upper three quartiles combined. By contrast, the proportion of 11-year-old children with bronchial hyper-responsiveness

![Figure: Predicted mean values for lung function in males at ages 11, 16, and 22 years by length-adjusted infant VmaxFRC](image-url)
to methacholine was unrelated to their VmaxFRC as infants (28·6%, 27·8%, 25·0%, and 31·3% for the lowest to highest quartiles respectively, trend χ² p=0.9).

Table 4 shows that, concordant with previous reports from this same cohort, infants in the lowest quartile for VmaxFRC had an increased risk for development of lower respiratory illnesses in the first 3 years of life (77%) compared with children in the upper three quartiles combined (45%, p=0.005). Infants in the lowest quartile did not differ in ethnicity, sex, or maternal asthma or smoking from those in the upper three quartiles, and they were not more likely to have wheeze at ages 11, 16, or 22 years (table 4).

### Discussion

We showed that up to 14% of the variance in measurements of airway function (FEV₁, FEV₁/FVC ratio, and FEF₂₅–₇₅%) in young adults was related to the maximal flows at functional residual capacity (VmaxFRC), measured in the same individuals at 2 months. Infant lung function was correlated with all measurements of airway function at ages 11–22 years, but more strongly with measurements taken before bronchodilator use than with those after bronchodilation. Moreover, individuals who had low airway function as infants had much greater responses to bronchodilators than others. We did not measure infant lung function after bronchodilator use, and thus we do not know if the weaker association between infant lung function and bronchodilator responsiveness was due to variability between individuals in congenital responses to bronchodilators. However, both reversible and irreversible determinants of maximal flows during forced expirations could explain the correlations recorded before bronchodilator administration. We recorded no association between infant lung function and subsequent bronchial responses to methacholine, which suggests that structural characteristics of the lung, and not intrinsic airway hyper-responsiveness, were responsible for the recorded tracking of airway function from birth to early adult life (ie, individuals remained at a constant deviation from the mean over time).

A detailed analysis of our data suggested that the correlation between infant airway function and lung function in adult life could be attributed to some individuals in whom airway function was already diminished shortly after birth. These individuals, who were so classified because they were in the lowest quartile for length-adjusted infant VmaxFRC, had, for example, mean predicted FEV₁/FVC ratios of 75·1% (95% CI 73–77) at age 22 years, which was 5·2% lower than mean values for infants in the other three quartiles. This finding suggests that individuals with airflow obstruction at birth will be more likely to remain in the lowest end of the distribution until early adult life, whereas tracking of airway function might be less evident in children with normal airways. However, we cannot exclude the possibility that, by use of the passive chest-compression technique to obtain partial flow-volume curves, maximal flows could have been more readily obtained in infants with congenitally narrower airways than in those with larger airway. If this were the case, however, our results would underestimate the correlation between infant airway function and lung function obtained with full flow-volume curves in older children and adults.

Previous studies had shown that spirometric parameters tracked within cohorts during school age.²⁻⁹ Our results suggest that the lowest levels of airway function can be tracked from shortly after birth, and that individuals who are born with low VmaxFRC have persistently poor lung function up to 22 years of age. Similarly, Turner and colleagues²⁰ reported that airway function in infancy was positively correlated with lung function measured at ages 6 and 11 years in children with different wheezing phenotypes. Filippone and co-workers²⁰ reported that in children with bronchopulmonary dysplasia, airway function tracks from age 2 to 9 years. Hoo and colleagues²¹
showed strong tracking of airway function between birth and 9 months of age in infants of both normal and low birthweight. Taken together, these findings support the hypothesis that factors which control airway development in utero determine the degree of airway function that an individual will attain by early adult life. This hypothesis is compatible with the observation that branching of the bronchial tree is complete by 16 weeks of gestation, and that the number of terminal bronchiolar duct endings does not increase postnatally. Elastic recoil also affects maximal expiratory flow, not only because it is the motive force behind flow, but also because it maintains airway patency, or openness. We did not measure static recoil because methods of measurement are invasive. It is, however, not inconceivable that our findings could be explained by life-long changes in the static recoil of the lung, either alone or in combination with altered airway conductance.

The main strength of our study was the large proportion of participants in our newborn cohort for whom airway function was measured shortly after birth and one or more times thereafter up to the age of 22 years. Nevertheless, we did not test a sufficient number of infants to allow us to accurately determine the relative contributions to lung function in early adult life of congenital deficits in airway function and of acquired factors such as lower respiratory infections, ongoing symptoms, and environmental exposures.

With data obtained from these participants, we previously showed that children who wheezed during viral infection in the first years of life, and especially those whose symptoms had remitted before the age of 6 years (so-called transient wheezers), had lower premorbid $V_{max}$ than children who never wheezed during the preschool years. Other long-term birth-cohort studies had previously shown that adults who had lower respiratory illnesses in early life had worse lung function than those with no such history. Our results suggest that in-uterine alterations in airway development predispose individuals both to lower respiratory illnesses and to subsequent deficits in lung function during adult life. This hypothesis does not exclude the possibility that lower respiratory illnesses in early life, especially in children whose symptoms persist beyond the preschool years, might themselves cause additional deficits in development of lung function that become apparent after birth. Moreover, other studies have shown that passive smoking, air pollution, and other factors, can affect airway function.

Chronic obstructive pulmonary disease is the fourth leading cause of death in the USA, and is projected to become the third leading cause of death worldwide by 2020. Its defining characteristic is irreversible airflow obstruction, which is conventionally defined as a postbronchodilator FEV$_1$/FVC ratio of 70% or lower. Although cigarette smoking is known to be the major risk factor for this disease, 5–10% of non-smoking young adults and up to 30% of non-smoking adults aged 65 years or older have evidence of chronic obstructive pulmonary disease. In non-smokers, impaired lung function is also a known predictor of mortality due to ischaemic heart disease and stroke. Individuals who enter adult life with lung-function deficits are at risk of chronic obstructive pulmonary disease in their later adult years, especially if they had lower respiratory illnesses in early life. In our cohort, infants who had lung function in the lowest quartile started adulthood with deficits in FEF$_{25-75}$, FEV$_{1}$, and the FEV$_{1}$/FVC ratio. We postulate that, even if the lung function of these individuals was to diminish during adult life at rates similar to those recorded in non-smokers, they would reach the threshold of FEV$_{1}$ and FEV$_{1}$/FVC ratio that define chronic obstructive pulmonary disease at an earlier age than their peers. Fetal determinants of airway function could therefore predispose not only to airflow obstruction and chronic obstructive pulmonary disease, but also to non-respiratory morbidity and mortality during adult life.

The factors that affect pulmonary development in utero are not well understood. Lung morphogenesis is a highly regulated process that could be impaired in utero by both genetic and environmental factors. Among these factors, maternal smoking during pregnancy has been consistently associated with poor lung function in both infants and older children. Children with chronic lung disease of prematurity have impaired lung function growth, as do, to a lesser extent, premature children who did not have chronic lung disease of prematurity. Our results suggest that a better understanding of the mechanisms that control normal lung growth in utero would contribute to development of strategies for the prevention of chronic obstructive pulmonary disease in adult life.

**Contributors**

FDM designed the study, and DAS analysed the data with input from FDM. WJM did the infant pulmonary function tests. All authors contributed to interpretation of the data. FDM and DAS drafted the manuscript with input from WJM, SG, and ALW. All authors approved the final version of the manuscript.

**Conflict of interest statement**

We declare that we have no conflict of interest.

**Role of the funding source**

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Global burden of COPD: risk factors, prevalence, and future trends

David M Mannino, A Sonia Buist

Chronic obstructive pulmonary disease (COPD) continues to be an important cause of morbidity, mortality, and health-care costs worldwide. It is a global health issue, with cigarette smoking being an important risk factor universally; other factors, such as exposure to indoor and outdoor air pollution, occupational hazards, and infections, are also important. As the global population ages, the burden of COPD will increase in years to come. Prevalence estimates of the disorder show considerable variability across populations, suggesting that risk factors can affect populations differently. Other advances in our understanding of COPD are increased recognition of the importance of comorbid disease, identification of different COPD phenotypes, and understanding how factors other than lung function affect outcome in our patients. The challenge we will all face in the next few years will be implementation of cost-effective prevention and management strategies to stem the tide of this disease and its cost.

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in countries of high, middle, and low income. Estimates from WHO’s Global Burden of Disease and Risk Factors project1 show that in 2001, COPD was the fifth leading cause of death in high-income countries, accounting for 3·8% of total deaths, and it was the sixth leading cause of death in nations of low and middle income, accounting for 4·9% of total deaths. In this same report, COPD was also estimated to be the seventh and tenth leading cause of disability-adjusted life years in countries of high income, and it was the sixth leading cause of death in high-income countries, accounting for 3·8% of total deaths. In this same report, COPD was also estimated to be the seventh and tenth leading cause of disability-adjusted life years in countries of high income, and it was the sixth leading cause of death in nations of low and middle income, accounting for 4·9% of total deaths. In this same report, COPD was also estimated to be the seventh and tenth leading cause of disability-adjusted life years in countries of high income, and it was the sixth leading cause of death in nations of low and middle income, accounting for 4·9% of total deaths.

COPD has been the focus of recent Reviews in The Lancet, including one from 2003 by Calverley and Walker2 and another published in 2004 by Pauwels and Rabe.3 Our Review will focus on advances in understanding of COPD and its risk factors, prevalence, and natural history since these Reviews were published, address some of the questions that still persist, and raise some of the issues that health-care planners will have to consider as the burden of COPD increases as the world’s population ages.

Definition

The working definition of COPD, as noted in the 2006 update of the Global Initiative for Obstructive Lung Disease (GOLD) guidelines, is that COPD is “a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.” Some of the key components of this definition, which are similar to those in the definition adopted by the American Thoracic Society and European Respiratory Society,4 are described below.

First, COPD is a preventable disease. Primary, secondary, and tertiary prevention strategies exist for COPD. These
range from increasing smoking cessation and adequate treatment of asthma (primary)\textsuperscript{2} to early detection of disease and subsequent modification of risk factor exposure (secondary)\textsuperscript{7} to prevention of complications in patients with established disease (tertiary).\textsuperscript{8,9,10}

Second, COPD is a treatable disorder. Treatment of stable COPD and exacerbations are the subject of other Reviews to be published in The Lancet.\textsuperscript{11,12}

Third, extrapulmonary effects are seen frequently in patients with COPD and some of these other diseases are probably related to the respiratory disorder. These include muscle wasting,\textsuperscript{13} cardiovascular disease,\textsuperscript{14} depression,\textsuperscript{15} reduced fat free mass, osteopenia, and chronic infections.\textsuperscript{16}

Fourth, individuals with similar smoking and exposure histories can vary a great deal in the severity of their disease and response to intervention.\textsuperscript{17,18} Interventions should be tailored to the individual, with recognition that the disease process we call COPD has many different phenotypes (see Disease classification section). Use of lung function to characterise severity is, currently, the best system available to clinicians, but it clearly falls well short of being ideal.

Fifth, the airflow limitation or obstruction that happens in COPD is caused by a mixture of small airway disease, parenchymal destruction (emphysema), and, in many cases, increased airways responsiveness (asthma).\textsuperscript{4} These findings tend to worsen with age but are also affected by exacerbations or other events marked by an acute worsening.\textsuperscript{20}

Sixth, COPD is not fully reversible: the obstruction noted does not revert either in response to bronchodilators, anti-inflammatory treatment, or spontaneously.\textsuperscript{4} This lack of full reversibility is a means of trying to distinguish COPD and asthma, although many patients have features of both.\textsuperscript{20}

The final key component of this COPD definition relates to the inflammation present in the lung. Although the definition states that this effect is in response to noxious particles or gases, such as those in tobacco smoke, there is also some evidence that infections can have an important role in the presence of chronic inflammation in the lung.\textsuperscript{21}

**Disease classification**

COPD can be classified with respect to both phenotype and disease severity. It is a heterogeneous disease process that varies greatly from person to person with respect to lung pathology, natural history of disease, and comorbidity. A result of this heterogeneity is that different researchers have championed alternative hypotheses about COPD development over the past four decades: the British hypothesis stated that the presence of cough and sputum was the key factor in COPD,\textsuperscript{22} and the Dutch hypothesis pointed to the presence of increased airways responsiveness.\textsuperscript{4} Less widely known hypotheses stressed abnormal cellular repair, and development of complications or comorbid disorders.

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**Table 2: Classification of COPD severity according to the 2006 revision of the GOLD criteria**

<table>
<thead>
<tr>
<th>GOLD 1 (mild)</th>
<th>FEV₁/FVC &lt;0·70 and FEV₁ ≥80% predicted</th>
<th>1.5799</th>
<th>15,116</th>
<th>14,906</th>
<th>14,631</th>
<th>14,135</th>
<th>14,135</th>
<th>3797</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 2 (moderate)</td>
<td>FEV₁/FVC &lt;0·70 and 80% &gt;FEV₁ ≥50% predicted</td>
<td>15,840</td>
<td>15,840</td>
<td>15,840</td>
<td>15,840</td>
<td>15,840</td>
<td>15,840</td>
<td>15,840</td>
</tr>
<tr>
<td>GOLD 3 (severe)</td>
<td>FEV₁/FVC &lt;0·70 and 50% &gt;FEV₁ ≥30% predicted</td>
<td>16,632</td>
<td>16,632</td>
<td>16,632</td>
<td>16,632</td>
<td>16,632</td>
<td>16,632</td>
<td>16,632</td>
</tr>
<tr>
<td>GOLD 4 (very severe)</td>
<td>FEV₁/FVC &lt;0·70 and FEV₁ &lt;30% predicted or FEV₁ &lt;50% predicted plus chronic respiratory failure</td>
<td>17,424</td>
<td>17,424</td>
<td>17,424</td>
<td>17,424</td>
<td>17,424</td>
<td>17,424</td>
<td>17,424</td>
</tr>
</tbody>
</table>

People with an FEV₁/FVC<0·70 and respiratory symptoms of chronic cough and sputum production are no longer included as a COPD stage (formerly GOLD stage 0). Patients with an FEV₁/FVC≥0·70 but an FVC<80% predicted meet spirometric criteria for a restrictive process. Although this is not regarded as COPD, patients might present with several symptoms similar to those seen in COPD, and these patients have an increased risk of death.

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**Figure 1:** Kaplan-Meier survival curves for patients in the Atherosclerosis Risk in Communities Study, stratified by level of lung function impairment

Reprinted from reference 33, with permission of Elsevier. Lung function strata are defined in table 2.
Table 1 lists the key diseases to be considered in the differential diagnosis of COPD. However, these diseases can coexist with COPD and contribute to disease prevalence or severity. For example, results of the Burden of Lung Disease (BOLD) study—a multinational investigation of the prevalence of COPD using a standard methodology and reported in this issue of The Lancet, show that one of the highest prevalences of COPD was recorded in South Africa, a country that also has a high prevalence of tuberculosis. Asthma can coexist with COPD in clinical settings and is a risk factor for development of COPD. Another example of disease overlap can be noted in the cluster of cases of so-called popcorn workers’ lung, which is related to diacetyl exposure, in which affected individuals were diagnosed with COPD and, in fact, would meet criteria for COPD diagnosis.

Table 2 shows classification of disease severity, according to the current GOLD criteria. Classification should be done on post-bronchodilator lung function, although in many epidemiological studies, prebronchodilator lung function has been used, which can overestimate the presence of airflow obstruction by up to 50%. Missing from the 2006 GOLD guidelines is what was previously called GOLD stage 0, consisting of patients with normal lung function but presence of chronic respiratory symptoms. Also omitted from the GOLD classification are individuals with so-called restrictive spirometry—ie, an FEV1/FVC ratio (forced expiratory volume in 1 s/forced vital capacity) of at least 0-70 but an FVC of less than 80% of the predicted value. Some would argue that this group of individuals have airflow limitation in the absence of airways obstruction and that this pattern can be seen in many patients who have a clinical COPD diagnosis. Lung function impairment is a strong predictor of mortality (figure 1). Although simple, use of lung function alone to classify disease severity does not capture the multi-dimensional component of COPD. Celli and colleagues showed that by incorporating the measures of body-mass index, lung function, dyspnoea score, and exercise level (as measured with a 6-min walk test) into a common index (BODE index) the ability to predict mortality was enhanced (figure 2).

Risk factors
Risk for COPD is related to an interaction between genetic factors and many different environmental exposures, which could also be affected by comorbid disease. Risk factors for the disease are described below.

Genetic factors
The best known genetic factor linked to COPD is a deficiency of the serine protease α1 antitrypsin, which arises in 1–3% of patients with COPD. Having low concentrations of this enzyme, particularly in combination with smoking or other exposures, increases the risk of panlobular emphysema.
lower left corner of graph). Conversely, of children with both parents in the highest quintile of lung function, 41% were in the highest quintile of function when compared with their peers (blue part of upper right corner of graph).

Several genes have been implicated in COPD, including those coding transforming growth factor β1,6 tumour necrosis factor α,7 and microsomal epoxide hydrolase 1.7 To date, however, work done to examine specific polymorphisms in these genes for the development of disease has been, at best, inconsistent.

**Tobacco smoke**

Worldwide, tobacco smoke remains the most important cause of COPD. WHO estimates that in high-income countries, 73% of COPD mortality is related to smoking, with 40% related to smoking in nations of low and middle income.1 This relation is affected highly by genes, because not all smokers go on to develop COPD. Lately, however, a much higher proportion of smokers—perhaps as much as 50%—have been noted to develop COPD.34,35,36 Furthermore, smoking during pregnancy can negatively affect fetal lung growth and result in development of lung disease.45 Smoking of marijuana has been linked to respiratory symptoms but not conclusively to development of COPD.41,42

**Occupational dust, vapours, and fumes**

Exposure to various dusts, chemicals, vapours, and fumes in the workplace is a factor for many people with COPD. In one report, estimates showed that 19.2% of COPD cases in the USA were attributable to work exposures, with this proportion being 31.1% in never-smokers.44 In countries of low and middle income, where occupational exposures to dust and fumes could be greater than in high-income nations because of less stringent laws, work exposures can assume high importance as a risk factor. Data of another study showed that people who reported a diagnosis of COPD or chronic bronchitis were twice as likely to recall previous worksite exposures to gases, dusts, vapours, or fumes.46

**Indoor air pollutants**

Globally, the most important risk factor for development of COPD might be exposure to biomass fuels such as coal, straw, animal dung, crop residues, and wood, which are used to heat and cook in poorly ventilated homes. WHO estimates that, in countries of low and middle income, 35% of people with COPD developed the disorder after exposure to indoor smoke from biomass fuels.43 Furthermore, WHO suggests that 36% of mortality from lower respiratory disease is also related to indoor smoke exposure.44 Findings of a report from China showed that COPD prevalence in never-smoking women is two to three times higher in a rural area where women are exposed to biomass smoke compared with urban women without this exposure.45 Second-hand smoke, which is another form of biomass smoke, has been linked to respiratory symptoms but not to development of COPD.46

**Outdoor air pollutants**

The risk attributable to outdoor pollutants in development of COPD is much smaller than that for indoor air pollutants. WHO estimates that urban air pollution causes 1% of COPD cases in high-income countries and 2% in nations of low and middle income.1 Air pollution is also linked to lower respiratory infections and acute cardiopulmonary events, which are also important in both the development and progression of COPD.

**Ageing**

COPD prevalence, morbidity, and mortality increase with age. Lung function, which reaches its peak level in young adults, starts to decline in the third and fourth decades of life.47 Although this diminished function is judged normal, some researchers have reported that elderly people with high levels of lung function live longer than do those with low levels of lung function.48 One reason for the increasing prevalence of COPD in recent years is the changing demographic of the world’s population, attributable to good nutrition and elimination or reduction of some childhood infectious diseases and falling mortality rates from diseases that kill young people, such as cardiac disease and acute infections. The result is that a larger proportion of the world’s population is living longer and is at risk for chronic medical disorders, such as COPD.49

**Infections**

Infections have an important role in both development and progression of COPD. Exposure to infection in early life could predispose an individual to bronchiectasis or changes in airway responsiveness. Most COPD exacerbations are related to bacterial or viral infections and are the subject of a separate Review in this issue of The Lancet.50

**Asthma**

According to the Dutch hypothesis, increased bronchial responsiveness, a hallmark of asthma, leads to development of COPD, although this topic remains controversial. Findings of cross-sectional studies have shown a large overlap of up to 30% between people who have a clinical diagnosis of COPD and asthma.51 Other work has shown that people with asthma, especially if they are smokers, can lose lung function more rapidly than individuals without asthma.52

**Gender**

The role of gender in development and progression of COPD is controversial and has been the topic of a great deal of research.53 Historically, COPD has been far more frequent in men than in women, related to patterns of...
smoking and occupational exposures.\textsuperscript{24,25} Lately, however, COPD prevalence seems to be becoming equal in men and women from high-income countries in which smoking habits are similar between the sexes. Whether women are more susceptible to development of COPD than men, given equal exposures, continues to be a topic of investigation, but some evidence lends support to this hypothesis.\textsuperscript{26,27} This question is important since women in countries of low and middle income have, historically, had a low prevalence of smoking but are increasingly targeted by advertising to increase their use of cigarettes.

**Socioeconomic and related factors**

Poor populations tend to have a higher risk of developing COPD and its complications than their wealthier counterparts.\textsuperscript{25–27} However, poverty is regarded as a surrogate measure for many factors that subsequently increase the risk of COPD, such as poor nutritional status, crowding, exposure to pollutants including high work exposures and high smoking rates (in countries of low and middle income), poor access to health care, and early respiratory infections.\textsuperscript{25–27}

**Prevalence estimates**

Two reviews have been published\textsuperscript{14,15} in which the prevalence of COPD was noted to be highly variable, probably because of differences in methods for establishment of disease prevalence. Figure 4 shows the findings from the 12 sites of the BOLD study\textsuperscript{26} and the five sites in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study.\textsuperscript{60} These estimates, even with identical methodologies, show a large amount of variability. For example, in the BOLD study,\textsuperscript{26} GOLD stage II COPD in women ranged from 5·1% in Guangzhou, China, to 16·7% in Cape Town, South Africa, and in men it ranged from 8·5% in Reykjavik, Iceland, to 22·2% in Cape Town, South Africa (figure 4). In both the BOLD and PLATINO studies, post-bronchodilator lung function was used to obtain estimates of disease burden. Other researchers, as noted above, have shown that disease prevalence after use of a bronchodilator could be 5–50% lower than the prebronchodilator prevalence.\textsuperscript{25,26} Whereas post-bronchodilator lung function is the standard according to current GOLD guidelines, most studies in which health effects and outcomes related to lung function impairment are examined have used prebronchodilator measurements.\textsuperscript{61} Moreover, we do not know whether post-bronchodilator lung function is better or worse at predicting mortality and other adverse outcomes. Finally, in studies that look at prebronchodilator and post-bronchodilator lung function, the process by which individuals actually increase their FEV$_1$/FVC is not well-defined—ie, small increases in FEV$_1$, versus small decreases in FVC, or both. Additional understanding of how the FEV$_1$/FVC increases in response to a bronchodilator is needed to accurately classify patients.

**Morbidity and mortality**

Additional measures of the burden of COPD, such as morbidity, mortality, and costs, present challenges similar to those seen in attempting to measure disease prevalence. Table 3 shows WHO estimates of deaths and disability-adjusted life years attributable to COPD for the world’s 25 most populous nations.\textsuperscript{1} This table highlights some of the difficulties with these other measures of COPD. For example, the estimated COPD death rate in Japan of 4·4/100 000 is nearly 30 times lower than that in China (130·5/100 000). Findings of an epidemiological study of COPD in Japan, however, showed that 16·4% of men and 5·0% of women aged 40 years and older had disease of GOLD stage I or higher,\textsuperscript{62} which is similar to the 15·3% of men and 7·6% of women with a similar COPD stage in the Guangzhou study reported in the BOLD study.\textsuperscript{26} The difference between Japan and China in mortality rates versus the similarity in prevalence suggests that other factors might affect how disease is diagnosed and cause of death is attributed between countries.

We also know that patients with COPD typically have comorbid diseases, such as muscle wasting, cardiovascular disease, depression, reduced fat-free mass, osteopenia, and chronic infections.\textsuperscript{63} These disorders contribute to a high disease burden and early mortality in patients with COPD. As figure 1 shows, people with moderate and severe COPD die more quickly than do those with normal lung function.\textsuperscript{13} Deaths in individuals with COPD, however, are frequently attributed to a cause other than COPD. For example, in a large prospective cohort from the USA of deaths in people with GOLD stage III or IV disease, 31·5% were recorded as a respiratory cause, 23·9% were due to lung cancer, 13·0% were due to cardiovascular disease, and 31·5% were from other causes.\textsuperscript{26} Of those with GOLD stage II disease at baseline, only 3·5% of deaths were attributed to respiratory causes.
These data suggest that COPD might be underappreciated as a contributor to mortality, particularly when it could be an important comorbid disorder that leads to development of a lethal disease, such as lung cancer or stroke.

A similar difficulty in underestimating the negative effects of disease is seen when looking at admissions for COPD, which are the largest contributor to the direct medical costs of the disease in the USA and many high-income countries. From 1979 to 2001, in the USA, COPD was the primary reason for hospital discharge 9·8 million times and a secondary reason for discharge an additional 37·5 million times. In this study, COPD as a primary or secondary cause of admission was associated with a higher mortality and more comorbid disease when compared with admission without COPD mentioned. These data also suggest that the role of COPD as a contributor to admissions and their high costs might also be underappreciated.

Estimating the costs of COPD is similarly challenging, related to some of the difficulties noted above, such as under-diagnosis and presence of comorbid disease. Many different methodologies are used to estimate costs of chronic diseases such as COPD. There are direct costs of health-care services (ie, admissions, medications, durable medical equipment) and indirect costs (ie, lost work and productivity, premature death) that can be included in total costs. Furthermore, one can look at either attributable costs (ie, costs related specifically to COPD) or excess costs (additional costs of treatment in COPD vs non-COPD patients for both COPD and non-COPD illnesses).

In a review of annual direct medical costs of COPD in the USA, in 2005, the cost per patient was estimated at US$2700–5900 for attributable costs to US$6100–6600 for excess costs (figure 5). In 2003, the US National Heart, Lung, and Blood Institute estimated that total costs (direct and indirect) of COPD were US$32·1 billion, with direct costs of US$18·0 billion. Globally, costs vary between countries that have reported them (table 4), although more severe disease consistently incurs more costs than less severe disease.

Another means of measuring costs is to ascertain how expensive a specific intervention would be per quality-adjusted life year of improvement. Using this approach, WHO estimates that costs per quality-adjusted life year for COPD range from US$6700–8900 for inhaled ipratropium to US$13 400 for inhaled corticosteroids to US$238 200 for lung transplantation. Although one would expect smoking cessation to also be very cost effective, this invention has not been assessed with respect to quality-adjusted life years for COPD.

Future trends
When Calverley and Walker reviewed COPD in 2003 they made some predictions about progress in disease. With respect to pathogenesis, they forecast that there would be greater phenotypic characterisation of COPD,
identification of candidate susceptibility genes, clarification of the basis of steroid resistance, and enhanced animal models of the disease. With respect to clinical characteristics, they predicted that there would be better methods of detecting flow limitation and staging systems that go beyond lung function measurement. For treatment, which is the focus of another Review in this issue of The Lancet,\textsuperscript{11} they suggested several potential advances, such as enhanced smoking cessation treatments, better antioxidant treatments, biological agents targeting specific cytokines, and development of interventions to mechanically decrease lung hyperinflation. Some of their predictions have been partly realised, such as the development of the BODE index to predict COPD mortality,\textsuperscript{7} greater understanding of the role of inflammation in disease,\textsuperscript{11} and enhanced understanding of mechanisms of steroid resistance.\textsuperscript{11} We still, however, have many important questions, which will provide the basis for future research in COPD.

Projections for COPD prove challenging and can differ between high-income countries and those of low or medium income. In general, the disease is associated strongly with ageing and factors that allow people to survive into old age, such as enhanced interventions for acute cardiovascular disease, and acute infections, will result in higher COPD prevalence, morbidity, and mortality. Although smoking is a strong risk factor for COPD, the relation between changing smoking prevalence in a population and disease outcomes is complex. For example, in the USA, smoking prevalence in men has been falling since the mid 1960s whereas COPD mortality has been increasing.\textsuperscript{11} This occurrence is probably related to several factors, such as acute mortality from cardiac events being much higher in current smokers with a rapid decrease in risk after smoking cessation. Conversely, in populations in which smoking is increasing, there could be a time lag of many years before smoking-related COPD becomes apparent.

Occupational and environmental exposures are, in general, more frequent in countries of low and middle income than in those with high income. With the development and dissemination of better stoves and heating devices, these exposures should diminish with time. Similarly, prevalence of early respiratory infections and tuberculosis and malnutrition, which are all more typical in nations of low and middle income, hopefully will also decrease over time.

With the ageing of the global population, COPD is one of several chronic diseases that will continue to become more frequent. Such disorders will be best managed in an integrated and comprehensive way, with careful attention to prevention and cost-effectiveness of interventions.\textsuperscript{1,7,75}

### Conclusion

Our knowledge of COPD has grown over the past few years. Additional questions are raised by this new knowledge, which are discussed here. One of the biggest advances in COPD is greater understanding of disease burden in different countries and cultures. Publication of data from the PLATINO\textsuperscript{6} and BOLD\textsuperscript{6} studies is vital to establish how important COPD is, particularly in view of the disease’s consistent underdiagnosis at sites where it has been investigated.\textsuperscript{7,6} Other relevant components of disease burden relate to costs of treatment and disability associated with COPD. Why are there such striking differences between COPD prevalence in various countries even when using identical detection methods? Should we be talking about COPD phenotypes when we describe the prevalence of disease? Is so-called undiagnosed COPD clinically important and a predictor of bad outcomes? Does our current methodology fully capture the costs associated with COPD?

A second major advance in COPD over the past few years relates to the systemic nature of the disease process, with some of the most important effects arising in organs outside the respiratory system.\textsuperscript{7,8} What is a comorbid disease and what is a complication of COPD? Should comorbidity be part of the disease severity classification scheme? Should early treatment of COPD focus on prevention of comorbid disease? Should we be using the term polymorbid to indicate that many disease processes happen simultaneously?

In looking to the future, one cannot ignore the changing demographics of the world’s population and the reality that COPD is a disease of ageing. Furthermore, if every smoker in the world were to stop smoking today, the rates of COPD would probably continue to increase for the next 20 years.\textsuperscript{7,8} Are primary, secondary, and tertiary intervention strategies available that are low-cost, effective, and amenable to implementation in all parts of the world? After people have stopped smoking, are there additional means of preventing disease progression? Does early detection of disease with spirometry result in enhanced outcomes? Is the loss of lung function with ageing truly inevitable?

COPD remains an important disease globally. Our greater understanding of disease pathogenesis, prognosis, and treatment should result in better outcomes for many of our patients.
Conflict of interest statement

DMM has received research grants or served on advisory boards or speakers bureaus for GlaxoSmithKline, Pfizer, Ortho Biotech, Novartis, AstraZeneca, Dey, and Boehringer-Ingelheim. ASB has served on advisory boards for Altana, GlaxoSmithKline, Merck, Novartis, Pfizer, and Sepracor.

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What have we learned from large drug treatment trials in COPD?

Peter M A Calverley, Stephen I Rennard

Although the development of effective treatments for patients with chronic obstructive pulmonary disease (COPD) has not been seen as a high priority, the past decade has seen a substantial increase in the number of clinical studies examining different treatments for this disease. Large studies are needed to adequately assess the effectiveness of treatment because of the chronic nature of the disease and the intermittent occurrence of some key outcomes such as exacerbations. Data from randomised controlled trials show that treatment improves exercise performance by increasing lung volume rather than changing expiratory flow. Although assessment of lung function remains the cornerstone of drug assessment, improvements in health status, the number of exacerbations and admissions to hospital are now recognised as important treatment outcomes. Randomised controlled trial data provide the best evidence for treatment efficacy, but results of these studies can be affected by differences in inclusion criteria and patient dropout during the study. Bronchodilator reversibility testing does not reliably define subgroups that will respond to a particular treatment. Carefully done and adequately powered clinical trials continue to inform, not only our views about treatment, but also our understanding of COPD and how it is best assessed and managed. Ensuring that these expensive studies are done objectively to the highest standard is an important goal for the next decade.

Introduction

Until the past decade, chronic obstructive pulmonary disease (COPD) has been regarded, at least by doctors, as a rather dull and unrewarding illness. The reasons for this perception are complex and different factors are probably important to different people. However, prominent reasons include the longstanding arguments about the definition of the disease, uncertainties about its natural history, and, rather perversely, a belief that COPD could be a self-limiting problem because a fall in the number of people smoking and improvements in urban air quality would lead to a gradual reduction in the number of cases. The frequency of the illness defined objectively by spirometry has now been appreciated, although overinterpretation of the term irreversible airflow obstruction has encouraged the view that nothing can be done to improve it. In fact, some physicians seem to believe that even a modest degree of improvement in lung function in patients with COPD must be because of underlying asthma—since by definition the disease cannot improve. Unsurprisingly, researchers have little enthusiasm to do small, not to mention large, clinical treatment trials. The past 10 years, however, have seen a substantial shift in our approach to COPD, as many of the aforementioned views have been challenged.

A clear cohort effect is seen in people who smoke heavily, although the number of deaths due to COPD in any given age group is not falling as rapidly as those due to lung cancer. However, fewer people now die from serious illnesses like ischaemic heart disease early in life than they did 20 years ago, and so there is more opportunity to develop clinically important COPD as the population ages. Moreover, COPD is progressive. Although smoking cessation early in the disease slows progression, cessation after the disease has progressed probably has less benefit. In most people, even with smoking cessation, lung function will decline over time. The economic effect of COPD, especially on acute medical care, has been well documented with more than €38·6 billion spent on COPD in Europe and US$32·1 billion in the USA in 2002. COPD is now recognised as a major and growing public-health problem. Although present treatments have limited effects, the benefit of even modest improvements in lung function in people with severe disease is now recognised. This understanding has encouraged investment in large clinical trials, the analysis of which has in turn changed our perceptions of what can be achieved for patients with COPD. In this Review, we discuss some important changes in management resulting from large clinical trials of drug treatments. Inevitably, such an overview is selective but we have tried to highlight data that are generalisable and which aspects of disease continue to be controversial, and thus will shape our future understanding of COPD.

What is a large COPD trial?

Although most studies in the past 10 years have been funded by the health-care industry or with some Government sponsorship, the first studies defining the clinical course of COPD were entirely funded by governments. Thus, the landmark study of Fletcher and colleagues in a stratified random sample of 792 British men was supported by the British Medical Research Council. They tested the hypothesis that the presence of cough and sputum identified patients with a worse natural history of disease compared with those without cough or sputum production. The unexpected conclusion, that the degree of airflow obstruction determined disease progression, has affected the subsequent definition of COPD and provided a clear
rationale for the role of spirometry in diagnosis. This study also led directly to a difficult therapeutic target, namely the slowing of the decline in lung function over time, which has subsequently been studied in detail. Results in other general populations have supported the longitudinal findings of Fletcher and Peto about the association of decline in lung function with tobacco smoking, but the US National Heart Lung and Blood Institute (NHLBI)-supported Lung Health Study in nearly 6000 North American smokers with mild COPD showed beyond doubt that smoking cessation, and treatment in a smoking cessation programme had beneficial effects on lung function decline and other important outcomes such as mortality.

Before the Lung Health Study, the British Medical Research Council’s long-term oxygen trial in 89 patients with hypoxaemic COPD and the NHLBI nocturnal oxygen therapy trial, in 203 patients were thought to be large studies. Each of these studies lasted for 3 years with a clear endpoint of all-cause mortality. At about the same time, the NHLBI funded the intermittent positive pressure breathing trial in 985 COPD patients to establish whether this way of delivering bronchodilator drugs was most effective. Although this study had negative results, it led to many important findings about the natural history of COPD, not least about the pathological changes of COPD and inflammation in the smaller airways. Table 1 shows data for some of these important early studies.

Although exacerbations of COPD, especially those defined as being infectious, are quite frequent, the number of randomised placebo-controlled trials of antibiotics is surprisingly small. The largest reported study included 173 people with the smallest recruiting only 30 participants. Data from the first trial, which was reported in 1987, have dominated subsequent thinking and meta-analyses, and are at the core of recommendations about the use of antibiotics in present treatment guidelines. Specifically, the data suggest that the only patients to improve with antibiotic treatment are those reporting an increase in breathlessness, increased sputum volume, and purulence before treatment. In view of the frequency of COPD exacerbations, that these simple observations have not been revisited using present methods is surprising. Unfortunately, the criteria used to approve antibiotics are largely based on bacteriological cure rates, often with non-inferiority as an endpoint. As a result, the many antibiotic trials for exacerbations of COPD have done little to advance understanding or improve clinical care.

Other trials designed to improve symptoms in stable COPD have focused on bronchodilator drugs originally developed for the management of asthma. The number of participants needed to show a small but significant degree of bronchodilation is quite small. A well established assessment method used by US and European regulators includes the serial measurement of forced expiratory volume in 1 min (FEV1) to define the duration of drug action, then 12 weeks of regular treatment compared with a placebo or active comparator.
then a further FEV₁ assessment. Figure 1 shows a study of the combination of a short-acting inhaled β agonist and anticholinergic bronchodilator.21 However, effective management of COPD needs more than small changes in lung function, and to study this disease effectively, complex trial designs have emerged.

Clinical trials have been used to test specific hypotheses and to identify clinically important effects beyond spirometrical change. The best studied mechanisms include exercise physiology, for which trial hypotheses and to identify clinically important effects beyond spirometrical change. The best studied mechanisms include exercise physiology, for which trial designs have moved from individual investigators doing crossover studies of 12–20 patients25,26 to multicentre randomised placebo-controlled studies using complex exercise physiology assessments in 100–200 patients.27,28 Yet, the question of how well such changes relate to everyday activity remains unanswered.29 Even larger studies than those mentioned are needed to assess parameters that change slowly, for instance reduction in lung function, or that are intermittent (eg, exacerbations needing medical attention). Table 2 shows examples of such large studies. Assessment of these important endpoints has been a real logistical challenge. Data resulting from such trials, however, have taught us practical lessons about who should be included in clinical studies, and how they should be assessed, and have greatly advanced our understanding of COPD.

### Improving trial design and interpretation

Although that the results of a clinical trial only apply to the population under study seems obvious, small

<table>
<thead>
<tr>
<th>Duration</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Do inhaled corticosteroids reduce the rate of FEV₁ decline?</td>
<td></td>
</tr>
<tr>
<td>Vestbo,30 1999 (n=1207)</td>
<td>3 years In patients with mild COPD (FEV₁=68% of predicted) budesonide 800 μg daily had no effect</td>
</tr>
<tr>
<td>Pauwels,31 1999 (n=1277)</td>
<td>3 years In patients with moderate COPD (FEV₁=77% of predicted) budesonide 800 μg daily had no effect</td>
</tr>
<tr>
<td>Lung Health Investigators,32 2000 (n=1116)</td>
<td>3 years In patients with moderate COPD (FEV₁=80–90% of predicted) tiotropium 1200 μg daily did not affect rate of FEV₁ decline but reduced symptoms and physical visits</td>
</tr>
<tr>
<td>Burge,33 2000 (n=751)</td>
<td>3 years In patients with moderately severe COPD (FEV₁=50% of predicted) fluticasone did not affect FEV₁ decline, but reduced the number of exacerbations and improved health status</td>
</tr>
</tbody>
</table>

| Can a long-acting inhaled bronchodilator modify endpoints not usually associated with bronchodilation? |
| Casaburi,34 2002 (n=921) | 12 months In patients with severe or very severe COPD (FEV₁<50% of predicted) tiotropium improved lung function and health status, and reduced exacerbations compared with placebo |
| Vincen,35 2002 (n=535) | 12 months In patients with severe or very severe COPD (FEV₁<42% of predicted) tiotropium was better than ipratropium |
| Brusasco,36 2003 (n=1207) | 6 months In patients with severe or very severe COPD (FEV₁<38% of predicted) tiotropium reduced exacerbations significantly and both tiotropium and salmeterol improved health status and lung function compared with placebo |

| Does combining an inhaled corticosteroid with a long-acting beta-agonist have clinical benefit? |
| Calverley,37 2003 (n=1465) | 12 months In patients with moderately severe COPD (FEV₁<44% of predicted) salmeterol with fluticasone reduced exacerbations and improved health status, as did either drug on its own compared with placebo |
| Szafranski,38 2003 (n=612) | 12 months In patients with severe or very severe COPD (FEV₁<36% of predicted) budesonide 800 μg formoterol 9 mg daily improved lung function and exacerbations compared with placebo and formoterol on its own |
| Calverley,39 2003 (n=1022) | 12 months In patients with severe COPD (FEV₁<36% of predicted) who had previous oral corticosteroid and formoterol treatment, budesonide with formoterol improved health status and reduced exacerbations compared with placebo or either drug on its own |
| Calverley,40 2007 (n=512) | 3 years In patients with moderate or severe COPD (FEV₁<44% of predicted) salmeterol with fluticasone combination did not reduce mortality significantly compared with placebo. Significantly fewer exacerbations, admissions to hospital, and better health status were recorded with this therapy. Pneumonia was more commonly seen with inhaled corticosteroid treatment than with salmeterol and fluticasone |

| Does phosphodiesterase-4 inhibition improve lung function and clinical outcomes? |
| Rennard,41 2006 (n=647) | 24 weeks In patients with moderately severe COPD (FEV₁<50% of predicted) cilomilast 15 mg twice daily increased FEV₁, by mean 40 mL and reduced the number of exacerbations compared with placebo |
| Rabe,42 2005 (n=1411) | 24 weeks In patients with moderately severe COPD (FEV₁<51% of predicted) FEV₁, after bronchodilator increased by 97 mL with 500 mg roflumilast and exacerbations needing bronchodilator treatment were reduced |
| Calverley,43 2007 (n=1513) | 12 months In patients with moderate or severe COPD (FEV₁<41% of predicted) roflumilast 500 mg increased FEV₁, by 41 mL, but did not improve health status or number of exacerbations. More patients withdrew because of drug intolerance with roflumilast than with placebo |

| Does the antioxidant drug acetylcysteine reduce the rate of decline of FEV₁? |
| Decramer,44 2005 (n=523) | 3 years In patients with moderate or severe COPD (FEV₁<52% of predicted) 600 mg oral acetylcysteine did not change the decline in FEV₁, but reduced exacerbations in patients who were not taking inhaled corticosteroids |

*FEV₁ after taking bronchodilator.

Table 2: Large randomised controlled treatment trials done after 1997
differences in recruitment criteria can substantially affect outcome variables and restrict how results are generalised. This difficulty could help to explain conflicting results between seemingly similar studies. COPD is heterogeneous, both clinically and pathologically, but this heterogeneity is not the same for the pathological and clinical aspects of the disease. Thus, definition of reliable phenotypes on the basis of a patient having mostly emphysema or Airways disease, or presence or absence of specific symptoms has, to date, proven extremely difficult. Similarly, the failure to establish a surrogate endpoint for many clinically important outcomes (eg, admissions to hospital or mortality), has led to the need for large studies of long duration in patients who are sick enough for the events of interest to take place. Further work to establish the association between potentially important surrogate measurements, whether physiological or biochemical, is urgently needed if clinical trials are to be shorter and more discriminating than at present. Several other issues have been identified that have effects well beyond clinical trial design.

Bronchodilator reversibility

Bronchodilator reversibility (panel) in COPD as conventionally defined is not a useful marker in patients with established disease. One of the main concerns in the management of COPD and in the identification of treatment effects has been to avoid confusion between COPD and bronchial asthma. Asthma is characterised by variable airway calibre, either spontaneously or in response to treatment. Thus, an improvement in some measure of lung function, usually FEV₁, after taking a bronchodilator drug, either a β agonist or an anticholinergic, would seem to be a good way of distinguishing asthma from COPD. The definition of COPD based on clinical presentation and FEV₁ before taking bronchodilator led to some early confusion because inhaled corticosteroids seemed to have notable effects that many experts would have attributed to the presence of individuals with asthma in the study populations. Subsequently, and especially in Europe where these data originated, a bronchodilator response was redefined to try to overcome the inadvertent inclusion of asthmatic participants and this change emphasised that COPD was irreversible. In fact, a COPD phenotype based on the presence or absence of small increases in lung function after bronchodilator (panel) does not allow for spontaneous variation in airway smooth muscle tone, and the ability of bronchodilator drugs to reduce this tone in both health and disease.

If baseline lung function is relatively well preserved, small changes in FEV₁ after taking bronchodilator will probably not meet the threshold relative to baseline for patients to be reclassified as having asthma. When lung function is severely reduced in advanced COPD, similar

Panel: Definitions used in COPD trials

Bronchodilator reversibility

American Thoracic Society and GOLD criteria: a change in FEV₁ that is greater than 12% of baseline and encompasses an absolute change of 200 ml.

European Respiratory Society criteria: a change in FEV₁ that is greater than 9% of the value predicted for that person.

COPD exacerbation

An event in the natural course of the disease characterised by a change in the patient’s baseline dyspnoea and cough or sputum, or both, that is beyond normal day-to-day variations, is acute in onset, and might warrant a change in the patient’s regular medication.
changes in lung function can lead to an erroneous diagnosis of asthma (figure 2). Confusion about this point led to different requirements for drug regulators on either side of the Atlantic, with the European regulators insisting that the diagnosis of COPD needed the patient to have some bronchodilator response, but the US Food and Drug Administration did not regard such a response as an essential feature of COPD, if lung function after taking bronchodilator remained abnormal.

As a result of these differing criteria, clinical trials in the US showed larger improvements in lung function than was seen in Europe for the same drugs in similar patients.21,22 Some of this confusion was resolved by analysis of bronchodilator data from the ISOLDE study and in the Lung Health Study.19 In both studies, the most symptomatic patients did not show any relationship between the size of bronchodilator response and clinical outcomes such as exacerbation frequency or health status. Both studies showed that patients had significant day-to-day variability in airflow. Thus, the classification of an individual by some criteria would have changed on different days. Moreover, the number of people classified as having reversible disease was affected by the number of drugs tested. Taken together with the other problems of bronchodilator testing, such as its reproducibility, firm recommendations about using bronchodilator reversibility as a criterion for diagnosis, staging, and drug treatment in routine clinical practice are clearly undesirable—a view supported by subsequent national and international guidance.21,22

Large changes in lung function (ie, two standard deviations beyond the spontaneous variability of the measurement; about 400 mL) probably identify individuals who have an asthmatic clinical syndrome. Such individuals should be carefully assessed because they could have COPD. Proper prospective studies are needed in this small but important group of patients. The identification of so-called isolated volume responders, who show a clinically important reduction in forced expiratory vital capacity (FVC) with a small change in FEV1, is an attractive notion, but thus far we know little about how predictive such results are or how they can be reproduced. To date, bronchodilator response has been a poor predictor of short-term improvement in exercise ability or of other clinical outcomes such as exacerbation frequency or health status.21,22

Withdrawal from trials

Differences in withdrawal of patients from the two (or more) groups in a randomised clinical trial is a sign of treatment effect and not merely a statistical headache. Large studies of patients with COPD have investigated the rate of decline in lung function over time and most of these have studied the effects of inhaled corticosteroids.18-20 In studies in which most patients had more than 60% of predicted FEV1 and few symptoms, the dropout rate for the active treatment group was not different from the placebo group.21-24 However, in subsequent studies of inhaled glucocorticoids in severe COPD, in patients who generally had less than 50% of predicted FEV1, many patients had already been taking inhaled corticosteroids. As a result, participants assigned placebo were significantly more likely to have disease-related adverse events and to withdraw than were those assigned active treatment.25,26 The higher dropout rate in the placebo group creates a bias against the active intervention for outcomes such as exacerbations that take time to occur. Similar findings have been seen in long-term studies of bronchodilator drugs (with or without inhaled corticosteroids) lasting at least 1 year.27-29 This effect has been exploited in trials in which patients have been assigned to continue or stop their inhaled corticosteroids.27,28

Differing withdrawal between patients assigned placebo or active treatments tends to narrow the difference in results, because the sickest patients are those most likely to withdraw. This result was seen in ISOLDE,44 in which patients with the most rapid deterioration in health status and in FEV1, withdrew quickest.44 Differing rates of withdrawal can compromise primary outcomes as was seen in TORCH,44 BRONCUS,45 and OPTIMAL.46 In these studies, the reasons for withdrawal have been categorised in a standard way that permits further analysis. Exacerbations and patient dissatisfaction with treatment are major explanations for the differences in dropouts. Recognition that these factors can create both bias and logistical issues in long-term studies of patients with COPD is important for clinical study design. Moreover, informative dropout from a randomised blinded study can be viewed as a marker of overall treatment effectiveness—whether patients withdraw from placebo or because of treatment intolerability.29

Assessment of health status

One innovation in drug trials for COPD is the use of disease-specific health status questionnaires, which ask for data that is not strongly affected by the severity of airflow obstruction. Both the Chronic Respiratory disease Questionnaire and the St George’s Respiratory Questionnaire are used in treatment trials. The first questionnaire tends to detect small changes64,65 but the second has a useful summary score and an identified minimum clinical difference.22 However, recruitment into a clinical trial seems to have a positive effect on the health status of patients with COPD.23,66 This result might be a Hawthorne effect (ie, better care resulting from participation in the trial), or the expected consequence of previous exacerbations, following which health status can continue to improve for more than 12 weeks.66 These effects help to explain why the
health status of people assigned to placebo without other interventions commonly improves, at least for some months, although not by as much as those on active therapy.\textsuperscript{49} As noted previously, patients who leave a clinical trial tend to be those who are sickest at the beginning, leaving a healthy survivor population and affecting health status measurements. One way to overcome this drawback is to give intensive treatment with oral corticosteroids or additional long-acting beta-agonists, or both before randomisation.\textsuperscript{35,39} In these trials, no spontaneous improvement was seen in patients allocated to placebo.

Definition of exacerbation
The ISOLDE study looked at the number of episodes of symptomatic deterioration during its 3-year follow-up. An event was defined as contact with a health-care professional that resulted in a change in treatment, specifically a course of antibiotics or oral corticosteroids, or both.\textsuperscript{1,3,65} This definition has been developed further in the most recent version of the guidelines by the Global initiative for Obstructive Pulmonary Disease (GOLD).\textsuperscript{66} Careful study of daily diary cards showed that episodes of symptomatic deterioration persisting for many days occur more commonly than is seen with a definition based on use of health care.\textsuperscript{67} The importance of these episodes is unclear, neither their duration nor their cause has been robustly defined. However, data from both randomised controlled trials and observational studies show that health status is significantly worse in those who have more of them.\textsuperscript{68,69} Identification of exacerbations by daily diary cards is complex, but the high number of events recorded improves statistical power. Additionally, this method does not depend much on the availability of health care or on patterns of local clinical practice, which are important factors in international trials. Hopefully the EXACT-PRO initiative, which was started through a collaboration of the FDA, industry, and academics, can resolve many of these issues.

Statistical analysis of infrequent events
COPD exacerbations do not occur at regular intervals, nor do all patients have them. As a result, recruitment of individuals with frequent exacerbations might be seen as an advantage, but in a study of long duration many such patients could drop out early. Sufficient time must pass for an adequate number of exacerbations to take place, and most studies of 6 months or shorter are not usually large enough for such dropout to become a problem. Approaches include reporting the number of patients experiencing an exacerbation in each group or the time to first occurrence.\textsuperscript{6,7,9} However, clinicians want a sense not just of whether a treatment reduces the frequency of an event or of a statistical derivative, such as the time to first exacerbation, but they also would like an idea of the size of the change. Parametric statistics are clearly not appropriate for expression of exacerbation rates, but reporting data as a median can also be misleading, because of the very skewed distribution of exacerbations between individuals. To overcome this problem, complex statistical analyses such as Poisson distribution and the negative binomial approach have been done.\textsuperscript{72,73,75} These analyses model exacerbation rates for the whole population and give an idea of the size of an effect, but they are not literal representations of the number of events that have taken place. Pooling of cited data in meta-analyses can be misleading if exacerbations are the outcome, and caution is needed for interpretation of the reported exacerbation rates in earlier treatment trials.\textsuperscript{72}

Previous exacerbation history is a determinant of the likelihood of having further events,\textsuperscript{7,79} but, as the TORCH study\textsuperscript{80} showed, patients without exacerbations in the preceding year can subsequently have an exacerbation, and treatment in this subgroup can also be beneficial. Exacerbation analysis is further complicated by differential withdrawal as mentioned above, thus it is a difficult outcome to deal with, but one that is nonetheless important to patients and clinicians. However, care should be taken not to overinterpret the results of statistical modelling. The present approach probably gives an acceptable estimate of the effect of treatment on these events, if not for an individual, at least for a population of patients.

Underpowered studies
The expense and complexity of COPD trials is daunting, but as has been the case with cardiovascular disease, evidence that large and long-term studies are most informative is increasing. The effect of differences in patient recruitment, variations in initial treatment, differences in the natural history of each individual’s disease, not to mention previous and present smoking status (which as an outcome variable has made remarkably little difference to treatment effects reported in COPD trials) are all reduced as sample size increases. Large studies are more robust in the face of logistical problems, such as withdrawal of patients. Additionally, large trials allow for reasonable analysis of secondary hypotheses. Failure to account for these factors can raise uncertainty about the outcome of carefully designed studies.\textsuperscript{34,56}

Different trial designs give different answers
Randomised controlled trials have some important drawbacks when studying a disease such as COPD, in which change develops slowly. The criteria required for a patient to enter a randomised study, whether overtly stated or applied by investigators keen to recruit patients who will probably complete the trial, mitigate against the inclusion of patients with substantial comorbidities and those who are sickest. The availability of
computerised medical records documenting health-care consultations, diagnoses, and treatment should overcome these problems. Much research to validate such databases and investigate them has already been undertaken. However, database analyses have other forms of bias. Patients in databases are not necessarily from the same population as those in a clinical trial. Most importantly, these patients are not assigned to a treatment, but are given a therapy because an individual doctor believes it to be appropriate. Beneficial effects could be a direct result of treatment. However, outcomes could also be affected by other factors such as the organisation of health-care systems, or a physician giving other treatments, or selection bias because the patient has visited the physician. The creation of control populations to measure the effect of treatment is equally difficult. Untreated patients are those with mild disease who might not be directly comparable with treated individuals. The potential for time bias in database studies has been clearly identified. In view of the different limitations of these study methods, we should not be surprised that database studies and prospective randomised trials sometimes reach different conclusions.

What we have learned from clinical trials

Large clinical trials have prespecified primary outcomes and usually test a number of secondary hypotheses. Their results have substantial effects on treatment guidance, which for COPD is updated annually by GOLD. Smoking cessation early in the natural history of COPD undoubtedly has benefits for disease progression and risk of death, although at 14-5 years after randomisation in the Lung Health Study, few deaths were of a respiratory nature and most were related to cardiovascular disease and cancer. Smoking cessation can be helped with nicotine replacement therapy, and the antidepressant drug bupropion, which is associated with successful attempts to stop in COPD patients. Varenicline has proven more effective than nicotine replacement or bupropion in healthy volunteers and data for its effects in COPD are awaited.

Bronchodilator drugs, whether β agonists or anticholinergics, give small but consistent improvements in FEV₁ irrespective of baseline airway calibre. A combination of bronchodilator drugs is generally better than using one on its own, and a long duration of action of inhaled drugs is associated with greater clinical benefit than short-acting medications. Existing combinations of inhaled corticosteroids and long-acting inhaled β agonists result in greater improvement than either alone with generally acceptable side-effects. Long-acting drugs given by inhalation are preferred to short-acting ones, because they give important improvements not only in spirometry but also in health status and frequency of exacerbations. Adding an inhaled corticosteroid could result in additional clinical gains. Improvements in symptoms of COPD, especially exercise performance is related more to changes in lung capacity than to changes in expiratory flow. The improvement in vital capacity under resting conditions is probably due to a reduction in residual volume, a change which also occurs when high doses of bronchodilators are given during exacerbations. Additionally, bronchodilator drugs and bronchodilator-corticosteroid combinations reduce both the degree of dynamic hyperinflation seen during exercise and increase the duration of endurance exercise. These effects add to those of pulmonary rehabilitation or ambulatory oxygen, giving a clear rationale for combining different therapeutic approaches in the management of stable COPD.

Although still disputed by some researchers, most data suggest that inhaled corticosteroids reduce the number of exacerbations and improve the health status of patients. However, the TORCH study suggests that inhaled corticosteroids are associated with additional reports of pneumonia. This effect has been seen data from Canada. Both large clinical trials and database studies suggest a mortality benefit with bronchodilators or bronchodilator and corticosteroid combinations, but a beneficial effect of inhaled glucocorticoids was seen only in the database studies, not in the TORCH trial. Different meta-analyses with slightly different datasets have given conflicting estimates of the effect of inhaled corticosteroids and of the rate of reduction in lung function. Using many of the same studies and also incorporating data from studies lasting 1 year, a recent report suggests that such an effect seems absent. A preliminary report of a subanalysis of TORCH data suggests a positive effect on rate of decrease in lung function with all active treatments in 4000 patients studied prospectively. The UPLIFT study is comparing tiotropium with placebo on rate of reduction in lung function. The study is powered to detect a difference in rate of decline of 15 mL per year between treatment groups, a difference similar to that suggested by TORCH data. A smaller effect size than 15 mL per year reduction in lung function, would have needed an even larger or longer trial, than the 6000 participants and 3 years of follow-up in the TORCH trial.

Outcomes we did not anticipate

Large COPD trials have taught us much about aspects of COPD that we understood poorly or not at all before the studies. The limited usefulness of bronchodilator reversibility testing and the unexpected occurrence of pneumonia with inhaled corticosteroids have already been discussed. As also noted, patients who enter studies in COPD are often not as sick as many who attend their doctor’s office. Patients with substantial
comorbidities such as ischaemic heart disease, congestive heart failure, or known cancers are mostly excluded from clinical trials. The prevalence of these comorbidities in COPD patient populations has been described in epidemiological studies. However, even in trial participants, comorbidity is common. Thus in TORCH, which did not exclude individuals with comorbidities that were not expected to be rapidly fatal, more than a quarter of the subsequent deaths were thought to be from cardiovascular causes and 20% were from a tumour, with half of these being lung cancer. Additionally, more than 50% of the 654 TORCH participants who underwent measurement of bone mineral density showed osteoporosis or osteopenia at the time they were allocated to treatment. Moreover, their baseline disease was a much stronger predictor of subsequent outcome for bone-mineral density than of any identified effect of treatment.

The heterogeneity of COPD has been recognised for decades. Although not a drug trial, the National Emphysema Treatment trial (NETT) was the first to show a different response to treatment based on the phenotype of COPD. Specifically, in participants with upper-lobe emphysema seen by CT, and whose exercise performance did not improve after rehabilitation, surgical intervention resulted in large benefits on performance, but their ability to substantially reduce exacerbations has challenged existing thinking. This action could explain some of the benefits seen with these drugs. Studies with phosphodiesterase-4 inhibitors have shown consistent improvements in lung function over 6 months but these improvements have not been as notable in severe disease and have not affected frequency of exacerbations, except perhaps in patients with very severe disease. Additional data are needed to assess patient acceptability of these oral treatments because treatment-related nausea can be a drawback. Other approaches to anti-inflammatory therapy include the use of monoclonal antibodies against tumour necrosis factor-α, which, despite a good theoretical basis, has so far proved disappointing.

Future clinical trials

Large clinical trials have led to a substantial improvement in our understanding of COPD and of its management. Treatment strategies are now evidence-based and we can estimate the number of patients who need to be treated to prevent an event of interest taking place. The effect of this information will vary with the frequency with which a particular outcome occurs in a specific population of patients with COPD. We still do not have good algorithms to predict which patients will benefit from specific treatments. To develop these, we need to better define the clinical heterogeneity of this disease and establish how it relates to the symptoms of patients or their disease progression, or both. The search continues for validated intermediate outcome variables that will act as surrogates for treatment and so reduce the expense and delay inherent in clinical studies with agents unlikely to be of clinical benefit. Advances in CT and the identification of biochemical and cellular biomarkers hold great promise to help to address these needs. Application of these methods will be key in trials of new treatments such as retinoid drugs for emphysema.

The presence of comorbidities including cardiac disease, osteoporosis, muscle weakness, depression, and anaemia is being recognised as part of COPD rather than as separate medical disorders. This notion, which is supported by the increased risk of these non-pulmonary disorders in patients with COPD compared with similarly aged smokers without COPD, suggests a pathophysiological link. It also suggests that these disorders can be endpoints for COPD trials, which is a substantial diversion from the usual framework, in which patients with COPD who have important comorbidities are excluded from large clinical trials.
Inclusion of such individuals as study participants will not only allow results to be generalised, but will also offer opportunities to assess aspects of COPD that have thus far been poorly assessed. Additionally, trials of non-respiratory drugs such as angiotensin-2 inhibitors have been done, although results have so far been negative.\textsuperscript{10} Database studies suggest that patients with COPD who use statins have a better prognosis than those who do not,\textsuperscript{10,11} therefore the role of statins might be a useful area for future prospective study. Data like these are needed if we are to address the reasonable request for guidance about holistic management of patients.\textsuperscript{12}

Traditional randomised placebo-controlled trials have limitations as a practical instrument to establish treatment efficacy in a disease in which symptoms continue and complications such as exacerbations are distressing. The issues of differential withdrawal from studies, especially when the treatment under study is already available and licensed for another indication, have already been noted. Patients who are willing to participate might not be representative of the disease in the community and so findings can underestimate or overestimate how useful the treatment will be in general medical practice. The use of administrative databases to generate treatment hypotheses continues to be a reasonable way forward, but, as data for the use of inhaled corticosteroids and mortality from COPD show, they can generate findings opposing those from randomised controlled trials. We will probably follow the cardiologists in increasing the complexity of our treatment regimens, because future trials will investigate whether a new treatment augments or can be substituted for existing treatment, rather than showing efficacy compared with treatment with short-acting bronchodilators.

Perhaps the greatest challenge for future trials in a slowly progressive condition such as COPD will be the development of a robust and transparent funding model allowing the benefits of these large and costly studies done by industry to be retained, yet at the same time guaranteeing an independent role for investigators interested in the outcome for clinical rather than commercial reasons; traditionally, large trials in COPD have been sponsored by both industry and government. Generally, industry trials have focused on the effects of new products. Government trials, by contrast, have assessed both the effects of drugs and non-pharmaceutical interventions (eg, NETT, oxygen) and, to a lesser extent, have investigated the biology of the disease. However, several industry-funded trials in collaboration with academic centres now look at basic questions about genetics, natural history, and disease heterogeneity. As interactions between industry, academia, and government become more complex, the organisational structure that permits these studies and the regulatory policies that govern them need to evolve. Many of the studies discussed in this Review have helped us toward achievement of this goal, and as a result have greatly informed clinical practice, leading us to rethink the biology of COPD and to pose more specific questions relevant to our patients’ needs.

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COPD exacerbations: defining their cause and prevention

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Exacerbations of chronic obstructive pulmonary disease (COPD) are episodes of worsening of symptoms, leading to substantial morbidity and mortality. COPD exacerbations are associated with increased airway and systemic inflammation and physiological changes, especially the development of hyperinflation. They are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase airway inflammation. Some patients are particularly susceptible to exacerbations, and show worse health status and faster disease progression than those who have infrequent exacerbations. Several pharmacological interventions are effective for the reduction of exacerbation frequency and severity in COPD such as inhaled steroids, long-acting bronchodilators, and their combinations. Non-pharmacological therapies such as pulmonary rehabilitation, self-management, and home ventilatory support are becoming increasingly important, but still need to be studied in controlled trials. The future of exacerbation prevention is in assessment of optimum combinations of pharmacological and non-pharmacological therapies that will result in improvement of health status, and reduction of hospital admission and mortality associated with COPD.

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) impose a substantial burden on health-care systems worldwide; they are a major cause of morbidity, mortality, and reduced health status. COPD exacerbations are now the most common cause of medical hospital admission in the UK (accounting for 15·9% of hospital admissions), at a cost to the National Health System of over £253 million a year.2 Exacerbations are also important outcome measures in COPD, and thus a reduction in their frequency is a key target for intervention.

Although in half of community-treated exacerbations, patients recover to baseline symptoms by 7 days, a study of the time course showed that in 14% of these events patients had still not returned to baseline symptoms within 35 days of onset, and in a small proportion of exacerbations, symptoms never returned to the baseline level.3 Thus COPD exacerbations can be quite protracted, which accounts for some of the considerable morbidity associated with such an event. An audit of hospital admissions showed that around 30% of patients presenting with an index exacerbation will be seen again and possibly readmitted with another (or recurrent) event within 8 weeks.4 In a cohort of patients with moderate to severe COPD followed-up after exacerbation, 22% had a recurrent event within 50 days of the first (index) exacerbation. Thus, such events are complex, and an initial exacerbation seems to increase susceptibility to a subsequent one.5

Definition

An exacerbation of COPD is described as an acute worsening of respiratory symptoms associated with a variable degree of physiological deterioration.6 The guidelines of the WHO and US National Heart Lung and Blood Institute Global Initiative for Chronic Obstructive Lung Disease (GOLD)7 define an exacerbation as “an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD”.6

Definitions based on use of health care have also been proposed, eg, unscheduled physician visits, changes or increases in medication, use of antibiotics or oral steroids at exacerbation, and hospital admission.7 However, health-care use in COPD can vary depending on access, and thus there could be substantial difficulty in the standardisation of such a definition. Additionally, many COPD exacerbations are not reported to health-care professionals and are either self-treated or left untreated.1 The latest GOLD guidelines also indicate that exacerbations can be self-limiting, especially if of mild severity, and the phrase “may warrant a change in regular medication” has been incorporated.8 However, health-care use can be used to define exacerbation severity; often defined as mild if increases in regular inhaled medication are needed, moderate if courses of steroids or antibiotics are needed, and severe if the patient requires hospital admission.

Exacerbations are usually inflammatory events, with several airway and systemic inflammatory markers increasing.9 There has been substantial interest in developing a systemic biomarker as a diagnostic test for
an exacerbation. Hurst and colleagues did a large study of plasma biomarkers for COPD exacerbations, with 36 candidate molecules assessed in paired baseline and exacerbation plasma samples, and tested against a standard definition, meeting both health-care use and symptom-based criteria. To confirm the diagnosis of exacerbation, the most selective biomarker was C-reactive protein (CRP) but this was neither sufficiently sensitive nor specific alone. However, the combination of CRP with any increased major exacerbation symptom on that day (dyspnoea, sputum volume, or sputum purulence) increased the sensitivity and specificity. Further research will aid in the understanding of mechanisms of COPD exacerbations and will lead to the development of more specific biomarkers.

Pathophysiological changes
COPD exacerbations are associated with increased upper and lower airway and systemic inflammation (figure 1). There is little information available on the nature of the airway inflammatory changes especially when studied close to an exacerbation, because taking bronchial biopsies at exacerbation in patients with moderate to severe COPD is difficult. In stable COPD there is an increase in the CD8+ lymphocytes and macrophages in the bronchial mucosa and an increase in neutrophils with more severe disease. In one study, where biopsies were done at exacerbation in patients with chronic bronchitis, increased airway eosinophilia was reported, although the patients studied had only mild COPD. Modest increases were seen in neutrophils, T lymphocytes (CD3), and TNF alpha positive cells. However, in patients with more severe COPD, increases have been seen in airway neutrophils when stable that increase further at exacerbation. Qiu and colleagues have studied biopsies from patients with severe COPD, who were treated at exacerbation with tracheal intubation, and showed that there was pronounced airway neutrophilia, neutrophil elastase expression, and upregulation of neutrophil chemokine expression. However, studies in intubated patients with COPD are difficult, since the results can be complicated by secondary infection. Oxidative stress is a key factor in the development of airway inflammation in COPD. A study has shown that patients with severe exacerbations who needed hospital admission or assisted ventilation have evidence of increased large airway interleukin-8 (IL-8) levels and increased oxidative stress. Various markers of oxidative stress have been shown to rise in the airways with exacerbation such as hydrogen peroxide and 8-isoprostone and these markers can take some time to recover to baseline. Upper airway inflammation is increased in COPD patients, increases further at exacerbation, and is associated with lower airway inflammatory changes.

Systemic inflammation increases at exacerbation and although the causes of this response in COPD are not clear, there is probably a spill-over of inflammatory markers from the lungs. By contrast with stable disease, exacerbations seem to be associated with a direct correlation between the degree of airway inflammation and the size of the systemic acute-phase response. Systemic inflammation increases when the exacerbation is associated with bacterial and viral infection. Several inflammatory markers increase at exacerbation, such as plasma fibrinogen and CRP, that have been linked to increased cardiovascular risk. Respiratory infections have been associated with increased cardiac events and thus a COPD exacerbation, especially if triggered by an infection, might also be associated with increased cardiac morbidity.

The airway inflammatory responses during COPD exacerbations cause airway oedema, bronchospasm, and increased sputum production, leading to worsening airflow limitation and development of dynamic hyperinflation. Such hyperinflation is the main cause of dyspnoea, the most common symptom of an exacerbation, and has other effects including modulating gas exchange, mechanical, and cardiovascular effects. Generally the more severe the underlying disease, the greater the degree of physiological change at exacerbation leading to worsening of airflow limitation, and thus the more likely the patient is to develop respiratory failure.

Changes in airflow limitation result in changes in peak expiratory flow rate, but available data suggest that changes in peak flow are too small to be useful in

[Figure 1: Triggers of COPD exacerbations and associated pathophysiological changes leading to increased exacerbation symptoms]
assessing individual patients. This limitation might be because peak expiratory flow is mainly an assessment of large airway obstruction, although in COPD, most of the airflow limitation occurs in the small airways. Changes in exhaled nitric oxide also occur and are greater in the presence of viral infections, but are not suitable for monitoring of current exacerbations. Novel physiological methods to monitor exacerbations are being developed, and some data now suggest that inspiratory capacity measurements or within-breath forced oscillation measurements might be more useful to assess COPD exacerbations and indicate the degree of physiological impairment.

**Causes of COPD exacerbations**

COPD exacerbations are heterogeneous events that are now thought to be caused by complex interactions between the host, respiratory viruses, airway bacteria, and environmental pollution, leading to an increase in the inflammatory burden (panel).

### Panel: Most common bacterial and viral pathogens isolated from patients with COPD exacerbations

**Bacteria**

- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococcus pneumoniae*
- *Pseudomonas aeruginosa*

**Viruses**

- Rhinovirus
- Coronavirus
- Influenza
- Parainfluenza
- Adenovirus
- Respiratory syncytial virus

**Viral infections**

COPD exacerbations are frequently triggered by upper respiratory tract infections, which are more common in the winter months, when respiratory viral infections are prevalent in the community. Lung function also shows small but significant falls with reduction in outdoor temperature. Exacerbations triggered by respiratory viral infections are more severe and are associated with longer recovery times than those triggered by other factors. Molecular diagnostic techniques have now enabled detection of respiratory viruses at exacerbation, which have been isolated in around half of exacerbations, although this finding might be an underestimate due to difficulties in sampling at onset of symptoms. There have been few such studies in the developing world, but a study from Hong Kong detected viruses in only 22% of exacerbations. However, this study differed from others in the choice of assay and in that samples were taken from the upper airway rather than directly from the lower airway. A smaller study of 14 COPD patients admitted to hospital in Singapore reported that 64% of COPD exacerbations were associated with viruses although, like the Hong Kong study, most were associated with influenza virus, which was possibly due to less frequent use of the influenza vaccine.

The most common viruses isolated are human rhinoviruses (the most frequent viruses associated with exacerbations), and other viruses including coronavirus, respiratory syncytial virus, influenza, parainfluenza, and adenovirus. Since the introduction of influenza immunisation for patients with chronic lung disease, the virus has become a less prominent cause of exacerbation, though it is still likely to be an important factor at times of epidemics. Although respiratory syncytial virus infection has been seen at exacerbation, whether it was the sole cause is not entirely clear, since this virus has been detected in the airways of COPD patients when they are stable and is associated with increased airway inflammation in stable COPD. Latent expression of adenoviral E1A protein in alveolar epithelial cells can amplify the effects of lung inflammation induced by cigarette smoke. Thus, chronic viral infection might be linked to disease severity in COPD and further work is required on the relation between viruses detected in the stable state and at exacerbation.

With PCR techniques, rhinoviruses can be recovered from induced sputum more frequently than from nasal aspirates at exacerbation, suggesting that wild-type rhinoviruses can infect the lower airway and contribute to inflammatory changes at exacerbation. Low-dose experimental rhinovirus infection in patients with mild COPD has been shown produce symptoms that are typical of an exacerbation, confirming that respiratory viruses can infect the lower airway. Exacerbations triggered by respiratory viruses are also more severe, associated with longer recovery times, and have more chance of hospital admission than exacerbations where respiratory viruses were not detected.

**Bacterial infections**

The precise role of bacteria at COPD exacerbations has been difficult to assess, since airway bacterial colonisation in the stable state is associated with the same organisms as those isolated at exacerbations, including *Haemophilus Influenzae, Streptococcus Pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, and Pseu-

**Differential diagnosis**

- COPD exacerbations are heterogeneous events that are now thought to be caused by complex interactions between the host, respiratory viruses, airway bacteria, and environmental pollution.
- Viral infections, particularly rhinoviruses, are frequently associated with COPD exacerbations.
- Bacterial infections, particularly *Pseudomonas aeruginosa*, can also contribute to exacerbations.
- Monitoring of inspiratory capacity or within-breath forced oscillation measurements might be more useful than peak expiratory flow in assessing COPD exacerbations.

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Evidence for the involvement of bacteria has come from studies of antibiotic therapy, since exacerbations are often associated with increased sputum purulence and volume, and antibiotics have traditionally been used as first line therapy. A study investigating the benefit of antibiotics in more than 300 acute exacerbations showed a greater treatment success rate in patients treated with antibiotics, especially if their initial presentation was with the symptoms of increased dyspnoea, sputum volume, and purulence, than in patients who did not receive such treatment. Patients with mild COPD obtained less benefit from antibiotic therapy than those with more severe COPD. The results of a meta-analysis have shown that antibiotic treatment offered a small but significant benefit in treatment failure and mortality.

Substantial progress has been made on investigating the role of bacterial infection at exacerbation, with the development of molecular typing methods allowing the detection of changes in bacterial strains, rather than species. Sethi and colleagues have suggested that isolation of a new bacterial strain in COPD patients who were regularly sampled was associated with an increased risk of an exacerbation. However, this finding does not conclusively prove that bacteria are direct causes of exacerbations, because not all exacerbations were associated with strain change, and not all strain changes resulted in exacerbation. The strain-specific immune responses to colonising bacterial species provide some further evidence that bacteria are not just innocent bystanders in the lower airways during exacerbations.

However, the situation with airway infection is further complicated, since in many COPD exacerbations both respiratory viruses and bacteria could be isolated. A greater systemic inflammatory response has been reported in those exacerbations associated with both H influenzae and rhinovirus isolation, and if the isolation of H influenzae was associated with new or worsening coryzal symptoms (a surrogate of viral infection), such infections were more severe as assessed by changes in symptoms and lung function at exacerbation onset. This change has been confirmed in a further study which reported greater lung function impairment and longer hospitalisations in patients with exacerbations associated with viral and bacterial coinfection than in those without coinfection. Thus bacterial coinfection with viruses might be of greater importance than bacterial infection alone at COPD exacerbation but consensus within the field has not yet emerged.

Atypical bacteria such as chlamydia, legionella, and mycoplasma have also been implicated at COPD exacerbation, although evidence on their role is conflicting, and these microorganisms might also interact with airway bacteria and viruses. A recent study using real-time PCR detection methods found no role for these three atypical bacteria at COPD exacerbation.

COPD patients can have increased exacerbations and hospital admissions with increasing environmental pollution. In the APHEA study in six European cities, Anderson and colleagues reported a significant effect of air pollution levels on hospital admission for COPD, and similar results have also been seen in Taiwan and Brazil. However, common pollutants, especially nitrogen oxides and particulates, can interact with viral infection in asthma to precipitate exacerbation rather than acting alone, and a similar mechanism might occur in COPD. A study from Hong Kong has shown adverse effects of ambient concentrations of air pollutants (sulphur dioxide, nitrogen dioxides, ozone, and particulate matter with a diameter of less than 10 µg/m³ [PM₁₀] and 2.5 µg/m³ [PM₂.₅]) on hospitalisation rates for COPD, especially during the winter season. Thus measures to improve air quality can have an effect on exacerbation frequency.

Effects

In general, exacerbations become both more frequent and more severe as the severity of the underlying COPD increases. However, there remain large differences in yearly exacerbation incidence rates between patients of similar COPD severity. There is no agreed definition of a patient with frequent exacerbations, but in several studies they were defined as those with yearly exacerbation rates of greater than the median for the study, usually around three symptom-defined exacerbations per year or two per year if the exacerbation is defined by the requirement for therapy with courses of antibiotics, corticosteroids, or both.

Patients with a history of frequent exacerbations have worse quality of life than patients with a history of less frequent exacerbations, and have consistent exacerbation frequencies when studied from year to year. These patients also have an increased risk of hospital admission and greater mortality (figure 2). A UK study suggested that COPD exacerbations do not affect lung function decline, though this study was done in men of working age with fairly good lung function. However, results of subsequent studies suggest that exacerbations do play a part in disease progression in patients who are active...
smokers and those who have frequent exacerbations, although this effect is fairly small, at around 25% of the total decline in lung function. This observation might be due to the fact that not all exacerbations recover to baseline levels of symptoms and lung function. The results of one audit showed that around 30% of patients seen at hospital with an index exacerbation will be seen again and possibly readmitted with a recurrent exacerbation within 8 weeks. Patients with a history of frequent exacerbations also have increased airway inflammation, which could also contribute to the disease progression. Why some patients have frequent exacerbations is not clear, although they possibly have increased susceptibility to respiratory viral infection. Thus this group of COPD patients is important for targeting interventions that have the potential of reducing exacerbation frequency.

COPD exacerbations have functional consequences. Spruit and colleagues have shown that peripheral muscle weakness worsens during exacerbation, potentially contributing to reduced functionality and therefore to deconditioning (loss of fitness). Patients who do not improve their walking distance within a month after exacerbation are more prone to be readmitted to hospital. Donaldson and colleagues have also shown that exacerbations are associated with a decline in outdoor activity for up to 5 weeks after the onset of symptoms. Patients who have frequent exacerbations had a faster decline in functional status, as measured by time spent outdoors, than patients with infrequent exacerbations (figure 3). Thus, patients with frequent exacerbations are more likely to become housebound and are a subpopulation that needs targeting for pulmonary rehabilitation programmes.

COPD is associated with other comorbid conditions, and patients who are admitted to hospital are more likely to have associated comorbid conditions such as ischaemic heart disease, pneumonia, and diabetes than patients without a diagnosis of COPD. Increasing blood glucose concentrations have been shown to be associated with adverse clinical outcomes in patients with COPD exacerbations. Thus the disease burden of COPD exacerbations is likely to be much higher when these comorbidities are taken into account.

There have been several reports of associations between pulmonary embolism, deep venous thrombosis, and COPD exacerbation. Exacerbations could trigger pulmonary embolic events, since acute infections are known to predispose to deep venous thrombosis and pulmonary embolism. There might also be diagnostic difficulties because both COPD exacerbations and pulmonary embolism might present solely with dyspnoea. However, a recent study has shown that pulmonary embolism is not a common feature in uncomplicated exacerbations, but some patients with exacerbations can have prolonged recovery periods, complicated by respiratory failure and comorbidity, when the risk of pulmonary embolism could become greater.

**Prevention**

**Pharmacological therapies**

A few studies have shown that a decreased exacerbation rate is associated with improved quality of life. Thus lowering the exacerbation rate would be expected to decrease hospitalisations and have important health economic benefits. Several classes of drugs with potential for reducing exacerbations have been investigated, with variable evidence for their use: vaccines, bacterial extracts, inhaled steroids and long acting bronchodilators, phosphodiesterase inhibitors, and mucolytic agents.

**Vaccines and immunostimulants**

There are several studies of influenza and pneumococcal vaccinations, which are now routinely recommended for all patients with COPD of significant severity. One study that reviewed the outcome of influenza vaccination in a cohort of elderly patients with chronic lung disease found that influenza vaccination is associated with significant health benefits with fewer outpatient visits, fewer hospitalisations, and reduced mortality.

A Cochrane database review of four studies in COPD saw no evidence of efficacy for injectable anti-pneumococcal vaccines; however, in a study of the 23 serotype pneumococcal polysaccharide vaccine in COPD patients, Alfgäme and colleagues showed that the vaccine was effective in the prevention of community acquired pneumonia, compared with placebo in patients younger than 65 years or those with severe airflow obstruction. However, no difference in mortality between

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**Figure 3:** Time course of a COPD exacerbation over 51 days of time spent indoors (open circles) and symptom count (solid circles) for 136 patients who were monitored daily and had an exacerbation. Reproduced with permission from Fletcher and colleagues.⁵⁹
Inhaled corticosteroids and long acting bronchodilators

The success of oral corticosteroids in the treatment of COPD exacerbations with reduction of hospital length of stay has prompted much interest in the use of inhaled steroids to reduce exacerbation frequency in COPD. One of the early studies, the ISOLDE (Inhaled Steroid in Obstructive Lung Disease in Europe) study, was a 3-year study, powered to detect a significant change in FEV₁, decline, was negative for the primary outcome but showed that exacerbation frequency can be reduced with inhaled steroids by about 25%. Generally the effect of inhaled steroids was greater in patients with more impaired lung function, suggesting that this is the group to target with long-term inhaled steroid therapy. In another study from the USA (The Lung Health Study), the inhaled steroid (triamcinolone) group had significantly fewer visits to a physician due to respiratory illness, suggesting that triamcinolone also reduced the frequency of COPD exacerbations.

Inhaled long-acting beta 2 agonist (LABA) therapy has been shown to cause small reductions in exacerbation frequency, although most studies involved short periods of therapy at 12 weeks. Mahler and colleagues found that the time to the first exacerbation was longer with therapy with the long-acting beta agonist salmeterol, although the overall number of exacerbations during the study was small. The larger TORCH study of 6112 COPD patients reported that salmeterol reduced exacerbation frequency compared with placebo over a 3-year period. In another study comparing salmeterol with ipratropium when studied over a 1-year period, there was no difference in the effect in either treatment arm on exacerbation frequency.

Rossi and colleagues compared two different dosages of the inhaled bronchodilator formoterol with placebo or theophylline and concluded that formoterol was more effective and better tolerated than therapeutically appropriate doses of oral slow-release theophylline in symptomatic COPD patients. Furthermore, two studies reported that formoterol had no effect on total exacerbation frequency relative to placebo, though these studies did find that the rates of steroid-treated exacerbations were decreased in the formoterol group.

The balance of evidence favours a positive role for LABAs in decreasing exacerbation frequency, which might be the result of the inhibitory effect of beta-adrenoceptor agonists on plasma exudation and neutrophil migration, or possibly indicating an additional reduction in the expression of adhesion molecules. However, the likely pathway of action could be through a synergistic action on airway inflammatory cells in those patients already receiving inhaled corticosteroid therapy. All of the major recent studies of combination therapy have reported that the combination of inhaled steroid and LABA is more effective than either individual drug alone in reducing exacerbation frequency. Thus, inhaled steroids are unlikely to be used as sole therapy for COPD patients in the future. The data from the TORCH study have confirmed the effectiveness of the inhaled steroid-LABA combination in reducing exacerbation frequency, and the study has reported that the combination reduces hospital admission rates in COPD patients. However, most of these studies have been done in patients with more severe COPD with an FEV₁ at less than 60% predicted (figure 4). The effect of the inhaled steroid-LABA combination on reducing exacerbations in patients with milder COPD is not clear, especially in those patients who have an increased exacerbation frequency.

Long-acting anticholinergic agents such as tiotropium also reduce exacerbation frequency, and tiotropium has been shown to reduce exacerbations by 24%, compared with ipratropium when studied over a 1-year period. Niewoehner and colleagues in a well designed study have confirmed the potential of tiotropium to reduce exacerbation frequency and also have shown a reduction in hospitalisation. Tiotropium does not have any known
anti-inflammatory effect, and its effect on reducing exacerbations is most likely due to the reduction of dynamic hyperinflation that is the major cause of dyspnoea in COPD (figure 5). The combination of tiotropium with inhaled LABA and inhaled steroids has been explored in the Optimal Study. This randomised trial compared tiotropium-fluticasone-salmeterol versus tiotropium-salmeterol versus tiotropium-placebo, and the triple combination reduced hospitalisation as a result of exacerbation, but not the total number of exacerbations. However, a trend was seen in the reduction of the number of exacerbations with the triple combination, which failed to reach significance possibly due to the small size of the study and the high dropout rate. Triple therapy could be more effective than dual therapy, but further studies of these combinations are required with adequately powered studies.

**Phosphodiesterase inhibitors and other anti-inflammatory agents**

The phosphodiesterase inhibitors now form a class of non-steroidal anti-inflammatory drugs that might be useful in the prevention of COPD exacerbations. Studies of the phosphodiesterase inhibitor theophylline have suggested that small reductions in exacerbation rates can be achieved with therapy, though further studies are needed on the effect of low dose theophylline on exacerbation frequency in COPD. Two new receptor-specific phosphodiesterase inhibitors have been studied in COPD: cilomilast and roflumilast, which are both phosphodiesterase-4 inhibitors. A trial of cilomilast in COPD patients showed reduction in exacerbations in the cilomilast group. Two studies of roflumilast in COPD have been recently reported: Rabe and colleagues have reported a reduction in exacerbations after 24 weeks therapy with roflumilast, while Calverley and colleagues studied roflumilast in patients with GOLD stage III and IV in a 1-year trial and showed no overall effect on exacerbation rate, although patients with severe disease (GOLD stage IV) had fewer during the study period. Prevention of COPD exacerbations using this class of drugs is evolving and newer agents and more effective phosphodiesterase inhibitors will be developed with fewer adverse events.

Tumour necrosis factor (TNF)-a has an important role as a key mediator in COPD and has been a target for study. However, a trial of the anti-TNFα antibody, infliximab, showed no benefit on any of the main trial outcomes and no effect of the therapy on exacerbation rate.

**Mucolytic agents**

The BRONCUS trial using N-acetylcysteine has shown no overall benefit of mucolytics on reduction of COPD exacerbations, except a small effect was noted in those patients who were not taking inhaled steroids. A follow-up meta-analysis of 26 randomised trials involving mucolytic therapy in COPD revealed a 20% reduction in exacerbations, with a large number of patients treated with mucolytics having no exacerbations. A study from North America has shown that small airways occluded with inflammatory exudate in COPD patients were associated with early death. This finding might stimulate further research into the role of mucolytic agents in COPD therapy. However, the consensus view is that the evidence for mucolytics preventing COPD exacerbations is not convincing: this view is supported by the GOLD guidelines, although mucolytics are still used quite widely in some parts of the world.

**Long-term antibiotics**

Long-term antibiotic treatment has been used by physicians in clinical practice previously in patients with very frequent exacerbations, either continuously or in rotation, though there is little evidence for their effectiveness. There are some problems with using long-term antibiotics as resistant bacteria could emerge and cause increased airway inflammation and exacerbations. However, in view of the presence of lower airway bacterial colonisation in these patients and data from Patel and colleagues that such colonisation is related to exacerbation frequency, there has been renewed interest in this type of intervention and some continuing studies will soon be reporting their findings.

**Non-pharmacological therapies**

**Pulmonary rehabilitation and self management**

Pulmonary rehabilitation is now an accepted intervention in COPD and although it has important benefits for patients, its effect on preventing exacerbations is less clear. In a randomised trial from South Wales, UK, Griffiths and colleagues reported that those patients...
treated with a pulmonary rehabilitation programme including exercise training and education had shorter hospital stays than the control group and fewer primary-care home visits. This finding suggests that a course of pulmonary rehabilitation might reduce exacerbation severity rather than frequency by increasing the patient’s knowledge of COPD and how to access health care or self-manage during an exacerbation. Pulmonary rehabilitation could thus reduce hospital stay but also encourage early presentation for exacerbation therapy, which reduces exacerbation length and thus the severity of the event.101

Garcia-Aymerich and colleagues102 have also shown in a 1-year study that patients with high levels of usual physical activity were at reduced risk of readmission to hospital. An intensive disease-specific self-management programme done in Canada has been shown to reduce hospital admission rate,103 though a systematic review of nurse-led interventions failed to show a consistent effect on hospitalisation.104 Casas and colleagues105 have extended this approach by using a similar integrated care plan in two different environments (Barcelona, Spain, and Leuven, Belgium), with similar effects on decreased readmission rates for COPD exacerbation. Patients with COPD are elderly, often with a degree of cognitive impairment and might have difficulty with self-management at exacerbations. How optimum community support should be provided for patients who are at particular risk of hospital admission is not clear.

**Home oxygen therapy and ventilatory support**

Long-term oxygen therapy has several benefits in COPD patients who are chronically hypoxaemic, including reducing mortality, anxiety, and depression.106–108 In an epidemiological study, Garcia-Aymerich and colleagues109 noted that patients with hypoxaemia but not treated with long-term oxygen therapy had a higher risk of hospital admission. Another observational study from the Danish Oxygen Register110 has also suggested that long-term oxygen therapy reduces hospital admission rate. Controlled studies on home oxygen therapy and COPD exacerbations are difficult, since withholding therapy in a control hypoxaemic group would not be ethically justifiable.

COPD patients with chronic respiratory failure are particularly susceptible to exacerbations. After the early experience of domiciliary long-term non-invasive ventilation in patients with chest wall and neuromuscular disease, non-invasive ventilation has also been assessed in patients with hypercapnic COPD. Early observations on the effect of non-invasive ventilation in COPD showed a significant beneficial effect on health status, although data for exacerbations were not recorded.111 Because health status is such an important determinant of exacerbation frequency,112 improvement in health status could be due to a reduction of exacerbation frequency. In a controlled study lasting a year, no effect was seen of non-invasive ventilation on exacerbations but there was a reduction in hospital admission at the 3-month follow-up point.113 Thus, larger controlled studies are now required to assess the effect of non-invasive ventilation on exacerbation in hypercapnic COPD patients, particularly at risk of hospital admission.

**Conclusion**

COPD exacerbations are often triggered by airway infection and are an important cause of morbidity, impairment of health status, and mortality. Although many pharmacological and non-pharmacological interventions prevent exacerbations, the degree of reduction in exacerbation frequency is still restricted and we now need new interventions to be urgently developed and studied in well designed and adequately powered randomised trials. Combinations of these interventions will probably be most effective and this approach will need future development and assessment. One of the main objectives of therapy for COPD is to reduce the morbidity associated with exacerbations and thus improve the quality of life of patients with this disabling condition.

**Conflict of interest statement**

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**References**


Review


Review


From COPD to chronic systemic inflammatory syndrome?

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Chronic obstructive pulmonary disease (COPD) is characterised by poorly reversible airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, particularly cigarette smoke. A diagnosis of COPD should be considered in any current or previous smoker older than 40 years who has symptoms of cough, sputum production, or dyspnoea. Diagnosis and assessment of severity of COPD are based on the degree of airflow limitation at spirometry. However, increasing evidence suggests that clinical features of COPD and airflow limitation are poorly correlated and a comprehensive approach, including imaging and assessment of exercise tolerance and body-mass index, is needed. In this Viewpoint, we aim to convey the message that COPD can no longer be judged a disease only of the lungs. We propose to add the term chronic systemic inflammatory syndrome to the diagnosis of COPD to stimulate discussion around the frequent complex chronic comorbidities in people with COPD and to provoke a new view of the disease in general.

Cigarette smoking is the major risk factor for COPD and is one of the most important risk factors for all chronic diseases and some cancers. Up to now, definitions of COPD have focused on the lungs based on the simplified idea that inhalation of particles and gases will mainly affect the respiratory tract. However, cigarette smoke causes not only airway and lung inflammation but also systemic cellular and humoral inflammation, systemic oxidative stress, striking changes of vasomotor and endothelial function, and enhanced circulating concentrations of several procoagulant factors. These systemic effects of smoking could contribute substantially to the development not only of the airways and lung abnormalities characteristic of COPD but also of chronic diseases—eg, cardiovascular diseases, metabolic disorders, and some cancers that are induced by smoking in combination with or without other risk factors such as obesity, hyperlipidaemia, and increased blood pressure. Such chronic diseases can develop either with COPD or independently of the disorder.

The most common comorbidities described in association with COPD are skeletal muscle abnormalities, hypertension, diabetes, coronary-artery disease, heart failure, pulmonary infections, cancer, and pulmonary vascular disease. Chronic comorbid diseases affect health outcomes in COPD; in fact, patients with COPD mainly die of non-respiratory disorders such as cardiovascular diseases or cancer.

Chronic diseases account for a large proportion of human illness and include cardiovascular disease, cancer, chronic respiratory diseases, and diabetes. An unprecedented increase in chronic diseases is expected in the next few decades as populations age, a prospect that is of great concern to health authorities.

Chronic diseases typically develop together. COPD is associated with chronic heart failure in more than 20% of patients and with osteoporosis in up to 70% of patients—in part, independently from treatment with steroids, decreased physical activity, or both. Furthermore, in a small study, almost 50% of patients with COPD had one or more components of the metabolic syndrome. Conversely, chronic heart failure is associated, in more than 50% of patients, with arterial hypertension and coronary or peripheral artery diseases, with diabetes in 20–30%, and with anaemia in 20–30%. Type 2 diabetes is linked to hypertension in more than 70% of individuals and to cardiovascular diseases and obesity in more than 80%. Diabetes is independently associated with reduced lung function, which together with obesity could further worsen the severity of COPD.

Almost half of all people aged 65 years or older have at least three chronic medical conditions, and a fifth have five or more, with costs rising exponentially in patients with two or more comorbid chronic diseases. The strongest predictive factors of increased cost in COPD patients are age, chronic symptoms such as chronic dyspnoea and wheezing, and comorbidities; comorbid diseases account for more than 50% of health-care resources.

Potentially, the common mechanism by which major risk factors such as smoking, hyperlipidaemia, obesity, and hypertension lead to chronic disease is systemic inflammation. C-reactive protein is almost invariably increased in all components of the chronic systemic inflammatory syndrome, suggesting that this acute-phase protein could represent the sentinel biomarker to all chronic diseases.

Metabolic syndrome was defined by the clustering of specific risk factors for cardiovascular disease with common underlying pathophysiological findings (eg, insulin resistance). This paradigm was useful because it drew attention to the fact that cardiovascular disease risk factors sometimes cluster and it served as a helpful reminder to clinicians to take a broad approach to treatment for such patients. Since its definition, the metabolic syndrome has stimulated an enormous amount of interest and research, to the point that it now has its own ICD-9 (International Classification of Diseases, 9th edition) code (277.7). Although, strictly speaking, the metabolic syndrome is not a syndrome in its own right, introduction of the term stimulated development of three fundamental ideas. First, one or more risk factors can be associated with and cause simultaneous development of diseases—eg, diabetes, obesity, hypertension, and cardiovascular disease.
Second, a comprehensive diagnostic approach to chronic disorders is needed. Finally, all risk factors should be approached with lifestyle modifications (eg, smoking cessation, weight loss, physical activity), and every associated chronic comorbid disorder should be treated simultaneously.

We hereby propose an overarching approach to diagnosis, assessment of severity, and management of COPD and its frequent comorbidities. In patients older than 40 years, with a smoking history of more than 10 pack-years, who develop clinical and functional abnormalities compatible with COPD, we suggest not to restrict the diagnostic approach to COPD alone but to search for signs of the more general disorder chronic systemic inflammatory syndrome, with detailed description of clinical and functional abnormalities of the respiratory, cardiovascular, and metabolic systems. The term chronic refers to the slow and progressive development of the abnormalities; systemic refers to the fact that risk factors act directly or indirectly on all target organs simultaneously; inflammatory refers to the association of all components with inflammation; and syndrome refers to the association of several clinically recognisable features, signs, symptoms, or characteristics that generally arise together, so that the presence of one feature alerts the doctor to the presence of the others.

Diagnosis of chronic systemic inflammatory syndrome can be established by the presence of at least three of the six components listed in the panel. COPD, chronic heart failure, and metabolic syndrome are diagnosed according to current international guidelines after comprehensive assessment of lung, cardiac, and metabolic functions. Other chronic disorders, such as coronary and peripheral artery diseases, anaemia, osteoporosis, and rheumatoid arthritis, could be included either as additional comorbidities, as complications (eg, steroid-induced osteoporosis), or as independent modifiers of severity of the chronic syndrome (eg, depression).

Severity of chronic systemic inflammatory syndrome should be ascertained by combination of these different components. Indeed, the present approach of defining severity of COPD by spirometry has obvious limitations. For example, diagnosis of moderate COPD using a post-bronchodilator forced expiratory volume in 1 s (FEV1) of more than 50% but less than 80% and a FEV1/FVC (forced vital capacity) ratio of less than 0.7 has very limited clinical value if the simultaneous presence of chronic heart failure, diabetes, or both, is ignored.

Our main reason for suggesting the introduction of the term chronic systemic inflammatory syndrome is to emphasise the importance of complex risk factors (eg, smoking, obesity, hypertension) in development not only of primary disease (ie, COPD, chronic heart failure, or metabolic syndrome) but also of systemic and complex abnormalities affecting other organs, which are induced by smoking or by interaction of major risk factors. To ascertain the public-health perspective of this approach, the cost/benefit ratio of the assessment and treatment of every component will have to be tested in properly designed randomised clinical trials of appropriate disease-management plans. Implementation of these studies is feasible, and we expect that a proposal to search for the most frequent chronic comorbidities of COPD will be a helpful reminder to clinicians of the complexity of the effects of smoking.

Risk factors for chronic diseases are well recognised, and preventive and prophylactic approaches—such as smoking prevention and cessation, weight control and diet, and exercise and rehabilitation—are feasible and effective and possibly represent the only approach that can tackle all components of chronic systemic inflammatory syndrome. Amending pharmacological treatment algorithms to account for the many aspects of the syndrome will probably be more complex, because drugs are usually developed for individual diseases or target organs. However, since pharmacological treatment of chronic diseases—particularly COPD—is mainly symptomatic, a more comprehensive approach to management of COPD and its comorbidities might provide an opportunity to modify the natural history of COPD, allowing for identification of novel targets for treatment. This idea is especially relevant for disorders that seem to be more preventable and treatable than COPD, such as cardiovascular and metabolic disorders. Cardiovascular drugs have already been reported to have beneficial effects in COPD. Statins, which are used mainly as lipid-lowering agents for treatment of metabolic syndrome, have potent anti-inflammatory properties that positively affect COPD, chronic heart failure, and vascular diseases. Similarly, drugs developed and used to treat respiratory diseases (eg, inhaled bronchodilators and steroids) could have substantial beneficial effects for cardiovascular diseases.

Clinical practice guidelines in general seem to ignore the fact that most patients with a chronic disease have additional comorbidities. Guidelines designed largely by specialty-dominated committees for management of individual diseases provide clinicians with little advice for caring for people with several chronic diseases, resulting frequently in poly-pharmacia. We suggest that...
the introduction of an overarching idea such as chronic systemic inflammatory syndrome will improve recognition of chronic comorbid disorders and will affect patients’ care, particularly that of elderly people. Not only will clinicians have to agree to change their approach to treating chronic diseases but also our health-care system must rise to this major challenge.

Conflict of interest statement

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References


In January, 2006, a 21-year-old Norwegian woman presented to our emergency department with a 3-day history of wheeze, sore throat, cough, and shortness of breath. Asthma had been diagnosed in early childhood; she also had eczema, and a strong family history of asthma. She reported having at least two chest infections per year, and had eczema, and a strong family history of asthma. She was taking oral montelukast, inhaled salmeterol and fluticasone twice daily, and inhaled salbutamol as required.

On examination, she was distressed, had no fever, was taking 30 breaths per min, had a sinus tachycardia of 120 beats per min, and was normotensive. Her peak expiratory flow rate (PEFR) was 120 L per min; auscultation revealed diffuse wheeze, but no stridor. Chest radiography revealed compression of the lower trachea by a vascular ring. Magnetic resonance angiography (MRA) showed a double aortic arch, the left side of which was largely atretic.

The patient’s longstanding symptoms were caused by tracheal obstruction—and not by asthma. Corrective vascular surgery was done in Norway. On subsequent review, the patient was asymptomatic, and taking no respiratory medications. However, post-operative pulmonary function testing showed continuing upper airway obstruction: longstanding compression of the trachea had caused tracheomalacia.

A vascular ring is a congenital malformation, in which the trachea and oesophagus are encircled by arteries—sometimes together with the ligamentum arteriosum. The double aortic arch is the commonest cause of a vascular ring. Magnetic resonance angiography (MRA) showed a double aortic arch, the left side of which was largely atretic.

Surgical treatment eradicates symptoms in over 70% of patients—although airflow limitation may persist, because of residual tracheal compression or tracheomalacia—and is generally done in infancy, despite an estimated perioperative mortality rate of 3%. Only rarely does a double aortic arch present in adulthood. However, when apparent asthma is unresponsive to treatment, other diagnoses should be considered, and spirometry done.

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