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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

The Interaction of Genes and Smoking on Forced Expiratory Volume*

A Classic Twin Study

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Background: Genetic influences on lung function as measured by FEV₁ have been reported from twin and family studies. The aims of this study were to estimate heritability of the ratio of measured FEV₁ (mFEV₁) to expected FEV₁ (eFEV₁) in a white population, and to examine the interaction between genetic factors and smoking on this ratio.

Methods and subjects: The sample consisted of unselected monozygotic (MZ) and dizygotic (DZ) twin pairs from the TwinsUK registry. FEV₁ was measured with a spirometer, and mFEV₁/eFEV₁ ratio was calculated.

Results: A total of 475 MZ and 1,054 DZ twin pairs participated (mean age, 47 years; range, 18 to 84 years). mFEV₁/eFEV₁ ratio was 0.057 lower in smokers than nonsmokers ($p < 0.0001$). The difference in the correlation for mFEV₁/eFEV₁ ratio between MZ and DZ twin pairs was 0.32 in nonsmokers and 0.19 in current smokers, suggesting a significant genetic influence on lung function that was modified in current smokers. Using structural equation modeling, the heritability estimate for mFEV₁/eFEV₁ ratio was found to be 66% (95% confidence interval [CI], 59 to 72%) in nonsmokers but significantly reduced to 32% (95% CI, 12 to 53%) in current smokers. However, there was no clear difference in the heritability of mFEV₁/eFEV₁ ratio between nonsmokers and ex-smokers.

Conclusion: Genes are the major influence on the variability of mFEV₁/eFEV₁ ratio in nonsmokers. However, this strong genetic influence is strongly modified by an interaction with cigarettes. (CHEST 2007; 132:1772-1777)

Key words: FEV₁; genetics; measured to predicted FEV₁ ratio; smoking; twins

Abbreviations: AIC = Akaike information criterion; CI = confidence interval; DZ = dizygotic; eFEV₁ = expected FEV₁; mFEV₁ = measured FEV₁; MZ = monozygotic

FEV₁, a measure of lung function, is strongly associated with chronic lung disease and its associated mortality.¹ It is also evident from pop-

ulation studies that FEV₁ is a risk factor in cardiovascular disease, stroke, and lung cancer and is associated with mortality caused by these diseases,²⁻⁷ suggesting that FEV₁ has a predictive role in a wide range of conditions, as well as respiratory disease.²

Genetic influence on FEV₁ has been studied in different populations with inconsistent results. A significant genetic effect has been found in several studies of white twins⁸⁻¹⁰ but not in others.^{11,12} Many of these studies have been performed on small samples or suffered methodologic problems.

Smoking is known to be an important risk factor for lung function,¹³ yet clinical obstructive pulmonary disease does not develop in most smokers, and many patients with chronic bronchitis who continue

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to smoke do not have excessive deterioration in lung function,¹⁴ suggesting that some individuals may be more susceptible than others to the noxious effects of smoking.^{15,16} One study¹⁷ suggested a possible biological interaction between cigarette smoke and the airways of individuals with blood group A antigen and familial lung disease. Although some researchers^{8,18} have controlled for the effects of smoking in their analyses of FEV₁ heritability, the genetic correlation and gene-environment interaction between genetic factors and smoking to lung function has not yet been properly explored. The aims of the current study were to estimate the heritability of the ratio of measured FEV₁ (mFEV₁) to expected FEV₁ (eFEV₁) in a large white population, and to examine the gene-environment interaction between genetic factors and smoking to the mFEV₁/eFEV₁ ratio.

MATERIALS AND METHODS

The study participants were white monozygotic (MZ) and dizygotic (DZ) twin pairs from the TwinsUK adult twin registry, a group used to study the heritability and genetics of age-related diseases (www.twin-research.ac.uk). These unselected twins were recruited from the general population through national media campaigns in the United Kingdom and shown to be comparable to age-matched population singletons in terms of disease-related and lifestyle characteristics.¹⁹ The study was approved by St Thomas' Hospital Research Ethics Committee, and all twins provided informed written consent.

Anthropometric measurements including height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, during a visit to the clinic center. Questionnaires were administered, providing information for an extensive range of demographic variables and medical history. For the purpose of this study, smoking status (never-smoker, ex-smoker, and current smoker) and years of smoking duration were determined by the following questions: have you ever smoked cigarettes, cigars, or a pipe on a regular basis? Have you ever smoked? Are you a current smoker, or an ex-smoker? At what age did you start smoking? How many cigarettes do/did you usually smoke each day? If you are an ex-smoker, at what age did you stop altogether?

Spirometry (model 2150; Vitalograph; Buckingham, England) was conducted at the clinical center during a visit. Twins were instructed before the test, and FVC maneuvers were performed in a standing position without the use of nose clips. Three maneuvers were performed, and maximum obtained values for FEV₁ were obtained. eFEV₁ was calculated by the following formula derived from the National Health and Nutrition Examination Survey²⁰ for a white population. mFEV₁/eFEV₁ ratio was then calculated and used in the analysis, for men and women, respectively:

$$eFEV_1 = 0.5536 - 0.01303 * age - 0.000172 * age^2 + 0.00014098 * height^2$$

$$eFEV_1 = 0.4333 - 0.00361 * age - 0.000194 * age^2 + 0.00011496 * height^2$$

Statistical Analysis

Descriptive statistics of all variables were compared between MZ and DZ twin pairs. Intraclass correlations or polychoric correlations where appropriate were calculated for mFEV₁/eFEV₁ ratio and smoking status and compared between MZ and DZ twin pairs. Any significant higher correlation in MZ than in DZ twin pairs would indicate a genetic influence on the traits.

An interaction between genetic factors and smoking on lung function is present if genetic influence on ratio of mFEV₁/eFEV₁ differs from smokers to nonsmokers. This was examined by the following steps:

1. Discordant twin analysis was utilized to examine the environmental influence of smoking on mFEV₁/eFEV₁ ratio among twins with discordant smoking habits.

2. Insight into the nature of the association between mFEV₁/eFEV₁ ratio and smoking status is gained by examining the strength of the correlation between mFEV₁/eFEV₁ ratio in one twin and smoking status in their co-twin, which must be due to determinants shared by the twins. Thus, the degree of strength of the cross-trait, cross-twin correlation can help determine if genetic and/or environmental influences explain the association. There are two possible scenarios: a significant higher cross-twin, cross-trait correlation in MZ twins than that in DZ twins would be evidence for a genetic influence between mFEV₁/eFEV₁ ratio and smoking status. However, if the cross-trait, cross-twin correlation is significant but of similar magnitude in both MZ and DZ twin pairs, a shared environmental influence would be indicated; and a cross-trait, cross-twin correlation is absent if both MZ and DZ twin pairs fail to show any evidence of an association. This would be evidence for unique environmental influence.

3. Structural equation modeling implemented in Mx software was then utilized to estimate the heritability of mFEV₁/eFEV₁ ratio, and to examine the interaction between genetic factors and smoking to mFEV₁/eFEV₁ ratio. Heritability is defined as the proportion of total variance due to genetic effects, assuming that the phenotypic variance is due to additive genetic factors, dominant genetic factors, shared environmental factors, and nonshared environmental factors. The best-fitting saturated model was determined based on the comparison of the correlation in mFEV₁/eFEV₁ ratio among MZ and DZ twin pairs and the model-fitting test. Nested models were compared to the best-fitting saturated model, and the most parsimonious model was determined based on the likelihood ratio test or Akaike information criterion (AIC) and parameter estimates were then obtained from the best-fitting model. Analysis was performed using statistical software (STATA; StatCorp; College Station, TX),

Table 1—Descriptive Statistics of the Study Sample*

Variables	MZ (n = 950)	DZ (n = 2,108)	p Value
Male gender, %	5	9	< 0.0001
Age, yr	47.1 (14.2)	46.4 (12.5)	0.09
Height, m	1.63 (0.07)	1.64 (0.07)	< 0.0001
Weight, kg	64.9 (11.7)	67.5 (13.1)	< 0.0001
Body mass index, kg/m ²	24.5 (4.2)	25.2 (4.6)	< 0.0001
mFEV ₁ , L	2.77 (0.67)	2.86 (0.69)	0.0001
eFEV ₁ , L	2.89 (0.52)	2.98 (0.49)	0.0001
mFEV ₁ /eFEV ₁ ratio	0.96 (0.15)	0.97 (0.15)	0.20
Smoking status, %			
Ever-smokers	35	38	0.014
Current smokers	28	36	< 0.0001

*Data are presented as mean (SD) for continuous variables, unless otherwise indicated.

Table 2—Within-Twin Pair Difference in mFEV₁/eFEV₁ Ratio According to Smoking Status

Variables	Mean Difference in mFEV ₁ /eFEV ₁ Ratio	95% CI
Concordant nonsmoker twin pairs (n = 1,074)	-0.002	-0.02, 0.01
Concordant smoker twin pairs (n = 422)	0.008	-0.01, 0.03
Discordant smoker twin pairs (n = 378)	0.057*	0.03, 0.08
Concordant ex-smoker twin pairs (n = 476)	-0.014	-0.04, 0.01
Discordant ex-smoker twin pairs (n = 708)	0.014	-0.004, 0.03

except for structural equation modeling, and $p \leq 0.05$ was considered as statistical significance.

RESULTS

A total of 475 MZ and 1,054 DZ twin pairs (mean age, 47 years; range, 18 to 84 years) participated in the study. The sample was predominately female for historical reasons (www.twin-research.ac.uk). Table 1 presents the characteristics of the sample. mFEV₁ and eFEV₁ in MZ twin pairs were slightly lower than in DZ twin pairs, but mFEV₁/eFEV₁ ratios were similar, with 5% of the sample having an mFEV₁/eFEV₁ ratio < 0.70.

Table 2 presents the results of the discordant twin analysis. Compared to the within-pair difference in mFEV₁/eFEV₁ ratio for nonsmokers, the difference was pronounced in twin pairs discordant for smoking status. The difference was also larger in concordant smoker twin pairs and discordant ex-smoker twin pairs, although it was not significant.

Table 3 presents the correlation analysis and comparison between MZ and DZ twin pairs. Intraclass correlations in mFEV₁ and mFEV₁/eFEV₁ ratio were all significantly higher in MZ than in DZ twin pairs. Similarly, a polychoric correlation in smoking status was also higher in MZ than that in DZ twin pairs, suggesting genetic influences on all these

Table 4—Standardized Variance Components Estimates in mFEV₁/eFEV₁ Ratio*

Variables	Nonsmokers	Smokers
Total variance, %	0.021	0.026
Additive genetic variance	66 (59, 72)	32 (12, 53)
Non-additive genetic or shared environmental variance		29 (10, 46)
Unique environmental variance	34 (28, 41)	39 (30, 51)

*Data are presented as % (95% CI) unless otherwise indicated.

variables. However, the difference in the correlation of mFEV₁/eFEV₁ ratio between MZ and DZ twin pairs was significantly reduced by 41% in smokers compared to nonsmokers (Table 3).

The cross-twin, cross-trait correlations between mFEV₁/eFEV₁ ratio and smoking status are -0.13 (SE 0.05) and -0.15 (SE 0.03) for MZ and DZ twin pairs, respectively. Both correlations themselves were significantly different to zero ($p < 0.01$), but the difference between them was not ($p = 0.25$), indicating that mFEV₁/eFEV₁ ratio and smoking status is unlikely to be under common genetic control but more likely to be under shared environmental influences.

The correlation in mFEV₁/eFEV₁ ratio among MZ twin pairs is higher than two to four times the difference in the correlation among MZ and DZ twin pairs (Table 2), suggesting that there is no Mendelian dominant/recessive genetic effect on mFEV₁/eFEV₁ ratio. Structural equation modeling using Mx software is shown in the Appendix. The model-fitting test indicates that there is no dominant genetic effect on mFEV₁/eFEV₁ ratio. The best-fitting final model suggested a significant interaction between the fitting genotype and smoking to mFEV₁/eFEV₁ ratio. Total estimated variance for mFEV₁/eFEV₁ ratio was 0.021 in nonsmokers and 0.026 in smokers. The estimated absolute additive genetic variance was 0.014 in nonsmokers and reduced by 43% to 0.008 in smokers. Standardized variance component estimates are presented in Table 4. The heritability estimate for mFEV₁/eFEV₁ ratio was 66% in non-

Table 3—Correlation in Traits Among MZ and DZ Twin Pairs*

Variables	MZ (95% CI)	DZ (95% CI)	Difference (95% CI)
mFEV ₁	0.82 (0.79, 0.85)	0.69 (0.66, 0.72)	0.13 (0.07, 0.19)
mFEV ₁ /eFEV ₁ ratio	0.58 (0.53, 0.63)	0.36 (0.32, 0.41)	0.22 (0.16, 0.28)
mFEV ₁ /eFEV ₁ ratio in nonsmokers	0.68 (0.59, 0.76)	0.36 (0.21, 0.47)	0.32 (0.27, 0.37)
mFEV ₁ /eFEV ₁ ratio in smokers	0.62 (0.46, 0.75)	0.43 (0.24, 0.61)	0.19 (0.10, 0.28)
Smoking status†	0.86 (0.82, 0.90)	0.65 (0.61, 0.69)	0.21 (0.18, 0.24)

*Correlation is intraclass correlation except where indicated.

†Polychoric correlation.

smokers but was reduced to 32% in smokers. Due to the small number who had accurate quantitative data of smoking (only 10 MZ twin pairs in the current-smoker group), we did not have enough power to analyze a possible dose-response effect on the interaction between genes and smoking to FEV₁.

There was no difference in the heritability estimates between nonsmokers and ex-smokers. Average time since stopping smoking was 18 years in this sample, and there were only 94 individuals (15 MZ and 32 DZ twin pairs) with time elapsed since stopping smoking < 5 years, too few to analyze separately.

DISCUSSION

This largest twin study to date has confirmed a significant genetic influence on lung function measured by mFEV₁/eFEV₁ ratio in a white population and documented a significant interaction between genetic factors and smoking to lung function. The heritability estimate for mFEV₁/eFEV₁ ratio in non-current smokers is 66% but significantly reduces to 32% among current smokers.

Some previous studies⁸⁻¹⁰ have reported a significant genetic influence on FEV₁ after adjustment for body habitus and other factors. In contrast, Ghio et al²¹ found in 74 university student pairs of twins with an average age of 20 years, that heritability was not significant after adjustment for height. Small sample sizes and a relatively young sample are a likely explanation for this discrepancy. However, all the previous studies used measured FEV₁ in their analysis. This may not be the most appropriate phenotype to be analyzed. Miller et al²² suggested that correct interpretation of FEV₁ requires the use of appropriate reference values with which the individual's results are compared, and the reference equation has to be determined by published studies of large numbers of healthy individuals. We therefore used the formula derived from the National Health and Nutrition Examination Survey²⁰ for the calculation of predicted values for FEV₁, which is comparable to the predicted normal equations derived from other white samples including the one from the United Kingdom.²³ We found that a clinical relevant parameter—mFEV₁/eFEV₁ ratio—has a strong genetic component with the heritability estimate of 66%. McClearn et al,⁸ in a study of 230 Swedish twin pairs, showed a suggestion of age effects on the relative importance of genetic and environmental influences on lung function. However, in our larger sample, we did not find any difference in heritability estimates between people < 30 years and people > 30 years old (data not shown).

It is well known that smoking is a strong risk factor for lung function. Our discordant twin analysis

showed that nonsmokers had on average 5.7%-higher mFEV₁/eFEV₁ ratios than smokers. Chronic smoking itself has been shown to have a strong genetic component,²⁴ and this has been clearly confirmed in our data with a heritability of 62% (95% confidence interval [CI], 44 to 81%; data not shown). However, there are no clear data on whether a strong association between lung function and smoking is due to genetic sharing, although some studies^{8,9} adjusted for smoking before estimating the heritability.

Tishler et al²⁵ found in 352 male veteran twins that the twin-twin correlations of FEV₁ for concordant smoking in MZ and DZ twin pairs were estimated at 0.71 and 0.34, respectively. For twins with little or no difference in cigarette use, the intrapair correlations of FEV₁ did not differ according to cigarette exposure over a wide range of exposures. Even the most extreme twin-twin discordance in terms of number of cigarettes smoked had little effect on the correlation for FEV₁. Tishler et al²⁵ concluded that a constant factor such as genotype appears to be interposed between the environmental toxin (cigarette smoke) and FEV₁. However, due to the odd nature of their sample, all the twins were current smokers; they could not provide any information as to whether this is due to sharing common genes or gene-environment interaction.

Our results based on a larger unselected data set provide more information. The difference in the correlation for mFEV₁/eFEV₁ ratio between MZ and DZ twin pairs was reduced 41% in smokers compared with nonsmokers, suggesting that genetic influences on lung function are modified by smoking. The cross-trait, cross-twin correlation between mFEV₁/eFEV₁ ratio and smoking status was low, and there was no difference in the cross-trait, cross-twin correlation between MZ and DZ twin pairs, indicating that it is unlikely that lung function and smoking are under common genetic control. However, we found that there is a significant interaction between genetic factors and smoking to lung function as the positive path coefficient of additive genetic factors on mFEV₁/eFEV₁ ratio in nonsmokers was reduced by 24% in smokers. This equates to a 52% reduction in the heritability.

Interestingly, we did not find any difference between nonsmokers and ex-smokers, suggesting that this influence on lung function would diminish if people stopped smoking. Given that the mean time since stopping smoking in this sample was 18 years and only a small number of individuals quit recently, we could not make any inference as to the timescale of this influence.

A family based study²⁶ of 1,787 white, nonpatient adults has reported a role of gene-environmental interaction between genotype and smoking to chronic airways obstruction. They found that heavy

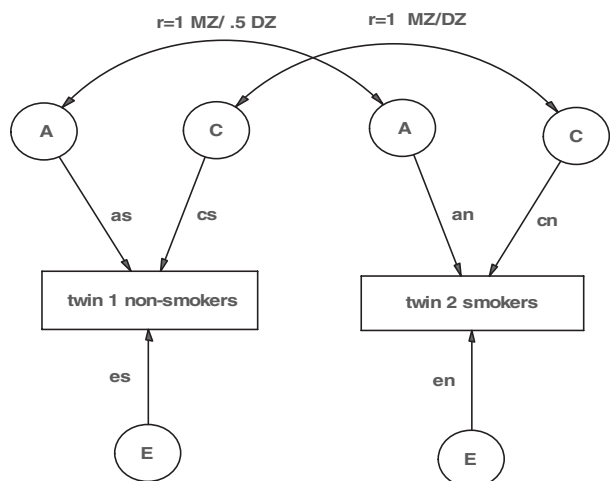


FIGURE 1. Path diagram for examining interaction between genetic factors and smoking to mFEV₁ to eFEV₁ ratio. The diagram shows the same additive genetic factors (A), shared environmental factors (C), and unique environmental factors (E) for twin 1 and twin 2 but different path coefficients for nonsmoker and smoker twins. See Table 5 for expansions of abbreviations not used in the text. The genetic correlation between twin 1 and twin 2 is 1 for MZ and 0.5 for DZ, while the shared environmental correlation is 1 for both MZ and DZ twin pairs. Interaction is indicated if the path coefficients are statistically significantly different between nonsmoker twins and smoker twins.

smokers who have blood group A antigen and are first-degree relatives of COPD or lung cancer patients not only have a higher prevalence of airways obstruction than heavy smokers without these two factors, but an excess prevalence that is more than that expected if blood group A and the familial component did not interact with smoking. Due to the small numbers in our sample who had chronic airways obstruction (based on mFEV₁/eFEV₁ ratio < 0.7), we could not confirm or refute these results.

Despite the significant findings, there are some caveats in the current study. The sample was a white, predominantly female population; therefore, the results may not be generalizable to other populations. The data on smoking were self reported, which might result in misclassification. Such misclassification would tend to indicate ex-smokers as never-smokers and current smokers as ex- or never-smokers; this would tend to blur any difference between smokers and nonsmokers and would not result in a statistically significant interaction as the one observed here. As we do not have enough quantitative measurements for number of cigarettes smoked, we could not examine a possible dose effect on the interaction between genetic factors and smoking to lung function. However, Tishler et al²⁵ found that the intrapair correlations of FEV₁ did not differ according to cigarette exposure over a wide range of exposures, suggesting this is not a major factor. Prevalence of smoking was slightly higher in DZ than MZ twin pairs, and thus may bias the heritability estimates. However, this bias would lead the estimate toward the null because it would increase the correlation of mFEV₁/eFEV₁ ratio in DZ twin pairs.

In summary, genetic influences on mFEV₁/eFEV₁ ratio are strong in healthy subjects not exposed to smoking. But this strong genetic influence is modified in current smokers, suggesting that smoking has an influence on the genetic expression of lung function; which, because it appears to disappear in ex-smokers, suggests it is reversible. The exact mechanism of this interaction deserves detailed study.

APPENDIX

The aim of structural equation modeling implemented in Mx software was to quantify the genetic and environmental effects on

Table 5—Parameter Estimates From Fitting Genotype × Smoking Interaction Models to mFEV₁/eFEV₁ Ratio*

Parameters	Model							
	I	II	III	IV	V	VI	VII	VIII
an	0.113	0.115	0.103	0.106	0.119	0.118		
cn	0.036	0.011	0.056	0.046			0.099	
en	-0.086	-0.091	-0.089	-0.089	-0.085	-0.087	-0.108	-0.147
as	0.065	0.099	0.108	0.106	0.090	0.123		
cs	0.102	0.087	0.056	0.072	0.086		0.111	
es	-0.106	-0.091	-0.104	-0.101	-0.101	-0.102	-0.118	-0.161
χ ²		6.108	6.801	5.404	1.634	1.0355	31.410	254.175
df		1	1	1	1	2	2	4
p Value		0.013	0.009	0.02	0.201	0.006	<0.0001	<0.0001
AIC	-5761.704	4.108	4.801	3.404	-0.366	6.355	27.410	246.175

*an = additive genetic path coefficient in nonsmokers; cn = shared environmental path coefficient in nonsmokers; en = unique environmental path coefficient in nonsmokers; as = additive genetic path coefficient in smokers; cs = shared environmental path coefficient in smokers; es = unique environmental path coefficient in smokers; df = degree of freedom; I = full G × E model; II = model with en = es. III = model with cn = cs; IV = model with an = as; V = model with cn fixed to zero; VI = model with cn and cs fixed to zero; VII = model with an and as fixed to zero; model VIII with an, as, cn, and cs fixed to zero.

lung function measured by $mFEV_1/eFEV_1$ ratio (Fig 1), by partitioning the total variance into additive genetic effect (A), dominant genetic effect (D)/shared environmental effect (C), and unique environmental effect (E); and examining the interaction between genetic factors and smoking to $mFEV_1/eFEV_1$ ratio by testing whether the path coefficients for additive genetic effect, dominant genetic effect, environmental effect, and unique environmental components were the same in smokers and nonsmokers; see Table 5 for expansion of abbreviations. The model-fitting test indicates that the A, C, E model (AIC = -5761.704) is the best-fitting saturated model compared to the A, D, E model (AIC = -5753.973). Subsequently, submodels were compared to the A, C, E model and heritability estimate, and interaction between $mFEV_1/eFEV_1$ ratio and smoking status was examined using structural equation modeling based on the path diagram presented in Figure 1. A comparison of the fit of a sequence of nested models to the saturated model is presented in Table 5. The equal unique environmental model (model II), equal shared environmental model (model III), and equal additive genetic model (model IV) were all rejected compared to the saturated unequal model (model I), indicating the path coefficients were significantly different between smokers and nonsmokers. The most parsimonious model was model IV, which dropped the shared environmental influence in nonsmokers but had a significant shared environmental component for smokers, in agreement with the above cross-twin, cross-trait correlation analysis. The best-fitting final model suggested a significant interaction between the fitting genotype and smoking to $mFEV_1/eFEV_1$ ratio.

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