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SERIES "THE GLOBAL BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE"
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The natural history of chronic obstructive pulmonary disease

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THE NATURAL HISTORY OF COPD LUNG FUNCTION AND THE ROLE OF EXACERBATIONS

Summary
Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the USA, and it remains one of the few diseases that continues to increase its numbers. The development and progression of COPD can vary dramatically between individuals. A low level of lung function remains the cornerstone of COPD diagnosis and is a key predictor of prognosis. Lung function, however, is not the only factor in determining morbidity and mortality related to COPD, with factors such as body mass index, exercise capability and comorbid disease being important predictors of poor outcomes. Exacerbations of COPD are additional important indicators of both quality of life and outcomes in COPD patients. Definitions of exacerbations can vary, ranging from an increase in symptoms to COPD-related hospitalisations and death. COPD exacerbations are more common in patients with lower levels of lung function and may lead to more rapid declines in lung function. Better understanding of the natural history of COPD may lead to better definitions of specific COPD phenotypes, better interventions and improved outcomes.

Introduction
COPD is a leading cause of morbidity and mortality both in the USA and globally [1, 2]. The current definition of COPD, established by the Global Initiative on Chronic Obstructive Lung Disease (GOLD) and recently adopted, in large part, by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), states that COPD is a ''preventable and treatable disease state characterised by airflow limitation that is not fully reversible'' [3, 4].

The predominant risk factor for COPD in the developed world is cigarette smoking [5, 6]. Other factors may also be important in some individuals, including occupational or environ-

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mental exposures to dusts, gases, vapours or fumes [7]; exposure to biomass smoke [8]; malnutrition [9]; early-life infections [10]; genetic predisposition [11–13]; increased airways responsiveness [14, 15]; and asthma [15–17]. This is particularly true in the developing world, where the prevalence and intensity of cigarette smoking is typically lower.

Lung function

GOLD has classified COPD as ''a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases'' [18]. This definition has also been adopted in the new ATS/ERS guidelines, with the important observation that COPD is both preventable and treatable [4]. Impaired lung function is of central importance in the diagnosis of COPD.

Airflow limitation is the slowing of expiratory airflow as measured by spirometry, with a persistently low forced expiratory volume in one second (FEV_1) and a low FEV_1/forced vital capacity (FVC) ratio despite treatment. The current GOLD and ATS/ERS definition for airflow limitation is an FEV_1/FVC ratio of $<70\%$ [4, 18]. Although this ''fixed'' ratio is easy to remember and simple, there is some concern that it may underestimate COPD in younger populations, overestimate it in older ones, and misclassify other patients [19, 20].

Declining lung function over time is an important component in understanding the natural history of COPD. The concept that different populations (*i.e.* susceptible smokers, nonsusceptible smokers, nonsmokers) have different trends in their lung function decline was developed by PETO *et al.* [21] and expanded by BURROWS *et al.* [22]. Interventions, such as smoking cessation, have been shown to alter this trend in populations, although individual patients may have a great deal of variability in their lung function decline over time [23].

Prevalent COPD in the USA is influenced predominantly by smoking and age. Figure 1 shows age-specific GOLD categories of COPD stratified by smoking status, and shows that a high proportion of people aged ≥ 65 yrs have evidence of COPD. Impaired lung function is an excellent predictor of both morbidity and mortality, including the development of lung cancer [25], functional impairments [26], elevated C-reactive protein levels [27], osteoporosis [28] and death [29]. However, people with similar levels of impaired lung function may have markedly different outcomes. In an analysis of participants in the first National Health and Nutrition Examination Survey (NHANES) and follow-up, current and former smokers with GOLD stage 3 or 4 COPD had a significantly increased mortality risk (compared with participants with no lung disease), whereas never-smokers with GOLD stage 3 or 4 COPD did not have an increased mortality risk [29]. The NHANES findings regarding lack of increase in mortality in nonsmokers with more severe disease has not been replicated in other studies. CELLI *et al.* [30] demonstrated that an index that includes body mass, dyspnoea and the 6-min walk, in addition to lung function, is much better at predicting mortality than lung function alone.

COPD is a heterogeneous disease, and future investigations of the natural history of COPD will have to incorporate better-defined COPD phenotypes into studies. This heterogeneity

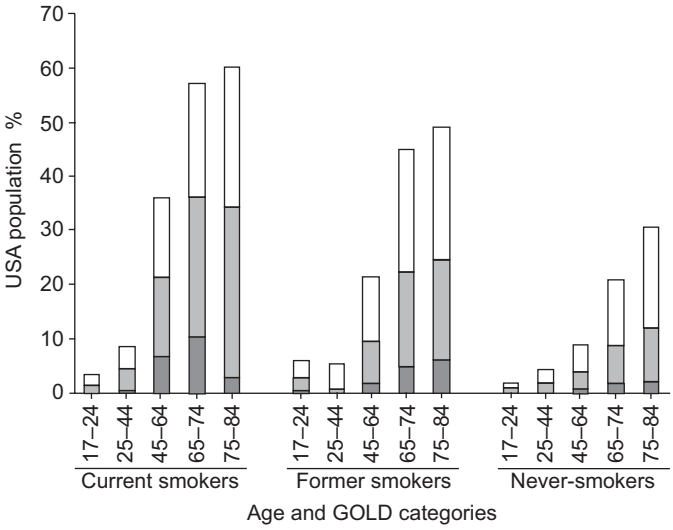

FIGURE 1. Proportion of USA population with spirometric evidence of chronic obstructive pulmonary disease, using criteria from the Global Initiative on Obstructive Lung Disease (GOLD) to classify subjects. GOLD stage 3 or 4 (■; forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.70 and $FEV_1 <50\%$ predicted), GOLD stage 2 (■; $FEV_1/FVC < 0.70$ and $FEV_1 \geq 50$ to $<80\%$ predicted), GOLD stage 1 (□; $FEV_1/FVC <0.70$ and $FEV_1 \geq 80\%$). Data are taken from [24].

extends to lung function. For example, there are several different trajectories that have been defined, including people who never reach their maximum level of lung function, people who have frequent exacerbations, and people who lose lung function at a faster rate than the rest of the population [31]. Another source of heterogeneity is the presence of reversibility, which can be present to varying degrees in patients with COPD [32]. This may represent an overlap with asthma or a subset of COPD apart from asthma.

The role of exacerbations

COPD exacerbations are an important part of the morbidity, mortality and progression of this disease. Several different definitions of exacerbations exist [33, 34], and exacerbations can be classified based on severity [3] or aetiology [34, 35].

COPD exacerbations probably represent a broad range from increased symptoms to hospitalisations, respiratory failure and death [4, 36]. Up to one-half of mild exacerbations are never reported by patients to their physicians [36]. People with lower levels of lung function are more likely to have more exacerbations, and frequent exacerbations may lead to lower levels of lung function [36].

Aetiologies for COPD exacerbations also vary and can be classified. A significant proportion of exacerbations are related to bacterial or viral infections, and changing subtypes of bacteria are a factor in some exacerbations [37]. Many exacerbations, however, do not have an identifiable aetiological factor.

Opportunities for research in COPD exacerbations include looking at how comorbid diseases, such as congestive heart failure, pulmonary hypertension or diabetes mellitus, affect the development and outcome of exacerbations. A second potential area of investigation is whether chronic respiratory

symptoms represent a form of ''chronic exacerbation''. The current guidelines for asthma aim for being ''symptom free''; perhaps the goal in COPD should be similar [38]. Measures unrelated to lung function should take precedence in future investigations of novel end-points of COPD.

Conclusion

The natural history of COPD remains an area of active study. Lung function decline is part of the natural history of COPD and is strongly predictive of COPD-related morbidity and mortality. However, many other factors also influence COPD outcome. In addition, COPD exacerbations can range from symptoms to respiratory failure and death, and can result in both more rapid declines in lung function and worse outcomes. Better understanding of the natural history of COPD may lead to better definitions of specific COPD phenotypes, better interventions and improved outcomes.

THE EPIDEMIOLOGY OF RESPIRATORY IMPAIRMENT AND DISEASE IN TWO GENERATIONS OF THE RENFREW AND PAISLEY (MIDSPAN) STUDY

Summary

Measures of respiratory symptoms and function have been studied in two successive generations over a 25-yr period, based on a larger original cohort of 15,411 males and females aged 45–64 yrs and a subsequent family study comprising 2,338 adult sons and daughters aged 30–59 yrs from 1,477 families. Poor respiratory health is a dominant feature of the original cohort, in association with high rates of socio-economic deprivation and mortality rates from all causes. Measures of COPD, such as the Medical Research Council (MRC) chronic bronchitis questionnaire, hospital admissions and death certification, underestimate the contribution of measured respiratory impairment to poor health and premature mortality. Cigarette smoking within families is a predictor of future ill health in family members, as shown by the associations between passive smoking and cardiorespiratory health in cohabiting adults and between maternal smoking and reduced FEV in adult offspring. The prevalence of chronic sputum production and cigarette smoking has fallen between the generations, whereas the prevalence of hay fever and atopic asthma has increased. These trends and the aggregation of respiratory impairment within families provide many opportunities for further investigation.

Introduction

The Renfrew and Paisley (MIDSPAN) Study is one the longest-running prospective population studies in the world, and spans two generations of adults living in west central Scotland, UK. Poor cardiorespiratory health has been a dominant feature of the study population and has given rise to many important and original observations. The current study provides a brief overview of the study and a review and commentary on the main respiratory findings.

Methods

Study populations

The original study cohort recruited 7,058 males and 8,353 females aged 45–64 yrs, between 1972 and 1976, comprising 80% of the general population in this age group in the two towns of Renfrew and Paisley. The towns are adjacent to the south-west border of the city of Glasgow, within the large, post-industrial Clydeside population, which is characterised by high levels of socio-economic deprivation and premature mortality.

The original cohort included 4,064 married couples, who were contacted again in 1995, either directly or *via* death certificate informants, to seek information on the number, dates of birth and current addresses of all natural offspring. Addresses were available for 3,445 couples, of whom 2,841 replied, providing the names and addresses of 4,829 offspring aged 30–59 yrs, from 2,365 couples with children. The 3,202 offspring from 1,767 couples lived locally and formed the eligible population for a second study. In 1996, 1,040 male and 1,298 female offspring from 1,477 families participated (the response rate for individuals was 73% and for families, 84%).

Measurements

Both studies included comprehensive questionnaires and physical measurements, for which the methods have been described previously [39–41]. Data common to both studies include assessments of cigarette smoking, responses to the MRC bronchitis and Rose chest pain questionnaires, and measurements of blood pressure, cholesterol, body mass index and electrocardiography. A large number of other variables were measured in blood samples taken from offspring [42]. Stored DNA was available for 2,225 offspring and 556 surviving parents. Reported and recorded birth weights were available for 1,714 and 678 offspring, respectively.

FEV_1 was measured in the original cohort [43] using a Garthur vitalograph (Vitalograph Ltd, Buckingham, UK) (best of two expirations with the subject standing) and in the offspring study using a Fleisch pneumotachograph (with Vitalograph Spirotrac III software, Vitalograph Ltd) and ATS standards to define spirogram acceptability [43, 44]. The spirometer's calibration was checked before every session. To improve spirometric quality, technicians were given performance feedback. A total of 2294 subjects attempted spirometry, of whom 2,195 (96%) provided at least two ATS acceptable curves. For a subsample who attended on two occasions, between-visit coefficients of variation for FEV_1 and FVC were 3%.

Predicted values of FEV_1 were obtained separately in each generation from linear regressions on age and height in healthy males and females who had never smoked and who did not have asthma or other respiratory symptoms [40, 43, 45].

Follow-up

All participants have been followed up for all-cause and disease-specific mortality, cancer incidence and hospital admissions. Deaths reported in this manuscript have been coded to International Classification of Diseases 9.

Results

Baseline findings in the original cohort

Over 80% of males in every age group had smoked at some stage of their lives; 54% of females had smoked, and only 7% had stopped by the time of the baseline study in 1972–1976 [39].

The age-related prevalence of chronic bronchitis, defined according to the MRC questionnaire, rose from 3.6% in males aged 45–49 yrs to 8.9% in males aged 60–64 yrs. Compared

with the figures for chronic bronchitis, more than twice as many males were breathless on effort while walking with people of their own age on level ground. Overall, 13.6% of males reported breathlessness and 5.9% reported symptoms of chronic bronchitis [39].

When walking with people of their own age on level ground, 16.4% of females were breathless, compared with 4.1% who had symptoms of chronic bronchitis. The youngest females had higher levels of breathlessness on effort compared with males (15.7% *versus* 8.8%). The oldest males, aged 60–64 yrs, had higher levels of chronic bronchitis than females at this age (8.9% *versus* 4.4%). Otherwise, there were only small sex differences in these variables. The prevalence of chronic bronchitis and breathlessness showed strong social-class gradients.

The prevalence of chronic bronchitis and other symptoms of respiratory impairment was higher than in other populations studied at the same time, including the Whitehall Study of Civil Servants, the Tecumseh Community Health Study, and the World Health Organization (WHO) Collaborative Study of employed males [46]. Prevalence rates in Renfrew were also higher than the prevalence observed some 10 yrs later in rural and more affluent urban settings in Scotland (Scottish Heart Health Study, 1984–1987; unpublished data). FEV_1 fell with age and showed strong social class gradients in males and females [39].

Follow-up of original cohort

Dividing males and females separately into fifths of the distributions of observed/expected FEV_1, relative hazard ratios for mortality after 15 yrs were highest in the bottom quintile, not only for respiratory causes of death, but also for most other major categories of death, including ischaemic heart disease, lung cancer, stroke and other ''causes'' [5]. This pattern of observation persisted after excluding deaths within the first 5 yrs of follow-up, and was also found in life-long nonsmokers.

In terms of percentage population attributable risk for all-cause mortality in males and females, reduced FEV_1 was second only to cigarette smoking, ranking substantially higher than blood pressure, social class and cholesterol. In the current study, FEV_1 was the most important physical measurement for predicting premature death [43].

Hospital use

Between 1972 and 1995, 79% of the cohort experienced at least one acute hospital stay, with an average of 4.6 episodes per person and a mean length of stay per episode of 11.9 days (reducing from 13.8 days in 1975 to 5.6 days in 1995). Follow-up of hospital admission data showed that diseases of the respiratory system provided the principal diagnosis for 5.1% of hospital admissions. Individuals in the lowest quartile of FEV_1 measurement were 27% more likely to be admitted to hospital than those in the top quartile, 50% more likely to have a ''serious'' admission, and 98% more likely to have a hospital admission resulting in death [47].

Death certificates

In the 25 yrs following the initial study, 4,267 males (61%) and 3,746 females (45%) died (table 1). Respiratory deaths ranked fourth in males (9.3%), after coronary heart disease, cancer and stroke, and fourth in females (8.4%), after cancer, coronary heart disease and stroke. COPD deaths comprised 49% of 397 respiratory deaths in males and 43% of 315 respiratory deaths in females.

TABLE 1 Ranking of causes of death after 25 yrs of follow-up of males and females aged 45–64 in the Renfrew and Paisley (MIDSPAN) Study

Ranking	Cause of death %	
	Males	Females
1	Coronary heart disease 36	Cancer 30
2	Cancer 30	Coronary heart disease 28
3	Stroke 10	Stroke 15
4	Respiratory 9	Respiratory 8
5	Other 7	Other 9
6	Other cardiovascular disease 6	Other cardiovascular disease 7
7	Digestive 2	Digestive 3

Passive smoking

The high response rates in the original study meant that there was often more than one participant per household [48]. Passive smoking could, therefore, be studied on the basis of a lifelong nonsmoking index case and whether the cohabitee had ever smoked or never smoked. Symptoms of breathlessness and excess sputum production were increased in passive smokers, although these findings did not reach statistical significance. FEV_1 adjusted for covariates was significantly lower in passive smokers than in controls. All-cause mortality was also higher in passive smokers, as were causes of death related to smoking and mortality from lung cancer and ischaemic heart disease. A dose–response relationship was found, based on the amount of cigarettes smoked by the cohabitee.

Intergenerational trends

Comparing age-standardised prevalence of respiratory illness, smoking and social class at age 45–54 yrs, the percentage of current smokers fell between 1972–1976 and 1996 from 55% in fathers to 26% in sons, and from 52% in mothers to 24% in daughters [41]. The percentage with chronic sputum production fell from 24% in fathers to 14% in sons and from 13% in mothers to 7% in daughters. The proportion of participants in nonmanual occupations rose from 32% in fathers to 55% in sons, and from 47% in mothers to 77% in daughters.

In never-smokers, age- and sex-standardised prevalence of asthma and hay fever was 3.0% and 5.8%, respectively, in 1972–1976, rising to 8.2% and 19.9% in 1996. In ever-smokers, the corresponding values were 1.6% and 5.4% in 1972–1976 and 5.3% and 15.5% in 1996. In both generations, the prevalence of asthma was higher in those who reported hay fever (atopic asthma). In never-smokers, reports of wheeze not labelled as asthma were about 10 times more common in 1972–1976 than in 1996. With a broader definition of asthma (asthma and/or wheeze) to minimise diagnostic bias, the overall prevalence of asthma changed little. However, diagnostic bias mainly affected nonatopic asthma. Atopic asthma increased

more than two-fold (prevalence ratio 2.52), whereas the prevalence of nonatopic asthma did not change (1.00).

Effect on offspring FEV1 of parental death from COPD

Analysis of FEV1 values for male offspring who smoked, and with a father who had died of COPD, showed striking reductions in FEV1 compared with controls (table 2). In cases with COPD mentioned anywhere on the death certificate, the average reduction in FEV1 in offspring was 235 mL. In cases with COPD mentioned as the underlying cause of death, the decrement was 255 mL. Confining these analyses to paternal deaths under 70 yrs gave decrements of 319 mL with any mention of COPD on the death certificate and 478 mL with COPD mentioned as the underlying cause of death.

Familial aggregation of FEV1

Strict comparison and interpretation of trends in spirometric data between the two studies are not possible because of the different measurement methods employed. It is possible, however, to rank individuals within generation-specific distributions and to observe the nature and extent of familial aggregation of FEV1.

The prevalence of high FEV1 (a value in the top quintile) was highest (41%) in the adult offspring of parents who both had high FEV1, whereas the prevalence of low FEV1 (a value in the bottom quintile) was highest (37%) in the offspring of parents who both had low FEV1 (fig. 2). However, there are exceptions: 6% of the adult offspring of parents with high FEV1 values had low personal values of FEV1, whereas 7% of the adult offspring of parents who both had low FEV1 values had high personal values of FEV1. Such observations, and the investigation and comparison of offspring from the different categories, may help to explain why respiratory impairment runs in some families but not others, and why some individuals appear to ''escape'' the phenotype shared by their parents.

Early origins of adult disease

An early analysis based on data from the two generations showed an inverse relationship between maternal smoking and FEV1 in adults [49]. Since FEV1 and FVC are strongly correlated, it was unclear whether the association in question reflected a link with lung volume, airflow limitation, or both. This analysis was extended, therefore, to investigate whether maternal and personal smoking synergise to increase airflow limitation [45]. Residual FEV1 was estimated as an expression of FEV1 variation that was not associated with FVC. Irrespective of personal smoking, maternal smoking was inversely associated with FEV1 and FVC, and also FEV1/FVC, forced mid-expiratory flow rates and residual FEV1 in current smokers but not in never- or former smokers. The clinical relevance of these findings was assessed in ever-smokers without asthma: 10 cigarettes per day of maternal cigarette smoking increased prevalent COPD in offspring by 1.7 (95% confidence interval 1.2–2.5) after adjustment for covariates. Within families, the effect of maternal smoking of 10 cigarettes per day over 20 yrs previously has the same effect on airflow limitation in offspring as 10 yrs of personal smoking. Maternal smoking impairs lung volume irrespective of personal smoking and appears to synergise with personal smoking to increase airflow limitation and COPD.

TABLE 2 Decrements of forced expiratory volume in one second (FEV1) in male offspring who smoke associated with various definitions of chronic obstructive pulmonary disease (COPD) death in a father compared with such offspring with no parental history of COPD death

Family history	Effect on FEV1 mL	p-value
COPD anywhere on the death certificate	-235 (-64– -407)	0.007
COPD as first cause of death	-255 (+36– -546)	0.086
COPD anywhere on death certificate and death at <70 yrs	-319 (-2– -636)	0.049
COPD as first cause of death at <70 yrs	-478 (-12– -943)	0.044

Values given in parentheses are 95% confidence intervals. All values are adjusted for age, height, maternal smoking, pack-yrs of personal smoking, parental social class, parental housing tenure, personal social class and personal housing tenure.

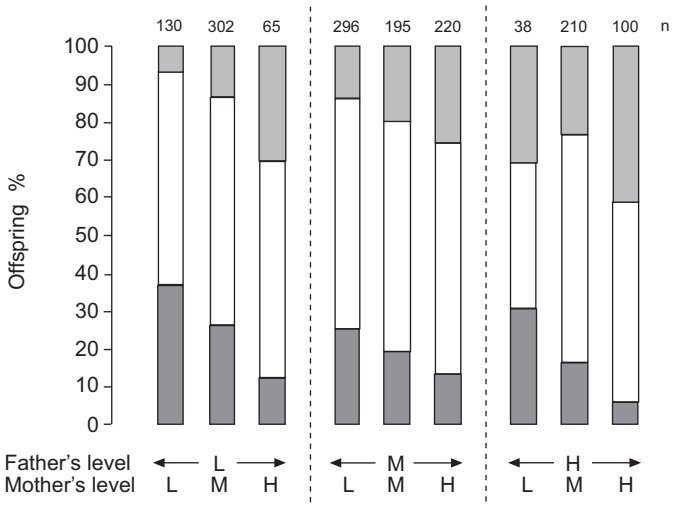

FIGURE 2. Familial aggregation of forced expiratory volume in one second (FEV1). Family descriptions are based on combinations of maternal and paternal FEV1 values in the highest (H; ■), middle three (M; □) and lowest (L; ■) quintiles of the distributions of age- and sex-specific z-scores. Data for the number of offspring are also shown.

FEV1 and cardiovascular risk status

In cross-sectional analyses of the offspring generation, taller males and females had more favourable cardiovascular profiles than shorter people [50]. Leg length was the component of adult height most strongly associated with cardiovascular risk. Genetic influences did not seem to underlie the height–coronary heart disease (CHD) associations. However, FEV1 was more strongly associated than height with the cardiovascular risk factors examined, suggesting that it may be a better biomarker for the factors underlying associations between pre-adult exposures and adult cardiovascular disease. The findings provide indirect evidence that measures of lung development and pre-pubertal growth act as biomarkers for childhood exposures that may modify an individual's risk of developing CHD [50].

Current work is proceeding to assess the effect of new risk factors in explaining familial aggregation and disease risk. For example, the strength of the association between C-reactive protein (CRP) and cardiovascular disease is sufficiently consistent that a recent joint American Heart Association/ Center for Disease Control statement produced guidelines for its potential incorporation into future risk factor stratification [51]. In the MIDSPAN offspring, an association has been shown between CRP levels and area-based definitions of socio-economic deprivation, which is independent of known confounding factors such as age, sex, smoking status, and obesity [52]. It is possible that socio-economic deprivation, assessed by place of residence in this study, is associated with an aggregation of features which results in an increase in systemic inflammation. Within the Renfrew and Paisley (MIDSPAN) study, low-grade background systemic inflammation assessed by an increase in the plasma concentration of CRP was not explained by associations with smoking and body mass index.

In a separate analysis, the current authors found that, after adjusting for potential confounders, there was a negative association between birth weight and CRP, whereby a 1-kg increase in birth weight is associated with a 10.7% decrease in CRP [53]. The current authors have also observed an inverse relationship between levels of CRP and raw FEV_1, with more than a doubling of CRP levels between the highest and lowest quartiles of FEV_1 (unpublished data).

Discussion

The Renfrew and Paisley general population study is one of the longest running prospective studies of cardiorespiratory risk and disease. It is unusual in several respects, including its setting in a population with very high levels of socio-economic deprivation and premature mortality, its initial 80% coverage of this population, and the inclusion of similar proportions of males and females. The setting in a single locality, combined with relatively low population mobility, has also enabled follow-up studies, including a major study of adult offspring using similar measurement methods. The baseline study established high levels of respiratory symptoms in association with known risk factors and hazards, such as cigarette smoking, short stature, and poor housing and air quality.

A major finding of the study has been the importance of respiratory impairment, as measured by FEV_1 and other measures of lung function, comparing observed with expected, in determining future risk of hospital admissions and mortality, not only for respiratory diagnoses, but also all other major causes of hospital admission and death. The observations of this pattern in lifelong nonsmokers and in people who were free of respiratory symptoms at baseline, and after exclusion of deaths within the first 5 yrs of follow-up, all point to a general effect of respiratory impairment on population health, which is not fully captured by focusing on respiratory symptoms and diagnoses.

The pervasive effect of respiratory impairment on mortality is confirmed by the observation that the population attributable risks for all-cause and for CHD mortality were higher for reduced FEV_1 than for any other measurable risk factor, including blood pressure and cholesterol, and were second only to cigarette smoking in terms of overall effect.

The current study shows that smoking in the home environment is harmful to other family members, not only *via* the cumulative effects of passive smoking on cardiorespiratory symptoms and disease, but also the long-term effect of impairing respiratory function in adult offspring who smoke.

An important feature of the MIDSPAN Family Study is that the adult offspring are old enough to demonstrate expression of their predisposition and susceptibility to adverse behaviours and environments. Thus, a family history of premature paternal death from COPD is associated with a substantial reduction in FEV_1 in adult offspring who smoke, while a history of maternal smoking is associated with both an increased prevalence of COPD and reduction of FEV_1 in adult offspring.

In general, symptoms of COPD are less prevalent in adult offspring than in the parent generation, particularly in families who smoke, suggesting improvements not only in general health, in association with increased stature and upward social mobility, but also in exposure to other respiratory hazards. At the same time, the study shows a tripling of the prevalence of atopy, based on the changing prevalence of hay fever, and a doubling of the prevalence of asthma, in both smokers and nonsmokers.

Levels of FEV_1 are seen to aggregate in families, at both ends of the population distribution, but there are fascinating exceptions to the general rule, with ''high'' offspring of ''low'' parents and *vice versa*, which call out for further investigation and explanation. The current study confirms that FEV_1, with height, may be a useful biomarker of future susceptibility to cardiovascular risk and disease, representing the combined and cumulative effects of early influences on growth and development. The observed, separate, associations between CRP levels and socio-economic deprivation, birth weight, and FEV_1 raise the possibility of an inflammatory basis to this early disease predisposition.

Although respiratory impairment is clearly important as a predictor of premature mortality and poor health, it is less clear whether there are any interventions, other than smoking cessation, that can be employed to improve future outcomes. Until such measures become available, population monitoring of respiratory function may nevertheless have a useful role to play in providing a general measure of current and future population health.

COPD, SYSTEMIC INFLAMMATION AND ITS RELEVANCE TO CARDIOVASCULAR DISEASE

Summary

COPD is a growing health burden worldwide. Traditionally, it was believed that most patients with COPD died from respiratory failure; however, emerging epidemiological data indicate that many COPD patients develop cardiovascular complications and die from cardiovascular causes of mortality. In the Lung Health Study, for instance, which studied over 5,800 patients with mild-to-moderate COPD, 42–48% of all hospitalisations, which occurred over a 5-yr follow-up period, were related to cardiovascular complications. Various population-based

studies suggest that, independent of smoking, age and sex, COPD increases the risk of cardiovascular morbidity and mortality two-fold. Despite these strong epidemiological associations, the mechanism(s) by which COPD can be linked with cardiovascular diseases are not clear. In the current study, one potential pathway linking COPD with cardiovascular events is discussed.

Introduction

COPD affects over 5% of the adult population and is the only major cause of death for which the morbidity and mortality are increasing in the USA and elsewhere [54]. Globally, COPD is the fourth leading cause of mortality and the twelfth leading cause of disability and, by the year 2020, it is estimated that it will be the third leading cause of death and the fifth leading cause of disability worldwide [55]. Although these figures are alarming, they are likely to be gross underestimates of the true health and economic burdens of COPD because COPD is an important risk factor for other causes of morbidity and mortality, including cardiovascular disorders [56, 57]. Even relatively small reductions in lung function increase the risk for ventricular arrhythmias, coronary events and cardiovascular mortality by two-fold, independent of the effects of smoking [43, 57, 58]. Moreover, among those with established COPD, the leading cause of hospitalisation and mortality is related to the cardiovascular system, accounting for 40–50% of all hospitalisations and for 30–50% of all deaths among COPD patients [56, 57]. Indeed, a 10% decrease in FEV_1 among COPD patients increases the cardiovascular event rate by approximately 30% [57]. The mechanism(s) linking COPD with cardiovascular events is (are) not very clear.

Pathogenesis of atherosclerosis

Atherosclerosis is a progressive disease characterised by accumulation of lipids, fibrous tissue and inflammatory cells in arteries [59, 60]. One of the pivotal events that initiates this process is thought to be the accumulation of low-density lipoprotein (LDL) in the subendothelial matrix of vessel walls. The rate of LDL deposition is proportional to the circulating LDL levels in plasma. Once LDL penetrates into the vessel wall, it undergoes modification (*e.g.* oxidation). One product of this process is oxidised LDL, which subsequently initiates a variety of events that lead to atherosclerosis [59, 60]. First, it stimulates the endothelial cells to overexpress adhesion molecules (*e.g.* selectins and integrins) and growth factors (*e.g.* macrophage colony-stimulating factor). Secondly, it inhibits production of endothelial nitric oxide, which leads to overactivity of vasoconstrictive forces and endothelial dysfunction. Thirdly, it signals the entry of monocytes into the vessel wall, where they transform into macrophages. These macrophages then ingest the oxidised LDL particles, leading to the formation of foam cells in the subendothelial matrix. The foam cells release a variety of growth factors to promote the proliferation of fibrous tissue and smooth muscle cells, which, over time, result in plaque formation. Homocysteine, angiotensin II and CD40, with its CD40 ligand, are cofactors in this process; thus, increased expression of these factors accelerates plaque formation. Surrounding these plaques are fibrous caps. The most vulnerable plaques (*i.e.* those that are most likely to rupture) have very thin caps and contain a large number of inflammatory cells. The highest concentrations of inflammatory cells are found at the edges of plaques (*i.e.* shoulder regions), where plaques are most likely to rupture. Once plaques rupture, platelets and other blood coagulants come into direct contact with tissue factor, which then binds to factor 7, initiating a process that eventually leads to the formation of fibrin clot through the extrinsic pathway. Thrombosis then ensues. Coronary events are therefore a by-product of both atherosclerosis and thrombosis (*i.e.* atherothrombosis) [59, 60].

Association of atherosclerosis and systemic inflammation

Although the pathogenesis of atherosclerosis is complex and multifactorial, persistent, low-grade systemic inflammation is believed to be one of the centrepiece events leading to plaque formation [59–61]. There are strong epidemiological data linking systemic inflammation to atherosclerosis, ischaemic heart disease, strokes and coronary deaths [61–63]. Under normal physiological conditions (and without external insults), the human endothelium does not support leukocyte adhesion, which is the building block of plaque genesis. However, in an inflammatory state (such as diabetes, COPD or obesity), the endothelium begins to overexpress surface adhesion molecules, such as vascular cell adhesion molecule-1, that allow circulating white blood cells to adhere to damaged endothelial surfaces [64, 65]. Once the white cells become adherent to the endothelium, they trigger a whole series of inflammatory reactions. Certain molecules can promote (or amplify) this inflammatory process. The most studied of these molecules is CRP. It is an acute-phase protein that responds to infectious or inflammatory stress. When released into the systemic circulation, CRP can upregulate production of other inflammatory cytokines, activate the complement system, promote uptake of LDL by macrophages, and foster leukocyte adhesion to vascular endothelium, thereby amplifying the inflammatory cascade. CRP can also upregulate the expression of adhesion molecules and monocyte chemotactic protein-1 [62–65], promote macrophage uptake of LDL [63–66], and interact with endothelial cells to stimulate the production of interleukin (IL)-6 and endothelin-1 [65, 66]. Physiologically, CRP is produced in the liver, and is massively induced as part of the innate immune response to infection and tissue injury [67]. CRP and serum complements act in concert to promote the clearance of apoptotic cells [67]. Not surprisingly, given these physiological functions of CRP, the serum CRP level is a strong, independent predictor of cardiovascular morbidity and mortality [62, 68]. In the Women's Health Study, for instance, CRP levels of <1, 1–3 and 3 $mg \cdot L^{-1}$ corresponded to low-, moderate- and high-risk groups for future adverse cardiovascular events [69]. Other acute-phase proteins released by the liver such as plasma fibrinogen can also be used to predict future cardiovascular events [61]. CRP has a serum half-life of 18 h, and its measurement is reproducible with a correlation coefficient for two values repeated years apart in the same individual of 0.5 [67]. Importantly, the serum half-life of CRP has little diurnal variation and is determined primarily by the hepatic synthesis rate which, in turn, is influenced by the inflammatory signal arising from other cells and organs [66]. When that inflammatory signal dissipates, the hepatic synthesis of CRP normalises and the CRP levels rapidly decrease. This makes CRP a very attractive molecule in estimating the burden of systemic inflammation in health and disease, irrespective of

whether or not CRP is directly involved in the pathogenesis of cardiovascular disease. The ''quantification'' of the systemic inflammatory burden through CRP measurements permits the conduct of large clinical and population-based studies to evaluate the effects of systemic inflammation on salient outcomes, such as the level of lung function, rate of decline of lung function, risk of cardiovascular events and all-cause mortality.

Association of cardiovascular disease and systemic inflammatory disorders

If systemic inflammation is a key mechanism for atherosclerosis, patients suffering from conditions associated with systemic inflammation should have an excess risk of cardiovascular morbidity and mortality. Indeed, this appears to be the case. There is compelling epidemiological evidence that patients with rheumatoid arthritis, for example, have an elevated risk of cardiovascular disease. A recently published meta-analysis evaluating this relationship indicated that rheumatoid arthritis increases mortality rates by 70%; nearly half of this excess risk is directly attributable to cardiovascular causes [70]. Treating rheumatoid arthritis with disease-modifying agents, however, appears to mitigate this risk. In a recent report by CHOI *et al.* [71], therapy with methotrexate reduced the overall mortality by 60%, primarily by reducing cardiovascular deaths. Methotrexate had little impact on other causes of mortality. Since there is no compelling reason to believe that methotrexate had direct salutary effects on the cardiovascular system, these data suggest that, by dampening disease activity, cardiovascular risks can be modified in these patients. Similarly, systemic lupus erythematosis (SLE), another condition associated with systemic inflammation, is also associated with an excess risk of atherosclerosis. Those with SLE have a two- to three-fold increase in the risk of atherosclerosis compared with controls [72, 73]. Importantly, the risk increases linearly along the severity gradient such that those with the most active inflammation and the greatest amount of tissue damage have the highest risk of atherosclerosis. Interestingly, the use of cyclophosphamide or prednisone to dampen disease activity and systemic inflammation is associated with a reduced risk of atherosclerosis in SLE [70]. These data further support the notion that systemic inflammation is an important component in the pathogenesis of atherosclerosis and provides a very strong rationale for determining its role in the pathogenesis of cardiovascular events in COPD.

COPD is an inflammatory disorder

An inflammatory response in the airways and lung parenchyma is an established feature of COPD [74]. HOGG *et al.* [74] have shown that small airways of COPD patients are persistently inflamed and that the intensity of the inflammatory process correlates with the severity of COPD. Once COPD is established, airway inflammation persists, even after many years of smoking cessation [75]. The inflammatory process is thought to play a central role in mediating excess mucus secretion, fibrosis and proteolysis, which, in turn, lead to clinical phenotypes of chronic bronchitis, airway obstruction and emphysema. Several cell lines and inflammatory mediators are likely to be involved in the pathogenesis. Cigarette smoke and other environmental irritants and infectious organisms may activate alveolar macrophages, bronchial epithelial cells, and other cellular elements in the airways of genetically susceptible individuals [76]. Once activated, these cells produce a variety of signalling molecules, chemokines and cytokines, such as IL-8, which recruits neutrophils; macrophage chemotactic protein (MCP)-1, which recruits monocytes; and interferon-γ-inducible protein-10, which recruits lymphocytes. Additionally, they stimulate the synthesis and release of growth factors, elastolytic enzymes and metalloproteinases, which, by themselves, may promote emphysematous changes in lung parenchyma and airway remodelling [76]. Systemic inflammation is also present in COPD [77] and, on a cross-sectional basis, has been linked with cardiac ischaemic events [78]. Interestingly, the strength of the relationship between reduced lung function and cardiovascular events could be significantly attenuated by considering plasma inflammatory proteins in risk models, even among nonsmokers. This suggests that systemic inflammation may contribute to the causal pathway, linking COPD with cardiovascular complications. More clinical and animal studies are needed to validate this hypothesis.

Animal models linking pulmonary and systemic inflammation with atherosclerosis

The relationship between lung inflammation, systemic inflammation and cardiovascular disease is supported by several studies. The current authors have shown, in both animals and humans, that exposure to cigarette smoke [79, 80] and atmospheric particles [81–84] stimulate the bone marrow, an integral component of the systemic inflammatory response, to release leukocytes, such as neutrophils and monocytes, as well as platelets. The magnitude of the bone marrow's response is related to the number of particles phagocytosed by alveolar macrophages [85, 86] and to the level of mediators they produced when processing these particles [87]. Studies from the current authors' laboratory have also shown increased levels of circulating IL-6 and IL-1β in some healthy smokers, and elevated circulating levels of IL-1β, IL-6 and granulocyte macrophage colony-stimulating factor [81] in some subjects exposed to increased levels of ambient particles. All these cytokines are known to stimulate the marrow. Tumour necrosis factor-α and IL-1β are ''acute response'' cytokines and, together with IL-6, are responsible for initiation of the acute-phase response [88]. Together, these cytokines have the ability to elicit a systemic inflammatory response characterised by an increase in circulating leukocytes, platelets, proinflammatory and prothrombotic proteins. This response generates CRP, fibrinogen and other coagulation factors that have all been associated with thromboembolic cardiovascular events. They also have the ability to activate circulating leukocytes and the endothelium of the vascular bed to promote leukocyte–endothelial adhesion and migration.

To test this hypothesis, the Watanabe heritable hyperlipidaemic rabbit, which develops atherosclerosis naturally, was studied [85]. Rabbits were exposed to fine atmospheric particulate matter for 4 weeks; a brisk systemic inflammatory response (including bone marrow stimulation) was demonstrated in the exposed animals compared with controls. Furthermore, the extent of the atherosclerosis in both the coronary arteries and aorta was higher in the exposed animals compared with controls. Quantitative histological studies

showed an increase in plaque lipid content, a higher cell turnover in the plaques and a thinner plaque cap, all of which are morphological changes characteristic of plaque instability and vulnerability [89]. The extent of the atherosclerotic burden was directly proportional to the concentration of alveolar macrophages that contained the particulate matter. Collectively, these data suggest that inhalation of noxious environmental substances (*e.g.* pollution, cigarette smoking) can induce a state of systemic inflammation, possibly through activation of alveolar macrophages, which influences the progression of pre-existing diseases in distant organ systems, such as blood vessels. These studies identify lung inflammation as a potential risk factor for the development of atherosclerosis and its complications, such as ischaemic heart disease, stroke and peripheral vascular disease.

Association of COPD and cardiovascular disease

Consistent with the animal work described previously, there is a growing body of epidemiological data linking COPD with cardiovascular diseases. Indeed, cardiovascular disease caused by atherosclerotic or ischaemic heart disease is one of the leading causes of mortality in COPD [90]. Large population-based studies suggest that patients with COPD have two to three times the risk for cardiovascular mortality, which accounts for ~25–40% of the total number of deaths [58]. Although not generally recognised, poor lung function has been shown to be as powerful a predictor of cardiac mortality as established risk factors such as total serum cholesterol [43]. In the ''Men Born in 1914'' Study, ENGSTROM *et al.* [91] showed that individuals in the lowest quintile of FEV_1/FVC (ratio $\leqslant$66.3%) had risks of coronary events that were, on average, 73% higher than those in the highest quintile (ratio $\geqslant$77.3%), adjusted for tobacco consumption, former smoking, alcohol consumption, angina pectoris, physical activities and diabetes. The risk for frequent or complex ventricular arrhythmia was 83% higher in the lowest FEV_1/FVC quintile compared with the highest quintile. There was a synergistic effect between presence of frequent or complex ventricular arrhythmias on a 24-h ambulatory electrocardiographic recording and reduced FEV_1/FVC ratio on coronary event rates. Reduced FEV_1/FVC ratio by itself was a modest independent risk factor for coronary events (relative risk (RR) 1.30). Presence of arrhythmias in those with normal FEV_1/FVC ratio was not associated with coronary events (RR 1.01). However, the combination of reduced FEV_1/FVC ratio and presence of arrhythmias increased the risk of coronary events by over two-fold (RR 2.43; 95% confidence interval 1.36–4.32). These data suggest that COPD is a major independent risk factor for arrhythmias and coronary events, including cardiovascular mortality. Importantly, the cardiotoxic effects of obstructive airways disease appeared to be amplified in those who have co-existing ventricular dysrhythmias. In the Lung Health Study [57], which followed >5,000 individuals with mild-to-moderate COPD, ~13% of the cohort experienced at least one hospitalisation during the 5-yr follow-up. Cardiovascular events accounted for 42% of the first hospitalisations and 48% of the second hospitalisations. The rate of hospitalisation for lower respiratory tract infection was only one-third of that for cardiovascular illnesses. In this study, for every 10% decrease in FEV_1, all-cause mortality increased by 14%, cardiovascular mortality increased by 28%, and nonfatal coronary event increased by almost 20%, after adjustments for relevant confounders, such as age, sex, smoking status and treatment assignment [57].

In summary, there is a growing body of evidence to indicate that persistent low-grade systemic inflammation is present in stable COPD. Low-grade systemic inflammation has been implicated in the pathogenesis of cardiovascular events. Since COPD patients suffer from excess morbidity and mortality related to cardiovascular events, the present authors postulate that systemic inflammation may, in part, mediate this process. More experimental work, including animal studies, is needed to provide a stronger biological rationale for this hypothesis. Moreover, since temporality is an absolute necessity for a causal association (*i.e.* the cause must precede the effect [92]), future prospective longitudinal studies are needed to determine whether: 1) circulating CRP and other markers of systemic inflammation predict all-cause and cardiovascular causes of morbidity and mortality in COPD; and 2) by modulating systemic inflammation, the health outcomes of COPD can be favourably altered.

COMORBIDITIES IN COPD

Summary

The percentage of predicted FEV_1 has been the primary outcome measure in COPD studies. The contribution of comorbid conditions on clinical outcomes has not been studied extensively. Analyses were conducted using the Lovelace Health Plan database of COPD patients. Almost all comorbid conditions were increased in the COPD population, particularly those that were also smoking related. There was a linear relationship between the number of chronic comorbid illnesses in the COPD population and annual total costs. The average total healthcare cost per patient in the study year was US$13,538. Patients in this cohort averaged slightly more than two comorbidities. The most strongly predictive factors of increased future costs were advanced age, chronic symptoms and chronic illnesses. Comorbidities are among the strongest predictors of increased future costs and should therefore be accounted for in any project examining the financial impact of therapy in COPD. In summary, half of the increased healthcare utilisation and costs found in COPD patients are attributable to comorbid conditions, which are at least as important as airflow obstruction in their effects on future prognosis. Due to the high prevalence of comorbid conditions in COPD patients and the increased utilisation related to them, they may be used to efficiently identify and treat individuals with a high risk of undiagnosed COPD.

Introduction

Comorbid conditions, or comorbidities, may be defined as the other serious diseases and chronic medical conditions that afflict persons who have COPD. Chronic airflow obstruction clearly has a devastating effect on health status, healthcare costs and overall prognosis; this has been demonstrated in hundreds of studies over the last 40 yrs and several other studies presented at the symposium ''The Global Burden of COPD'' (Vancouver, Canada). Because of the correlation between the degree of airflow obstruction and poor outcomes, the percentage of predicted FEV_1 has traditionally been the primary outcome measure in clinical studies of COPD, and

pulmonologists have tended to neglect the contribution that comorbid conditions have on outcomes. In fact, randomised clinical trials of new treatments for COPD usually exclude persons with serious comorbid conditions. However, for every smoker who succumbs to COPD (98,007), three others die of smoking-related cardiovascular disease (148,605), cancer (155,761), or some other nonrespiratory related illness (40,025) [93]. Therefore, comorbidities are highly likely to affect health outcomes in COPD, and COPD patients are more likely to die of cardiovascular complications or cancer than from respiratory failure.

Over the last few years, several projects have been conducted by the current authors that have described the epidemiology of comorbid conditions in population-based cohorts of COPD patients and how comorbidity affects healthcare costs and overall prognosis. In these projects, it has consistently been found that the increased prevalence of comorbid conditions found among COPD patients has impact on utilisation that is as great as or greater than the respiratory effects, and that they are also accurate predictors of poor outcomes. Finally, the increased prevalence of comorbidities in COPD may provide an opportunity to efficiently identify persons at risk for undiagnosed COPD and to get them appropriately evaluated, diagnosed and treated.

The prevalence of comorbidities and their impact on costs

In most of the current authors' COPD projects, patients were examined who were cared for by the Lovelace Health Plan, which is a regional managed care organisation with ~200,000 members based in Albuquerque, NM, USA. The Lovelace Health Plan is primarily a staff-model health maintenance organisation with its own network of hospitals and clinics, but it also has a network of >1,000 contracted physician and other providers from across New Mexico.

In one of the authors' earliest projects, case–control comparisons were used to examine the healthcare costs and utilisation of persons with COPD [94]. Every person at Lovelace was identified who had at least two outpatient visits or one hospitalisation for COPD in 1996 and who was continuously enrolled in 1997 (n=1,522); they were matched to three control patients without COPD by age, sex and ethnicity, and their entire healthcare utilisation for 1997 was then compared. To validate the current authors' methods, and to help capture comorbidities, medical record abstracting of 200 randomly selected persons from the COPD cohort and 200 of their matched controls was conducted [95].

As expected, it was found that COPD patients had a substantially higher prevalence of coronary artery disease (22.0 cases·100^{-1}) and congestive heart failure (13.5 cases·100^{-1}), and twice as much cancer (18.0 cases·100^{-1}). Unexpectedly, the most common chronic illness in the control population was peptic ulcers/gastritis (17.0 cases·100^{-1}). Additionally, COPD patients were far more likely than the controls to have gastritis (32.0 cases·100^{-1}). The most likely explanation for these observations is that ulcers and gastritis are also smoking-related illnesses and, not surprisingly, the COPD patients currently studied were far more likely to have ever smoked or still to be smoking during this time period [96]. This clearly has a huge impact on utilisation. Most of these patients are chronically taking proton pump inhibitors and H_2 blockers, and the current authors found that COPD patients were four times more likely to have upper gastrointestinal endoscopy and other gastrointestinal procedures during the study period. In other diseases not traditionally associated with smoking, such as chronic liver disease or diabetes, there were only slight increases in the COPD population in this study. However, depression (17.0 cases·100^{-1} *versus* 13.0 cases·100^{-1}) and other psychiatric illnesses were also far higher in the COPD population, indicating more than simply the health effects of smoking being a factor.

In summary, this analysis shows that almost all comorbid conditions are increased in the COPD population, particularly those that are smoking related. However, there are also substantial increases in chronic pain syndromes, psychiatric illnesses and other important conditions that are not obviously smoking related.

To look at the impact on healthcare costs, the current authors divided utilisation into inpatient (or in-hospital) costs, outpatient (or clinic) costs, and outpatient pharmacy costs [94]. Of the COPD population, 25% was hospitalised at least once during the study year, as compared with only 10% of the control group (table 3).

The average length of stay (4.7 *versus* 3.9 days) was slightly, but significantly, longer in the COPD group, but the average cost per stay ($11,314 in COPD *versus* $11,921 in controls) was not statistically significant. The primary discharge diagnosis was compared between the case and control groups and, unsurprisingly, approximately one-half of the additional hospitalisations among COPD patients were primarily for respiratory complaints. However, COPD patients had a substantially higher incidence of hospitalisations for every diagnostic category. As one would anticipate from the data previously discussed, admissions for cardiovascular disease were much higher among COPD patients, and admissions for digestive system complaints were also increased. However, admissions for injury, poisoning and diseases of musculoskeletal systems, which have no obvious association with COPD, were also increased. The current authors suspect that some of these increases reflect an increase in risky or otherwise poor health behaviours found among persons who smoke, and their associated health consequences. When a similar analysis was applied to patients with chronic osteoarthritis and low back pain, it was found that chronic pain syndrome sufferers also had a higher prevalence of cardiovascular and other smoking-related diseases [97]. Overall, the marginal cost increase for COPD, which is the difference in the costs between COPD and their matched controls, averaged $1,333 per patient for respiratory-related hospitalisation, but the marginal cost for all nonrespiratory related hospitalisations was even greater ($1,740 per patient per yr).

In the next comparison, the present authors examined the impact of COPD on outpatient visits and costs for the same study year, dividing the visits into the various service areas and comparing the annual cost difference between cases and controls (table 3). If the marginal cost difference for COPD is viewed as simply the increased costs for visits to a pulmonologist ($127.44 per patient), one would falsely assume that

TABLE 3 The annual incidence of hospitalisation among chronic obstructive pulmonary disease (COPD) patients and age- and sex-matched non-COPD controls by discharge diagnosis; the annual mean outpatient visits for COPD patients and matched controls by specialty area, and the associated increase in costs; and the annual prescription fills for COPD patients and matched controls by therapeutic class, and the associated increase in costs

	COPD	Control	Cost difference US$
Subjects n	1522	5466	
Diagnosis group discharges/100			
Respiratory	14.1	0.8	NA
Cardiovascular	7.3	4.3	NA
Signs and symptoms	4.7	1.7	NA
Injury and poisoning	4.5	2.0	NA
Digestive system	3.6	2.2	NA
Musculoskeletal	3.4	1.8	NA
Annual mean outpatient visits			
Primary	7.86	5.10	391.65
Pulmonary	0.81	0.06	127.44
Cardiology	0.62	0.37	77.23
Radiology	1.80	1.06	142.59
Laboratory	4.92	3.38	101.63
Surgical	2.12	1.68	101.49
Total	27.82	16.18	1992.45
Mean prescription fills·patient^{-1}			
Respiratory	8.44	0.69	404.07
Cardiovascular	9.59	6.55	74.56
Psychiatric and pain	5.44	3.02	81.18
Antibiotics	2.58	1.20	72.25
All nonrespiratory	27.04	17.73	402.39
Total	35.48	18.42	806.46

NA: not applicable. For all comparisons, $p < 0.01$.

COPD has only a minor impact. COPD obviously has a tremendous impact on primary care visits, cardiology visits and ancillary service areas, such as radiology and the outpatient laboratory. One of the greatest advantages of working with a managed care database is that it can capture these outpatient visits and associated costs, which are not well accounted for in Medicare or similar databases. Overall, the increased costs for all outpatient services averaged $1,992 per COPD patient.

Outpatient pharmacy costs were analysed, using the same system used to compare COPD patients with their controls by system or drug class (table 3). Again, as expected, the biggest differential between the COPD and control groups was found in respiratory-related utilisation. However, for every occasion a COPD patient gets a prescription for a respiratory drug filled in, they also get one or more prescriptions filled in for a cardiovascular agent. For every classification of drugs, utilisation was increased by 50% to $\geq$100% in the COPD cohort. As one might predict, COPD patients had more than twice as many prescription fills for antibiotics, which the current authors found can be directly related to visits for respiratory infections. However, if the increased costs for antibiotics ($72.25 per person) are compared with those for antidepressants and pain medications ($81.18), this is clearly a population that is suffering in ways one might not anticipate, and the increased cost for nonrespiratory drugs ($402) was almost as great as that for the respiratory drugs ($404).

The impact of comorbid conditions on prognosis in COPD

In the next phase of the current authors' work, they set out to examine what clinical factors best predicted increased future costs in COPD [98]. In the first project, 300 patients were recruited from the Lovelace Health Plan, which was not a random sample, but was a population that closely reflected the total population of COPD patients treated in this system. A complete clinical assessment was performed on each patient (medical history, physical examination, symptoms and quality of life questionnaires, and spirometry and exercise tests) and then each patient was followed for up to 2.5 yrs to see which of these factors were most predictive of increased costs. A linear relationship was found between the number of chronic comorbid illnesses in the COPD population and annual total costs. The average total healthcare cost per patient in the study year was $13,538, and patients in this cohort averaged slightly more than two comorbidities.

When all of the various factors were put into a multivariate model to see which were most strongly predictive of increased future costs, advanced age, chronic symptoms, such as chronic wheezing or a worse quality of life score (*e.g.* the St. George's respiratory disease questionnaire activity subscale), and chronic illnesses (as described by the Charlson–Deyo index) were found to be the most significant factors. Spirometry results, entered as either percentage of predicted FEV_1 or FVC, or by the GOLD staging systems, were also statistically significant predictors, but were weak in comparison with these other factors [18].

In another study, which was also designed to determine which clinical factors were most predictive of increased future costs, the current authors abstracted the medical records of all Lovelace Health Plan COPD patients who had a diagnosis of COPD in 1998, and then captured the direct medical costs for each patient for calendar 1999 using the administrative database [99]. Again, the idea was to see what clinical information available to a physician on any outpatient visit would best predict that a COPD patient is going to have increased costs in the subsequent year. The medical records of 2,116 patients who had at least two outpatient or one in-patient diagnoses were abstracted for information regarding chronic symptoms, smoking status, smoking pack-yr history, and pulmonary function testing (available for only 1,041 patients in this cohort during 1998). The information about comorbidities and healthcare utilisation was abstracted from the administrative database. Total costs in this population were log-normally distributed, so the various clinical factors observed in 1998 were compared with the log of the total direct medical costs expended in 1999.

In univariate comparisons, age was again important, with younger persons (age <50 yrs) being substantially less

expensive than all subsequent age groups. Those who were still smoking in 1998 had significantly lower costs than those who had stopped, mostly because those who were still smoking tended to be young and have less severe lung disease as compared with ex- or never-smokers. Not surprisingly, hospitalisation for any reason in 1998 and home oxygen use were strongly correlated with increased future costs, showing once again that the predictor of future behaviour is past behaviour. Comorbidities were highly predictive of increased future costs, with every form of chronic illness in 1998 having a strong and highly statistically significant correlation. Pulmonary function tests, according to the GOLD severity classifications, were also predictive of increased future costs, but the correlation coefficients were weaker.

These various clinical factors were entered into a multivariate model to see which were most predictive, after adjusting for the other factors included in the model. As was observed in the smaller 300-patient prospective cohort, other clinical factors, including comorbidities, were still strongly predictive of future costs, while pulmonary function tests lost their statistical significance.

In summary, the degree of airflow obstruction as assessed by the GOLD staging system is a valid predictor of increased future costs and utilisation, but the correlation is weak and rather noisy. This fits with the observations of most pulmonologists, who can usually cite several patients in their clinics who seem to exist adequately for many years with minimal lung function. Comorbidities are among the strongest predictors of increased future costs and should, therefore, be accounted for in any project examining the financial impact of therapy in COPD.

Conclusions

The current study shows that one-half of the increased healthcare utilisation and costs found in COPD patients are attributable to comorbid conditions and that comorbid conditions are at least as important as airflow obstruction in their effects on future prognosis. Treatments for COPD are likely to have effects on these comorbid conditions, both positively and negatively, so they must be described and followed carefully both in randomised clinical trials and in observational cohort studies. Due to the high prevalence of comorbid conditions in COPD patients and the increased utilisation related to them, the current authors believe that they may soon be able to use this phenomenon to efficiently identify those at high risk for having undiagnosed COPD, and to appropriately evaluate and treat these persons.

CHARACTERISTICS OF THE PERFECT COPD NATURAL HISTORY STUDY

Summary

To explore which characteristics, if any, define the perfect COPD natural history study is potentially challenging and provoking, but may prove to be fruitful. By critically assessing the limitations and, equally important, what is already known about COPD's natural history, the understanding of the condition currently called COPD might be advanced.

The natural history of COPD is generally well described [100]. To date, the knowledge comes from large epidemiological studies spanning years, and even decades, describing aspects of the natural history of chronic respiratory symptoms and of obstructive lung function impairment [101]. Standardised questionnaires, as well as spirometry, have been applied to different populations around the globe, such as Tucson, AZ, USA [102], Vlagtwedde-Vlaardingen, the Netherlands [103], the Po River Delta, Northern Italy [104] and Copenhagen, Denmark [105]. Even the framework of the European Community Respiratory Health Survey asthma survey is suitable for a COPD follow-up [106].

Measuring lung function in very young children is technically feasible, but rather invasive, and unpleasant for both the child and their parents [107]. Spirometry can be conducted reliably and safely from $\geqslant$4 yrs of age [108]. Although no single study has followed its participants with lung function measurements from birth to death, it is possible to combine the information from studies covering different life stages and present a relatively clear picture of the natural history of FEV_1.

Perinatal factors are likely to affect lung function. For instance, EDWARDS *et al.* [109] described a positive linear trend between birth weight and adult lung function. However, as a follow-up of detailed studies over 40 yrs is not feasible, the mechanisms underlying this phenomenon are not really understood. Subsequently, there is a gap between the programming of the disease early in life and its mechanism later in life. Furthermore, most of what has been carried out in early life studies has been related with a focus on childhood asthma and subsequent asthma.

Lung function growth is probably associated with early onset of lung function decline. However, it is unclear whether or not there is a ''plateau'', or whether this is a reflection of individuals meeting their maximum lung function at different ages. GOLD *et al.* [110] evaluated lung function growth and smoking habits in teenagers. Lung function growth was affected by smoking. By the age of 18 yrs, smoking females already had a decline in lung function; they skipped the ''plateau'' and went directly from decreased lung function growth to accelerated decline in lung function. Although an increasing amount of information about lung function growth is being gathered, there is still not as much known about lung function decline.

Since the perfect COPD natural history study has not been carried out, respiratory epidemiologists often claim a need for such a study. The most common concept is that a perfect COPD natural history study should be an enlarged pulmonary version of the Framingham study [111], enabling pulmonologists to ''do what the cardiologists have done''. In addition, pulmonologists' knowledge (or lack) of genetics and early origin of late-onset disease should be taken into account. From this somewhat naïve view, the perfect COPD natural history study should be large, following participants from before birth until death, and should be extremely comprehensive in terms of all information collected. It should include a few hundred pages of questionnaire forms, full pulmonary function tests, biomarkers, imaging and direct exposure measures. Continuous information should be collected periodically every few years (or even monthly). Finally, it should also obtain, store and analyse all biological and genetic information collected to

disentangle any meaningful current or future biomarker to any COPD outcome.

Just as the perfect COPD natural history study has never been done (the current authors believe it never will be, and never should be), it may be worth considering what is already known. So far, the majority of studies describing the natural history of COPD have focused on decline in FEV_1 in adulthood, but studies in childhood and adolescence are sufficient to describe the natural history of FEV_1 in detail. However, FEV_1 is merely a biomarker, albeit probably a very good one, and having a novel look at the natural history of COPD might be beneficial. Reasonable questions to the epidemiology of the natural history of COPD would therefore be the following. Is it necessary to know more about decline in FEV_1? Will COPD ever be understood if COPD is constantly viewed as ''just COPD''? Is a new paradigm needed?

It is probable that no more new data on FEV_1 decline are needed. However, more time might need to be spent considering how to analyse these data. Exceptions could be the association of FEV_1 with exposures other than smoking, and further exploration of the interaction of FEV_1 with race, sex and exposures. Focus should be on the development of the respiratory system and growth of lung function, as well as structural changes during growth. COPD will never be fully understood if it is constantly viewed simply as COPD. Simple definitions work well for raising awareness, for public health purposes, for initial understanding of the natural history of COPD and for specific outcome studies. The authors doubt whether much progress will be made in the future understanding of the natural history of COPD if the complex and varied features underlying COPD continue to be simplified down to ''reduced FEV_1''. As anticipated, a new paradigm might be needed. Recognising that COPD is a heterogeneous disease should lead to a realisation that the natural history of COPD is a mixture of the natural history of the various phenotypes making up the umbrella term COPD (fig. 3). Future epidemiological studies need to overcome the hurdle of introducing more detailed, and costly, measures enabling the various phenotypes to be addressed; there is a need to ''split'' phenotypes and not just consider them all together [112].

FEV_1 decline is perhaps not the best thing to study if it is the natural history of the disease that is of interest. Patients who might be diagnosed with COPD, and who have the same smoking history and FEV_1, might be considered as having completely different diseases after looking at high-resolution computed tomography scans. Looking at just FEV_1 or FEV_1/FVC will not give the complete clinical picture because there are actually many ongoing processes that are not measured by these simple tests. Use and cost of high-resolution computed tomography scans may not be as prohibitive in clinical trials as some may think. In the future, clinicians may be able to obtain certain single sections to determine the degree of emphysema; this would be no more expensive than a radiograph of the chest, would not result in excessive radiation, and could be carried out in large studies.

Finally, incorporating an epidemiologist mindset into clinical trial design will ensure that the resulting natural history of the disease and the extrapolation of information either to or from the patient population is appropriately defined. Being speculative, it can be concluded that the perfect chronic obstructive pulmonary disease natural history study should consist of multiple studies, each addressing a specific scientific question, and it should split phenotypes instead of considering them all together.

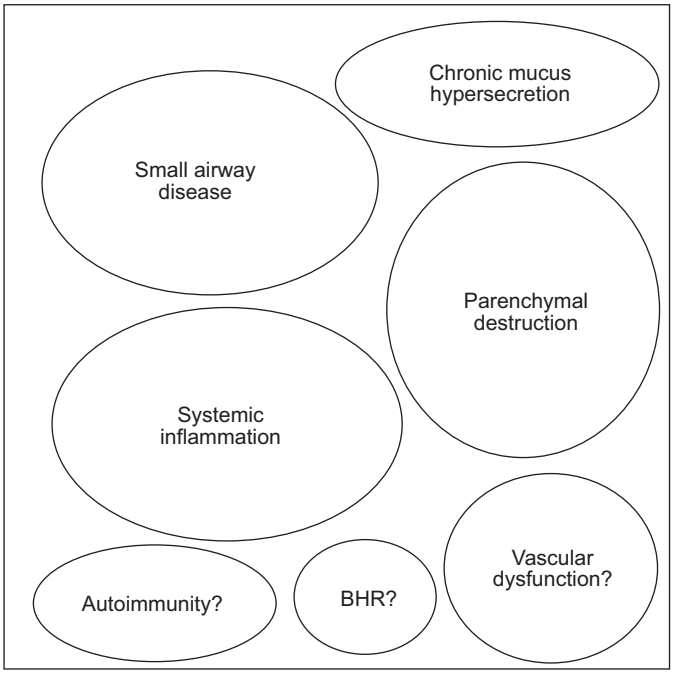

FIGURE 3. The natural history of chronic obstructive pulmonary disease (COPD) is a mixture of the natural history of the various phenotypes making up the umbrella term COPD. The potential phenotypes implicated in the natural history of COPD are shown. BHR: bronchial hyperresponsiveness.

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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/elearning.

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