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Clinical Determinants of Exacerbations in Severe, Early-onset COPD

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Exacerbations in Early-Onset COPD

Abstract

Rationale: COPD exacerbations impair health. We analyzed participants in the Boston Early-Onset COPD Study for familial aggregation and propensity for COPD exacerbations.

Methods: Two exacerbation outcomes, episodes of cough and phlegm and frequent exacerbations, were analyzed with multivariable modeling and generalized estimating equations.

Results: In early-onset probands, passive tobacco smoke exposure within the home strongly associated with episodes of cough and phlegm ($p = 0.002$), OR 10.8 [95% CL 2.3, 49.9]. Chronic phlegm production associated with both exacerbation phenotypes in probands. In first-degree relatives, chronic bronchitis ($p < 0.0001$), OR 5.2 [2.6, 10.4], episodic wheezing ($p < 0.0002$), OR 3.1 [1.7, 5.7], pneumonia ($p = 0.006$), OR 2.3 [1.3, 4.2] and active smoking ($p = 0.01$), OR 2.1 [1.2, 3.9] were associated with the episodes of cough and phlegm phenotype. In relatives, identical characteristics plus exertional dyspnea 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 ($p = 0.005$).

Conclusions: Passive smoke exposure increases morbidity in severe early-onset COPD probands. COPD exacerbations correlate with chronic sputum production in probands and relatives. Familial aggregation of exacerbations suggests a genetic basis for susceptibility to COPD exacerbations.

Introduction

Individuals with chronic obstructive pulmonary disease (COPD), a progressive and irreversible illness, manifest symptoms of cough, phlegm, dyspnea, 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 utilization, 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 hospitalizations.[9, 10] The fundamental reasons underlying the propensity to frequent exacerbations have not been determined.

Silverman and colleagues have 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.[11] DeMeo et al demonstrated that both smoking and non-smoking first-degree relatives of severe early-onset COPD probands have significantly lower spirometric mid-flow parameters.[12] We analyzed 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. We

hypothesized that frequent exacerbations in early-onset COPD probands and first-degree relatives would be increased by chronic cough and phlegm production, active smoking, passive environmental tobacco smoke exposure, and lower lung function. We hypothesized 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 administered a survey at study enrollment by a trained research assistant. Probands met the following criteria: 1) age $\leq$ 52 years, 2) FEV_1 < 40% predicted, 3) no evidence of severe alpha 1-antitrypsin deficiency, and 4) physician-diagnosed COPD, and were enrolled between 1994 and July 2002. This analysis was restricted to 139 probands and 465 adult first-degree relatives (parents, siblings, and children) $\geq$ 18 years of age. Other details concerning study participant enrollment and baseline physiologic testing have been published previously.[13]

Survey

The enrollment survey is a modification of the 1978 ATS-DLD 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) dyspnea 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. Two exacerbation outcomes, ***episodes of increased cough and phlegm*** and ***frequent exacerbations*** were analyzed 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 years have you had any chest illnesses that kept you off work, indoors, at home, or in bed?" The ***frequent exacerbations*** phenotype was dichotomized at a threshold of $\geq$ 3 episodes in 3 years. 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 two years. Chronic cough was defined as the presence of a cough at least 3 months annually for the past two years. Chronic bronchitis was defined as chronic cough plus chronic phlegm. The episodes of wheezing with dyspnea 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 years (2 months – 8.1 years). The follow-up survey was specifically focused on determining the prevalence of important clinical events (respiratory or other

hospitalizations, mechanical ventilation and respiratory failure), surgical procedures (lung volume reduction surgery or lung transplantation), and complications such as pneumothorax. We 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 means $\pm$ standard deviations. The following variables were tested in the univariate analysis: chronic cough, chronic phlegm, episodes of wheezing with dyspnea, chronic bronchitis, walks slower than age due to dyspnea, self-reported pneumonia, history of lung disease before the age of 16, current smoking, other individuals actively smoking in the home, age, age at onset of smoking, gender, pack-years, and FEV_1 percent predicted. In the univariate analysis, categorical variables were compared with chi-square tests and continuous variables were analyzed with 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, we elected to include FEV_1 and pack-years regardless of statistical significance. Generalized estimating equations were used to adjust and assess for familial aggregation. An alpha level of 0.05 was considered as an acceptable level of statistical significance. All analyses were performed with SAS, version 9.1.3, SAS Institute, Cary, NC.

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

	mean ± sd
n = 139	
Age	48 ± 5
FEV_1 (% predicted), preBD/postBD	19 ± 7 / 22 ± 9
FVC (% predicted)	51 ± 17
FEV_1/ FVC (preBD/postBD)	0.32 ± 0.11 / 0.31 ± 0.10
FEV_1 bronchodilator response (% of baseline)	16 ± 15
BMI	25 ± 6
Pack-years of smoking	39 ± 22
	%
Gender (% female)	101 (73%)
Current smoker	20 (14%)
Beta-agonist therapy	98%
Inhaled corticosteroid therapy	79%
Current prednisone use	35%
Anticholinergic inhaler therapy	75%

PreBD = before bronchodilator administration

PostBD = after bronchodilator administration

Episodes of Cough and Phlegm Phenotype in Probands

73 probands (53%) 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 years vs. 48 ± 4 years, p = 0.5), baseline FEV_1 (0.58 ± 0.24 L vs. 0.57 ± 0.27 L, p = 0.7), or pack-years of smoking (39 ± 24 vs. 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 vs. 16 ± 3, p = 0.046), the presence of chronic cough (67% vs. 44%, p = 0.006), the presence of chronic phlegm production (62% vs. 33%, p = 0.0009), history of chronic bronchitis (55% vs. 27%, p = 0.001), and exposure to passive smoke (6% vs. 30%, 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

Table 2. Clinical Predictors of *Episodes of Cough and Phlegm P*henotype in Severe Early-Onset COPD Probands

	Unadjusted Odds [CL]	p-value	Adjusted Odds[§] [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
Pack-years	1.0 [0.98, 1.0]	0.9	1.0 [0.98, 1.0]	0.9
FEV_1, post BD (% predicted)‡	1.0 [0.98, 1.1]	0.4	1.0 [0.97, 1.1]	0.5

‡Post BD spirometry was unavailable for 11 probands. A model using the pre BD FEV_1 was also not statistically significant.
[§]The full model includes all four variables.

chronic phlegm. Individuals with chronic phlegm production were greater than three times more likely to experience acute episodes of cough and phlegm production, OR 3.5 [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 [2.3, 49.9], p = 0.002, retaining significance in a revised model eliminating current smokers, OR 8.2 [1.7, 39], p = 0.009. Twenty-six probands (19%) 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% vs. 12%, p = 0.2), pack-years of smoking (42 vs. 38, p = 0.4), or post-bronchodilator FEV_1. Exposure to current

Table 3.
Impact of Acute Passive Environmental Tobacco Smoke Exposure
Probands from the Boston Early-onset COPD Study

	ETS (+) n = 26	ETS (-) n = 113	p-value
Episodes of cough and phlegm	22/73 (30%)	4/66 (6%)	0.0004
Self-reported pneumonia	25/26 (96%)	88/113 (78%)	0.047
Active smoking	6/26 (23%)	14/113 (12%)	0.2
Pack-years	42	38	0.4

ETS = environmental tobacco smoke exposure

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 hours. In contrast, 21% of individuals without the episodes of cough and phlegm phenotype reported exposure to secondhand tobacco smoke within the past 24 hours.

Frequent Exacerbations Phenotype in Probands

84 probands (60%) reported a history of frequent exacerbations defined as $\geq$ 3 chest illnesses resulting in loss of work, remaining indoors, or bed rest in the past three years. Exacerbation frequency in the frequent exacerbations group ranged from 3 – 35 events over 3 years, 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-years). Passive tobacco smoke exposure was not associated with the frequent exacerbations phenotype. In a multivariable model

Table 4. Clinical Predictors of the Frequent Exacerbations Phenotype in Severe Early-Onset COPD Probands

	Unadjusted Odds [CL]	p-value	Adjusted Odds[§] [CL]	p-value
Chronic phlegm production	2.5 [1.3, 5.1]	0.01	3.7 [1.7, 7.9]	0.0009
Pack-years	1.0 [0.99, 1.03]	0.3	1.01 [0.99, 1.03]	0.2
FEV_1, post BD (% predicted)‡	0.98 [0.94, 1.02]	0.3	0.98 [0.94, 1.02]	0.3

‡Post BD spirometry was unavailable for 11 probands.
A model using the pre BD FEV_1 was also not statistically significant.
[§]The full model includes all three variables.

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 Table A in the online depository.

Episodes of cough and phlegm phenotype in first-degree relatives

78 first-degree relatives (17%) reported experiencing episodes of cough and phlegm. Airflow obstruction was present in 51% of these individuals (FEV_1 < 80% predicted). The FEV_1 was severely reduced (FEV_1 < 50% predicted) 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-years (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 FEV_1 (p = 0.0006) and increased bronchodilator responsiveness as defined by the following three definitions: % of baseline FEV_1 (p = 0.0009), change in absolute FEV_1 (p = 0.04), and % of predicted FEV_1 (p = 0.01). (Data presented in Table B in the online depository). 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, we constructed regression models using the Global Initiative for

Table 5. Clinical Predictors of the Episodes of Cough and Phlegm Phenotype in All First-degree Relatives in the Boston Early-onset COPD Study

	Unadjusted Odds [CL]	p-value	Adjusted Odds§ [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 dyspnea	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
Pack-years	1.0 [1.0, 1.03]	0.0005	0.99 [0.98, 1.01]	0.3
FEV_1*	0.97 [0.96, 0.98]	<0.0001	0.99 [0.97, 1.00]	0.1

*Forced expiratory volume in 1 second, post-bronchodilator administration, % predicted
§The full model includes all six variables. FEV_1 and pack-years were included in the final model.
Age, gender, and dyspnea were non-significant and not included.

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 odds of episodes of cough and phlegm was 2.8 [CL 1.6, 4.8], p = 0.0002. For GOLD stage III and below, the odds 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

Forty-three first-degree relatives (9%) exhibited the frequent exacerbations phenotype. 65% of these individuals manifested an abnormal FEV_1 (<80% predicted). Severe airflow obstruction (FEV_1 <50% predicted) was present in 35%. Individuals with this

phenotype were more likely to be current or former smokers, p = 0.02 (81% vs. 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, and self-reported pneumonia.

Table 6. Clinical Predictors of the Frequent Exacerbations Phenotype in First-degree Relatives in the Boston Early-onset COPD Study

	Unadjusted Odds [CL]	p-value	Adjusted Odds[§] [CL]	p-value
Episodes of wheezing with dyspnea	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 dyspnea	2.3 [1.2, 4.6]	0.02	1.6 [1.04, 2.5]	0.04
Pack-years	1.0 [0.99, 1.02]	0.07	0.99 [0.97, 1.0]	0.2
FEV_1*	0.97 [0.96, 0.98]	<0.0001	0.99 [0.97, 1.0]	0.3

*Forced expiratory volume in 1 second, post-bronchodilator administration, % predicted
[§]The full model includes all six variables. Active smoking, age, and gender were non-significant and not included

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 (OR 3.8 [1.7, 8.1], p = 0.0007), chronic bronchitis (OR 2.6 [1.1, 6.2] p = 0.03), and exercise limitation due to dyspnea (OR 1.6 [CL 1.04, 2.5], p = 0.04). (Table 6)

Familial Aggregation

Exacerbations in Early-Onset COPD

The presence of significant familial aggregation for a phenotype is suggestive of a genetic component. To assess for familial aggregation, generalized linear models were constructed where the phenotypes in probands were analyzed 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, we analyzed whether the exacerbation phenotypes were predictive of clinical events in the probands at follow-up. Because of the variable duration of follow-up time, we only analyzed events occurring within the year prior to the date of the follow-up survey. A composite variable was created to reflect hospitalizations for respiratory events consisting of pneumonia, bronchitis, and respiratory failure. The episodes of cough and phlegm phenotype was associated with increased odds of being hospitalized 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 hospitalization for respiratory events within the past year (OR 4.8 [CL 1.4, 16.4], p = 0.01).

Discussion

Exacerbations in Early-Onset COPD

COPD exacerbations are important causes of morbidity and mortality, but the biological basis for variation in exacerbation frequency is not well understood. We confirm that COPD exacerbations correlate with chronic phlegm production and we demonstrate this relationship in subjects with severe early-onset disease. Uniquely, we also demonstrate that passive exposure to tobacco smoke increases exacerbation morbidity in severe early-onset COPD. In the first-degree relatives of early-onset COPD subjects, we 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 our knowledge, our 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 and colleagues reported on a cohort of 101, predominantly male COPD patients monitored with daily symptom cards and followed for 2.5 years.[16] The median exacerbation rate was 2.4 exacerbations per patient per year. In a previous analysis with a shorter duration, the same group reported a median exacerbation frequency of 3 events per year in their study population where they defined frequent exacerbators as experiencing 3 or more 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 ($p = 0.001$). Our data and others substantiate the relationship between phlegm production and risk for exacerbations.[18] Our exacerbation frequency is similar

to that reported in other community-based cohorts.[16, 19] Though we did not utilize daily symptom diaries that are purported to be more likely to prospectively identify exacerbations[20], symptom diaries are also associated with under-report of exacerbations in almost 50% of closely monitored patients.[7, 16] It is therefore conceivable that our exacerbation frequency has been underestimated. Though our 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 hospitalization.[9, 21-26]

The definition of a COPD exacerbation is not without controversy. [20, 27-29] Our phenotype definitions have some distinctions. For instance, the duration of ***episodes of cough and phlegm*** phenotype exceeds the median 7-day duration of symptoms reported by Seemungal and colleagues.[16] Additionally, this phenotype definition may also be limited by residual correlation between the outcome and the predictors resulting in an over estimation of the odds ratio. Our study utilized 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] We recognize that our 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. We also acknowledge the lack of quality of life measurements that are known to be associated with exacerbation frequency.[7]

Exacerbations in Early-Onset COPD

Familial aggregation studies are often the initial procedures when evaluating whether a trait is inherited. Our phenotypes, e*pisodes of cough and phlegm* and *frequent exacerbations*, may reflect different mechanisms for exacerbation risk such as increased risk for infection, but our epidemiologic study could not confirm this in the absence of microbiologic or serologic 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 that suggests that other factors may be operative, potentially reflecting an enhanced innate susceptibility to infection. Our 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. We also acknowledge that though our 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 (ETS) and its importance as a public health issue has been re-emphasized by the Office of the Surgeon General of the United States. It is estimated that ETS exposure results in 50,000 excess deaths annually, of which approximately 3,000 are lung cancer deaths in non-smokers.[30] There is less conclusive support to substantiate a causal relationship in adults between ETS exposure and acute or chronic respiratory symptoms or as a cause of COPD or asthma. Developing a definitive

conclusion is complicated by methodologic issues that limit the comparison of studies such as differing study designs, misclassification of former smokers as non-smokers, 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] Our data supports a role for passive tobacco smoke exposure in precipitating COPD exacerbations and reinforces the public health message concerning the hazard of second hand smoke. Our data suggests that recent exposure to environmental tobacco smoke affects respiratory symptomatology in probands with severe, early-onset COPD. Although we found that passive tobacco smoke exposure increased the risk for acute exacerbations in probands with severe, early-onset COPD, we acknowledge the limitation of our small sample size. Based on the structure of the survey question on ETS, we know that the passive smoke exposure is current but its duration and intensity were not quantified. The advantages and disadvantages of questionnaires for assessing the manifestations of ETS exposure on health have also been reviewed.[40] Questionnaires are cost-effective, provide information on sources of exposure, may provide retrospective information on ETS 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. We also recognize that our 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.

Exacerbations in Early-Onset COPD

In summary, individuals with severe early-onset COPD who are exposed to passive environmental tobacco exposure have increased morbidity with more frequent reports of COPD exacerbations. Furthermore, the presence of phlegm production enhances the risk of COPD exacerbations even in younger patients with COPD. Though the probands in our study population had severe, early-onset disease, their relatives often had COPD at later stages in life suggesting that our results will generalize to other COPD 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 COPD exacerbations.

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