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Increasing COPD awareness

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EARLY DETECTION OF COPD BY HIGH RISK-POPULATION SCREENING

Summary

Early diagnosis and smoking cessation are the only available methods to stop the progression of chronic obstructive pulmonary disease (COPD). The aim of this study was to evaluate the effects of early detection of airflow limitation (AL) in a population with high risk for COPD, using spirometric screening.

Smokers aged $\geqslant$40 yrs with a smoking history of $\geqslant$10 pack-yrs were invited to visit a local outpatient chest clinic for simple spirometry (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)). Smoking history was recorded, followed by smoking cessation advice relating the results of spirometry to the smoking behaviour. Subjects who did not fulfil the above criteria (younger and/or nonsmokers) were also screened.

A total 110,355 subjects were investigated; they were aged 53.5$\pm$11.5 yrs and 58.2% were males. Of the total amount of subjects, 64% were current smokers, 25.1% were former smokers and 10.9% were lifelong nonsmokers. Spirometry tests were within normal values for 70.3%, and 20.3% showed signs of AL: this was mild in 7.6%, moderate in 6.7% and severe in 5.9%. The remaining 8.3% of subjects presented with a restrictive pattern of ventilatory impairment. Airflow limitation was found in 23% of smokers aged $\geqslant$40 yrs with a history of $\geqslant$10 pack-yrs.

This study concluded that large-scale voluntary spirometry screening of the population with high risk for COPD detects a large number of subjects with AL.

Introduction

COPD is a major cause of morbidity and mortality worldwide, and evidence suggests that the mortality rate is increasing [1–3]. Assuming that the current trends in mortality continue, COPD will move from the sixth leading cause of death worldwide in 1990, to the third in 2020 [4].

Recent epidemiological studies in Europe demonstrated that COPD affects ~9% of the adult population, mostly smokers [5–7]. A national survey on spirometric signs of AL in a representative sample of the US population of $\geqslant$25 yrs, has shown that AL was present in 8.8% of the investigated subjects [8].

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COPD is diagnosed very late in its natural history. In the National Health and Nutrition Examination Survey (NHANES) III, 71.7% of subjects with a mild AL did not have a current diagnosis of obstructive lung disease [8]. Only half of the subjects with moderate-to-severe pulmonary function impairment had been diagnosed and treated.

A late diagnosis results in high cost of treatment (direct medical costs) and indirect costs [9, 10]. There is no effective pharmacological treatment known to reduce the progression of the disease [11–13]. Early detection of the disease combined with smoking-cessation counselling and treatment seems to be the only currently available method to control COPD [14, 15]. There are two approaches to detection of COPD at an early preclinical phase: case finding [16, 17] and high risk-population screening [18].

The aim of this study was to evaluate the effects of large-scale detection of COPD by offering free spirometric screening to the population at high risk for COPD. The high-risk population was defined as smokers aged $\geqslant$40 yrs with a smoking history of $\geqslant$10 pack-yrs.

Methods

Organisation of the project

The Know the Age of Your Lung project was sponsored by the Ministry of Health, Warsaw, Poland. The National Tuberculosis and Lung Diseases Research Institute in Warsaw (Poland) was responsible for implementation and coordination of the project. The Institute developed a questionnaire on respiratory symptoms and smoking history for persons screened. Written educational and smoking cessation materials were developed for study participants. A central database was developed and managed by the Institute, which performed final analysis of the results. The Institute was also responsible for a publicity campaign (TV, radio broadcasts, and local and national press) regarding the causes and symptoms of COPD.

The project was conducted in 98 outpatient chest clinics throughout the country. All physicians received 2 days of training to ensure consistency of interrelated reliability in the use of the protocol for the investigations. Data from each of the participating centres were electronically downloaded into the study database.

Target population

The target population consisted of current and former smokers aged $\geqslant$40 yrs with a smoking history of $\geqslant$10 pack-yrs. They were invited to undergo free spirometry through mass media appeals and advertisements displayed in public places. Primary care physicians in the cities involved were asked to encourage eligible patients to participate in the project. Although the target population was defined as smokers aged $\geqslant$40 yrs, it was decided that all persons who were concerned with their lung health would be included in the programme.

Procedures

All subjects completed a questionnaire containing demographic and anthropometric data, a short history of any previous or present lung disease and a history of smoking. Subjects declaring past diagnosis of asthma, bronchiectasis or sequelae of tuberculosis were excluded. Simple spirometry was then performed by an experienced certified technician at the lung function laboratory of the clinic. All health professionals involved in the project had undergone 2 days of training to assure quality control of spirometry. FVC and FEV_1 were recorded following American Thoracic Society (ATS) guidelines [19]. The following spirometers were used in this study: Alpha 3 spirometer (Vitalograph Ltd, Maids Moreton, Buckingham, UK), Pneumo 2000 (ABC Med., Kraków, Poland), Lungtest 500 or Lungtest 1000 (MES, Kraków, Poland) and the Pneumoscreen (Jaeger, Würtzburg, Germany). All models used in the study fulfilled ATS criteria [19]. Models requiring frequent calibration were calibrated daily.

AL was diagnosed if the FEV_1/FVC ratio was <0.7 [1]. The severity of AL was classified according to the European Respiratory Society (ERS) guidelines as mild (FEV_1 $\geqslant$70% predicted), moderate (FEV_1 50–69% pred) and severe (FEV_1 $<$50% pred) [20]. Predicted values were those of the European Community of Coal and Steel approved by the ERS [21].

The visit was concluded by an interview with the physician involved in the project. During the interview, the physician showed the patient their spirometry result on the modified Flecher's and Peto's graph and explained the relationship between smoking and the progression of the disease, as well as the benefits of quitting smoking. Current smokers were strongly advised to stop smoking and received a booklet on how to stop smoking. The relatively high risk of lung cancer, myocardial infarction and stroke in subjects with a low FEV_1 was also addressed. Subjects with newly detected AL received a referral letter to their primary care physician recommending further diagnostic evaluation and treatment.

Statistical analysis

Tests were considered significant when $p<0.05$. Data distribution was analysed using the Kologomorov–Smirnov test with Lilliefors correction. Quantitative data are expressed as mean$\pm$SD.

Between-group characteristics were described using ANOVA. Homogeneity of variance was assessed using Levene's test. If data showed normal distribution and homogenous variance, Fisher's ANOVA was applied. *Post hoc* comparisons were performed using Scheffe's test, verified with Tukey's for different N tests (Spjotvoll–Stoline modification). For non-normal data distribution or non-homogenous variance, a nonparametric Kruskal–Wallis H test was used. To characterise relation strength between variables, Pearson correlations were used. Categorised qualitative between-group analyses were performed using the Pearson Chi-squared test with appropriate corrections for N.

Results

Demographic

Between October 2000 and December 2003, 110,355 subjects were investigated. Their mean age was 53.5$\pm$11.5 yrs. Of the subjects, 64,189 (58.2%) were males and 46,166 (42.8%) were females; the mean age was 54.28$\pm$11.8 yrs for males and 52.75$\pm$11.0 yrs for females. There were 16,829 subjects (15.25% of the total) who were $<$40 yrs or never-smokers, or both.

Attitudes towards smoking

The smoking status was not reported in 2% of the participants. Of the participants, 64% were current smokers and 25.1% were former smokers. The remaining 10.9% declared themselves as lifelong nonsmokers. Smoking history of current and former smokers averaged 29.09±18.9 pack-yrs.

Spirometry

Of the 110,355 spirometries performed, 1.5% (n=1,693) were technically unsatisfactory and were not included in the analysis; 70% (77,616) of the results were within normal limits. AL was diagnosed in 20.3% (22,022) of the subjects, mild in 7.6% (8,244), moderate in 6.7% (7,319) and severe in 5.9% (6,459). The remaining 8.3% (9,024) had a restrictive pattern of ventilatory impairment.

Of the current and former smokers (⩾10 pack-yrs) aged ⩾40 yrs, 23% (18,479) had spirometric signs of AL. Mild AL was found in 8.43% of those subjects, moderate in 7.6% and severe in 6.97%. Detailed results of spirometry in current and former smokers stratified for age and smoking intensity categories are shown in table 1. Prevalence and severity of AL increased with age and tobacco exposure.

AL was more frequent in males than females (23.9% *versus* 15.7%, p<0.001), reflecting higher tobacco exposure in males. In addition, the severity of AL was more advanced in males than in females (7.55% *versus* 3.88%, p<0.001). However, there was no difference in frequency of restrictive pattern of ventilatory impairment between males and females (8.34% in males and 8.36% in females, p=0.91).

AL was found in 12% (1,262) of lifelong nonsmoking subjects (table 2). There was no difference in the frequency of AL and its severity between males and females. Restriction was more frequent in females (p<0.001). There was also a significant trend in AL prevalence with increasing tobacco exposure (table 3). When the cohort of current and former smokers was stratified to specific age groups (<35, ⩾35, ⩾40 and ⩾45), the prevalence of AL detected was 7.53%, 21.88%, 22.32% and 23.97%, respectively.

Respiratory symptoms

Respiratory symptoms and sputum production were reported by 52.53% of participating subjects with normal lung function. One-third (33.48%) of subjects with AL did not report any respiratory symptoms, whereas the rest declared chronic cough or chronic cough with sputum production.

TABLE 1 Results of spirometry in 95,185 current and former smokers stratified for age and smoking exposure groups

Category	Airflow limitation				Restricted	Normal
	Mild[#]	Moderate[¶]	Severe[+]	Total		
Aged ⩾40 yrs, ⩾10 pack-yrs	6777 (8.43)	6100 (7.60)	5602 (6.97)	18479 (22.98)	7047 (8.76)	54877 (68.25)
Aged ⩾40 yrs, <10 pack-yrs	495 (5.67)	436 (4.99)	370 (4.24)	1301 (14.90)	583 (6.68)	6847 (78.42)
Aged <40 yrs, ⩾10 pack-yrs	161 (4.69)	92 (2.68)	28 (0.82)	281 (8.18)	99 (2.88)	3054 (88.93)
Aged <40 yrs, <10 pack-yrs	97 (3.71)	63 (2.41)	23 (0.88)	183 (6.99)	100 (3.82)	2334 (89.19)
Total	7530 (7.90)	6691 (7.02)	6023 (6.33)	20244 (21.27)	7829 (8.23)	67112 (70.51)

Data are presented as n (%). [#]: classified as forced expiratory volume in one second (FEV_1) ⩾70% predicted; [¶]: FEV_1 50–69% pred; [+]: FEV_1 <50% pred.

TABLE 2 Spirometry in 10,195 lifelong nonsmokers

Variable	Total	Males	Females	Males *versus* females p-value
Subjects n	10195	3458	6737	
Normal lung function	8038 (78.84)	2781 (80.42)	5257 (78.03)	<0.01
Airflow limitation	1262 (12.38)	434 (12.55)	828 (12.29)	0.73
Mild[#]	554 (5.43)	201 (5.81)	353 (5.24)	0.25
Moderate[¶]	422 (4.14)	125 (3.61)	297 (4.41)	0.06
Severe[+]	286 (2.81)	108 (3.12)	178 (2.64)	0.18
Restriction	895 (8.78)	243 (7.03)	652 (9.68)	<0.001

Data presented as n (%), unless otherwise stated. [#]: classified as forced expiratory volume in one second (FEV_1) ⩾70% predicted; [¶]: FEV_1 50–69% pred; [+]: FEV_1 <50% pred.

TABLE 3 Results of spirometry in current and former smokers according to smoking-exposure categories

	Pack-yrs				
	<10	10–19	20–29	30–39	⩾40
Airflow limitation	1486 (13.08)	3346 (15.97)*	4412 (19.00)§	4232 (23.06)§	6784 (31.83)§
Mild#	592 (5.21)	1415 (6.75)f	1717 (7.39)f	1637 (8.92)**	2170 (10.18)***
Moderate¶	501 (4.41)	1060 (5.06)f	1495 (6.44)f	1382 (7.53)*	2266 (10.63)§
Severe+	393 (3.46)	871 (4.16)f	1200 (5.17)f	1213 (6.61)*	2348 (11.02)§

Data presented as n (%). #: classified as FEV1 ⩾70% predicted; ¶: FEV1 50–69% pred; +: FEV1 <50% pred. Significant differences between first and other columns are as follows: *: p<0.05; **: p<0.01; ***: p<0.001; §: p<0.0001; f: nonsignificant.

Discussion

The present study reports the results of the first large-scale attempt to detect COPD by spirometric screening of the population with high risk of the disease. Of the investigated current or former smokers aged ⩾40 yrs exposed to ⩾10 pack-yrs of smoking (fulfilling the entry criteria for the high-risk population), 23% presented with spirometric signs of AL.

The high yield of subjects with AL in the present study was comparable to results from the Lung Health Study, which screened >73,000 smokers aged 35–60 yrs [22]. Of the subjects screened for that study, 30% presented with signs of AL. The higher yield of subjects with AL in the Lung Health Study may be explained by higher tobacco exposure. The present subjects had a history of 29 pack-yrs, whereas patients in the Lung Health Study group had a history of 40 pack-yrs. The prevalence of AL in lifelong nonsmokers in the present study was 12%. Contrary to NHANES III survey results, there was no difference in prevalence of AL between never-smoking males and females [8].

The results of the study confirmed that AL was largely undiagnosed. Of the 6% of the study population who were found to have severe AL on spirometry, none had been diagnosed previously by a physician. This study also confirmed that the prevalence of AL increased with cumulative tobacco exposure.

The results of the present study may be compared with the effectiveness of the case-finding method. VAN SCHAYCK *et al*. [23] reported the results of spirometric screening of smokers aged 35–70 yrs who were seeking medical attention in a general practitioner's office. Of 201 smokers who were not taking drugs for a pulmonary condition, 169 produced a reliable spirogram. Of these, 18% presented with FEV1 <80% pred. However, effectiveness of the method was low. By testing one smoker per day, an average practice could identify one patient with an impairment of lung function per week. Such a low yield was probably related to the characteristics of patients attending the primary care physician's office. Usually, middle-aged ''healthy'' smokers seek medical advice for an acute medical condition, which is not a suitable time to perform spirometry.

Presence or absence of cough and sputum production was not helpful in heralding AL. Slightly more than half of subjects with normal spirometry presented with respiratory symptoms. In contrast, AL was found in 67% of subjects with symptoms and also in 33% of subjects who reported no respiratory symptoms. These findings are in agreement with the results of a recent study by BUFFELS *et al*. [24], who analysed the usefulness of spirometry performed by general practitioners in early diagnosis of COPD. They found that the number of newly diagnosed cases of COPD increased by 42% with spirometry compared to the diagnosis based on a questionnaire on signs and symptoms of COPD alone.

The main problem with spirometric measurements performed in the primary care setting is their accuracy. EATON *et al*. [25] found that only 30% of 1,000 spirometries performed in the primary care setting included at least two acceptable recordings. Insufficient quality of spirometries performed in the primary care setting was also reported recently by SCHERMER *et al*. [26], which is in contrast with the high repeatability of spirometries performed by experienced personnel reported by ENRIGHT *et al*. [27].

Another potentially negative effect of spirometric screening is the risk of reinforcing the smoking habit in smokers with normal spirometry. It seems that those fears are unsubstantiated. A recent study by GORECKA *et al*. [28] showed that 8.4% of smokers with normal lung function stopped smoking after spirometry combined with simple smoking-cessation advice.

There is no agreement regarding the lower age limit for screening of subjects for early diagnosis of COPD; it ranges from 35 to 45 yrs [23, 29]. The present data suggest that screening should start from 35 yrs of age. However, the difference in the overall yield of subjects with AL in the age group ⩾35 yrs and ⩾45 yrs is only 2% (21.88% *versus* 23.9% of AL detected, respectively). This would support the opinion that screening should start from 45 yrs of age. However, at that age, the prevalence of severe AL diagnosed during screening was already one-third of the total number of the current subjects with AL. This can hardly be called an early diagnosis.

The present study has some limitations. The index FEV1/FVC <70% was arbitrarily accepted as a sign of AL [1, 2]. The use of such a fixed cut-off point may lead to underestimation of AL in the youngest subjects and overestimation of AL in the oldest subjects. Although the mean age of the studied subjects was 53 yrs, 27% of subjects were aged >60 yrs in whom the lower limit of normal for FEV1/FVC was <70% [30, 31]. The number of subjects <30 yrs of age in whom AL may have been underestimated was 2.8%.

Another problem is the reliability of the spirometric measurements. It has been assumed that the quality of measurements was good. They were performed in specialised lung function labs by experienced certified technicians. Only 1.5% of spirometric results were not evaluable. Recently, ENRIGHT *et al*. [27] confirmed very high reliability of spirometric measurements performed by pulmonary function technicians in a laboratory setting.

Both methods (case-finding and high risk-population screening) have positive and negative aspects. Considering the large number of middle-aged smokers that should be screened for COPD, there is a function for both. Primary care physicians should perform forced spirometry in patients fulfilling the criteria for high risk of COPD. This approach could be reinforced by inviting (*via* a letter or phone call) smokers aged $\geqslant$40 yrs registered in their practice to report for spirometric tests. Such a method was used recently by STRATELIS *et al*. [32]. All smokers aged 40–55 yrs from a community of 88,000 inhabitants were invited (by posters) to visit their primary health centre for a free spirometry testing. A total of 512 (9.6%) of invited smokers responded. Spirometry showed signs of AL in 27% of participants; AL was mild in 85% of participants. In countries where office spirometry equipment is uncommon in the primary care setting, large-scale spirometric screening of healthy smokers should be developed.

Early diagnosis and effective behavioural and pharmacological interventions have led to substantial reductions in the prevalence of and mortality from cardiovascular diseases over the last 40 yrs. The time has now come to adopt a similar strategy to control the disease that is the third leading cause of death in developed countries. An increasing number of sustained quitters among subjects with mild-to-moderate AL would substantially reduce morbidity and mortality from COPD.

COPD AND FEMALES

Summary

This section is mainly based upon two *Monographs* [33, 34] and the *European Lung White Book* [35] published by the ERS.

Gender differences in obstructive airway diseases result from the interaction of sex-dependent genetic factors and socio-cultural gender differences in childhood, adolescence and adulthood. Gene/environmental interactions occur in asthma and COPD. Sex differences in lung physiology and immune response influence the patterns of obstructive pulmonary diseases. Increasing evidence supports the view that sex hormones influence airway behaviour throughout the human lifespan. There are also differences in environmental factors between genders, relating to the frequency and the type of exposure (smoking, occupation, air pollution *etc*.) for which females appear to be at greater risk. More attention should therefore be paid to the home environment.

In addition, the clinical pattern of diseases may differ between genders. There are gender differences in the perception and reporting of symptoms, which are also reflected in diagnostic labelling and management. Thus, more epidemiological research should be devoted to studying hormonal influences and sociocultural-dependent risk factors. Standardisation for gender is to be replaced by stratification. Information about the reproductive history of females and their current endocrine status should be further pursued in aetiological research and in the evaluation of the treatment outcomes.

Finally, some original findings on gender-related differences from the Po Delta [7, 36–40] and Pisa [38, 39, 41] surveys in Italy are presented in this section.

Introduction

In November 2003, the ERS released the first comprehensive report on lung diseases in Europe, the *European Lung White Book* [35]. Taken together, lung diseases in 1990 were responsible for 9.4 million deaths worldwide, representing 18.7% of overall mortality and ranking first among the specific causes of death. In 2010, COPD will represent the fourth cause of death in Europe and, in 2020, the third worldwide [4]. There were 2.2 million deaths caused by COPD worldwide in 1990, which is likely to become 4.7 million in 2020. COPD also costs more than asthma (€38.7 *versus* €17.7 billion), due in particular to in-patient care and lost working days [35].

Much of what is known about the epidemiology of obstructive pulmonary diseases in females has recently been reviewed in two issues of the *European Respiratory Monograph* [33, 34]. Two other review articles were also published in 2004 [42, 43].

Sex and gender

KAUFFMANN and BECKLAKE [44] describe the influence of sex and gender on the development of respiratory diseases. In particular, sex differences concern genetic and biological factors, whereas gender resemblance concerns environmental and sociocultural factors. These two aspects influence the path that leads from risk factors to perception of health effects, as reported by the subject. There are the following sex and gender differences in risk factors of obstructive pulmonary diseases.

1) Sex-specific risk factors: hormonal levels (androgens, oestrogen, progesterone), for which there are limited data; menstrual cycle (follicular phase, luteal phase), for which there are epidemiological data on premenstrual asthma; pill (during, after), for which there are limited data; pregnancy (which includes three different trimesters, labour, the influence of the mother on the foetus, the influence of the foetus on the mother, number of pregnancies, treatment for having a baby, changes in respiratory treatment during pregnancy, lactation), for which there are epidemiological data on changing asthma status during pregnancy, but few data on determinants of change; menopause (natural/other, hormone replacement therapy), for which there is evidence of decreased asthma incidence with partial reversal under hormone replacement.

2) Environmental factors that are common to both genders, with marked differences in the prevalence or nature between genders or for which sex/gender may be a modifying factor, are shown in table 4.

An example of greater female susceptibility to smoking is found in a paper by GOLD *et al*. [46], who presented a decreased FEV_1 growth rate in females who smoked more than five cigarettes per day compared with males. Another example pertains to the relative risk of hospitalisation for COPD in the

TABLE 4 Environmental factors common to both genders

Factors with a marked difference in prevalence or nature between genders
Passive smoking. Evidence suggests more females are exposed and that they may be more susceptible than males [44].
Alcohol consumption. Evidence suggests more males are exposed [44].
Hygiene/cosmetic products. Evidences suggests more females are exposed [44].
Time-activity patterns, which are gender related [44].
Indoor exposures [44].
Home environment (cleaning and cooking), which is known to be more under the control of females, thus more females are exposed [44].
Hobbies. It is known that males are more likely to be involved in industrial processes in home workshops (wood and metal work, automobile restoration, use of low molecular weight asthmagens, *e.g.* isocyanates) [44].
Occupational exposure, which is almost male-specific for exposure to mineral dust (*e.g.* coal, hard rock mine dust) and to asthmagens (such as chemicals, isocyanates), whereas more females are exposed in textiles/manufacturing/dry cleaning. In agriculture there are fewer gender differences [44].
Income, which is generally higher in males [44].
Factors in which sex/gender may be a modifying element
Active smoking. Current knowledge shows gender-specific cohort changes (cultural) and females tend to be more susceptible [44].
Childhood infections, for which it is known that young males are more susceptible (genetic?) [44].
Sport/exercise, which is generally practiced more by young males and is more valued in males [44].
Occupational factors [44].
Nutrition, which appears more under the control of females [44].
Socioeconomic status [44].
Air pollution, to which females may be more susceptible [45].

Glopstrup Population Studies [47], which showed this to be much higher in females than males either in those smoking 1–30 pack-yrs or in those smoking >30 pack-yrs. Similar results were found by the same authors in the Copenhagen City Heart Study [47], in which smokers were stratified into three groups (1–20, 21–40 and >40 pack-yrs). It is also important to point out the presence of diagnostic bias of asthma in relation to gender [48]. The incidence of attacks of shortness of breath with wheezing are always higher in males than in females in every age group, while the reverse is true for incidence of asthma diagnosis.

BECKLAKE [49] comprehensively reviewed the factors accounting for the differences between males and females in airway physiology. They occur throughout the lifespan from the prenatal period. There is evidence that the female foetus is more mature than the male foetus in terms of surfactant production from 32 to 38 weeks' gestation. In the peri- and post-natal period of <1 yr, there is evidence that female neonates are at a lower risk for respiratory distress syndrome and more responsive to hormone accelerators of surfactant production than male neonates. Moreover, the lungs of female infants are smaller on average than those of male infants but they have higher absolute as well as size-corrected flow rates than male neonates. In childhood, up to ~10 yrs, although young females' lungs continue to be smaller than young males' lungs, their specific airway resistance is lower. From 6–10 yrs, large airways grow proportionally to lung volumes in young females' lungs but lag behind in young males' lungs, whereas small airways grow faster than lung volumes in young females' lungs but grow proportionally in young males' lungs. Furthermore, forced expiratory flow rates are higher in young females' lungs than in young males' lungs, controlling for volume. From early adolescence up to mid-teens, the peak velocity for increase in height occurs ~2 yrs earlier in adolescent females than in adolescent males. FEV_1 in relation to height and FEV_1/FVC remain higher in female than in male adolescents. In later adolescence (mid-to-late teens), growth velocity for FVC plateaus in females after height stabilises, but continues at a lower pace in males until their mid-20s. Further growth of total lung capacity (TLC) is slower in female than male adolescents and growth of flow rates relative to TLC appear to be dysanaptic in females and isotropic in males. Finally, effort-independent flow rates remain higher in females than in males. In early adulthood (late teens to mid-20s), lung volumes (TLC, FVC) remain stable in young females but continue to increase in young males. These physiological factors have been the basis for the explanation of higher incidence of bronchial responsiveness in females than in males, and for the higher susceptibility of females to air pollution, including cigarette smoking [45–47].

There is also evidence of sex differences in markers of atopy in the female's life cycle, presented in a longitudinal study in Tucson, Arizona (USA) [50–52]. For example, below the age of 5, more females appear to be skin-test positive than males; the same appears to be the case in those aged 15–54 yrs and >75 yrs. In contrast, levels of immunoglobulin (Ig)E are always higher in males. Thus, the sex differences in IgE are consistent, whereas those in skin-test positivity are inconsistent. There are also gender differences in the relationship of reported shortness of breath with FEV_1. Data from the French study PAARC (Pollution Atmospherique Affections Respiratoires Chroniques) show that for each quintile of FEV_1, females report a much higher prevalence of shortness of breath [53]. In the same study, there are also data on the incidence of asthma, which is higher in males up to the age of 14; between 15 and 19 yrs of age, the incidence is the same in both sexes, while it becomes higher in females up to 49 yrs of age. In the eldest age group examined (50–54 yrs), the incidence becomes higher again in males. In the Po Delta survey [36], females have been shown to have higher rates of bronchial hyperresponsiveness than males. Confirmation of these findings came from a recent general population survey in

six Canadian locations [54]. In a multivariate model, female gender has been associated with an increased risk for bronchial hyperresponsiveness (provocative dose causing a 20% fall in FEV1 $\leqslant$1 mg); odds ratio (OR) 2.16, 95% confidence interval (CI) 1.64–2.84.

Smoking

Issues pertaining to active smoking are reviewed in a paper by SLAMA [55]. In two important cohort studies (one performed in the United States, the other in Copenhagen, Denmark), the risk of disease incidence is still higher in males for cancer of the lung, while all tobacco-related cancer incidences and the risk of all respiratory disease in those with >15 cigarettes smoke daily are higher in Danish females; in the American study, females show an increased risk of cancer of the oesophagus and COPD [56, 57]. In the Copenhagen Centre for Prospective Population Studies, PRESCOTT *et al*. [58] found that females have higher relative risks of death from respiratory disease than males in each smoking category; for example, in females and males, respectively, in ex-smokers OR 2.96 (CI 1.80–4.87) *versus* 1.39 (0.77–2.51), in current smokers of 1–14 g·day^{-1} OR 5.21 (3.23–8.41) *versus* 2.42 (1.34–4.37), and in current smokers of >24 g·day^{-1} OR 23.71 (12.30–45.73) *versus* 4.68 (2.52–8.69). Furthermore, Danish female smokers have also shown a steeper decline in FEV1 than male smokers [47].

The World Health Organization (WHO) Atlas, published in 2003, provides recent data on smoking prevalences across the world [59]. Currently, about 1 billion males and 250 million females across the world smoke, with marked geographical differences between the sexes. The highest rates in males are found in Asia, especially China. Conversely, in females, the highest rates are in France, Germany, and Norway. In Norway and Sweden, the proportion of female smokers is similar to the proportion of males. EZZATI and LOPEZ [60] have estimated that in the year 2000, 3.84 million deaths in males and 1 million in females worldwide were due to smoking. The mortality fraction attributed to smoking ranged between 91/92% for lung cancer and 84/77% for COPD in males, whereas in females it ranged between 70/72% for lung cancer and 62/61% for COPD.

In their studies, ULRIK [61] and WATSON *et al*. [62] reported on gender similarities in smoking habits and dissimilarities in the natural history of asthma and COPD. According to recent data from the US and Denmark, the historical trend of decrease in smoking habit has been much steeper in males than females, and in the year 2000, more females were smokers than males (>40% in Denmark and 25–30% in the US) [63, 64]. This phenomenon is explained by the sequential birth cohorts *versus* mean age at smoking initiation in males and females in the US [65]. Mean age was almost steady (around 17–18 yrs) in males from 1901 to 1951, whereas females from the 1901 birth cohort started to smoke at a mean age of 30 yrs; female mean age decreased substantially up to the same age as males in the 1951 birth cohort. PRIDE and SORIANO [66] have described the historical trend in tobacco consumption in the UK for the period 1905–1987 and the prevalence of smoking in England for the last quarter of the 20th century. In the last decade, the gender differences have almost vanished. It is clear that in some countries, like Denmark, the observed number of deaths from COPD after the 1990s has already risen higher in females than in males. Furthermore, MANNINO [67] recently reported that in the year 2000 the absolute numbers of female deaths due to COPD in the US exceeded male deaths for the first time.

COPD and gender

The number of females hospitalised due to COPD in Canada was estimated to exceed the number of males by the year 2001, with the gap increasing steeply up to 2016 [68]. Similarly, the number of COPD deaths in females was projected to exceed that in males by the year 2006, with the gap increasing steeply up to 2016. Conversely, in Singapore, rates per 10,000 COPD hospitalisations (18.2 *versus* 94.1) and mortality (6.9 *versus* 28.2) have been lower in females than in males, respectively, in the period 1991–1998.

The distribution of COPD between the two genders shows a link to latitude [35]. In countries in Northern Europe, the difference in age-adjusted COPD death rates between males and females is slight, whereas it is quite large in Eastern and Southern European countries. The data of SORIANO *et al*. [69] show an increasing trend in COPD diagnosis in females from 1990 to 1997 (a 69% increase compared with a 25% increase in males). At the end of the period, in patients 20–44 yrs old, UK physicians diagnosed more COPD in females than in males; in patients aged 45–65 yrs, they diagnosed slightly more in males. The prevalence difference remained elevated among males and females >65 yrs. However, after the diagnosis had been made, although females with COPD had the same pattern as males, survival in males was worse at any given level of severity. CHAN-YEUNG *et al*. [68] recently reviewed the data for developing countries, indicating the persistence of a male–female gradient in terms of COPD hospitalisation and mortality rates, as well as tobacco-smoking habit. For the year 2001, they reported a world COPD prevalence of 1.01%, with a range from 0.18% in Africa to 1.68% in Western Pacific regions of WHO.

HALBERT *et al*. [70] summarised the prevalence estimates of COPD, showing clearly that there are still differences between males and females but that these differences are lower in the populations in which spirometry has been applied, such as Italy and Norway. In addition, the authors show that the figures based on WHO were largely underestimated.

The Italian phase of the European Community Respiratory Health Survey determined that in subjects aged 20–44 yrs in the general population, the prevalence of chronic bronchitis was 11.8% in males and 12.0% in females [71]. In a multiple logistic regression model, female sex was associated with a significantly increased OR (1.22, 95% CI 1.10–1.36) of having the condition.

The present author's own epidemiological data collected in the Po Delta Study in Italy were used to compare the prevalence rates of COPD severity, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [2], between males and females of the general population (age range: 8–78 yrs; fig. 1) [7, 36–40]. The author found an additional stage, called ''pre-risk 0'', in which people with habitual cough or phlegm did not meet the definition of chronic symptoms. About 35% of males were classified as

GOLD stage pre-risk 0, 0, 1, 2, 3 or 4 compared to almost 23.4% of females. A total of 17.7% males have shown signs of pre-risk 0 and 0 *versus* 13.6% of females. In 12.3% of males and 7.3% of females, signs of mild COPD were noted. Moderate and severe COPD were around 5% in males and 2.5% in females. By definition, 100% of those with neither cough nor phlegm were in the absence category, 100% of those with either habitual cough or phlegm (not meeting the definition of ''chronic'') were in the pre-risk 0 category, and 100% of those with either chronic cough or phlegm were in the at risk category (fig. 2).

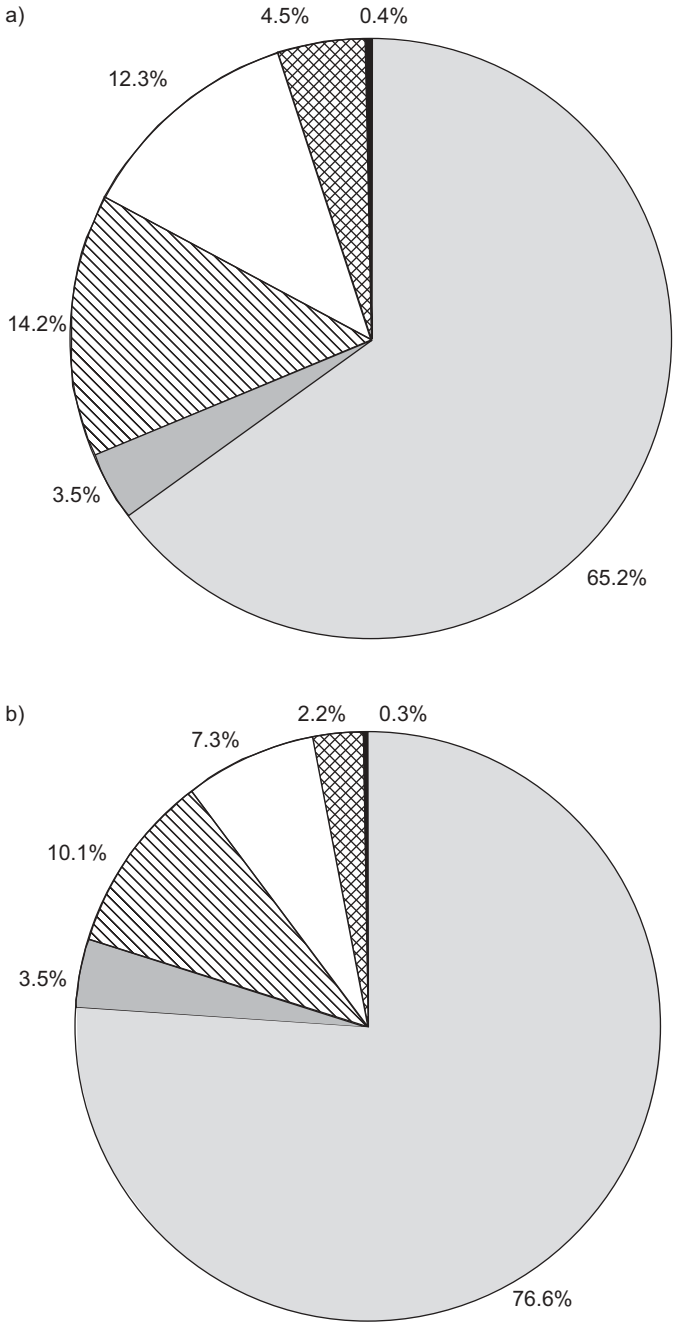

FIGURE 1. Prevalence of chronic obstructive pulmonary disease (COPD) severity by gender in the Po Delta survey, in a) males (n=1,214) and b) females (n=1,250). ▫: absence; ■: pre-risk 0; ▨: at risk of COPD; □: mild COPD; ▪: moderate COPD; ■: severe COPD.

Although GOLD classification does not take into account symptoms when airflow obstruction is already present to gradual severity of COPD, there is an increasing trend to have a larger proportion of patients with airflow obstruction and simultaneous presence of symptoms in mild-to-severe COPD both in males and females. In the latter category, ~80% of subjects are symptomatic.

Environmental risk factors in females

A paper by BLANC [72] discusses domestic environmental exposures and their potential contribution to respiratory diseases among females. These environmental factors are as follows: 1) biomass fuels, which expose females to particulates and can cause airway obstruction; 2) gas fuels, which expose females to nitrogen dioxide and can cause asthma exacerbations; 3) cleaning agents, which can expose females to hypochlorite/chlorine gases or other irritants and can produce irritant lung injury, irritant bronchitis and asthma; and 4) environmental tobacco smoke, which exposes females to irritants and carcinogens and can cause respiratory symptoms and cancer.

In their paper, WAI and TARLO [73] cite examples of lung diseases in occupations that are relatively common amongst females, as

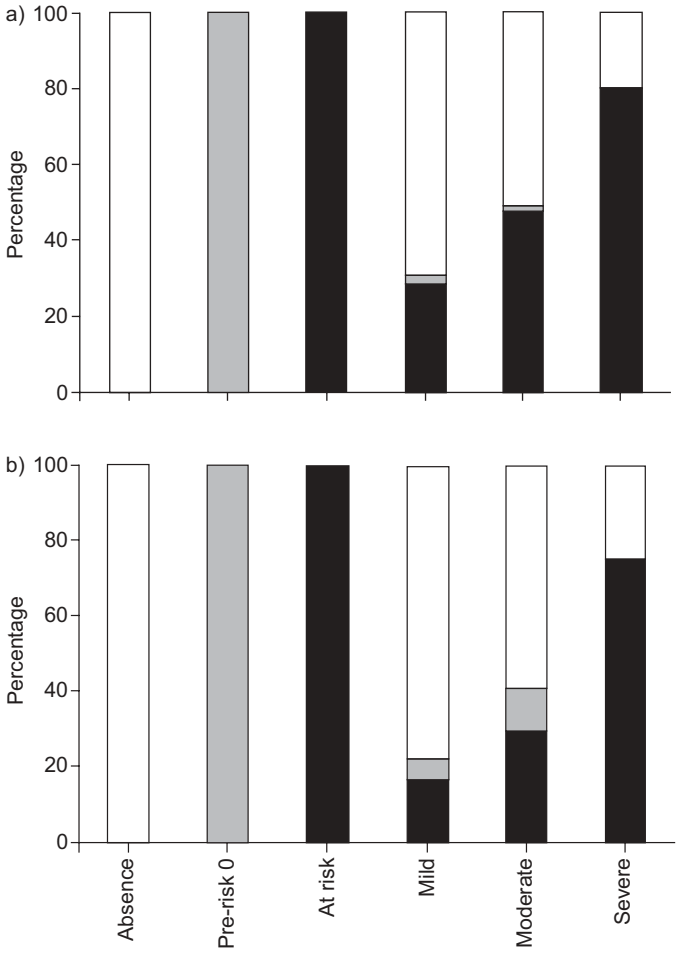

FIGURE 2. Distribution of chronic obstructive pulmonary disease severity according to symptoms in Po Delta survey, in a) males and b) females. □: absence of symptoms; ▪: occasional symptoms; ■: chronic symptoms.

well as some causative agents, such as occupational asthma, which can occur in: 1) healthcare workers exposed to natural rubber latex or psyllium and other pharmaceutical agents or formaldehyde; 2) food industry workers (*e.g.* bakers, farmers, food processors) exposed to flour, enzymes, storage mites, eggs and other foods; and 3) house cleaners, exposed to common indoor allergens, cleaning agents, and irritant mixtures. Bronchitis can occur in other industries/occupations in which workers are exposed to irritant dusts, fumes and smoke.

A recent ATS Statement reported estimates on the population attributable risk due to occupational exposure. They were: 15% for asthma; 15% for chronic bronchitis; 19% for lung function impairment; 14% for dyspnoea; and 14% for wheezing [74].

Gender differences in obstructive airway diseases

To summarise, gender differences in obstructive airway diseases result from the interaction of sex-dependent genetic factors and sociocultural differences during childhood, adolescence and adulthood [44]. These are aspects of gene/environmental interactions, which occur in asthma and COPD. Sex differences in lung physiology and immune response influence the patterns of obstructive pulmonary diseases. There is increasing evidence to support the view that sex hormones influence airway behaviour throughout the human lifespan [49]. There are also differences in environmental factors between genders, related to the frequency and the type of exposure (smoking, occupation, air pollution *etc.*), for which females appear at greater risk. More attention should therefore be paid to the home environment. Also, the clinical pattern of diseases may be different between genders. Gender differences in the perception and reporting of symptoms and subsequently in diagnostic labelling and management should also be taken into account. Thus, more epidemiological research should be devoted to studying hormonal influences and sociocultural-dependent risk factors. It is important that standardisation for gender is replaced by stratification. The reproductive history of females and their current endocrine status should also be further pursued in aetiological research and in the evaluation of treatment outcomes.

Changing COPD epidemiology

Finally, it is important to point out that COPD epidemiology is changing. In a follow-up study in Tucson, Arizona (USA), SILVA *et al*. [75] clearly showed that active asthma at baseline is a significant risk factor for subsequent development of chronic bronchitis, emphysema and COPD. VIEGI *et al*. [40] have recently published a paper describing the proportional Venn diagram of obstructive lung disease in the Italian general population. These data confirm that there is overlap between asthma, chronic bronchitis and emphysema, and indicate that up to 15 categories of subjects can be classified with the diagnoses related to COPD [76]. Overall, ~18% of the Italian general population samples report either the presence of obstructive lung diseases or show spirometric signs of airflow obstruction. After stratifying by sex (figs 3 and 4) in the Po Delta Sample [7, 36–40], this percentage climbed to 21.9% of

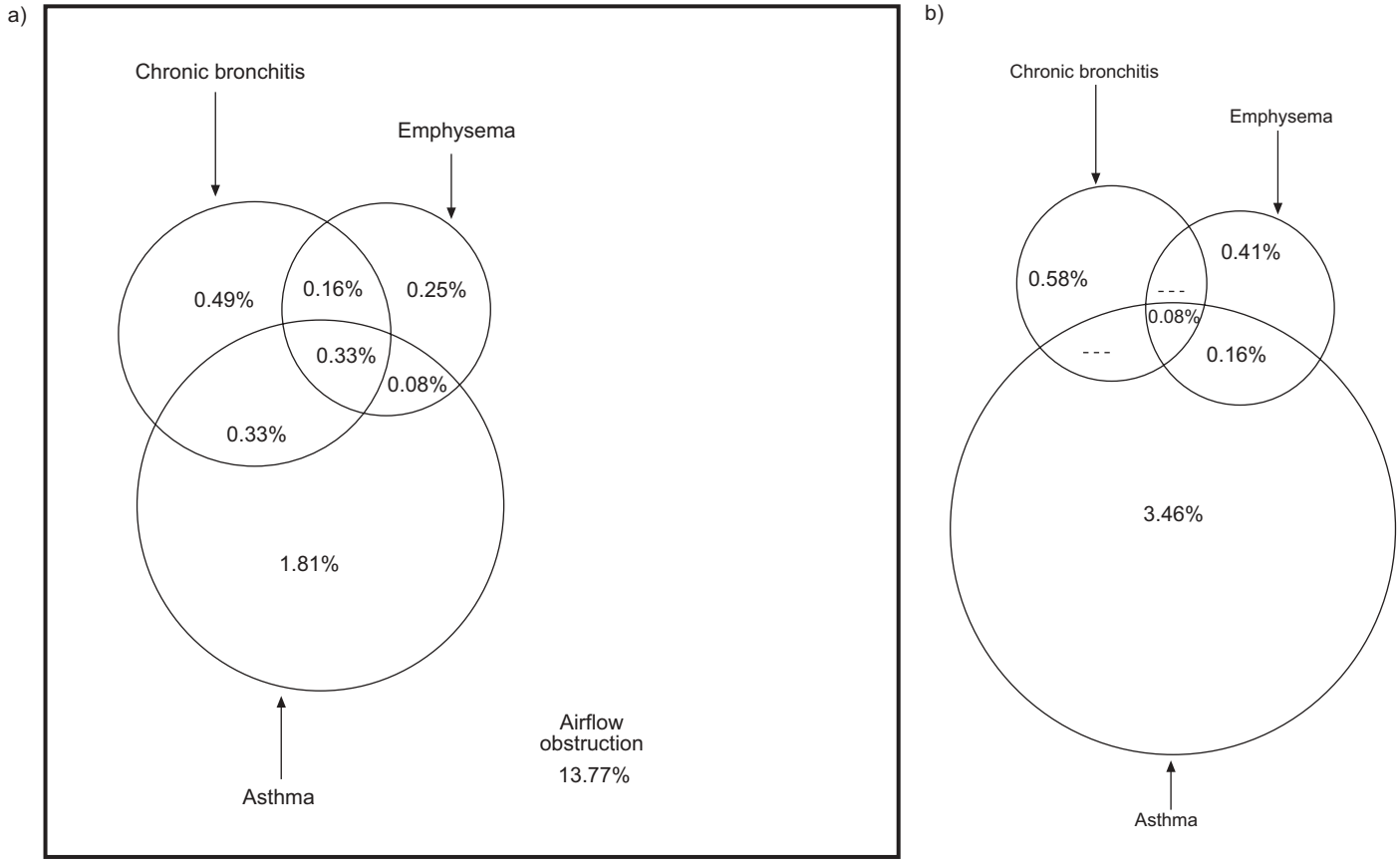

FIGURE 3. Distribution of obstructive lung diseases a) with and b) without airflow obstruction in Po Delta sample males.

males compared with 13.9% of females. The proportion of those with airflow obstruction in the absence of any respiratory diagnosis is 10.96% in the whole population sample (13.77% in males; 8.24% in females). In the Pisa sample, rhinitis has been shown to be an independent risk factor for developing cough, with the exception of common colds, in a 6-yr follow-up, without any difference between males and females [41].

Conclusion

In conclusion, the priorities of epidemiological research on COPD should be as follows [35]. 1) To perform long-term general population surveys with subjective (questionnaires) and objective (spirometry, biomarkers) tools in order to improve the knowledge of the natural history (inception, exacerbations, deaths, costs) of COPD. 2) To implement studies to determine the most effective smoking-cessation interventions and smoking-prevention techniques. 3) To develop new therapeutic modalities that inhibits the decline in lung function.

RAISING AWARENESS OF COPD

Summary

With the exception of smoking cessation, factors in the development and manifestation of COPD have not received the attention of scientists or experts in healthcare delivery warranted by the public health importance of this chronic lung disease. To raise awareness of COPD and for subsequent effective management of the disease, a team approach is required that includes multiple disciplines.

At a local level, effective dissemination and implementation of healthcare recommendations seem to be based on the characteristics of the message, the recognition of external barriers that require change, and how prepared clinicians are to make change. Judging from the success of the asthma coalition groups, developing coalition groups for COPD should be a valuable mechanism that brings awareness campaigns to the local level.

Various initiatives of the GOLD programme and the US COPD Coalition that aim to raise global awareness of COPD, are described in this section. Raising awareness of COPD at global, national and local levels, should eventually result in reduction of the global burden of COPD.

Introduction

Healthcare professionals, community leaders, policy makers, government agencies, the pharmaceutical industry and the public must all work together to develop and provide effective healthcare delivery strategies for patients with COPD. However, with the exception of smoking cessation, factors in the development and manifestation of COPD have not received the attention of scientists or experts in healthcare delivery warranted by the public health importance of this chronic lung disease.

Programmes that raise awareness about COPD, its importance as a public health problem, its symptoms, how to make a diagnosis and how to manage those who are afflicted with this chronic condition are being implemented in several countries. These are based on GOLD [1, 2]. Through the network of individuals involved in the GOLD programme, it is anticipated that much will be learnt about how the diagnosis, treatment and prevention of COPD can be promoted and effectively implemented in a variety of healthcare settings.

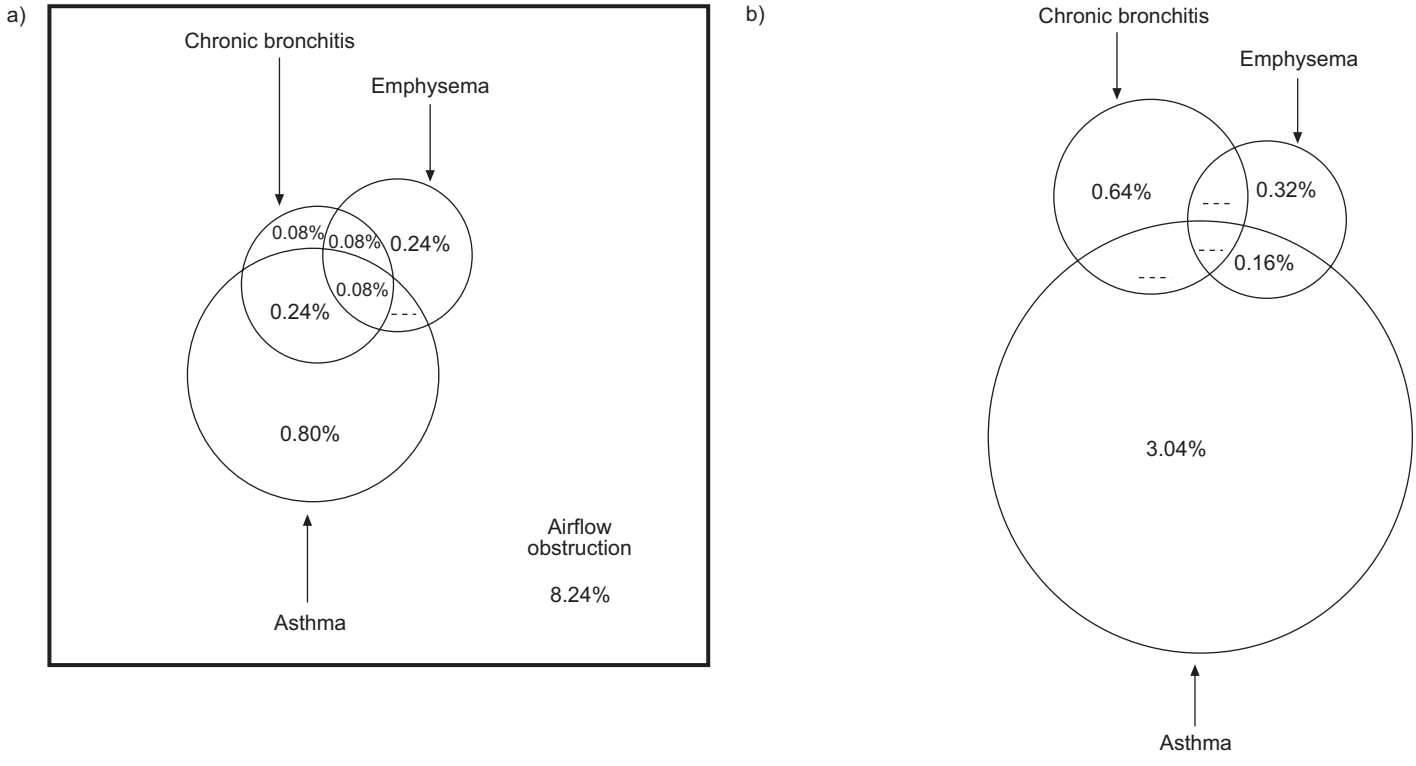

FIGURE 4. Distribution of obstructive lung diseases a) with and b) without airflow obstruction in Po Delta sample females.

For many years, healthcare workers have had a rather nihilistic approach to the care of COPD patients. Awareness programmes designed to make a positive impact will be required. Effective management of COPD is no longer the responsibility of the pulmonary disease specialist alone, but requires a team approach that includes multiple disciplines. At all stages, patients and their families should be actively involved in programmes designed to raise awareness of COPD.

Interventions to promote behavioural changes among health professionals

The translation of research findings to impact on public health requires strategies to promote behaviour changes among healthcare professionals. Many approaches have been taken and there is increasing literature on dissemination and implementation. A Cochrane Group [77] convened to examine the literature on interventions that promote the implementation of research findings, including: dissemination and implementation of guidelines; continuing medical education; strategies, such as audit, feedback and computerised decision support systems; target groups, including nurses and primary healthcare professionals; and particular types of behaviour, such as diagnostic testing, prescribing or aspects of preventive care. Although there were common methodological problems in many of the studies, and heterogeneous issues were addressed, a number of consistent themes were identified that may help to design programmes of awareness for COPD.

For example, passive dissemination of information (such as publication of consensus conferences in professional journals or the mailing of educational materials) was generally found to be ineffective in altering practices. The use of computerised decision support systems led to improvements in performance in such areas as decisions on drug dosage, provision of preventive care and general clinical management of patients, but not in diagnosis (an important issue in the area of COPD). Patient-mediated interventions seemed to improve the provision of preventive care (in studies conducted in North America). At a local level, effective dissemination and implementation of healthcare recommendations seemed to be based on the characteristics of the message, the recognition of external barriers requiring change and how prepared clinicians are to make change.

Raising the awareness of patients/families

Outreach education programmes of the National Heart, Lung and Blood Institute (NHLBI) and the National Institutes of Health (NIH) have taken several approaches to raising the awareness of patients and their families in relation to specific health topics, such as high blood pressure, cholesterol and obesity as risk factors for cardiovascular disease and stroke. In 1990, the NHLBI initiated the National Asthma Education and Prevention Program to raise awareness of the burden of asthma and to implement recommendations for effective treatment and prevention [78].

The NHLBI education outreach programmes are conducted through a coordinating committee comprised of representatives from member organisations, including government agencies, medical and healthcare organisations and patient groups. For example, the National Asthma Education and Prevention Program includes allergy, respiratory, emergency care, and primary care medical organisations; organisations representing respiratory therapists, nurses, allied health personnel and teachers; NIH institutes supporting asthma research; and patient groups, such as the Mothers of Asthmatics. Together, these organisations developed recommendations for asthma management and prevention (guidelines), established avenues for programme dissemination of information (programme awareness) and worked on tools to evaluate programme effectiveness. Multiple indicators (including reduction in mortality; fig. 5) provide evidence that a coordinated programme of good scientific information and a network of partner organisations (stakeholders) to assure programme awareness and information dissemination can impact on patient care.

Among the ''lessons learned'' from the NHLBI National Asthma Education and Prevention Program has been the importance of establishing local ''coalition groups'' to work at the community level to raise awareness of asthma and to improve asthma care. This approach utilizes local networks to enhance the dissemination and utilization of science-based information to change knowledge, practice, and behaviour. It provides information about the target audience (demographics, behaviours, local media, local leaders), and is a means to raise the resources for patient awareness campaigns. The programme has also developed and tested a variety of communication channels including television/video, audio/radio, print, and support materials targeted to local news media outlets. Based on the success of the asthma coalition groups, developing coalition groups for COPD should be a valuable mechanism to bring COPD awareness campaigns to the local level.

Raising global awareness of COPD: the GOLD programme

GOLD was initiated in 1997 in cooperation with the WHO and the NHLBI to increase awareness of COPD, and with the ultimate goal of decreasing morbidity and mortality from this disease. The objective of GOLD is to improve prevention and

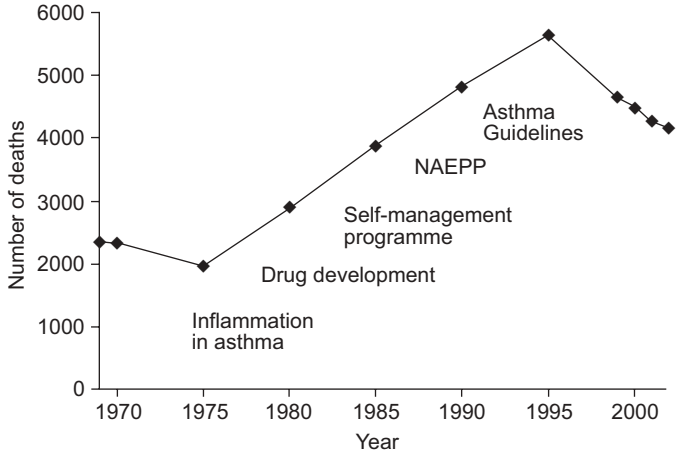

FIGURE 5. Annual mortality from asthma (total population). NAEPP: National Asthma Education and Prevention Program. Reproduced from a lecture delivered by C. Lenfant, during the President's Lecture, at the American Thoracic Society meeting 2004. With permission from C. Lenfant (personal communication, Gaithersburg, MD, USA).

management of COPD through a concerted worldwide effort of people involved in all facets of healthcare and healthcare policy, and to encourage a renewed research interest in this extremely prevalent disease. As a global initiative, the programme is made up of an executive committee, comprised of COPD medical experts, and a representative from four respiratory medical societies (the ATS, the ERS, the Asociación Latinoamericana del Tórax and the Asian Pacific Society of Respirology).

The first step in programme development was to prepare a Workshop Report, ''Global Strategy for Diagnosis, Management and Prevention of COPD'', developed by an expert panel and presented during its development at the annual meetings of the ATS and ERS for wide community comment and input. Prior to its publication in 2001, it was widely circulated and comments received were incorporated. In addition to the Workshop Report, there is an Executive Summary, a Pocket Guide for Health Care Workers, and a Patient Guide [1, 2]. All GOLD reports have been translated into multiple languages and widely distributed. The management segments are updated each year based on published literature [79]. See [2] for the most recent updated report (2004).

The GOLD programme sponsors World COPD Day, held each year on the third Wednesday in November (November 15, 2006) with the theme ''Raising Awareness of COPD''. Through a network of GOLD National Leaders from dozens of countries, World COPD Day brings awareness about COPD at the local level. Every effort is made to develop interactive programmes that directly engage the audience, such as health fairs and conferences about COPD conducted by local doctors. Press materials are made available, which can be tailored to local conditions. Because early diagnosis is an important objective of GOLD, a simple questionnaire, ''Breathing for Life!'', has been developed and is being evaluated as a means to raise public awareness of the symptoms of COPD. The questionnaire has appeared in several public places, such as local newspapers and magazines, as posters on public transport (including buses, subways *etc.*), and in doctors' offices.

Raising national awareness of COPD: the US COPD coalition

Awareness of a chronic disease and implementation of effective treatment and management is a difficult and complex matter. Although the role of the specialist is pivotal, the participation of other healthcare professionals and of communities and families is just as critical. To realise this objective, in 2001 a US COPD Coalition was initiated to raise awareness of COPD in the USA, among patients, health professionals, policy makers and the public [80]. The US COPD Coalition includes medical organisations representing a variety of medical disciplines, government agencies and patient groups.

The work of the US COPD Coalition is just beginning but already some important steps have been taken. In November 2003, the 30 organisations that comprise the US COPD Coalition conducted a workshop to identify specific actions [81]. In March 2004, a Congressional COPD Caucus was formed to raise COPD awareness among Members of Congress and to promote policy to improve the lives of Americans with COPD. The Caucus leadership includes Senator M. Crapo (ID), Senator B. Lincoln (AR), Congressman C. Stearns (FL) and Congressman J. Lewis (GA). A major objective of the Caucus is to develop regulatory and legislative proposals that address the unique challenges and opportunities of COPD communities.

In conclusion, a concerted effort, at the global, national and local levels, will be required before the public and healthcare community are aware of the public health significance of COPD, an important requirement for those interested in reducing the burden of COPD. However, much can be learned from programmes on other chronic diseases about how to reach a variety of target audiences. Working with a multidisciplinary team, including actively participating patients and their families, to raise awareness about COPD, should eventually result in reduction of the global burden of COPD.

COPD: THE JAPANESE EXPERIENCE

Summary

In the recently updated Japanese guidelines for the diagnosis and treatment of COPD, there is an increased emphasis on inflammatory processes occurring in the lung and on the identification of patients in the early stages of COPD through the use of spirometry.

In this section, the authors describe preliminary results of the first nationwide COPD epidemiological study (Nippon COPD Epidemiology Study (NICE)) in Japan [82]. Out of 23,949 eligible households successfully contacted, 19,637 were eligible to participate. Of these, 2,711 (14%) completed the study. After excluding 368 (13.6%) invalid measurements, the NICE study population comprised 2,343 Japanese subjects aged $\geqslant$40 yrs. The prevalence of AL was 10.9%. AL was significantly more frequent in males than females (16.4% *versus* 5.0%). The protocol for the Confronting COPD Study, which has been conducted in four Asian countries, will also be presented in this section.

This section concludes that COPD is largely underdiagnosed in Japan but that it is hoped that the data from these studies will continue to raise the awareness and importance of COPD for practicing physicians and the general public in Japan.

Introduction

According to the updated 2004 Japanese Respiratory Society (JRS) Guidelines for the diagnosis and treatment of COPD, the use of spirometry to establish a diagnosis of COPD is essential in the presence of symptoms (chronic cough/sputum and exertional dyspnoea) and a long-term history of tobacco smoking [83]. The JRS Guidelines were based on the GOLD guidelines and were updated in 2004.

Unlike the traditional concept of the Venn diagrams contained in previous guidelines, the JRS Guidelines put forward the concept of the clinical features of COPD. Emphasis is placed on the importance of peripheral airway inflammation as a result of inflammatory processes caused by noxious particles or gases invading the airways. Recently published data provide compelling evidence to support this concept [84, 85]. While noxious particles might influence lung parenchyma or the central airways directly, there is some unknown mechanism by which this inflammation in peripheral airways

may preferentially advance to lung parenchyma destruction (*i.e.* emphysema) or inflammatory processes in the central airways (*i.e.* chronic bronchitis). The main concept is that all of these inflammatory processes should be called COPD, not just a clinical presentation of chronic bronchitis or emphysema. These are two extreme profiles of clinical entities of the inflammatory processes occurring in the lung.

In order to detect the early stages of this disease before the inflammatory processes manifest as clinical symptoms, a physiological assessment must be performed to detect AL. In the JRS guidelines, staging and degree of AL, measured by varying degrees of reversibility, is similar to that described in the GOLD and ERS/ATS Guidelines [83].

There seems to be a time lag between consumption of tobacco and mortality due to respiratory disease such as lung cancer and COPD. In Japan, male mortality due to COPD parallels the increase associated with the tobacco consumption epidemic, which occurred 25–30 yrs earlier [83]. However, in the clinical setting, there was not much a difference between the total numbers of patients with COPD in 1996 (220,000) and 1999 (212,000), which corresponded with 0.2% of those >40 yrs of age [84]. The percentage of male and female patients diagnosed with COPD in 1996 was 59% and 41% (n=220), respectively, compared with 66% and 34% (n=212), respectively, in 1999.

The discrepancy between predicted mortality increases and the number of COPD patients in the Japanese clinical setting may be explained by genetic differences. SILVERMAN *et al*. [86] described an association between family history and development of COPD. Having a parent with COPD increased the likelihood of developing COPD. It can be hypothesised that Japanese people may be somewhat protected from the development of COPD, up to a given amount of tobacco consumption. In Korean and Japanese studies, α_1-antitrypsin deficiency is extremely rare. Only 18 families in Japan have documented α_1-antitrypsin deficiency. Genotype analyses in patients with α_1-antitrypsin deficiency showed that the Z-type aberrations are not expressed, indicating a reduced risk of COPD [87, 88]. The predominant genotype among the Japanese for α_1-antitrypsin deficiency is the S-variant.

The present authors conducted the first nationwide epidemiological study (NICE) in Japan to explore the prevalence of COPD in the Japanese general population [82]. The results from this study suggest that the low number of clinical COPD cases in Japan is largely due to marked underdiagnosis of the disease rather than the hypothesised genetic tolerance to COPD. The data from this study have been published and comprehensively presented in detail elsewhere [82], but are summarised below.

Methods

Sampling

Eighteen prefectures were selected for participation (fig. 6). Thirty-five institutes were selected to perform spirometric testing. Out of 40,000 randomly selected households, over 23,949 eligible households inhabited by persons >40 yrs of age were successfully contacted. Of these households, 19,637 were eligible for participation. Because cluster sampling by age and sex were applied during recruitment, suitable comparisons with the total population of Japan are presented.

Fieldwork

The GOLD definition of COPD AL of FEV1/FVC <70% was applied. Bronchodilator reversibility testing was not

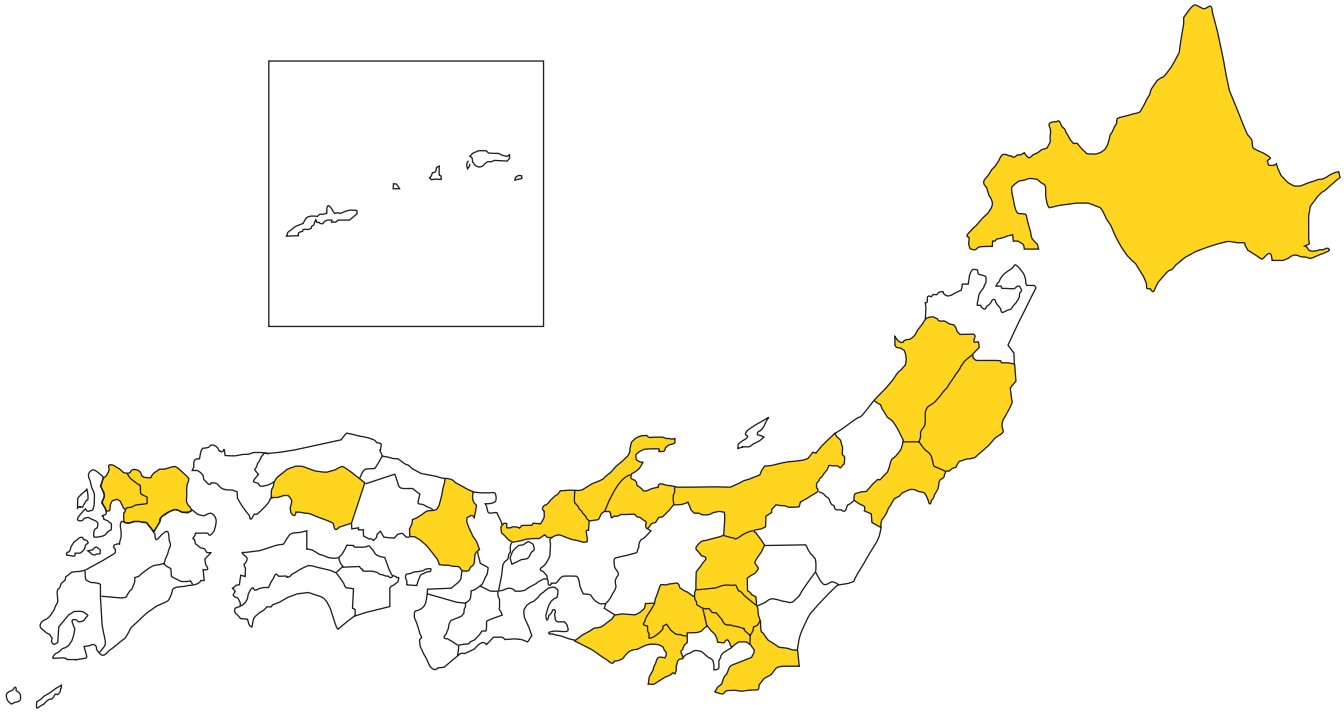

FIGURE 6. Map of Japan, showing the 18 prefectures (shaded in orange) selected for participation in the Nippon COPD Epidemiology Study. The boxed area shows the Okinawa Islands.

conducted; instead, questionnaires were administered to exclude possible asthmatic cases. Questionnaire items were completed by subjects prior to their visit to the institute. Four questions related to asthmatic components of AL. A sensitivity analysis was performed to assess the proportion of AL cases that were likely to be caused by COPD or asthma. Probable COPD was determined according to study diagnostic criteria ($\geqslant$40 yrs of age and FEV1/FVC <70% with no positive symptoms suggestive of asthma).

Results

Of the 19,637 households eligible for participation, 2,711 (14%) completed the study protocol. After excluding 368 (13.6%) invalid measurements, the study population comprised 2,343 Japanese subjects aged $\geqslant$40 yrs. In general, the study cohort was similar to the overall population of Japan with regard to age and sex.

The prevalence of COPD was varied 8.6–10.9%, depending on the diagnostic criteria employed. This number is much higher than the prevalence of COPD reported by the National Ministry of Health and Welfare (0.3%) from nationwide clinical diagnoses [84]. The total number of COPD cases in patients aged $\geqslant$40 yrs was estimated to be 5.3 million compared with the 0.2 million reported by the National Ministry of Health and Welfare. It is of particular significance that physicians did not diagnose 90% of the subjects with suspected COPD.

The prevalence of COPD increased three-fold in those aged >70 yrs compared with those of 50–59 yrs. The ratio of COPD prevalence in males to females was ~3:1. The prevalence of COPD in current smokers and ex-smokers was 12.3% and 12.4%, respectively. COPD was found in 4.7% of non-smokers. Only 10% of respondents reported having a prior diagnosis of COPD. These data indicate that COPD is largely underdiagnosed in Japan.

Discussion

NICE was the first Japanese nationwide epidemiological study conducted using population-based sampling. The results disclosed an unexpectedly high prevalence of COPD, in sharp contrast to the much lower burden of the disease reported by the Ministry of Health and Welfare of Japan in 1996 (0.3%) [84].

Previous occidental studies in COPD prevalence showed figures in the range of 6–9% for AL [70]. A recent Korean study [89] reported that AL occurred at a prevalence of 10.3% in subjects >18 yrs of age. Thus, the prevalence of COPD in Asia is similar to that found in the rest of the world.

There are some limitations to this study. First, NICE did not employ reversibility testing to rule out asthmatic subjects. However, it is unlikely that this represents a substantial number of the study subjects since electively scheduled tests would not be likely to find obstruction of the level required for diagnosis in patients without fixed AL. Secondly, the response rate was too low to validate the study and to truly reflect the Japanese population. The low response rate was mainly due to the stringent timelines in which participant subjects were to complete all fieldwork. The response rate among sites of different prefectures was relatively homogenous.

It is hoped that the data from this study will renew a sense of urgency in the medical community regarding the heavy burden of COPD in Japan in the coming years. The results from this study will also stimulate increased public awareness and promote recognition of COPD in this country.

Conclusion

COPD is largely underdiagnosed in Japan. The epidemiological assessment of the prevalence of COPD in Japan will raise awareness not only among practicing physicians but also in the general public through various public media. Educating the general public about the importance of COPD and the cessation of smoking, in particular, will hopefully bring more patients into the clinics at earlier stages of the disease for appropriate assessment, evaluation and treatment.

COPD: THE CHINESE EXPERIENCE

Summary

COPD is a major public health problem in China. Epidemiological studies have shown that 14.6% and 17% of ever-smokers in mainland China and Hong Kong, respectively, might be suffering from this disease, defined by an FEV1/FVC <70%. Though significantly less prevalent than in smokers, 4.6% and 4.1% of never-smokers in these respective areas have met this spirometric criterion, suggesting that non-tobacco-related causes may also be important in the pathogenesis of COPD. Indeed, although the prevalence of smoking has decreased in the elderly in Hong Kong in the past decade, there is evidence that the prevalence of COPD has increased amongst the population. The infrequent use of spirometry may have led to an underdiagnosis of COPD; only 2.7% of adults in mainland China had a diagnostic label of this condition, despite the fact that 8.8% had spirometric evidence of airflow obstruction.

COPD is a major public health problem in mainland China and Hong Kong. Strategies to reduce tobacco consumption and non-tobacco-related exposures are urgently required to lessen the burden of COPD in these two areas.

Introduction

COPD is a common respiratory illness that causes considerable morbidity and mortality worldwide. This is particularly true in Western Pacific countries. In its 2002 World Health Report, WHO estimated that the Western Pacific region has the highest mortality (79.8 per 100,000 population), prevalence (1,675 per 100,000 population) and disability adjusted life yrs (DALY; 13.7 million) for COPD than the other regions in the world [90]. With its huge population of 1.2 billion and a smoking prevalence of >30%, which is likely to continue to rise, China is expected to bear the brunt of this disabling disease. Indeed, COPD is currently the fourth leading cause of death in China's cities and the first leading cause in the rural areas [91]. It is expected that it will become the third leading cause of death for the whole country by 2020.

Similarly, COPD has consistently ranked among the top 10 causes of death in Hong Kong in the past decade, with a mortality rate of 31.1 per 100,000 population in 1998–1999. It is also the third most common cause of acute hospital admissions, after cancer and chronic renal failure, and accounts for 3.5–3.7% of all hospitalised patients in the territory. These

acute admissions have also been rising steadily in recent years, from 39,393 cases in 1996 to 49,452 in 2000.

Despite this considerable burden, very little information on this disease in the Chinese population is available in the English literature. This article reviews the recent data on the burden and management issues of COPD in mainland China and Hong Kong.

Prevalence

In the early 1990s, a community-based questionnaire survey conducted in Hong Kong on >2,000 elderly subjects aged ⩾70 yrs revealed that: 10% of the subjects had a history of chronic cough productive of sputum for 3 consecutive months in the past 2 yrs; 6.8% had been diagnosed with chronic bronchitis; 2.4% were with diagnosed emphysema; and 5.1% were with diagnosed asthma [92]. Using a mathematical model derived from the local prevalence of known risk factors for COPD (smoking, exposure to high-risk occupations, biomass fuel and air pollutants), the Asia Pacific COPD working group projected the prevalence of this disease in 12 countries/areas in the region in 2000. The estimated prevalence rates for moderate-to-severe COPD for the population aged ⩾30 yrs were 6.3% for the region, 6.5% for China and 3.5% for Hong Kong [93]. However, neither of these two studies used lung function tests to document airflow obstruction, the primary feature in COPD, and estimate the prevalence of this condition.

In the last few years, community-based surveys in mainland China and Hong Kong have begun to include spirometry in their designs. In 2003, the Burden of Obstructive Lung Disease (BOLD) study group conducted a population-based survey in Guangzhou, a city in southern China with a population of 6,300,000, using a standardised protocol [94, 95]. A total of 702 adults (344 males) aged ⩾40 yrs, stratified by sex, were randomly selected from the database in the local police department. They were asked to complete a respiratory questionnaire and perform pre- and post-bronchodilator spirometry. Of these subjects, 602 (291 males) completed the study. The majority of male participants were either current smokers (52.9%) or ex-smokers (26.6%), while only 7.4% of females had ever smoked (5.8% current smokers and 1.6% ex-smokers). COPD prevalence, as defined by the GOLD criteria, was 8.8% for the whole population, with the majority of subjects having mild-to-moderate disease and males having more than twice the prevalence rate of females, except in the most severe category (stage IV; fig. 7) [1, 2].

As expected, the prevalence of COPD was higher in smokers than non-smokers (14.6% *versus* 4.6%) and increased with advancing age; it was 10 times higher in subjects aged >70 yrs than in those aged 40–49 yrs (table 5).

Another recent study in Hong Kong aiming to establish reference values of lung function for the adult Chinese population has provided some clues on the prevalence and severity of COPD in the community. This study was carried out from January 2001 to March 2003. Subjects, stratified according to age and sex, were selected from the community by random digital dialling. A total of 2,721 subjects aged 18–80 yrs were invited to take part and 1,811 (1,089 males) completed the study, representing a response rate of 66.6%.

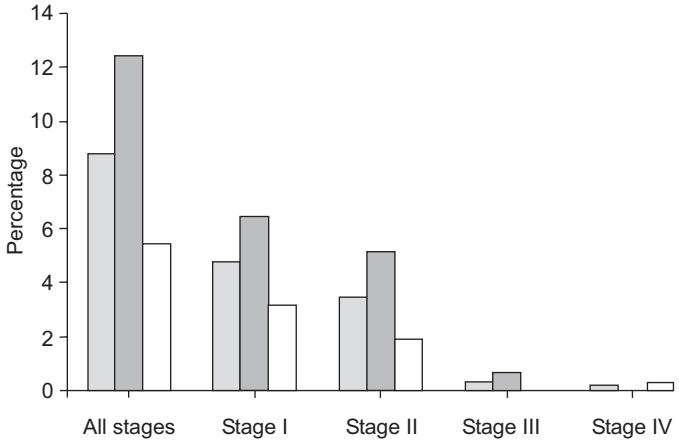

FIGURE 7. Prevalence and severity of chronic obstructive pulmonary disease in adults aged ⩾40 yrs in Guangzhou (China), according to the classification of the Global Initiative for Chronic Obstructive Lung Disease. ▫: overall; ▪: males; □: females.

TABLE 5 Prevalence of chronic obstructive pulmonary disease in relation to age and sex

	Age yr				
	40–49	50–59	60–69	70+	Total
Male	3.8 (1.9)	10.0 (3.9)	34.9 (7.3)	40.7 (9.5)	15.3 (2.3)
Female	4.1 (2.0)	1.5 (1.5)	13.0 (4.6)	30.0 (10.2)	7.6 (1.7)
Total	3.9 (1.4)	5.6 (2.1)	22.7 (4.2)	36.2 (7.0)	11.4 (1.5)

Data are presented as % (SEM). Data taken from the BOLD study in Guangzhou, China, 2003 [95].

Over one-third of the participants (671, 576 of which were males) were smokers. The study protocol involved completion of a questionnaire based on the ATS Questionnaire for Chronic Respiratory Symptoms, as well as performance of a full lung function test including measurements of dynamic and static lung volumes and diffusion capacity, without the use of any bronchodilator [96]. The prevalence of COPD, defined as having a pre-bronchodilator FEV_1/FVC <70%, was 8.9%, with more males (11.7%) being affected than females (4.7%). Similar to the situation in Guangzhou, the majority of subjects had mild-to-moderate disease at GOLD stages I (4.9%) and II (3.5%; fig. 8). Smokers also had a higher prevalence (17%) than never-smokers (4.1%), in both males (18.6% *versus* 4.9%) and females (7.4% *versus* 4.3%).

There is some evidence that the prevalence of COPD may be increasing in the elderly population in Hong Kong. The study method mentioned previously in this article was repeated in 2003, using the same questionnaire and study population, *i.e.* those aged ⩾70 yrs were randomly selected from the community [92]. It was found that the prevalence rates of 12-month respiratory symptoms, including wheeze, morning chest tightness, breathlessness at rest, and nocturnal breathlessness, have increased in the past decade. Furthermore, symptoms of

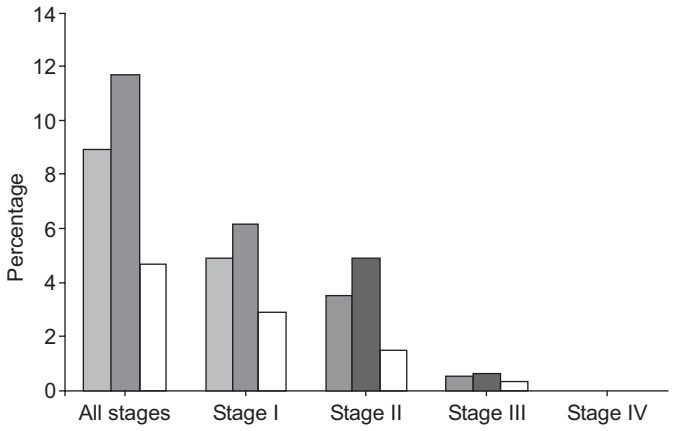

FIGURE 8. Prevalence and severity of chronic obstructive pulmonary disease in adults aged 18–80 yrs in Hong Kong according to the classification of the Global Initiative for Chronic Obstructive Lung Disease, using pre-bronchodilator spirometric data. ▫: overall; ▪: males; □: females.

chronic bronchitis, diagnosed chronic bronchitis, emphysema and asthma have also become slightly more prevalent (fig. 9).

Interestingly, there was a higher proportion of never-smokers in the more recent study (71.1% *versus* 52.7%), suggesting that other aetiological factors may be important. In support of this, it is worth noting that 30.2% and 29.2% of COPD subjects in Guangzhou and Hong Kong, respectively, were never-smokers. Amongst the never-smokers, 4.6% in Guangzhou and 4.1% in Hong Kong were showing spirometric evidence of COPD. Future studies to assess whether possible causes such as passive smoking, air pollution, exposure to biomass fuel and occupational dusts, may be responsible for the development of COPD, will shed light on its pathogenetic mechanisms.

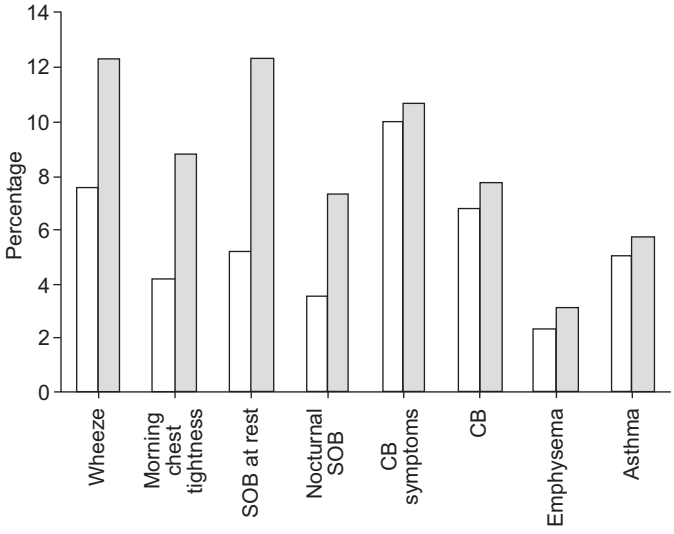

FIGURE 9. Increasing prevalence of respiratory symptoms over 12 months and diagnosed chronic bronchitis, emphysema and asthma in the Hong Kong elderly, comparing data from 1991 (□) and 2003 (▫). SOB: shortness of breath; CB: chronic bronchitis.

Management issues

Early diagnosis of COPD is vital in preventing disease progression, improving the patient's well-being and reducing its burden on society. However, preliminary analysis of the BOLD data from Guangzhou indicated that only one-third of the subjects (16 out of 53) with spirometric evidence of the disease had been diagnosed with chronic bronchitis, emphysema or COPD [1, 2]. This underdiagnosis is slightly worse in males, where only nine out of 36 (25%) had one of the diagnostic labels of COPD, compared with seven out of 17 (41.2%) in females. This is probably due to under-use of spirometry and a diagnosis based largely on symptoms. Indeed, only one-third of COPD patients in hospitals have ever been tested for spirometry in mainland China (Q. Wang, personal communication: Institute of Respiratory Disease, First Affiliated Hospital, China Medical University, Shenyang, China). Education of healthcare professionals in using lung function tests more readily to evaluate subjects with a high risk of developing COPD (*e.g.* smokers) and patients with respiratory complaints are important in the early detection of the disease.

From 1992 to 1999, a comprehensive intervention programme aimed at reducing the burden of COPD was implemented in some rural areas of mainland China [97]. The major intervention measures included public health education, formation of community groups for the prevention and treatment of COPD, education of doctors and nurses to provide appropriate outpatient care, improvement of living environment, public campaigns on smoking cessation, and the use of standard pharmacological therapy. Compared with areas where intervention measures were not implemented, those areas with intervention for the period (1992–1999) as a whole showed a downward trend in COPD mortality during this 8-yr period (fig. 10). This reduction in mortality was associated with a higher smoking cessation rate (28.2% *versus* 23%), a slower decline in FEV1 (32.0 mL·yr^{-1} *versus* 37.9 mL·yr^{-1}) and FVC

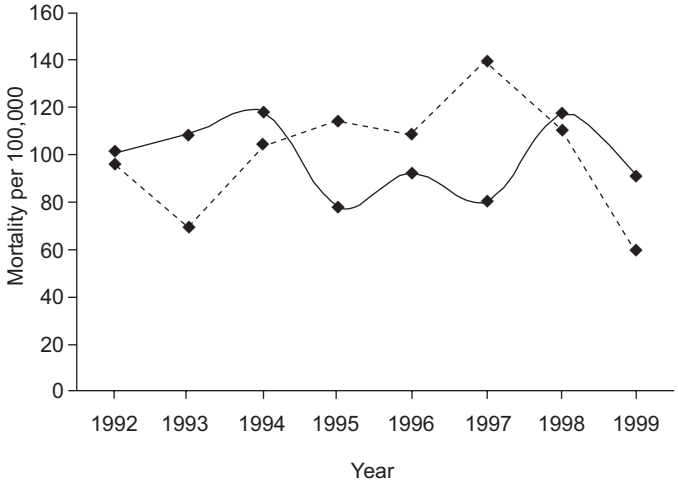

FIGURE 10. Chronic obstructive pulmonary disease mortality in rural China from 1992–1999. Regions with implementation of the intervention programme (——) showed a downward trend in mortality rates from 1995–1999, whereas regions with no intervention (-------) showed an upward trend during the same period. Modified from reference [97].

(42 mL *versus* 48.3 mL), and a smaller increase in COPD prevalence (5.6% *versus* 8% increase from baseline survey in 1992).

Acute exacerbations of COPD (AECOPD) are frequently encountered in those with severe disease (GOLD Stages III and IV) and are associated with a faster decline in lung function and a poor quality of life [98, 99]. Many of the exacerbations are triggered by infections, with 40–60% of cases due to bacteria [100]. A recent retrospective study in a teaching hospital in Hong Kong has revealed that 37.8% of all cases of AECOPD had a positive bacterial culture from sputum [101]. *Haemophilus influenzae* was the most common organism (23.1%) found, followed by *Pseudomonas aeruginosa* (6.3%) and *Streptococcus pneumoniae* (4%). The choice of antibiotics in the treatment of AECOPD should provide cover against these organisms. *Mycobacterium tuberculosis* was also found in 1.1% of sputum specimens. The latter finding mirrors an earlier study in Hong Kong, which found that 12% of hospitalisations for community-acquired pneumonia were due to *M. tuberculosis* [102]. The empiric use of fluoroquinolones in the treatment of AECOPD should therefore be cautioned, as this group of antibiotics, with their weak anti-tuberculosis effect, may result in a delay in the diagnosis and treatment of pulmonary tuberculosis in areas such as Hong Kong and China, where the disease is still prevalent [103].

Conclusion

In conclusion, chronic obstructive pulmonary disease is a major public health problem in mainland China and Hong Kong. With the increase in smoking prevalence in the former and the aging population in the latter, it is expected that the prevalence of the disease will continue to rise in coming years. Strategies to reduce tobacco consumption and non-tobacco-related exposures (air pollution, biomass fuel and occupational dusts) are urgently required to reduce the burden of this disabling disease in these two areas.

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A question and answer document file following each of the manuscripts presented during the workshop is available at www.ersnet.org/learning.

REFERENCES

1 Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.

2 GOLD Guidelines 2003. www.goldcopd.org/Guidelineitem.asp?11=2&12=1&intId=989. Last updated: September 2005. Last accessed: Febuary 5, 2005.

3 Mortality patterns - preliminary data, United States, 1996. *MMWR Morb Mortal Wkly Rep* 1997; 46: 941–944.

4 Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; 349: 1498–1504.

5 Lundback B, Nystrom L, Rosenhall L, Stjernberg N. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Respir J* 1991; 4: 257–266.

6 SobradilloPena V, Miravitlles M, Gabriel R, *et al.* Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. *Chest* 2000; 118: 981–989.

7 Viegi G, Pedreschi M, Pistelli F, *et al.* Prevalence of airways obstruction in a general population: European Respiratory Society *vs* American Thoracic Society definition. *Chest* 2000; 117: 339S–345S.

8 Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988–1994. *Arch Intern Med* 2000; 160: 1683–1689.

9 Morbidity & Mortality: chart book on cardiovascular, lung, and blood diseases. National Heart, Lung and Blood Institute. Bethesda, US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1998.

10 Sin DD, Stafinski T, Ng YC, Bell NR, Jacobs P. The impact of chronic obstructive pulmonary disease on work loss in the United States. *Am J Respir Crit Care Med* 2002; 165: 704–707.

11 Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343: 1902–1909.

12 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive

pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
13 Pauwels RA, Lofdahl CG, Laitinen LA, *et al.* Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999; 340: 1948–1953.
14 Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002; 166: 675–679.
15 Xu X, Dockery DW, Ware JH, Speizer FE, Ferris BG Jr. Effects of cigarette smoking on rate of loss of pulmonary function in adults: a longitudinal assessment. *Am Rev Respir Dis* 1992; 146: 1345–1348.
16 Albers JMC, Schermer TRJ, van den Boom G, *et al.* Efficacy of inhaled steroids in undiagnosed subjects at high risk for COPD: Results of the detection, intervention, and monitoring of COPD and asthma program. *Chest* 2004; 126: 1815–1824.
17 Van den Boom G, Rutten-van Mölken MPMH, Folgering HTM, van Weel C, van Schayck CP. The economic effects of screening for obstructive airway disease: An economic analysis of the DIMCA program. *Prev Med* 2000; 30: 302–308.
18 Zielinski J, Bednarek M. Early detection of COPD in a high-risk population using spirometric screening. *Chest* 2001; 119: 731–736.
19 Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
20 Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995; 8: 1398–1420.
21 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 16: Suppl., 5–40.
22 Connett JE, Bjornson-Benson WM, Daniels K. Recruitment of participants in the Lung Health Study: II Assessment of recruiting strategies. Lung Health Study Research Group. *Control Clin Trials* 1993; 14: 38S–51S.
23 van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. *BMJ* 2002; 324: 1370–1375.
24 Buffels J, Degryse J, Heyrman J, Decramer M. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. *Chest* 2004; 125: 1394–1399.
25 Eaton T, Withy S, Garrett JE, Mercer J, Whitlock RM, Rea HH. Spirometry in primary care practice: the importance of quality assurance and the impact of spirometry workshops. *Chest* 1999; 116: 416–423.
26 Schermer TR, Jacobs JE, Chavannes NH, *et al.* Validity of spirometric testing in a general practice population of patients with chronic obstructive pulmonary disease (COPD). *Thorax* 2003; 58: 861–866.
27 Enright PL, Beck KC, Sherrill DL. Repeatability of spirometry in 18,000 adult patients. *Am J Respir Crit Care Med* 2004; 169: 235–238.
28 Gorecka D, Bednarek M, Nowinski A, Puscinska E, Goljan-Geremek A, Zielinski J. Diagnosis of airflow limitation combined with smoking cessation advice increases stop-smoking rate. *Chest* 2003; 123: 1916–1923.
29 Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. *Chest* 2000; 117: 1146–1161.
30 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159: 179–187.
31 Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002; 20: 1117–1122.
32 Stratelis G, Jakobsson P, Molstad S, Zetterstrom O. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. *Br J Gen Pract* 2004; 54: 201–206.
33 Annesi-Maesano I, Gulsvik A, Viegi G, eds. Respiratory epidemiology in Europe. *Eur Respir Mon* 2000; 5: 1–454.
34 Buist S, Mapp CE, eds. Respiratory diseases in women. *Eur Respir Mon* 2003; 8: 1–241.
35 European Respiratory Society. European Lung White Book. The first comprehensive survey on respiratory health in Europe. Huddersfield, European Respiratory Society, 2003.
36 Paoletti P, Carrozzi L, Viegi G, *et al.* Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking and level of pulmonary function. *Am J Respir Crit Care Med* 1995; 151: 1770–1777.
37 Sapigni T, Biavati P, Simoni M, *et al.* The Po River Delta Respiratory Epidemiological Survey: an analysis of factors related to level of total serum IgE. *Eur Respir J* 1998; 11: 278–283.
38 Viegi G, Paoletti P, Carrozzi L, *et al.* Prevalence rates of respiratory symptoms in Italian general population samples exposed to different levels of air pollution. *Environ Health Perspect* 1991; 94: 95–99.
39 Viegi G, Pedreschi M, Baldacci S, *et al.* Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. *Int J Tuberc Lung Dis* 1999; 3: 1034–1042.
40 Viegi G, Matteelli G, Angino A, *et al.* The proportional Venn diagram of obstructive lung disease in the Italian general population. *Chest* 2004; 126: 1093–1101.
41 Guerra S, Sherrill DL, Baldacci S, *et al.* Rhinitis is an independent risk factor for developing cough apart from colds among adults. *Allergy* 2005; 60: 343–349.
42 Chapman KR. Chronic obstructive pulmonary disease: are women more susceptible than men? *Clin Chest Med* 2004; 25: 331–341.
43 Varkey AB. Chronic obstructive pulmonary disease in women: exploring gender differences. *Curr Opin Pulm Med* 2004; 10: 98–103.

44 Kauffmann F, Becklake MR. Sex and gender. In: Annesi-Maesano I, Gulsvik A, Viegi G, eds. Respiratory epidemiology in Europe. *Eur Respir Mon* 2000; 5: 288–304.

45 Annesi-Maesano I, Agabiti N, Pistelli R, Couilliot MF, Forastiere F. Subpopulations at increased risk of adverse health outcomes from air pollution. *Eur Respir J* 2003; 21: Suppl. 40, 57s–63s.

46 Gold DR, Wang XW, Wypij D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med* 1996; 335: 931–937.

47 Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997; 10: 822–827.

48 Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980; 122: 567–575.

49 Becklake MR. Gender differences in airway behaviour (physiology) over the human lifespan. In: Buist A, Mapp CE, eds. Respiratory diseases in women. *Eur Respir Mon* 2003; 8: 8–25.

50 Lebowitz MD, Knudson RJ, Burrows B. Tucson epidemiologic study of obstructive lung diseases: methodology and prevalence of disease. *Am J Epidemiol* 1975; 102: 137–152.

51 Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B. Longitudinal changes in allergens skin test reactivity in a community population sample. *J Allergy Clin Immunol* 1987; 79: 16–24.

52 Cline MG, Burrows B. Distribution of allergy in a population sample residing in Tucson, Arizona. *Thorax* 1989; 44: 425–431.

53 Kauffmann F, Becklake MR. Maladies obstructives pulmonaires: un paradigme de la complexité des differences de santé entre hommes et femmes [Obstructive lung disease: a paradigma of the complexity of the differences in health between men and women]. In: Saurel-Cubizolles MJ, Blondell B, eds. La santé des femmes [The health of women]. Paris, Medecine et Sciences, 1996; pp. 209–233.

54 Manfreda J, Sears MR, Becklake MR, *et al.* Geographic and gender variability in the prevalence of bronchial responsiveness in Canada. *Chest* 2004; 125: 1657–1664.

55 Slama K. Active smoking. In: Annesi-Maesano I, Gulsvik A, Viegi G, eds. Respiratory epidemiology in Europe. *Eur Respir Mon* 2000; 5: 305–321.

56 Doll R. Risk from tobacco and potentials for health gain. *Int J Tuberc Lung Dis* 1999; 3: 90–99.

57 Prescott E, Osler M, Andersen PK, *et al.* Mortality in women and men and relation to smoking. *Int J Epidemiol* 1998; 27: 27–32.

58 Prescott E, Godtfredsen N, Vestbo J, Osler M. Social position and mortality from respiratory diseases in males and females. *Eur Respir J* 2003; 21: 821–826.

59 WHO Atlas maps global tobacco epidemic. *Cent Eur J Public Health* 2003; 11: 106.

60 Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. *Lancet* 2003; 362: 847–852.

61 Ulrik CS. Smoking and mortality in women: ''smoke like a man, die (at least) like a man''. In: Buist S, Mapp CE, eds. Respiratory diseases in women. *Eur Respir Mon* 2003; 8: 103–117.

62 Watson L, Boezen HM, Postma DS. Differences between males and females in the natural history of asthma and COPD. In: Buist S, Mapp CE, eds. Respiratory diseases in women. *Eur Respir Mon* 2003; 8: 50–73.

63 Pierce JP, Fiore MC, Novontny TE, Hatziandreu EJ, Davis RM. Trends in cigarette smoking in the United States: projections to the year 2000. *JAMA* 1989; 261: 61–65.

64 Centers for Diseases Control and Prevention. Cigarette smoking among adults – United States, 1993. *JAMA* 1995; 273: 369–370.

65 Mannino DM, For DE, Giovino GA, Thun M. Lung cancer mortality rates in birth cohorts in the United States from 1960 to 1994. *Lung Cancer* 2001; 31: 91–99.

66 Pride NB, Soriano JB. Chronic obstructive pulmonary disease in the United Kingdom: trends in mortality, morbidity, and smoking. *Curr Opin Pulm Med* 2002; 8: 95–101.

67 Mannino DM. Chronic obstructive pulmonary disease: definition and epidemiology. *Respir Care* 2003; 48: 1185–1191.

68 Chan-Yeung M, Ait-Khaled N, White N, Ip MS, Tan WC. The burden and impact of COPD in Asia and Africa. *Int J Tuberc Lung Dis* 2004; 8: 2–14.

69 Soriano JB, Maier WC, Egger P, *et al.* Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax* 2000; 55: 789–794.

70 Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? *Chest* 2003; 123: 1684–1692.

71 Cerveri I, Accordini S, Corsico A, *et al.* Chronic cough and phlegm in young adults. *Eur Respir J* 2003; 22: 413–417.

72 Blanc PD. The role of household exposures in lung disease among women. In: Buist S, Mapp CE, eds. Respiratory diseases in women. *Eur Respir Mon* 2003; 8: 118–130.

73 Wai Y, Tarlo SM. Occupational lung disease in women. In: Buist S, Mapp CE, eds. Respiratory diseases in women. *Eur Respir Mon* 2003; 8: 131–145.

74 Balmes J, Becklake M, Blanc P, *et al.* Environmental and Occupational Health Assembly, American Thoracic Society. American Thoracic Society Statement. Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003; 167: 787–797.

75 Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004; 126: 59–65.

76 Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 2003; 124: 474–481.

77 Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings.

The Cochrane Effective Practice and Organization of Care Review Group. *BMJ.* 1998; 317: 465–468.
78 National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute, NIH. http://www.nhlbi.nih.gov. Last accessed: February 5, 2005.
79 Fabbri LM, Hurd SS, for the GOLD Scientific Committee. Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. *Eur Respir J* 2003; 22: 1–2.
80 US COPD Coalition. URL: http://www.uscopd.org. Last accessed: February 5, 2005.
81 Buist AS, Bailey W, Hurd SS. National COPD Conference Summary. *J COPD* 2004; 1: 293–302.
82 Fukuchi Y, Nishimura M, Ichinose M, *et al.* COPD in Japan: the Nippon COPD epidemiology study. *Respirology* 2004; 9: 458–465.
83 Japanese Respiratory Society Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease. Nihon Kokyuki Gakkai Zasshi 2004: 1–137.
84 Statistics Bureau, Director-General for Policy Planning, Ministry of Internal Affairs and Communications. www.stat.go.jp/english/index/official/215.htm#1. Last accessed: February 6, 2006.
85 Hogg JC, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 2645–2653.
86 Silverman EK, Chapman HA, Drazen JM, *et al.* Genetic epidemiology of severe, early onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998; 157: 1770–1778.
87 Shim YS. Epidemiological survey of chronic obstructive pulmonary disease and alpha-1 antitrypsin deficiency in Korea. *Respirology* 2001; 6: S9–S11.
88 Seyama K. State of alpha$_1$-antitrypsin deficiency in Japan. *Respirology* 2001; 6: S35–S38.
89 Shin C, In KH, Shim JJ, *et al.* Prevalence and correlates of airway obstruction in a community-based sample of adults. *Chest* 2003; 123: 1924–1931.
90 World Health Organisation. World Health Report 2002. www.who.int/whr/2002. Last accessed: February 5, 2005.
91 Ministry of Public Health of China. Yearbook of China Healthcare 1998. Beijing, People's Health Publishing House, 1998; pp. 355–361.
92 Lai CKW, Ho SC, Lau J, *et al.* Respiratory symptoms in elderly Chinese living in Hong Kong. *Eur Respir J* 1995; 8: 2055–2061.
93 Regional COPD working group. COPD prevalence in 12-Asia Pacific countries and regions: Projections based on the COPD prevalence estimation model. *Respirology* 2003; 8: 192–198.
94 Buist S. Cookbook of the Burden of Obstructive Lung Disease. March 2004. www.goldcopd.com. Last accessed: February 5, 2005.
95 Zhong NS, Ran PX, Lau JC, *et al.* The burden of obstructive lung disease (BOLD) project in China: Prevalence of COPD in Guangzhou. *Am J Respir Crit Care Med* 2004; 169: A603.
96 Ferris BG. Recommended respiratory disease questionnaire for use with adults and children in epidemiology research. *Am Rev Respir Dis* 1978; 118: 7–53.
97 Cheng XS, Xu X, Zhang ZX. Results of community intervention trial for chronic obstructive pulmonary diseases and chronic cor pulmonale from 1992 to 1999. *Chinese Journal of Tuberculosis and Respiratory Diseases* 2001; 24: 579–583.
98 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
99 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
100 Sethi Sanjay. Bacterial exacerbations of chronic obstructive pulmonary disease: phenomenon or epiphenomenona? *Proc Am Thorac Soc* 2004; 1: 109–114.
101 Ko FW, Ng TK, Li TS, *et al.* Sputum bacteriology in patients with acute exacerbations of COPD in Hong Kong. *Respirat Med* 2005; 99: 454–460.
102 Chan CHS, Cohen M, Pang J. A prospective study of community acquired pneumonia in Hong Kong. *Chest* 1992; 101: 442–446.
103 Dooley KE, Golub J, Goes FS, Merz WG, Sterling TR. Empiric treatment of community acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis. *Clin Infect Dis* 2002; 34: 1607–1612.