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Occupational Exposures and Longitudinal Lung Function Decline

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Abstract

Background—Few longitudinal studies have been conducted on occupational exposure and lung function. This study investigated occupational dust exposure effects on lung function and whether genetic variants influence such effects.

Methods—The study population (1,332 participants) was from the Framingham Heart Study, in which participant lung function measures were available from up to five examinations over nearly 17 years. Occupational dust exposures were classified into “more” and “less” likely dust exposure. We used linear mixed effects models for the analysis.

Results—Participants with more likely dust exposure had a mean 4.5 mL/year excess loss rate of FEV_1 over time. However, occupational dust exposures alone or interactions with age or time had no significant effect on FEV_1/FVC. No statistically significant effects of genetic modifications in the different subgroups were identified for FEV_1 loss.

Conclusions—Occupational dust exposures may accelerate the rate of FEV_1 loss but not FEV_1/FVC loss.

Keywords

job exposure matrix; forced expiratory volume in one second; chronic obstructive pulmonary disease; environmental lung disease; environmental health; occupational health; occupational respiratory disease

Introduction

Chronic obstructive pulmonary disease (COPD) affects between 6% and 20% of people worldwide [Buist et al., 2008]. Diagnosis of COPD usually employs a measure of the forced expiratory volume in one second (FEV_1) and ratio of FEV_1 to forced vital capacity (FVC). FEV_1 is a stable measure of lung function and has been shown to predict clinical outcome, as well to reflect the severity and natural history of obstructive lung disease. Smoking is a

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well-known important risk factor for COPD. However, in the United States, 15% to 20% of COPD cases are attributable to occupational exposure [Balmes et al., 2003].

Occupational exposure to dust has been associated with COPD or poor lung function in both industry-based [Higgins, 1973; Kauffmann et al., 1982; Oxman et al., 1993; Johnsen et al., 2008] and community-based [Korn et al., 1987; Krzyzanowski and Kauffmann, 1988; Bakke et al., 1991; Viegi et al., 1991; Heederik et al., 1992] cross-sectional studies, although some results are controversial [Petran et al., 2000]. Industry-based longitudinal studies have shown that occupational exposure is associated with accelerated lung function decline in the furniture industry [Jacobsen et al., 2008], in blue-collar workers [Thaon et al., 2012], in smelters [Johnsen et al., 2010], and in flavoring manufacturing workers [Kanwal et al., 2011; Kreiss et al., 2011]. Other longitudinal studies have shown that lung function declines in occupational settings [Wang and Petsonk, 2004; Wang et al., 2006; Hnizdo et al., 2010].

Few community-based studies have been published based on *longitudinal* pulmonary function data; importantly, the follow-up times were short (<10 years), and the numbers of repeated measurements were few (only two or three repeated measurements) for those studies. A recent review of occupational chronic obstructive pulmonary diseases summarized the results of the lung function/COPD studies using either industry-specific or population-based data [Omland et al., 2014].

A community-based longitudinal study offers several advantages. For example, studies in industry-based populations tend to focus on workers who are less susceptible participants, such as blue-collar workers who are usually healthier or stronger than the general population and thus more prone to healthy worker effect bias. Community-based studies, however, can provide more generalizable information since they include participants from many different industries. Additionally, in contrast to cross-sectional studies, longitudinal studies can help characterize aging and normal development as well as improvement or decline in lung function, to distinguish the effects of time. Longitudinal studies also allow for consideration of time-dependent variables such as change in smoking status between different examinations.

The pathophysiological mechanisms of all cause (e.g., aging and cigarette smoking) accelerated decline of FEV_1 are thought to be multifactorial, involving genetic factors, cellular repair, and inflammatory response and resolution [MacNee and Tuder, 2009]. Genes and environmental interaction such as occupational exposure may thus interact with each other and affect the lung function. In a previous gene-environmental interaction study on cross-sectional lung function, we found a single nuclear polymorphism, rs9931086, in the gene *SLC38A8* on chromosome 16, that significantly modified the association of occupational dust exposure with cross-sectional FEV_1, and another single nuclear polymorphism, rs17051547, on chromosome 4, that modified the association of occupational dust exposure with cross-sectional FEV_1/FVC (using the SNP with the smallest *p* value which did not, however, reach genome-wide significance) [Liao et al., 2013].

In this study, we stratified our participants into two genetic groups and assessed whether the single nucleotide polymorphisms rs9931086 or rs17051547 also modified the association of

occupational dust exposure with *longitudinal* lung function. The purpose of the study was to determine how occupational dust exposures affect lung function change over time and whether genetic variants influence occupational dust exposure effects on lung function change over time in a longitudinal community-based study population with an average of 17 years of follow-up.

Materials and Methods

Study Population

Our study used the Framingham Heart Study (FHS) population, which includes mainly Whites who live in Framingham, Massachusetts, USA. Manufacturing, such as automobile production, had been a key economic feature of Framingham at the time of the first generation study, but in the past 3–4 decades, as in other United States industrial towns, manufacturing left and now Framingham is a retail center for the region. The FHS has recruited participants since 1948, and participants have returned approximately every two years for spirometry measurement, detailed medical history, physical examination, and laboratory tests. Three generations have participated in the FHS: the original cohort, their offspring, and the third generation. Here, we used the offspring cohort, which has available longitudinal lung function measurements. The study population comprises participants with at least one spirometry measurement, current occupation information, and covariates. A total of 1,332 participants (261 families and 352 individuals without relatives) with 4,734 observations were used for our longitudinal analysis.

Ethics Statement

Written informed consent was provided by all participants. Protocols were approved by local institutional review boards.

Spirometry Phenotypes, Covariates, and Genotypings

Spirometry data from participants having acceptable pulmonary function were used in our study. Accessible examinations were obtained from Offspring Exams 3, 5, 6, 7, and 8. FEV_1 and FEV_1/FVC values were used as continuous outcomes. Gender and baseline age were time-independent variables; height (inches), pack-years, years after baseline, and smoking status at the time of each examination were time-dependent variables and were used as covariates in our analysis. Smoking status (never, former, and current smokers) was coded as a dummy variable. The genotyping was conducted with Affymetrix 500 K mapping plus Affymetrix 50 K supplemental array. The method has been described in detail in our previous study [Liao et al., 2013].

Occupational Dust Exposure

Although the lung function was measured longitudinally (exams 3, 5, 6, 7, 8), the occupation information was only measured at exam 8. We did not have information on how long participants remained on the job or whether their occupations changed during the follow-up period. We excluded participants who retired or reported their jobs as unknown or other (retired, other, and unknown are three separate categories). For occupational dust exposure classification, we used a mini population-specific job exposure matrix (JEM) (Table I) [Liao

et al., 2013] modified from the UCSF COPD Job Exposure Matrix (January, 2009 revision) [Blanc et al., 2009] for occupational exposure (with job category codes rather than specific occupational codes in the UCSF COPD JEM). Occupational dust exposure was classified as "more likely dust exposure" for job categories (factory/assembly/mechanic, skilled labor, general labor, and heavy labor) that were classified as high exposure in the UCSF COPD Job Exposure Matrix. Occupational dust exposure was classified as "less likely dust exposure" for homemakers and the remaining job categories. There were 29 job categories in the FHS occupations classification, which were less detailed than the UCSF COPD Job Exposure Matrix. For example, in the FHS occupational classification, the category of skilled labor (classified as more likely dust exposure) included some jobs (e.g., plumber, carpenter, and painter) classified as job with dust exposure and some jobs (e.g., hairdresser) classified as no dust exposure in the UCSF COPD Job Exposure Matrix.

Statistical Analysis

For longitudinal analysis we used a linear mixed effects model for the association between FEV_1 or FEV_1/FVC and dust exposure groups, adjustment for relevant covariates. Random effects were used to account for the correlation between repeated measures within each subject and the correlation among observations from multiple individuals within a family. Specifically, we used a family random intercept to account for the correlation of the measures of different individuals within the same family, and individual random intercept/random age slope to account for correlation of repeated measures over time within the same individual. In addition to main effects, we also included two interaction terms, dust exposure (E) and baseline age (centered by mean baseline age for whole the population, $Age-Age_{mean}$) and years after baseline in which the lung function was measured (T). These two interaction terms are presented as $E_{ij}*(Age-Age_{mean})_{ij}$ and $E_{ij}*T_{ijt}$ below. Y_{ijt} denotes the outcome (FEV_1 or FEV_1/FVC) for subject j of family i measured at year t. The mixed effects model can be written as below:

$$Y_{ijt}=\beta_0+\beta_1^*E_{ij}+\beta_2^*(Age-Age_{mean})_{ij}+\beta_3^*T_{ijt}+\beta_4^*E_{ij}^*(Age-Age_{mean})_{ij}+\beta_5^*E_{ij}^*T_{ijt}+aX_{ijt}+b_i+a_{ij}+c_{ij}T_{ijt}+e_{ijk},$$

where the X_{ijt} are other covariates at year t, the b_i are family random effects, the a_{ij} and c_{ij} are subject-specific random intercept and slopes and e_{ijk} are residuals. Analyses were performed using SAS PROC MIXED (version 9.2; SAS Institute Inc., Cary, NC).

We stratified our participants into subgroups based on the genotype of the single nucleotide polymorphisms rs9931086 and rs17051547 that we previously identified as potential interacting variants for occupational exposure and lung function [Liao et al., 2013]. For analysis of the genetic modification of rs9931086, one subgroup comprised participants with one or two C alleles on rs9931086 (AC/CC), and the other subgroup comprised participants without a C allele (AA). For analysis of the genetic modification of rs17051547, one subgroup comprised participants with one or two A alleles on rs17051547 (AC/AA), and the other subgroup comprised participants without an A allele (CC). We analyzed the data separately and compared the effect of occupational dust exposures in these subgroups. We

also tested the difference of the effects in these subgroups using three way interaction analyses with the model written as below:

$$\begin{aligned} Y_{ijt} = & \beta_0 + \beta_1^* E_{ij} + \beta_2^* (Age - Age_{mean})_{ij} \\ & + \beta_3^* T_{ijt} + \beta_4^* E_{ij}^* (Age - Age_{mean})_{ij} \\ & + \beta_5^* E_{ij}^* T_{ijt} \\ & + \beta_6^* G_{group} + \beta_7^* G_{group}^* T_{ijt} \\ & + \beta_8^* G_{group}^* E_{ij} \\ & + \beta_9^* G_{group}^* E_{ij}^* T_{ijt} \\ & + aX_{ijt} + b_i + a_{ij} + c_{ij} T_{ijt} + e_{ijk}, \end{aligned}$$

where G_{group} are coded as 1 and 0 to represent the two subgroups and tested for β_9.

Results

There were 1,332 participants with an average of 3.55 (median = 4) repeated lung function measurements/per person. Among them, 1,188 participants were in the less likely dust exposure group, with an average of 3.58 (median = 4) repeated measurements/per person, and 144 participants were in the more likely dust exposure group with an average of 3.38 (median = 4) repeated measurements/per person.

Table II summarizes the baseline characteristics for groups with different dust exposure likelihood at final follow-up (Exam 8). The mean follow-up time was about 17 years in both groups. At baseline, FEV_1 was higher in the group with more likely dust exposure, but the FEV_1/FVC ratio was the same for both groups. Additionally, the prevalence of current and former smokers at baseline was higher in the group with more likely dust exposure.

Table III shows the results of the linear mixed model fit of FEV_1 and FEV_1/FVC on centered baseline age, years after baseline, centered baseline age by dust exposure interaction, and years after baseline by dust interaction, adjusting for covariates. The association of dust exposure as a main effect on FEV_1 was not significant at baseline for subjects with a mean age of 47.44 years old. The decrement in FEV_1 associated with a one-year increase in the baseline age (cross-sectional age effect) for the less likely dust exposure group was − 30.6 ± 1.3 mL/year, adjusted by gender, height, smoking, and pack-years at baseline (*P*-value < 0.0001). Some evidence indicated different cross-sectional age effects between the two dust exposure groups (*P*-value = 0.05), with a bigger mean difference between the two dust exposure groups for older subjects.

The FEV_1 annual loss rate (longitudinal time effect) for the less likely dust exposure group was −25.8 ± 0.6 mL/year adjusted by other covariates (*P*-value < 0.0001). Subjects with more likely dust exposure had a statistically significant 4.5 ± 1.7 mL/year mean excess loss of FEV_1 over time compared to those with less likely dust exposure (*P*-value = 0.0074). No significant effect of occupational dust exposure was observed on the FEV_1/FVC ratio.

As expected, males had a significantly higher (712.6 ± 34.1 mL) mean FEV_1 than females. Current smokers (−135.9 ± 22.4 mL) and former smokers (−92.8 ± 19.6 mL) had a significantly lower mean FEV_1 than never smokers. Each increase in pack-years significantly decreased the mean FEV_1 by 2.8 ± 0.4 mL. For each one-inch increase in height, the FEV_1 significantly increased by 61.5 ± 4.2 mL.

Comparing the two subgroups stratified by genotype of rs9931086, there was a mean 6.5 ±3.4 mL/year mean excess loss of FEV_1 over time ($P = 0.05$) among those with more likely dust exposure compared to those with less likely dust exposure in the AC/CC group (at least one C allele in rs9931086) and a 3.8 ±2.1 mL/year mean excess loss of FEV_1 over time ($P = 0.07$) in the AA group (no C allele in rs9931086). However, the difference in FEV_1loss across dust exposure strata was not significant across the two genotype subgroups ($P = 0.53$ in the three way interaction analysis). No significant effect of occupational dust exposure was observed on the FEV_1/FVC ratio loss in either the CC ($P = 0.19$) or the AA/AC group ($P = 0.42$) stratified by genotype of rs17051547 although the difference in FEV_1/FVC loss across dust exposure strata was significant across the two genotype subgroups ($P = 0.03$ in the three way interaction analysis).

Figure 1 demonstrates different annual FEV_1 loss for a male who was 67 inches tall across the different dust exposure groups, baseline age, and pack-years. The more likely dust exposure group had a larger FEV_1 annual loss. Compared to former smokers with 20 pack-years smoking history but no dust exposure, former smokers with dust exposure had greater loss in FEV_1 after 8 to 9 years, even with 10 pack-years less smoking history. The effect of occupational dust exposure on the FEV_1 annual loss (4.5 mL/year) was greater than the effect of each pack-year (2.8 mL). For older participants (e.g., baseline age of 60 years old), the mean difference between different dust exposure groups was larger than for younger participants.

Discussion

We found that occupational dust exposure was not associated with cross-sectional FEV_1 cross-sectional FEV_1/FVC, or longitudinal FEV_1/FVC annual loss in a general population study. However, we did find dust associated accelerated longitudinal FEV_1 annual loss, and this effect was greater than the effect of each pack-year increase. Dust exposure also modified the effect of age at baseline on cross-sectional FEV_1.

We distinguished the age effect as two components: cross-sectional age effect and longitudinal time effect. In our model, the coefficient of baseline age represents the cross-sectional age effect, and the coefficient of years after baseline represents the longitudinal time effect. For the cross-sectional age effect, we found that, for participants at baseline, each year of age decreased the FEV_1 significantly when other covariates remained constant. This effect was modified by dust exposure. For example, at baseline, the difference between each male non-smoker of 67-inch height and a matched male one year older was greater in the group with dust exposure. The difference between different exposure groups was higher in older subjects.

For the longitudinal time effect, we found that participants having the same baseline age had significant annual FEV_1 loss, but the annual loss were higher in participants in the more likely dust exposure group. This result implies that, in populations similar to the Framingham Offspring Cohort, occupational dust exposure may not affect FEV_1 (occupational dust exposure is not significantly associated with lower average FEV_1 in this population), but may accelerate FEV_1 loss. The effect of dust exposure (4.5 mL/year excess loss) is greater than the loss caused by each pack-year increase in smoking (2.8 mL). This accelerated FEV_1 annual loss rate is consistent with a previous study [Johnsen et al., 2010]. Estimates of moderate to heavy smoking in a review of FEV_1 decline by age and smoking show a mean excess loss of 15 mL/year compared to non-smokers [Kerstjens et al., 1997]. The mean excess loss of FEV_1 attributable to occupational dust exposure in our study is about 1/3 of that due to smoking and therefore can be clinically significant over a lifetime. The absence of an overall effect of dust exposure on FEV_1 is also consistent with some previous studies [Petran et al., 2000; Zock et al., 2001].

The non-significant occupational dust exposure main effect may result from population selection. For our studies, occupational information was only available at exam 8 (the latest exam). Therefore, our participants were assumed to be active workers at exam 8. Participants without occupational information included retired individuals. This could skew selection toward healthier workers, especially in the job categories that require heavy labor (e.g., workers with respiratory diseases might not enter high-exposure jobs or might leave these jobs before the end of the study), causing a healthy worker effect confounding bias [Monson, 1990; Eisen et al., 1995; Li and Sung, 1999]. Since heavy labor job categories were classified as more likely for dust exposure, and if we assume that participants in the group were those in better health, then the magnitude of dust exposure's effect on FEV_1 is an underestimate. In addition, a healthy smoker effect confounding bias [Becklake and Lalloo, 1990] may explain why mean FEV_1 was higher in the more likely exposure group despite a higher prevalence of smoking.

However, even though these participants might be healthier, their FEV_1 loss rates were a significant 4.5 mL/year higher than participants in the less likely dust exposure group. Our observed accelerated loss is lower than a previous study that reported an excess loss in FEV_1 of 5.7 to 6.4 mL/year, although that study was industry-based [Johnsen et al., 2010]. One study of blue-collar workers exposed to welding fumes concluded that the absence of a significant effect of occupational dust exposure on lung function in smokers was because of a healthy worker effect [Thaon et al., 2012], but we did not find a significant joint effect (interaction) of tobacco use and occupational dust exposure (data not shown). Genetic factors may also play an important role in the lung function through interactions with occupational dust exposure, but we did not find a significant effect of genetic modifications on FEV_1or FEV_1/FVC loss.

Even though our results have merit in offering insights into the effects of occupational dust exposures on lung function loss in a community-based study, we acknowledge some limitations. One limitation concerns the assessment of the occupational dust exposure. We constructed a population-specific JEM for dust exposure based on 29 job categories that were less detailed than the UCSF COPD Job Exposure Matrix. This may cause exposure

misclassification. This bias can be viewed as non-differential misclassification since the exposure assessment was not related to outcome [Blair et al., 2007]. This misclassification might reduce statistical power and may bias the estimate toward the null, but would not affect the direction of the results (i.e., relation to outcome in the same direction) [Goldberg et al., 1993]. This may explain why we did not find a significant association between dust exposure and cross-sectional FEV_1.

In addition, the actual dust exposure level may vary among people who have the same job categories but have different job tasks. We included “students” and “homemaker” in our analysis, i.e., viewed them as having an occupation; although they are not currently employed for salary they can be categorized as low exposure. Another limitation is that we did not exclude participants with pre-existing conditions such as COPD or asthma, due to a lack of such information. Future research that aims at finding the effect of dust exposure on lung function loss in a population-based study will be improved by more detailed job classifications and by direct personal measurements on at least a representative sample of individual job categories.

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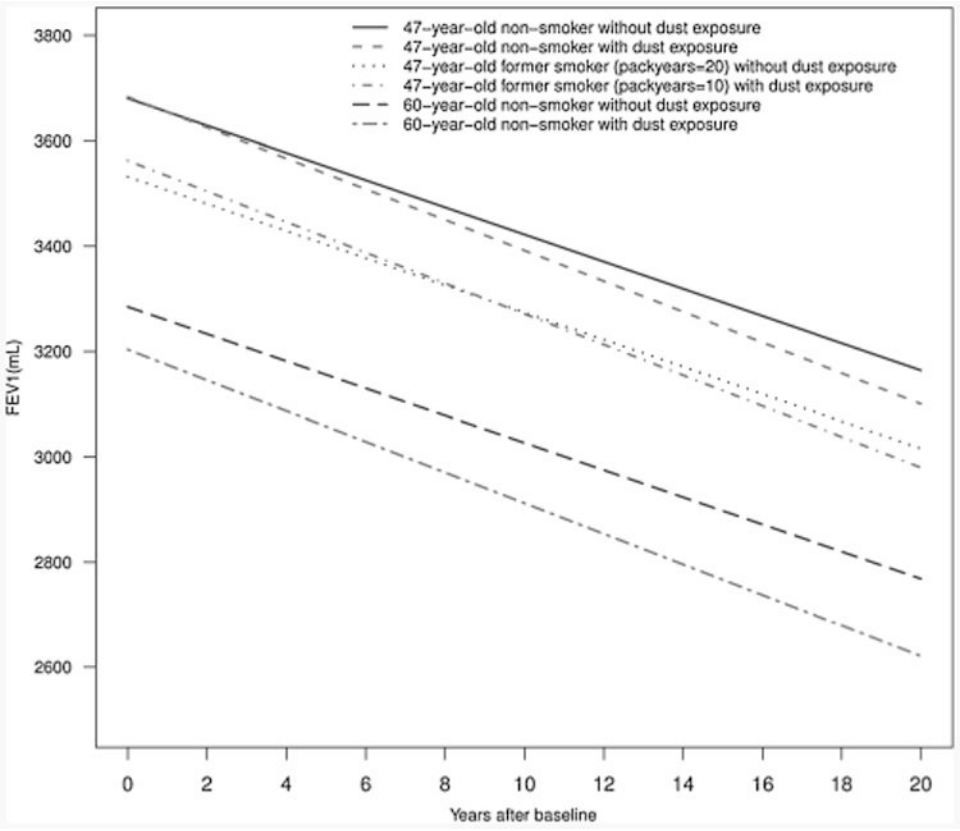

Figure 1.

Annual FEV_1 loss for a male of 67-inch height in different dust exposure groups, different smoking status, baseline age, and pack-years based on the linear mixed model.

Table I
Job Categories for Dust Exposure Classification

Dust exposure groups	Job categories
More likely dust exposure	Factory/assembly/mechanic
	Skilled labor (e.g., plumber, carpenter, painter, hairdresser)
	General labor (e.g., custodian, delivery, mailman, truck driver)
	Heavy labor (e.g., construction, landscaping)
Less likely dust exposure	Nurse/medical personnel/laboratory technician
	Physical/occupational/speech therapist
	Homemaker
	Self-employed business owner
	Physician/dentist/scientist/research
	Lawyer/judge
	Psychologist/social worker/mental health counselor
	Engineer/computer science
	banker/accountant
	Manager/consultant (e.g., production manager)
	Administrative (e.g., personnel)
	Educator
	Secretary/clerk/data entry
	Retail/cashier
	Sales/marketing/insurance
	Realtor
	Police/fire/security/military
	Restaurant/food worker
	Writer/editor
	Artist/graphic Designer/craftsperson
	Musician
	Clergy (minister, priest, rabbi)
	Sports pro/coach/exercise instructor/other
	Statistician
	Student

Table II

Characteristics of Participants at the Baseline Examination, Stratified by Dust Exposure Groups Classified at the Final Examination

	Total (n =1332)	More likely dust exposure (n =144)	Less likely dust exposure (n =11 8 8)
Male, n (%)	570 (42.79)	118 (81.94)	452 (38.05)
FEV_1, mL (SD)	3130 (820)	3520 (820)	3080 (800)
FEV_1/FVC, (SD)	0.77 (0.07)	0.76 (0.08)	0.77 (0.07)
Follow-up time, years (SD)	16.88 (5.44)	17.25 (4.36)	16.96 (4.53)
Age, years (SD)	47.44 (10.55)	45.89 (11.15)	47.63 (10.47)
Height, inches (SD)	66.30 (3.72)	68.10 (3.32)	66.08 (3.71)
Pack-years*, (SD)	21.35 (19.80)	27.80 (21.24)	20.30 (19.38)
Smoking status, n (%)			
Never smokers	583 (43.77)	40 (27.78)	543 (45.71)
Former smokers	429 (32.21)	52 (36.11)	377 (31.73)
Current smokers	320 (24.02)	52 (36.11)	268 (22.56)
Genotyping, n (%)			
rs 9931086**			
AC/CC genotypes	370 (27.78)	32 (22.22)	338 (28.45)
AA genotype	733 (55.03)	80 (55.56)	653 (54.97)
rs17051547**			
AC/AA genotypes	239 (17.94)	20 (13.89)	219 (18.43)
CC genotypes	990 (74.32)	111 (84.09)	879 (73.99)

FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; SD: Standard deviation; rs: Reference single nucleotide polymorphism number.
Values reported as means unless otherwise noted.

* Pack-years mean and standard deviation calculated among current and former smokers.

** Not all participants had genotyping.

Table III
Characteristics Affecting FEV_1 and FEV_1/FVC by Linear Mixed Model

	FEV_1 (mL)		FEV_1/FVC	
Covariate	**Estimate (SE)**	**P value**	**Estimate (SE)**	***P* value**
Time-independent				
More likely vs. less likely dust exposure	−15.1 (41.6)	0.7173	−0.0039 (0.0058)	0.5030
Male vs. female	712.6 (34.1)	<0.0001	−0.0128 (0.0048)	0.0083
Baseline Age*	−30.6 (1.3)	<0.0001	−0.0027 (0.0002)	<0.0001
Time-dependent				
Years after Baseline	−25.8 (0.6)	<0.0001	−0.0029 (0.0001)	<0.0001
Current vs. never smoker	−135.9 (22.4)	<0.0001	−0.0175 (0.0036)	<0.0001
Former vs. never smoker	−92.8 (19.6)	<0.0001	−0.0125 (0.0031)	<0.0001
Pack-years	−2.8 (0.4)	<0.0001	−0.0004 (0.0000)	<0.0001
Height	61.5 (4.2)	<0.0001	−0.0036 (0.0006)	<0.0001
Interaction terms				
Baseline age*×More likely dust exposure	−7.1 (3.7)	0.0573	0.0001 (0.0005)	0.8907
Years after baseline age×More likely dust exposure	−4.5 (1.7)	0.0074	−0.0001 (0.0003)	0.6643

FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; SD: Standard deviation.

*Baseline age was centered on mean baseline age (47.44 years old).