Respirology (2006) **11**, 523–532 doi: 10.1111/j.1400-1843.2006.00886.x

INVITED REVIEW: PRESIDENT SERIES

Epidemiology of chronic obstructive pulmonary disease: Health effects of air pollution

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VIEGI G, MAIO S, BALDACCI S. *Respirology* 2006; **11**: 523–532

Abstract: COPD is one of the leading causes of morbidity and mortality in the industrialized and the developing countries. According to the prediction of the World Health Organization, COPD will become the third leading cause of mortality and the fifth cause of disability in 2020 worldwide. In epidemiology, distinct phenotypic entities converge on the term COPD, so that prevalence and mortality data may be inclusive of chronic bronchitis, emphysema and asthma; moreover, the assessment of prevalence rates may change considerably according to the diagnostic tools used. Thus, a considerable problem is to estimate the real prevalence of COPD in the general population. COPD is determined by the action of a number of various risk factors, among which, the most important is cigarette smoking. However, during the last few decades, evidence from epidemiological studies finding consistent associations between air pollution and various outcomes (respiratory symptoms, reduced lung function, chronic bronchitis and mortality), has suggested that outdoor air pollution is a contributing cause of morbidity and mortality. In conclusion, epidemiological studies suggest that air pollution plays a remarkable role in the exacerbation and in the pathogenesis of chronic respiratory diseases. Thus, respiratory physicians, as well as public health professionals, should advocate for a cleaner environment.

Key words: COPD/ emphysema/ chronic bronchitis, environmental and occupational health and epidemiology, respiratory structure and function, tobacco.

INTRODUCTION

COPD is a major global health problem that increasingly constitutes a burden for the society and has large effects on health-care expenditure. COPD has recently been described by the World Health Organization (WHO) Global Obstructive Lung Disease (GOLD) initiative[1] and by American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines on COPD[2] as a disease 'characterised by airflow limitation that is not fully reversible'. The airflow limitation (AL) in most cases is both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. This progressive and relentless loss of lung function is the result of emphysema due to destruction of lung parenchyma and narrowing of small airways caused by chronic inflammation.[3]

COPD is one of the most important causes of morbidity and mortality in the industrialized and developing countries. According to WHO, COPD, which in 1990 was estimated to be the 12th cause of disability and the sixth cause of mortality, will be the fifth cause of disability and the third cause of mortality by 2020 all over the world.[4]

Its socioeconomic burden is also expected to increase. In Europe, direct and indirect costs of COPD were estimated at about 38.7 billion euros in 2000, as compared with 17.7 for asthma.[5]

MORTALITY AND MORBIDITY

Worldwide considerable differences are shown in COPD mortality rates among different countries, in relation to the different distributions of tobacco smoking and other risk factors. Remarkable differences are shown even in Europe, where 200 000–300 000 people die each year because of this disease.

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Received 1 April 2006; accepted 6 April 2006.

Still according to the WHO, in 1997, COPD was the cause of death for 4.1% of men and 2.4% of women in Europe. In general, COPD mortality was two to three times higher in men than in women, showing an increasing trend in the elderly. Moreover, a COPD mortality increase among women was observed in the North European countries in 1980–1990. Overall, among European countries, there is a considerable variation in the age-standardized death rate per 100 000 population from respiratory diseases. In particular, mortality rates of COPD range from 6 per 100 000 in Greece to 95 per 100 000 in Kyrgyzstan. The reasons for these discrepancies are not clear and should certainly become an area of future research.[5]

For morbidity, studies from the last two decades indicate that 4–6% of the adult European population suffered from clinically relevant COPD. The prevalence largely increases with age and recent surveys show signs of diminishing differences between the two gender in this still predominantly male-related disease.[5]

RISK FACTORS

Risk factors for developing COPD may be divided into two categories: exogenous (tobacco smoke, air pollution, work exposure, etc.) and endogenous (age, gender, genetic factors, etc.). Such factors, separately or in synergy, determine the subject's susceptibility level for disease. Among these factors the most important is still cigarette smoking.

Tobacco smoking

Ezzati and Lopez estimated the global and regional mortality caused by smoking in the year 2000 to be: 4.83 million premature deaths in the world attributable to smoking; 2.41 million in developing countries and 2.43 million in industrialized countries; 3.84 million of these deaths were in men. The leading causes of death from smoking were cardiovascular disease (1.69 million deaths), COPD (0.97 million deaths) and lung cancer (0.85 million deaths).[6]

Gender

Mannino *et al*. calculated that during 2000 in the USA, COPD was responsible for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726 000 hospitalizations and 119 000 deaths. During the analysed period, the most substantial change was the increase in the COPD death rate among women, from 20.1/100 000 in 1980 to 56.7/100 000 in 2000, compared with the more modest increase in the COPD death rate among men, from 73.0/100 000 in 1980 to 82.6/100 000 in 2000. It is important to highlight that in the year 2000 for the first time the absolute number of deaths in women exceeded that in men.[7]

Soriano *et al*. studied a total of 78 172 patients in England and Wales with a physician diagnosis of COPD. From 1990 to 1997 the annual prevalence rates of physician diagnosed COPD in women rose from 0.80% (95% confidence interval (CI): 0.75–0.83) to 1.36% (95% CI: 1.34–1.39), reaching the rate observed in men in 1990. The prevalence rate increased by 68.7% in women compared with 25.3% in men and differed according to age. In fact, in the first age-group (20–44 year) more women suffered from COPD than men, whereas in the older age groups (>65 year) there was a clear difference with greater occurrence among men.[8]

A possible explanation for the gender-related differences was given by Prescott *et al*. who, following two independent Danish population samples, showed that adverse effects of smoking on lung function were greater in women than in men. Moreover, after adjusting for smoking, women exhibited a higher risk of being admitted to hospital for COPD than men.[9]

INTERPRETATION OF PREVALENCE MEASUREMENTS

Estimates of the real prevalence of COPD in the general population may change considerably according to the diagnostic tools used: respiratory symptoms reported by the patient, physician's diagnosis, presence of lung function impairment. The term COPD may be used as a contributing factor to, rather than the main cause of, death. It may lead to misclassification and omissions from medical records and vital statistics. Therefore, mortality data from COPD patients should always be interpreted with caution. The diagnostic term COPD has not been widely used by physicians or other health professionals and is not generally recognized by the public.[5]

Lindström *et al*. assessed under-diagnosis of COPD. Two cross-sectional studies on respiratory symptoms and diseases, in two population samples of the same age living in the same areas in northern Sweden, were carried out 6 years apart. Of the subjects diagnosed with airflow obstruction (AO) only 25% in 1986 and 23% in 1992 had been diagnosed prior to the study as having chronic bronchitis, emphysema or COPD.[10]

A recent review by Halbert *et al*. reported on 32 studies assessing COPD prevalence rates, representing 17 countries and eight WHO-classified regions. Prevalence estimates were based on spirometry (11 studies), respiratory symptoms (14 studies), patient-reported disease (10 studies), or expert opinion. There was considerable variation in the reported prevalence of COPD. The overall COPD prevalence rates ranged from <1 to >18%, and tended to vary by the method used to estimate prevalence. In general, rates tended to be higher for male than female subjects. Some of the variations attributed to differences in risk exposure or population characteristics may be influenced by the methods and definitions used to measure disease.[11]

In the Po Delta Valley Study, Viegi and colleagues assessed the influence of different spirometric COPD definitions on prevalence estimates. Applying different COPD definitions, they found rates of obstruction

ranging from 11% to 57% of their study population. They found a disparity based on a large prevalence of mild obstructive abnormalities when the old ATS criterion ($FEV_1/FVC < 75\%$) was applied, as compared with a clinical criterion later adopted by GOLD ($FEV_1/FVC < 70\%$) and, especially, with the ERS criterion ($FEV_1/FVC < 88\%$ predicted in men and <89% predicted in women).[12]

Celli *et al*. evaluated the impact of different definitions of airways obstruction on the estimated prevalence of obstruction in a population-based sample. On the basis of the Third National Health and Nutrition Examination Survey, obstructive airway disease was defined using the following criteria: (i) self-reported diagnosis of chronic bronchitis or emphysema; (ii) $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted (GOLD Stage IIA); (iii) FEV_1/FVC below the lower limit of normal; (iv) $FEV_1/FVC < 88\%$ predicted in men and <89% predicted in women; and (v) $FEV_1/FVC < 0.70$ ('fixed ratio', GOLD criterion Stage I+). The rates in adults varied from 77 per 1.000 (self-report) to 168 per 1.000 (fixed ratio, GOLD criterion Stage I+). For persons aged >50 year, the fixed ratio criterion produced the highest rate estimates, ranging from 182 per 1000 in subjects aged 50–54 years, to 417 per 1000, in subjects aged 75–80 years. The GOLD criterion Stage I+ can overestimate the prevalence of COPD, because it does not take into account the natural decline of FEV_1/FVC rate with age.[13]

Hardie *et al*. criticized the applicability of the GOLD criterion to the whole population regardless of age. The authors examined the extent of COPD misdiagnosis using GOLD definition in healthy, never-smoker, asymptomatic adults aged >70 year in Bergen, Norway. The results suggest that the GOLD criterion would probably lead to a significant degree of over-diagnosis of COPD in those aged >70 year. Indeed, using the GOLD threshold for defining COPD, about 35% of the healthy elderly subjects in the reference sample would be diagnosed as having at least mild COPD. This percentage increases by age, and in the ≥80 year age group about 50% would have a COPD diagnosis.[14]

Johannessen *et al*. have evaluated the implications of reversibility testing on prevalence of COPD in a general population sample in Bergen, Norway: they have found a 27% reduction in prevalence after bronchodilatation in respect to the pretest prevalence value.[15]

De Marco *et al*. analysed data from the European Community Respiratory Health Survey (ECRHS) on more than 18 000 young adults (20–44 years) in order to assess the prevalence of COPD according to GOLD stages in high income countries and to evaluate their association with the known risk factors for AO. The results showed that in those young adults the overall prevalence of subjects with COPD was: 11.8% (95% CI: 11.3–12.3) in stage 0 (chronic cough and phlegm) and 3.6% (95% CI: 3.3–3.9) in stages I+.[16]

Using the same ECRHS dataset, Cerveri *et al*. had shown that the prevalence of subjects with chronic cough and phlegm was startlingly high among young adults (20–44 years). Indeed the adjusted prevalence of subjects with chronic cough and phlegm was 11.8% in men and 12.0% in women.[17]

The PLATINO study, launched in 2002, had the aim to describe the epidemiology of COPD in subjects, more than 40 years old, living in five major Latin American cities: São Paulo (Brazil), Santiago (Chile), Mexico City (Mexico), Montevideo (Uruguay) and Caracas (Venezuela). Adjusted prevalence rates ranged from approximately 12% in Mexico City to around 20% in Montevideo.[18]

Viegi *et al*. quantified the GOLD categories in two Italian general population samples, living in North Italy (Po Delta) and in Central Italy (Pisa), to assess their prognostic roles. Prevalence rates of GOLD stages pre-0 (habitual symptoms cough or phlegm were present for less than 3 month per year or for less than 2 years), 0, I, II, III–IV were 3.5, 14.2, 12.3, 4.5 and 0.4% in men, 3.5, 10.1, 7.3, 2.2 and 0.3% in women, within the samples. The proportion of people with chronic bronchitis symptoms increased from near 30% in GOLD stage I to near 80% in GOLD stage III–IV in Po Delta men and from near 20% to near 75% in Po Delta women, respectively. Similar figures were shown in the Pisa sample.[19]

A population-based epidemiological survey on COPD in a representative national sample was conducted using spirometry in Korea. The prevalence of COPD based on GOLD criterion was 17.2% (men, 25.8%; women, 9.6%) among subjects older than 45 years. Among adults of all ages (aged >18 years), the prevalence of AO was 7.8% (10.9% in men, 4.9% in women). The majority of these cases were found to be mild in degree, and only a minority of these subjects had received physician diagnosis or treatment.[20] Comparing these data with the previously reported prevalence rates by Viegi *et al.* using the same criteria among subjects older than 45 years, Italians had a higher COPD prevalence rate among women (which might be due to the higher reported smoking rate among Italian women, compared with Korean women) and also among non-smokers of both genders, whereas the difference among male smokers was rather small. This difference in the prevalence of COPD between the two populations was even greater when the 1986 ATS criterion for COPD was used. For subjects over 45 years of age, 33.8% of Koreans and 57% of Italians had AO; among adults more than 18 years of age, 18.4% of Koreans and 40.4% of Italians were obstructed. Interestingly, using the ERS criterion the prevalence of AO was similar in the two populations in all age groups. This study confirmed that the fixed criterion for the FEV_1/FVC ratio might result in an overestimation of the prevalence of COPD, especially among the elderly.[20]

INCIDENCE

Longitudinally, the GOLD categories can vary. In the Italian Po Delta study, among men, most subjects with GOLD Stage I+ or without the disease retained the same category after 8 years; of those at pre-risk or at risk, 20–60% worsened and about 40% improved. Among women, most subjects with GOLD Stage I, III+

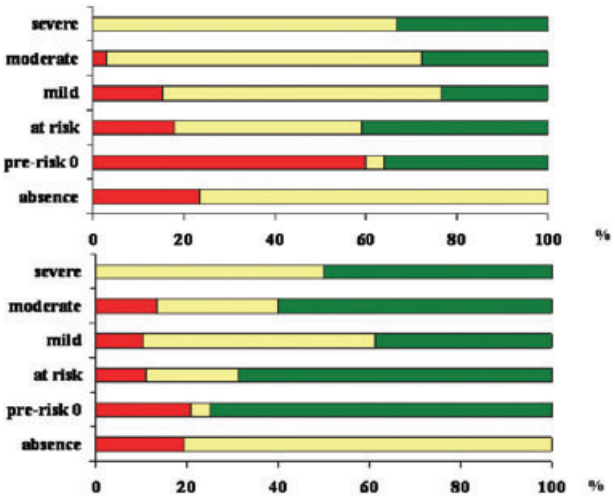

Figure 1 Variation of COPD status (respiratory symptoms/lung function) at follow up in subjects also participating in Po Delta baseline survey, in men (top) and women (bottom). (■) Worsened, (□) stable, and (■) improved.

or without disease retained the same category after 8 years; of those with GOLD Stage II and of those at pre-risk or at risk, 60–75% improved (Fig. 1). The GOLD classification of COPD in the general population is a dynamic process which requires periodical collection of respiratory symptoms and performance of spirometry.[19]

Lindberg *et al.* determined the 10-year cumulative incidence of COPD in a cohort of subjects with respiratory symptoms (GOLD stage 0) using the British Thoracic Society (BTS) and GOLD spirometric criteria. In this cohort, the 10-year cumulative incidence of COPD was 8.2% (using BTS criterion) and 13.5% (using GOLD criterion). Moreover the incidence of COPD among persistent smokers was close to three times the incidence among persistent non-smokers (24.5% vs. 9.4%, respectively, using GOLD criteria). In addition, they suggested that GOLD stage 0 appears to identify subjects who are at risk of COPD, but men and women presented different risk profiles.[21]

Johannessen *et al.* estimated the cumulative 9-year GOLD-defined COPD incidence in a general adult Norwegian population, accounting for the role of gender, age, smoking habits and residential area as predictors, and assessed the level of under-diagnosis. The study indicated that seven per 1000 of the general population aged 18–74 years develop GOLD-defined COPD each year. More than 90% of the 9-year cumulative incident cases were mild or moderate. Age, smoking and the amount smoked were important predictors for COPD incidence; in fact, the cumulative population weighted 9-year COPD incidence among current smokers (>20 pack-years) was 22.7% (95% CI: 8.3–37.1). The study suggested a substantial under-diagnosis of COPD among adults in this community: indeed, less than half of the incident cases had physician-diagnosed asthma, bronchitis, emphysema and/or COPD prior to the study examination.[22]

Recently, the ATS/ERS task force suggested, for the definition of obstructive pulmonary defect, to use a cut-off value of the FEV_1/VC ratio at the 5th percentile of the predicted value. In fact, the use of 5th percentile does not lead to an overestimation of the ventilatory defect in older people.[23]

SCREENING

Stratelis *et al.* used the definition of COPD of the ERS to evaluate a method to detect COPD at an early stage in smokers in an adult age group (40–55 years). The prevalence of COPD was 27%. COPD was classified as mild obstruction in 85%, moderate in 13% and severe in 2%.[24]

Gorecka *et al.* assessed how the diagnosis of AL combined with advice to stop smoking in middle-aged smokers influence the smoking cessation rate and identify predictors of successful outcome. In a population spirometric screening of 11 027 subjects who were at risk for COPD in 12 Polish cities, AL was detected in 30.6% of smokers who were >39 years of age and had a smoking history of >10 pack-years. Of the patients with AL, 40% had moderate AO and 20% had severe AO. At the end of the study all smokers, irrespective of their lung function, tried to modify their habit as the result of screening for COPD combined with smoking cessation advice. Smokers who had been shown to have AL had a larger success in their attempts to quit smoking.[25]

ASTHMA AND COPD

For several years, asthma and COPD have been regarded as separated entities, with distinct clinical courses. However, the Dutch Hypothesis sustains that various forms of airway obstruction as asthma and chronic bronchitis should not be considered as separate diseases but rather as different expressions of a single diseases entity, a chronic non-specific lung disease. The hypothesis sustains also that both endogenous and exogenous factor play a role in pathogenesis of this disease entity. Moreover, both diseases involve genetic predisposition related to altered immune or atopic responses to irritants and pollutants resulting in inflammation and bronchial hyper-responsiveness.[26] Indeed, it seems that despite distinctive physiological features at the time of diagnosis, the two diseases over time may share some risk factors and develop features that are quite similar (i.e. hyperreactivity and inflammation).

Silva *et al.* studied a cohort of 3099 adult subjects from Tucson (AZ, USA) and showed that physician-diagnosed asthma is significantly associated at follow up with an increased risk for chronic bronchitis, emphysema and COPD.[27]

A relationship of asthma and COPD has recently been shown from the estimation of overlapping prevalence in the general population (proportional Venn diagram). Viegi *et al.* aimed to quantify the proportion of the general population with obstructive lung disease (OLD), and the intersections of physician-diagnosed asthma, chronic bronchitis and emphysema in two Italian general population samples, in

relationship to AO determined through spirometry. About 18% of the Italian general population samples either reported the presence of OLD or showed spirometric signs of AO.[28]

OUTDOOR POLLUTION

Air pollution represents an important risk factor for COPD and other respiratory health effects. The statement of the ATS published in the year 2000 was aimed at enlisting the respiratory health effects of air pollution, emphasizing the interpretation of the epidemiological evidence. The statement recognized the spectrum of responses to air pollution, which has been characterized as a pyramid, with the most common consequences of exposure (increased prevalence and incidence of respiratory symptoms/diseases, reduction of lung function …) at the base and mortality, the least common and most severe consequence, at the tip. The statement included a table that lists adverse respiratory health effects, ranked in order of declining severity.[29]

Respiratory diseases and related mortality have been associated, with increasing evidence, to air pollutants. Conventional outdoor pollutants are 'black smoke' (particulates produced by fossil fuel), sulphur dioxide (SO_2), nitrogen oxides (NO_x) (products coming from vehicular-traffic and combustion processes) and ozone (O_3) (originated by photochemical reactions correlated to town traffic). Chronic exposure to elevated air pollution levels is related to chronic bronchitis and lung function impairments. In the last years, the research about the effects of suspended particulates with aerodynamic diameter <10 μm (PM_{10}) or <2.5 μm ($PM_{2.5}$), in relation to death for cardiopulmonary causes, originated much interest in the scientific community. Epidemiological surveys have shown that suspended particulates and NO_x were associated to COPD mortality risk and to COPD hospital admissions.[30]

In particular, a 16-year follow-up study carried out in US metropolitan areas on over half million people has evidenced that each 10 μg/m^3 elevation in fine particulate air pollution ($PM_{2.5}$) was associated with approximately a 6%, 9% and 14% increased risk of all-cause, cardiopulmonary and lung cancer mortality, respectively[31] (Table 1).

European confirmation of the association between long-term air pollution exposure and cardiopulmonary mortality comes from the study of Hoek *et al.* They showed in a Dutch cohort ($n = 4492$) that cardiopulmonary mortality was associated with living near a major road (relative risk 1.95, 95% CI: 1.09–3.52) and, less consistently, with the estimated ambient background concentration (relative risk 1.34, 95% CI: 0.68–2.64).[32]

Schikowski *et al.* evaluated the relation between long-term exposure to traffic air pollution and lung function and exacerbations of COPD, too. The results showed that a 7 μg/m^3 increase in 5-year mean of PM_{10} (interquartile range) was associated with an odds ratio (OR) of 1.33 (95% CI: 1.03–1.72) for COPD and that a 16 μg/m^3 increase in 5-year mean of nitrogen dioxide (NO_2) (interquartile range) was associated with an OR of 1.43 (95% CI: 1.23–1.66) for COPD. Moreover, women living less than 100 m from a busy road also had a significantly decreased lung function; among them, COPD was 1.79 times more likely (95% CI: 1.06–3.02) than for those living farther away[33] (Table 1).

The impact of outdoor (total) and traffic-related air pollution on public health was estimated in Austria, France and Switzerland, in terms of attributable cases of morbidity and mortality. Epidemiology-based exposure-response functions for a 10 μg/m^3 increase in PM_{10} were used to quantify the effects of air pollution. Air pollution caused 6% of total mortality or more than 40 000 attributable deaths per year. About half of all mortality caused by air pollution was attributed to motorized traffic, accounting also for: more than 25 000 new cases of chronic bronchitis (adults); more than 290 000 episodes of bronchitis (children); and more than 16 million person-days of restricted activities.[34]

Epidemiological surveys have shown that the exposure to air pollution can cause short-term effects too, such as increases in daily hospital admissions and increase in daily number of deaths.

Anderson *et al.* investigated the short-term effects of air pollution on hospital admissions for COPD in Europe (Air Pollution and Health, a European Approach—APHEA). For all ages, the relative risks (95% CI) for COPD hospital admissions for a 50 μg/m^3 increase in daily mean level of pollutant (lagged 1–3 days) were: SO_2 1.02 (95% CI: 0.98–1.06); black smoke 1.04 (95% CI: 1.01–1.06); total suspended particulates 1.02 (95% CI: 1.00–1.05), NO_2 1.02 (95% CI: 1.00–1.05) and O_3 (8 h) 1.04 (95% CI: 1.02–1.07). The results confirmed that air pollution is associated with daily admissions for COPD in European cities with widely varying climates[35] (Table 1).

More recently, Gryparis *et al.* (APHEA 2) demonstrated that, for the warm season, an increase in the 8-h O_3 concentration by 10 μg/m^3 was associated with a 0.31% (95% CI: 0.17–0.52) increase in the total daily number of deaths, 0.46% (95% CI: 0.22–0.73) in the number of cardiovascular deaths and 1.13% (95% CI: 0.74–1.51) in the number of respiratory deaths. The corresponding figures for 1-h O_3 were similar[36] (Table 1).

Yang *et al.* examined the association between gaseous pollution and hospitalization for COPD among elderly people living in Vancouver, British Columbia, Canada (1994–1998). The combined relative risk for NO_2, carbon monoxide (CO), O_3 and SO_2, on COPD hospitalization was 1.21[37] (Table 1).

Forastiere *et al.* evaluated the association between daily air pollution levels (PM_{10}, PNC—particle number concentration, CO, NO_2, O_3) and the occurrence of fatal, non-hospitalized coronary events; the association was statistically significant for PNC, PM_{10} and CO. The effect was stronger among people over 65 years of age, but was not limited to a group with specific comorbidity, even if there was a major risk in subjects with COPD[38] (Table 1).

The MISA study (the Italian Meta-analysis of Short-term effect of Air pollution) is another important

Table 1 Health effects of air pollution (long-term and short-term effect)

Study	Effect	Population sample investigated	Health outcome	Pollutants (unit of measures)	Measures (RR, 95% CI)
Anderson *et al.* 1997[35]	Short-term	More than 18 millions adults hospitalized for COPD six European cities (APHEA)	Daily COPD hospitalization	BS ($\mu g/m^3$) STP ($\mu g/m^3$) NO_2 ($\mu g/m^3$) O_3 ($\mu g/m^3$)	RR for an increase of 50 $\mu g/m^3$ of pollutants: 1.04 (1.01–1.06) 1.02 (1.00–1.05) 1.02 (1.00–1.05) 1.04 (1.02–1.07)
Pope *et al.* 2002[31]	Long-term	500.000 adults USA	Mortality: all-cause cardiopulmonary lung cancer	$PM_{2.5}$ ($\mu g/m^3$)	RR for an increase of 10 $\mu g/m^3$ of $PM_{2.5}$: 1.06 (1.02–1.11) 1.09 (1.03–1.16) 1.14 (1.04–1.23)
Yang *et al.* 2005[37]	Short-term	6027 adults hospitalized for COPD Vancouver (Canada)	Daily COPD hospitalization	NO_2 (p.p.b.) CO (p.p.m.)	RR for interquartile range of 7-days average level of pollutants (5.5 p.p.b. NO_2; 0.3 p.p.m. CO): 1.11 (1.04–1.20) 1.08 (1.02–1.13)
Gryparis *et al.* 2004[36]	Short-term	More than 50 millions adults 23 European cities (APHEA 2)	Daily mortality: total respiratory cardiovascular	O_3 ($\mu g/m^3$)	Increase percentage of mortality for an increase of 10 $\mu g/m^3$ of ozone: 0.31 (0.17–0.52) 1.13 (0.74–1.51) 0.46 (0.22–0.73)
Gauderman *et al.* 2004[45]	Long-term	1759 children (average age, 10 year) California	Clinical low of FEV_1	NO_2 (p.p.b.) $PM_{2.5}$ ($\mu g/m^3$) PM_{10} ($\mu g/m^3$) CO ($\mu g/m^3$)	Correlation between average level, over an 8-year period, of pollutants and low of FEV_1
Forastiere *et al.* 2005[38]	Short-term	5144 subjects died out of hospital Italy (Rome)	Fatal, non-hospitalized coronary events	PNC (particles/cm^3) CO ($\mu g/m^3$)	Increase percentage in risk for interquartile range of pollutants (27.8 particles/cm^3 PNC; 1.2 $\mu g/m^3$ CO): 7.6 (2.0–13.6) 6.5 (1.0–12.3)
Schikowski *et al.* 2005[33]	Long-term	4757 women (55 years old) Germany	Pulmonary function and COPD	NO_2 ($\mu g/m^3$) PM_{10} ($\mu g/m^3$)	OR for an interquartile range increases of pollutants (16 $\mu g/m^3$ NO_2; 7 $\mu g/m^3$ PM_{10}): 1.33 (1.03–1.72) 1.43 (1.23–1.66)

APHEA, Air Pollution and Health, a European Approach; BS, black smoke; CI, confidence interval; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM_{10} and $PM_{2.5}$, particulate matter with aerodynamic diameter <10 µm and <2.5 µm, respectively; PNC, particle number concentration; RR, relative risk; STP, suspended total particulate.

study about the effect of the exposure to air pollution. The survey was planned on 15 Italian cities, summing up to 9.1 million inhabitants at the 2001 census. The results showed an increase of mortality for all natural causes associated to increase of air pollutants concentration. Similar findings were found for cardiorespiratory mortality and hospital admissions for respiratory and cardiac diseases.[39]

Baldacci *et al.* analysed the effect of air pollution on respiratory symptoms in two Italian prospective studies carried out in a rural and in an urban area: the prevalence of respiratory symptoms/diseases was always higher in the urban area (Fig. 2). Moreover, bronchial reactivity level was higher in the urban area, after adjusting for percent predicted FEV_1.[40]

Iversen *et al.* investigated the epidemiology of self-reported chronic respiratory diseases throughout Scotland, and the relationship between quality of life and geographic location in those reporting a disease. The results suggested that living in a rural area was associated with a lower prevalence of asthma, chronic cough/phlegm, breathlessness and wheeze (significantly), and other chronic respiratory disorders (not significantly). Although the prevalence of COPD or emphysema did not significantly differ between rural and urban areas, rural residency appeared to be associated with better health status among subjects with these conditions.[41] Similar results were found by Xu *et al.* in Nanjing (China).[42]

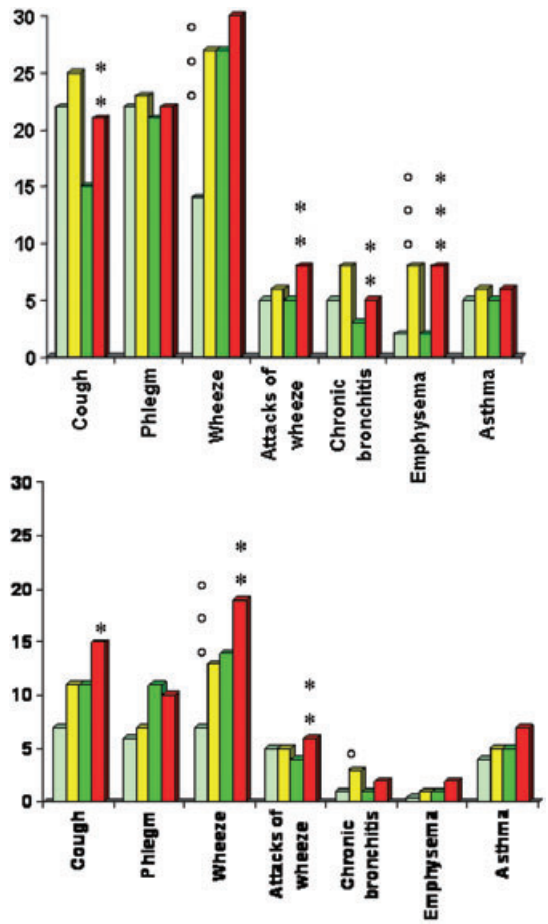

Figure 2 Cross-sectional comparison of prevalence rates of respiratory symptoms/diseases in men (top) and women (bottom), 25–64 years, participating in the first and second surveys of Po Delta, rural area ((□) PD1, (□) PD2) and of Pisa, urban area ((■) PI1, (■) PI2). °$P < 0.05$, °°°$P < 0.001$ (PD1 vs. PI1); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (PD2 vs. PI2).

The effect of exposure to air pollution has been investigated in children as well. The focus of the SIDRIA (Italian Studies on Respiratory Disorders in Children and the Environment) project was the respiratory disorders in children and the environment: more than 54% of the SIDRIA-2 sample reported a high/moderate traffic density in their zone of residence. High frequency of lorry traffic in the street of residence was associated with significantly increased risks for chronic cough or phlegm (OR 1.85, 95% CI: 1.43–2.39 for continuous truck traffic). These results, confirming previous findings (SIDRIA, 1994–1995),[43] showed that children living near streets with intense traffic consisting of heavy vehicles are at higher risk for adverse respiratory effects, especially for productive cough.[44]

A US study of children from the age of 10–18 years indicated that current levels of air pollution have chronic adverse effects on lung development, leading to clinically significant deficits in maximal attained FEV_1 level as children reach adulthood, especially in boys. In particular, there was a significant positive correlation between the clinically low FEV_1 and the average level of exposure to NO_2 and $PM_{2.5}$[45] (Table 1).

EXPOSURE TO BIOMASS FUELS AND SMOKE

The main causal factor of COPD is chronic oxidative stress as a result of long-term smoking, use of biomass fuels and air pollution exposure.

A recent study aimed to compare the presence of chronic airway diseases (CAD) in two groups of non-smoking women older than 40 years with and without a history of exposure to biomass for cooking (liquid petroleum gas). The fraction of CAD attributed to exposure to biomass smoke after adjusting for possible confounding factors was 23.1% (95% CI: 13.4–33.2). Acute symptoms during exposure to biomass smoke were important predictors for the presence of CAD. Thus, biomass smoke pollution is an important contributing factor in the development of CAD in non-smoking women living in a rural area[46](Table 2).

Chapman *et al.* tested whether improvement in household coal stoves affected the incidence of COPD in Xuanwei County, Yunnan, China. The intervention was the installation of a chimney in households in which unvented stoves had been used previously. The Cox-modelled risk ratio was 0.58 (95% CI: 0.49–0.70) in men and 0.75 (95% CI: 0.62–0.92) in women, compared with people who did not have chimneys. In both genders, the reduction in risk became unequivocal about 10 years after stove improvement[47] (Table 2).

In the study of Ceylan *et al.* basal levels of DNA strand breaks were investigated together with some

Table 2 Effects of long-term exposure to biomass fuel

Study	Population sample investigated	Health outcome	Exposure	Measures
Ekici *et al.* 2005[46]	596 non-smoking women (>40 year) (Turkey)	Chronic airway diseases (CAD)	Liquid petroleum gas	Fraction of CAD: 23.1% (CI 95% 13.4–33.2)
Chapman *et al.* 2005[47]	20 453 subjects born into homes with unvented coal stoves (China)	Incidence of COPD	Reduction of households coal stoves	Cox Model RR: 0.58 (95% CI: 0.49–0.70) in men 0.75 (95% CI: 0.62–0.92) in women
Ceylan *et al.* 2005[48]	108 patients with COPD (Turkey)	DNA strand breaks	Fuel for cooking	High DNA damage levels in biomass-related COPD groups

CI, confidence interval.

additional markers of oxidative damage on other biomolecules such as proteins and lipids in patients with COPD who were exposed to smoking and biomass. The mean values of DNA strand breaks were significantly higher in smoking- and biomass-related COPD groups than in the control group. DNA damage levels were also higher in smoking-related COPD group than in biomass-related COPD group. Oxidative stress markers and DNA damage were strongly increased in both patient groups with smoking- and biomass-related COPD[48] (Table 2).

Girod and King sustained that the pathogenesis of COPD mirrors a chronic inhalational dust-induced disease. The putative inorganic dust in cigarette smoke is aluminium silicate or kaolinite. Kaolinite has been recovered in the alveolar macrophages of smokers and has been reported as a constituent of tobacco products. On inhalation, kaolinite deposition in the distal lung may promote macrophage accumulation within the terminal airways leading to a respiratory bronchiolitis. In the susceptible smoker, important genetic, environmental, immunological and mechanical factors interact and modulate the small airway inflammation, ultimately leading to the pathological lesion of emphysema. So, respiratory bronchiolitis, caused by dust exposure, may be the initial inflammatory lesion in smokers and precedes the development of COPD.[49]

PREVENTION

Recommendations for the prevention of COPD, beside the abatement of air pollution, may be the following: promotion of smoking cessation and control of occupational exposures; encouragement for health care systems to track their patients' smoking and occupational histories and to perform spirometry; development of early COPD identification programs for all smokers and those with occupational risk.

In this connection, Kunzli has recently estimated the health benefit that is possible to obtain through an abatement scenario of the main risk factors for respiratory diseases and, in particular, of smoking habit, environmental tobacco smoke (ETS) and outdoor air pollution. He has estimated that more than 70% of chronic bronchitis cases could be prevented if the prevalence rates of active smoking, ETS and PM_{10} annual mean were reduced to 5%, 2.5% and 5 $\mu g/m^3$, respectively.[50]

Previously, Friedmann *et al.* described traffic changes in Atlanta, during the 1996 Summer Olympic Games and concomitant changes in air quality and childhood asthma events (sample of children aged 1–16 years living in the five central counties of metropolitan Atlanta). They compared the 17 days of the Olympic Games (July 19–August 4, 1996) to a baseline period consisting of the 4 weeks before and 4 weeks after the Olympic Games. The results showed an association of the prolonged reduction in O_3 pollution with significantly lower rates of childhood asthma events. These data provide support for efforts to reduce air pollution and improve health via reductions in motor vehicle traffic.[51]

Particulate air pollution episodes have been associated with increased daily mortality, too. However, there is little direct evidence that diminished particulate air pollution concentrations would lead to reductions in death rates. Clancy *et al.* assessed the effect of air pollution controls—the ban on coal sales—on particulate air pollution and death rates in Dublin. Concentrations of air pollution and directly standardized non-trauma, respiratory and cardiovascular death rates were compared for 72 months before and after the ban on coal sales. Average black smoke concentrations in Dublin declined by 35.6 $\mu g/m^3$ (70%) after the intervention. Adjusted non-trauma death rates decreased by 5.7% (95% CI: 4–7%), respiratory deaths by 15.5% (95% CI: 12–19%) and cardiovascular deaths by 10.3% (95% CI: 8–13%). Reductions in respiratory and cardiovascular death rates in Dublin suggest that control of particulate air pollution could substantially diminish human deaths.[52]

CONCLUSION

In conclusion, epidemiological studies have characterized the disease at a population level, indicating possible removable causes and assessing its impact on the individual and on society as a whole.

Population ageing is not the only cause of the increased prevalence of COPD observed in the industrialized countries over the last decades, but other risk factors must be taken into account. Tobacco smoking is the most important cause, but work exposure to

noxious agents and air pollution play a remarkable role in the exacerbation and in the pathogenesis of chronic respiratory diseases, too. Thus, respiratory physicians, as well as public health professionals, should advocate for a cleaner environment.

In order to monitor the epidemiological situation of these diseases, routine statistical data on mortality and hospital admission are available. However, the performance of longitudinal epidemiological surveys in the general population in different geographical areas of the world is advisable to fully highlight the natural history of COPD. To facilitate this project, international respiratory societies should agree upon a standardized definition of COPD that can serve as a population-based measurement criterion as well as a guide to clinicians.

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