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Clinical determinants of exacerbations in severe, early-onset COPD

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) exacerbations impair health. The present authors analysed participants in the Boston Early-Onset COPD Study for familial aggregation and propensity for COPD exacerbations.

In the present study, two exacerbation outcomes, episodes of cough and phlegm, and frequent exacerbations were analysed with multivariable modelling and generalised estimating equations.

In early-onset COPD probands, passive tobacco smoke exposure within the home was strongly associated with episodes of cough and phlegm. Chronic phlegm production was associated with both exacerbation phenotypes in probands. In first-degree relatives of early-onset COPD probands, chronic bronchitis, episodic wheezing, pneumonia and active smoking were associated with the episodes of cough and phlegm phenotype. In relatives, identical characteristics plus exertional dyspnoea were associated with frequent exacerbations. Exacerbation risk increased with declining lung function. Familial aggregation for episodes of cough and phlegm was observed in relatives with severe obstruction.

In conclusion, passive smoke exposure increases morbidity in severe early-onset chronic obstructive pulmonary disease probands, and chronic obstructive pulmonary disease exacerbations correlate with chronic sputum production in probands and relatives. The familial aggregation of exacerbations suggests a genetic basis for susceptibility to chronic obstructive pulmonary disease exacerbations.

KEYWORDS: Chronic obstructive pulmonary disease, exacerbation, familial aggregation, passive smoking

Individuals with chronic obstructive pulmonary disease (COPD), a progressive and irreversible illness, manifest symptoms of cough, phlegm, dyspnoea and exercise limitation. A proportion of individuals experience exacerbations during which these symptoms are acutely intensified. These episodes reduce quality of life, alter activities of daily living and commonly compel additional medical therapy. COPD exacerbations result in substantive morbidity, increased resource utilisation and significant financial burden [1–4]. Unfortunately, some individuals experience COPD exacerbations frequently. Other individuals have longer periods of relative stability. Frequent exacerbations are associated with increased morbidity and mortality [5]. The magnitude of this effect is highlighted by reports linking exacerbation frequency to acceleration in loss of lung function [6], reduction in quality of life [7, 8], and risk for increased hospitalisations [9, 10]. The fundamental reasons underlying the propensity to frequent exacerbations have not been determined.

SILVERMAN *et al.* [11] previously demonstrated that current or former smoking relatives of severe, early-onset COPD probands in the Boston Early-Onset COPD Study had lower lung function and a higher relative risk of chronic bronchitis than controls who smoked. DEMEO *et al.* [12] demonstrated that both smoking and nonsmoking first-degree relatives of severe early-onset COPD probands have significantly lower spirometric mid-flow parameters. The present authors analysed probands from the Boston Early-Onset COPD Study and their first-degree relatives to determine the clinical characteristics associated with COPD exacerbations and to assess for familial aggregation of exacerbations. It was hypothesised that frequent exacerbations in early-onset COPD probands and first-degree relatives would be increased by chronic cough

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and phlegm production, active smoking, passive environmental tobacco smoke exposure and lower lung function. It was also hypothesised that exacerbations in first-degree relatives would be increased in relatives of early-onset COPD probands with frequent exacerbations.

METHODS

Boston Early-Onset COPD Study participants

Participants were given a survey at study enrolment by a trained research assistant. Probands met the following criteria and were enrolled between 1994 and July 2002: 1) age $\leqslant$52 yrs; 2) forced expiratory volume in one second (FEV_1) <40% predicted; 3) no evidence of severe α_1-antitrypsin deficiency; and 4) physician-diagnosed COPD. This analysis was restricted to 139 probands and 465 adult first-degree relatives (parents, siblings and children) aged $\geqslant$18 yrs. Other details concerning study participant enrolment and baseline physiological testing have been published previously [11, 13].

Survey

The enrolment survey is a modification of the 1978 American Thoracic Society Division of Lung Diseases Epidemiology Questionnaire [11, 14]. The questionnaire collects traditional demographic information and includes domains pertinent to symptoms, respiratory history, past medical history, environmental exposures and family history. The questions on breathlessness are modified from the Medical Research Council (MRC) dyspnoea scale questionnaire where the levels of exercise intolerance are graded from 1–5 [15]. Passive tobacco smoke exposure was assessed with questions concerning the smoking habits of others who currently and regularly smoked in the proband's home. The two exacerbation outcomes, ''episodes of increased cough and phlegm'' and ''frequent exacerbations'', were analysed as binary exacerbation phenotypes. The episodes of increased cough and phlegm phenotype was created from the survey question asking: ''Do you have periods of increased cough and phlegm lasting for 3 weeks or more each year?'' The frequent exacerbations phenotype was created from the survey question asking: ''During the past 3 yrs have you had any chest illnesses that kept you off work, indoors at home, or in bed?'' The frequent exacerbations phenotype was dichotomised at a threshold of at least three episodes in 3 yrs. This threshold provided a mean annual exacerbation rate of 2.3 events per person per year, which approximated the rate in other published reports [7, 16]. Chronic phlegm production was defined as phlegm production at least 3 months annually for the past 2 yrs. Chronic cough was defined as the presence of a cough at least 3 months annually for the past 2 yrs. Chronic bronchitis was defined as chronic cough plus chronic phlegm. The episodes of wheezing with dyspnoea phenotype derived from the inquiry whether the participant had ever experienced attacks of wheezing with shortness of breath.

Follow-up survey

Surviving participants and relatives of deceased probands were contacted by telephone interview between May and November 2002 [13]. The average follow-up time was 3.5 yrs (2 months to 8.1 yrs). The follow-up survey was specifically focused on determining the prevalence of important clinical events (respiratory or other hospitalisations, mechanical ventilation and respiratory failure), surgical procedures (lung volume reduction surgery or lung transplantation), and complications, such as pneumothorax. The present authors validated whether the original phenotypes, episodes of increased cough and phlegm and frequent exacerbations, were predictive of clinical events longitudinally by constructing logistic and linear regression models using responses from the follow-up survey as dependent variables.

Statistical analysis

Quantitative data are presented as mean$\pm$SD. The following variables were tested in the univariate analysis: chronic cough, chronic phlegm, episodes of wheezing with dyspnoea, chronic bronchitis, walks slower than age due to dyspnoea, self-reported pneumonia, history of lung disease before the age of 16 yrs, current smoking, other individuals currently smoking in the home, age, age at onset of smoking, sex, pack-yrs, and FEV_1 % pred. In the univariate analysis, categorical variables were compared with Chi-squared tests and continuous variables were analysed using two-tailed t-tests. To adjust for multiple covariates, multivariable regression models were constructed using a backward elimination algorithm and repeated with forward selection. A final set of significant variables was selected. For the multivariable models, it was elected to include FEV_1 and pack-yrs regardless of statistical significance. Generalised estimating equations were used to adjust and assess for familial aggregation. An α level of 0.05 was considered as an acceptable level of statistical significance.

RESULTS

Probands

The clinical characteristics of the 139 probands are presented in table 1. Severe functional limitation with breathlessness causing inability to leave the house or with activities of daily living, such as dressing (equivalent to MRC breathlessness questionnaire grade 5), was reported in 68% of probands.

TABLE 1 Clinical characteristics of probands with severe, early-onset chronic obstructive pulmonary disease

Subjects n	139
Age	48$\pm$5
FEV_1 pre-BD/post-BD % pred	19$\pm$7/22$\pm$9
FVC % pred	51$\pm$17
FEV_1/FVC pre-BD/post-BD	0.32$\pm$0.11/0.31$\pm$0.10
FEV_1 BD response % of baseline	16$\pm$15
BMI kg·m^{-2}	25$\pm$6
Smoking pack-yrs	39$\pm$22
Sex % female	101 (73)
Current smoker	20 (14)
β-Agonist therapy	98
Inhaled corticosteroid therapy	79
Current prednisone use	35
Anticholinergic inhaler therapy	75

Data are presented as mean$\pm$SD, n (%) or %, unless otherwise stated. FEV_1: forced expiratory volume in one second; % pred: % predicted; pre-BD: before bronchodilator (BD) administration; post-BD: after bronchodilator administration; FVC: forced vital capacity; BMI: body mass index.

TABLE 2 Clinical predictors of the episodes of cough and phlegm phenotype in severe early-onset chronic obstructive pulmonary disease probands

	Unadjusted odds ratio (CL)	p-value	Adjusted odds ratio# (CL)	p-value
Others actively smoke in the home	6.7 (2.2–20.7)	0.001	10.8 (2.3–49.9)	0.002
Chronic phlegm production	3.2 (1.6–6.5)	0.001	3.5 (1.6–7.7)	0.002
Number of pack-yrs	1.0 (0.98–1.0)	0.9	1.0 (0.98–1.0)	0.9
FEV1 post-BD % pred¶	1.0 (0.98–1.1)	0.4	1.0 (0.97–1.1)	0.5

CL: confidence limits; FEV1: forced expiratory volume in one second; post-BD: after bronchodilator administration; % pred: % predicted. #: the full model includes all four variables; ¶: post-BD spirometry was unavailable for 11 probands. The pre-bronchodilator FEV1 was also not statistically significant in a separate model.

Episodes of cough and phlegm phenotype in probands

In total, 73 (53%) probands reported a history of episodes of cough and phlegm. Probands with and without episodes of cough and phlegm did not significantly differ in terms of age (48±6 *versus* 48±4 yrs, p=0.5), baseline FEV1 (0.58±0.24 *versus* 0.57±0.27 L, p=0.7) or pack-yrs of smoking (39±24 *versus* 39±19, p=0.9). In the univariate analysis, probands with and without the episodes of cough and phlegm phenotype differed in age at onset of smoking (15±3 *versus* 16±3, p=0.046), the presence of chronic cough (67 *versus* 44%, p=0.006), the presence of chronic phlegm production (62 *versus* 33%, p=0.0009), history of chronic bronchitis (55 *versus* 27%, p=0.001) and exposure to passive smoke (30 *versus* 6%, p=0.004). The multivariable model is presented in table 2. After adjusting for potential confounders, the clinical characteristics that increased the odds of an individual with severe, early-onset COPD to experience acute episodes of cough and phlegm were current exposure to other smokers in the home and the presence of chronic phlegm. Individuals with chronic phlegm production were more than three times more likely to experience acute episodes of cough and phlegm production (odds ratio (OR) 3.5 (confidence limit (CL) 1.6–7.7), p=0.002).

The factor with the most dramatic impact on episodes of cough and phlegm was passive environmental smoke exposure (OR 10.8 (CL 2.3–49.9), p=0.002) and retaining significance in a revised model eliminating current smokers (OR 8.2 (CL 1.7–39), p=0.009). In total, 26 (19%) probands were currently exposed to other smokers in the home. Individuals with current passive tobacco smoke exposure did not significantly differ from those who were not exposed in terms of active smoking (23 *versus* 12%, p=0.2), pack-yrs of smoking (42 *versus* 38, p=0.4) or post-bronchodilator FEV1. Exposure to current passive environmental tobacco smoke was more likely to result in report of episodes of cough and phlegm and self-reported pneumonia (table 3). In the individuals with the episodes of cough and phlegm phenotype, 43% reported exposure to passive tobacco smoke within the past 24 h. In contrast, 21% of individuals without the episodes of cough and phlegm phenotype reported exposure to second-hand tobacco smoke within the past 24 h.

FREQUENT EXACERBATIONS PHENOTYPE IN PROBANDS

In total 84 (60%) probands reported a history of frequent exacerbations defined as at least three chest illnesses resulting in loss of work, remaining indoors or bed rest in the past 3 yrs. Exacerbation frequency in the frequent exacerbations group ranged from 3–35 events over 3 yrs, averaging 2.3 events per person per year. Probands with and without the frequent exacerbations phenotype did not significantly differ in lung function or tobacco use (age of initiation or pack-yrs). Passive tobacco smoke exposure was not associated with the frequent exacerbations phenotype. In a multivariable model controlling for potential confounding factors, the only significant predictor of the frequent exacerbations phenotype in probands was the presence of chronic phlegm production (OR 3.7 (CL 1.7–7.9), p=0.0009; table 4).

First-degree relatives

The characteristics of the first-degree relatives of severe, early-onset COPD probands are presented in the supplementary material (table 1).

Episodes of cough and phlegm phenotype in first-degree relatives

Of the first-degree relatives, 78 (17%) reported experiencing episodes of cough and phlegm. Airflow obstruction was present in 51% of these individuals (FEV1 <80% pred). The FEV1 was severely reduced (FEV1 <50% pred) in 26%. In a univariate smokers-only analysis, current and former smoking first-degree relatives with and without the episodes of cough and phlegm phenotype were comparable in terms of age (p=0.6), current smoking status (p=0.3), age at onset of smoking (p=0.1) and pack-yrs (p=0.3). Current and former smoking first-degree relatives with the episodes of cough and phlegm phenotype significantly differed from those without that phenotype by the presence of a reduced FEV1 (p=0.0006) and increased bronchodilator responsiveness as defined by the following three definitions: percentage of baseline FEV1 (p=0.0009), change in absolute FEV1 (p=0.04) and percentage of predicted FEV1 (p=0.01). Data are presented in table 2 of the supplementary material. In a multivariable model, clinical factors distinguishing first-degree relatives with the episodes of cough and phlegm phenotype from those without were the presence of active smoking (p=0.01), chronic bronchitis (p<0.0001), episodes of wheezing (p=0.0002) and self-report of pneumonia (p=0.006; table 5). To establish whether worsening lung function increased the risk of exacerbations, regression models were constructed using the Global Initiative for Obstructive Lung Disease (GOLD) classification [17] as the dependent variable. The odds of experiencing episodes of cough and phlegm increased as lung function declined. For GOLD stage II and below, the OR of episodes of cough and phlegm was 2.8 (CL 1.6–4.8), p=0.0002. For GOLD stage III and

TABLE 3 Impact of current household passive environmental tobacco smoke (ETS) exposure in probands from the Boston Early-Onset Chronic Obstructive Pulmonary Disease Study

	ETS		p-value
	Positive	Negative	
Subjects	26	113	
Episodes of cough and phlegm	22/26 (85)	5/113 (45)	0.0004
Self-reported pneumonia	25/26 (96)	88/113 (78)	0.047
Active smoking	6/26 (23)	14/113 (12)	0.2
Pack-yrs	42	38	0.4

Data are presented as n or n/n (%), unless otherwise indicated.

below, the OR of episodes of cough and phlegm increased to 5.2 (CL 2.6–10.3), p<0.0001.

Frequent exacerbations phenotype in first-degree relatives

In total, 43 first-degree relatives (9%) exhibited the frequent exacerbations phenotype. Of these individuals, 65% manifested an abnormal FEV_1 (<80% pred). Severe airflow obstruction (FEV_1 <50% pred) was present in 35%. Individuals with this phenotype were more likely to be current or former smokers, p=0.02 (81 *versus* 64%), with a trend towards heavier smoking intensity among frequent exacerbators that did not reach statistical significance (p=0.07). In the univariate analysis, the frequent exacerbations phenotype was associated with lower lung function, increased bronchodilator responsiveness by all three definitions, increased respiratory symptoms, a higher prevalence of lung disease before the age of 16 yrs, and self-reported pneumonia.

After adjustment for other covariates, the significant predictors of this phenotype were a history of episodes of wheezing (OR 4.3 (CL 2.0–9.3), p=0.0002), self-reported pneumonia (3.8 (1.7–8.1), p=0.0007), chronic bronchitis (2.6 (1.1–6.2), p=0.03) and exercise limitation due to dyspnoea (1.6 (1.04–2.5), p=0.04; table 6).

Familial aggregation

The presence of significant familial aggregation for a phenotype is suggestive of a genetic component. To assess for familial aggregation, generalised linear models were constructed where the phenotypes in probands were analysed as predictors of the phenotypes of their first-degree relatives, controlling for confounders and stratified by smoking history and lung function. Familial aggregation for episodes of cough and phlegm was observed in the subset of first-degree relatives with FEV_1 <50% (p=0.005). Familial aggregation was not demonstrated for the frequent exacerbations phenotype.

Longitudinal evaluation of probands

To determine the clinical relevance of the exacerbation phenotypes over time, the current authors analysed whether the exacerbation phenotypes were predictive of clinical events in the probands at follow-up. Due to the variable duration of follow-up time, only events occurring within the year prior to the date of the follow-up survey were analysed. A composite variable was created to reflect hospitalisations for respiratory events consisting of pneumonia, bronchitis and respiratory failure. The episodes of cough and phlegm phenotype was associated with increased odds of being hospitalised within the past year for respiratory events (OR 4.1 (CL 1.4–12.0), p=0.009). The frequent exacerbations phenotype was also associated with increased odds of hospitalisation for respiratory events within the past year (OR 4.8 (CL 1.4–16.4), p=0.01).

DISCUSSION

COPD exacerbations are important causes of morbidity and mortality, but the biological basis for variation in exacerbation frequency is not well understood. The present study confirms that COPD exacerbations correlate with chronic phlegm production and this relationship is demonstrated in subjects with severe early-onset disease. Uniquely, the present study also demonstrates that passive exposure to tobacco smoke increases exacerbation morbidity in severe early-onset COPD. In the first-degree relatives of early-onset COPD subjects, it was found that the presence of chronic bronchitis, wheezing and pneumonia are significantly associated with the occurrence of exacerbations, as well as more frequent exacerbations. To the current authors' knowledge, the present study is notable for the initial demonstration of familial aggregation for an exacerbation phenotype for COPD. This novel demonstration of familial aggregation for COPD exacerbations supports the plausibility of a genetic basis for susceptibility to exacerbations.

SEEMUNGAL *et al.* [16] reported on a cohort of 101, predominantly male, COPD patients monitored with daily symptom cards and followed for 2.5 yrs. The median exacerbation rate was 2.4 exacerbations per person per year. In a previous analysis with a shorter duration, the same group reported a median exacerbation frequency of three events per year in the

TABLE 4 Clinical predictors of the frequent exacerbations phenotype in severe early-onset chronic obstructive pulmonary disease probands

	Unadjusted odds ratio (CL)	p-value	Adjusted odds ratio[#] (CL)	p-value
Chronic phlegm production	2.5 (1.3–5.1)	0.01	3.7 (1.7–7.9)	0.0009
Number of pack-yrs	1.0 (0.99–1.03)	0.3	1.01 (0.99–1.03)	0.2
FEV_1 post-BD % pred[¶]	0.98 (0.94–1.02)	0.3	0.98 (0.94–1.02)	0.3

CL: confidence limits; FEV_1: forced expiratory volume in one second; post-BD: post-bronchodilator administration; % pred: % predicted. [#]: the full model includes all three variables; [¶]: post-BD spirometry was unavailable for 11 probands. The pre-bronchodilator FEV_1 was also not statistically significant in a separate model.

TABLE 5 Clinical predictors of the episodes of cough and phlegm phenotype in all first-degree relatives in the Boston Early-Onset Chronic Obstructive Pulmonary Disease Study

	Unadjusted odds ratio (CL)	p-value	Adjusted odds ratio# (CL)	p-value
Chronic bronchitis	9.3 (5.3–16.5)	<0.0001	5.2 (2.6–10.4)	<0.0001
Self-reported pneumonia	3.2 (1.9–5.2)	<0.0001	2.3 (1.3–4.2)	0.006
Episodes of wheezing with dyspnoea	4.8 (2.9–8.1)	<0.0001	3.1 (1.7–5.7)	0.0002
Active smoking	2.5 (1.5–4.1)	0.0003	2.1 (1.2–3.9)	0.01
Number of pack-yrs	1.0 (1.0–1.03)	0.0005	0.99 (0.98–1.01)	0.3
FEV1 post-BD % pred	0.97 (0.96–0.98)	<0.0001	0.99 (0.97–1.00)	0.1

CL: confidence limits; FEV1: forced expiratory volume in one second; post-BD: post-bronchodilator administration; % pred: % predicted. #: the full model includes all six variables. FEV1 and pack-yrs were included in the final model. Age, sex and dyspnoea were nonsignificant and not included.

study population, where they defined frequent exacerbators as experiencing at least three events annually [7]. Clinical factors predicting frequent exacerbations in this community-based cohort were daily cough ($p=0.018$), daily wheeze ($p=0.011$), daily cough and sputum ($p=0.009$), and exacerbations in the previous year ($p=0.001$). The present data and that of others substantiate the relationship between phlegm production and risk for exacerbations [18]. The exacerbation frequency of the present study is similar to that reported in other community-based cohorts [16, 19]. Although use was not made of daily symptom diaries, which are purported to be more likely to prospectively identify exacerbations [20], symptom diaries are also associated with under-reporting of exacerbations in almost 50% of closely monitored patients [7, 16]. It is therefore conceivable that the exacerbation frequency of the present study has been underestimated. Although the definition of episodes of cough and phlegm is not based on diagnosed illnesses, it is possible that it may capture exacerbations that did not receive medical attention. Other reports have determined that factors such as age, chronic mucus hypersecretion, low body mass index and hypercapnia increase the risk for severe or frequent exacerbations, but these studies primarily focused on risk for hospitalisation [9, 21–26].

The definition of a COPD exacerbation is not without controversy [20, 27–29]. The present phenotype definitions have some distinctions. For instance, the duration of the episodes of cough and phlegm phenotype exceeds the median 7-day duration of symptoms reported by SEEMUNGAL *et al.* [16]. Additionally, this phenotype definition may also be limited by residual correlation between the outcome and the predictors, resulting in an overestimation of the OR. The present study utilised a symptom-based definition of an exacerbation in contrast to symptoms plus an event, such as new prescriptions or urgent visits for medical care. Both definitions have been reported to have advantages and limitations [5]. The current authors recognise that their survey questions were based on symptom recall rather than recall of treated episodes, which would have been more consistent with most definitions of COPD exacerbation. They also acknowledge the lack of quality-of-life measurements that are known to be associated with exacerbation frequency [7].

Familial aggregation studies are often the initial procedures when evaluating whether a trait is inherited. The phenotypes episodes of cough and phlegm, and frequent exacerbations may reflect different mechanisms for exacerbation risk, such as increased risk for infection, but the present epidemiological study could not confirm this in the absence of microbiological or serological data. A genetic tendency for chronic bronchitis in the probands and their relatives could result in more frequent exacerbations. However, there were additional significant clinical factors, such as increased report of prior pneumonia, which suggests that other factors may be operative, potentially

TABLE 6 Clinical predictors of the frequent exacerbations phenotype in first-degree relatives in the Boston Early-Onset Chronic Obstructive Pulmonary Disease Study

	Unadjusted odds ratio (CL)	p-value	Adjusted odds ratio# (CL)	p-value
Episodes of wheezing with dyspnoea	8.3 (4.2–16.5)	<0.0001	4.3 (2.0–9.3)	0.0002
Self-reported pneumonia	5.0 (2.6–9.7)	<0.0001	3.8 (1.7–8.1)	0.0007
Chronic bronchitis	5.0 (2.6–9.8)	<0.0001	2.6 (1.1–6.2)	0.03
Exercise limitation due to dyspnoea	2.3 (1.2–4.6)	0.02	1.6 (1.04–2.5)	0.04
Number of pack-yrs	1.0 (0.99–1.02)	0.07	0.99 (0.97–1.0)	0.2
FEV1 post-BD % pred	0.97 (0.96–0.98)	<0.0001	0.99 (0.97–1.0)	0.3

CL: confidence limits; FEV1: forced expiratory volume in one second; post-BD: post-bronchodilator administration; % pred: % predicted. #: the full model includes all six variables. Active smoking, age and sex were nonsignificant and not included.

reflecting an enhanced innate susceptibility to infection. The present data therefore suggest that both of these factors may be important. Future studies will benefit from the investigation of familial clustering of more precise, physiologically defined phenotypes, such as neutrophil-predominant or eosinophilic-predominant exacerbations. The current authors also acknowledge that though their symptomatic first-degree relatives did not uniformly exhibit chronic airflow obstruction, the majority manifested abnormal lung function and are therefore at risk for COPD susceptibility.

Research into the adverse consequences of passive environmental tobacco smoke exposure and its importance as a public health issue has been re-emphasised by the Office of the Surgeon General of the USA. It is estimated that environmental tobacco smoke exposure results in 50,000 excess deaths annually, of which ~3,000 are lung cancer deaths in nonsmokers [30]. There is less conclusive support to substantiate a causal relationship in adults between environmental tobacco smoke exposure and acute or chronic respiratory symptoms or as a cause of COPD or asthma. Developing a definitive conclusion is complicated by methodological issues that limit the comparison of studies, such as differing study designs, misclassification of former smokers as nonsmokers, the precision in measurement of the exposure, consideration of confounding factors, or sample size sufficient enough to study an exposure where the effect is small [31–39]. The present data support a role for passive tobacco smoke exposure in precipitating COPD exacerbations and reinforces the public health message concerning the hazard of second-hand smoke. The present data suggests that recent exposure to environmental tobacco smoke affects respiratory symptomatology in probands with severe, early-onset COPD. Although it was found that passive tobacco smoke exposure increased the risk for acute exacerbations in probands with severe, early-onset COPD, the present authors acknowledge the limitation of their small sample size. Based on the structure of the survey question on environmental tobacco smoke, it is known that the passive smoke exposure is current but its duration and intensity have not been quantified. The advantages and disadvantages of questionnaires for assessing the manifestations of environmental tobacco smoke exposure on health have also been reviewed [40]. Questionnaires are cost-effective, provide information on sources of exposure, may provide retrospective information on environmental tobacco smoke exposure when biomarkers can no longer be measured, can provide information on long-term exposure, and may provide information on modifying factors. Disadvantages include recall bias and lack of a gold standard for validation of questionnaires. The current authors also recognise that their use of survey data has the inherent limitation of a retrospective study design, is restricted by the accuracy of patient recall, and is limited by the lack of objective data.

In summary, individuals with severe early-onset chronic obstructive pulmonary disease who are exposed to passive environmental tobacco smoke have increased morbidity with more frequent reports of chronic obstructive pulmonary disease exacerbations. Furthermore, the presence of phlegm production enhances the risk of chronic obstructive pulmonary disease exacerbations, even in younger patients with chronic obstructive pulmonary disease. Although the probands in the present study population had severe, early-onset disease, their relatives often had chronic obstructive pulmonary disease at later stages in life, suggesting that the present results will generalise to other chronic obstructive pulmonary disease subjects. The finding of familial aggregation of an exacerbation phenotype is a prime motivation for future research focusing on alterations in innate immunity as genetic determinants of chronic obstructive pulmonary disease exacerbations.

REFERENCES

1 Wedzicha JA, Wilkinson T. Impact of chronic obstructive pulmonary disease exacerbations on patients and payers. *Proc Am Thorac Soc* 2006; 3: 218–221.
2 Andersson F, Borg S, Jansson SA, *et al.* The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med* 2002; 96: 700–708.
3 Oostenbrink JB, Rutten-van Molken MP. Resource use and risk factors in high-cost exacerbations of COPD. *Respir Med* 2004; 98: 883–891.
4 Miravitlles M, Murio C, Guerrero T, Gisbert R. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest* 2002; 121: 1449–1455.
5 Donaldson GC, Wedzicha JA. COPD exacerbations. 1: Epidemiology. *Thorax* 2006; 61: 164–168.
6 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
7 Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
8 Donaldson GC, Wilkinson TM, Hurst JR, Perera WR, Wedzicha JA. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 446–452.
9 Garcia-Aymerich J, Monso E, Marrades RM, *et al.* Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study. *Am J Respir Crit Care Med* 2001; 164: 1002–1007.
10 Roberts CM, Lowe D, Bucknall CE, Ryland I, Kelly Y, Pearson MG. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2002; 57: 137–141.
11 Silverman EK, Chapman HA, Drazen JM, *et al.* Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998; 157: 1770–1778.
12 DeMeo DL, Carey VJ, Chapman HA, *et al.* Familial aggregation of FEF(25–75) and FEF(25–75)/FVC in families with severe, early onset COPD. *Thorax* 2004; 59: 396–400.
13 Hersh CP, DeMeo DL, Al-Ansari E, *et al.* Predictors of survival in severe, early onset COPD. *Chest* 2004; 126: 1443–1451.
14 Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis* 1978; 118: 1–120.
15 Fletcher C. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the

MRC committee on the aetiology of chronic bronchitis; MRC breathlessness score. *BMJ* 1960; 2: 1665.
16 Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1608–1613.
17 Calverley PM. The GOLD classification has advanced understanding of COPD. *Am J Respir Crit Care Med* 2004; 170: 211–212.
18 de Marco R, Accordini S, Cerveri I, *et al.* Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am J Respir Crit Care Med* 2007; 175: 32–39.
19 Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respir Care* 2003; 48: 1204–1213.
20 Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J* 2003; 21: Suppl. 41, 46s–53s.
21 Vestbo J. Clinical assessment, staging, and epidemiology of chronic obstructive pulmonary disease exacerbations. *Proc Am Thorac Soc* 2006; 3: 252–256.
22 Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med* 1996; 153: 1530–1535.
23 Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 158–164.
24 Miravitlles M, Guerrero T, Mayordomo C, Sanchez-Agudo L, Nicolau F, Segu JL. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. *Respiration* 2000; 67: 495–501.
25 Godtfredsen NS, Vestbo J, Osler M, Prescott E. Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. *Thorax* 2002; 57: 967–972.
26 Kim S, Emerman CL, Cydulka RK, Rowe BH, Clark S, Camargo CA. Prospective multicenter study of relapse following emergency department treatment of COPD exacerbation. *Chest* 2004; 125: 473–481.
27 Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000; 117: Suppl. 2, S398–S401.
28 Sapey E, Stockley RA. COPD exacerbations. 2: Aetiology. *Thorax* 2006; 61: 250–258.
29 MacNee W. Acute exacerbations of COPD. *Swiss Med Wkly* 2003; 133: 247–257.
30 Dhala A, Pinsker K, Prezant DJ. Respiratory health consequences of environmental tobacco smoke. *Clin Occup Environ Med* 2006; 5: 139–156.
31 Tredaniel J, Boffetta P, Saracci R, Hirsch A. Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. *Eur Respir J* 1994; 7: 173–185.
32 Samet JM, Lange P. Longitudinal studies of active and passive smoking. *Am J Respir Crit Care Med* 1996; 154, Suppl. 2: S257–S265.
33 Eisner MD. Environmental tobacco smoke and adult asthma. *Clin Chest Med* 2002; 23: 749–761.
34 Chan-Yeung M, Dimich-Ward H. Respiratory health effects of exposure to environmental tobacco smoke. *Respirology* 2003; 8: 131–139.
35 Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P. Passive smoking and evolution of lung function in young adults. An 8-year longitudinal study. *J Clin Epidemiol* 1995; 48: 317–327.
36 Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P. Effect of passive smoking on the development of respiratory symptoms in young adults: an 8-year longitudinal study. *J Clin Epidemiol* 1996; 49: 581–586.
37 Mannino DM, Siegel M, Rose D, Nkuchia J, Etzel R. Environmental tobacco smoke exposure in the home and worksite and health effects in adults: results from the 1991 National Health Interview Survey. *Tob Control* 1997; 6: 296–305.
38 Jayet PY, Schindler C, Schwartz J, *et al.* Passive smoking exposure among adults and the dynamics of respiratory symptoms in a prospective multicenter cohort study. *Scand J Work Environ Health* 2005; 31: 465–473.
39 Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. *Environ Health* 2005; 4: 7.
40 Jaakkola MS, Jaakkola JJ. Assessment of exposure to environmental tobacco smoke. *Eur Respir J* 1997; 10: 2384–2397.