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Familial aggregation and heritability of adult lung function: results from the Busselton Health Study

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ABSTRACT: Decreased spirometric indices are characteristic of asthma and other respiratory diseases. The aim of this study was to investigate the genetic and environmental components of variance of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) measured in adulthood in an Australian population-based sample of 468 Caucasian nuclear families. The inter-relationships of the genetic determinants of these traits with asthma and atopic rhinitis were also investigated.

Serial cross-sectional studies were conducted in the town of Busselton in Western Australia between 1966 and 1981 and follow-up of previous attendees was undertaken in 1995. Data from each subject included in this study were from a single survey in adulthood (25–60 yrs of age) when the subject was as close to age 45 yrs as possible.

Multivariate analysis suggested that FEV1 and FVC levels were associated with age, sex, height, tobacco smoke exposure, asthma and atopic rhinitis. After adjustment for relevant covariates, FEV1 levels had a narrow-sense heritability (h^2N) of 38.9% (SE 9.1 %). FVC levels had an h^2N of 40.6% (SE 8.9%). Extended modelling demonstrated little overlap in the genetic determinants of asthma or atopic rhinitis and either FEV1 or FVC levels.

The results of this study were consistent with the existence of important genetic determinants of adult lung function that are independent of asthma or other atopic disease, cigarette smoking, height, age or sex.
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Spirometric indices measure parameters of respiratory function in an individual which may reflect underlying pathological factors resulting in airflow obstruction. The most commonly used spirometric indices are the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC). FEV1 and FVC are strongly related to the severity of respiratory symptoms, atopy and elevated serum immunoglobulin E (IgE) levels in children and adults [1–4].

Population-based studies indicate that FEV1 and FVC are approximately normally distributed in the general population [5], suggesting that multiple factors are involved in determining these traits. Pedigree-based studies of unselected, asthmatic and chronic obstructive pulmonary disease (COPD) families give consistent evidence for familial aggregation of spirometric indices [6–11], suggesting that around 20–60% of total phenotypic variance may be accounted for by familial factors. Estimates of the narrow-sense heritability (h^2N) of the most commonly investigated spirometric measure, FEV1, have ranged from 28% [12] to 47% [13]. Twin studies also give consistent evidence of a genetic contribution to the variability of spirometric indices and a significantly higher concordance for these indices in monozygotic (MZ) twins [14–16], although estimates of the broad-sense heritability of spirometric indices in twin studies have ranged from just over 0% to almost 100% [8, 12, 14–16].

Few studies of general population samples with reasonable sample sizes have adequately adjusted for all known potential confounders such as sex, age, race, tobacco smoke exposure and body size. Those that have done so have reported inconsistent results [9, 17, 18].

There is substantial evidence that asthma and other atopic diseases aggregate within families and that a substantial proportion of this aggregation is due to genetic factors [19]. The extent to which the close

relationship of asthma with decreased spirometric indices reflects shared genetic determinants is unclear.

The aim of this study was to use variance components analysis to estimate the genetic and environmental components of lung function variance measured in adulthood in a population-based sample of nuclear families. A further aim was to investigate the interrelationships between any genetic determinants of these traits with asthma and atopic rhinitis.

Methods

Study population

Busselton is a rural town on the coast of South-Western Australia and the population is predominantly of European origin. Six cross-sectional surveys of adults in the town of Busselton were undertaken, approximately one every three years, over the period 1966–1981 and a follow-up survey of all survivors from these cross-sectional surveys was conducted in 1994/1995. A wide range of health related data was gathered in each survey, including demographic variables, general health and lifestyle variables, health history variables, and physical, biochemical, haematological and immunological measurements. General descriptions of the cross-sectional surveys have been reported previously [20, 21].

The current study is based on an analysis of the 468 nuclear families for whom lung function and other data were available for each family member from $\geqslant 1$ survey when they were aged 25–60 yrs. If a family member participated in >1 survey during this age range, then the data from the survey when their age was closest to 45 yrs was used. Data came from surveys conducted in 1966 (10.9%), 1969 (16.3%), 1972 (10.0%), 1975 (7.4%), 1978 (5.8%), 1981 (9.2%) and 1994/1995 (40.4%).

The ongoing cross-sectional studies were approved by the Human Rights Committee of the University of Western Australia, and informed personal consent was obtained from all subjects.

Questionnaire

Individual and family histories of respiratory symptoms, demographic information and smoking were completed at interview using a modified British Medical Research Council questionnaire [22]. Doctor diagnosed asthma (ever) was defined as a positive response to the question: "Has your doctor ever told you that you have asthma/bronchial asthma?" Doctor diagnosed atopic rhinitis (ever) was defined as a positive response to the question: "Has your doctor ever told you that you have hay fever?". Smoking was classified as never-smoked, exsmoker, light smoker (<15 cigarettes·day^{-1}) or heavy smoker ($\geqslant$15 cigarettes·day^{-1}).

Spirometry

In the surveys performed 1966–1978, FEV1 and FVC were measured using a McDermott dry spirometer (Pneumoconiosis Research Unit, Penarth, Wales, UK) calibrated daily with a 3-L syringe. All values obtained were corrected to body temperature and pressure, saturated (BTPS) assuming a fixed room temperature and atmospheric pressure. In the survey performed in 1981, spirometry was measured using wedge spirometers (Vitalograph, Buckingham, UK) and in 1994/1995 using a pneumotachograph spirometer (Welch Allyn, Skaneateles Falls, USA). At all time-points, the best FEV1 and FVC was measured according to the guidelines of the American Thoracic Society [23]. Results were recorded as the highest values from three maximum expiratory manoeuvres, provided that the best two recordings were within 5% of each other.

Because different methods and circumstances of lung function measurement were used in the different surveys, possible measurement biases in spirometric measures across the successive surveys were investigated. This analysis suggested a systematic study bias in the measurement of FEV1 and FVC in the 1969 and 1978 surveys (data not shown; the bias was unrelated to sex, smoking, height or other variables measured at the time of the studies). Therefore, FEV1 and FVC assessed in 1969 and 1978 were appropriately adjusted in order to correct for the apparent measurement bias. Height of subjects was measured at the time of spirometric assessment using a stadiometer.

Statistical analysis

The primary response variables modelled were FEV1 and FVC. Explanatory variables included sex, age, height, and smoking status. Asthma and atopic rhinitis status were also included as explanatory covariates in certain models. All explanatory variables except sex, asthma status, atopic rhinitis status and smoking were analysed as continuous covariates. Smoking was analysed as a categorical variable (never smoked=0; exsmoker=1; current light smoker=2; current heavy smoker=3). The marginal distributions of FEV1 and FVC levels were approximately normal. All continuous covariates were centred at or close to their mean. Bivariate analyses were performed using unpaired t-tests (two-tailed, equivariance not assumed) and analysis of variance (ANOVA) [24].

The software package FISHER (www.biomath.-medsch.ucla.edu/faculty/klange/software.html) [25] was used to undertake multivariate modelling and to partition observed phenotypic variance into genetic and nongenetic components by maximum likelihood methods. Each model assumed that the distribution of the response phenotype for a family was multivariate normal, with a mean that depended upon a particular set of explanatory covariates. The mean models and specification of variance and covariance structures are given in the appendices. Similar modelling methods were used in the investigation of familial aggregation of cardiovascular risk factors in Busselton families [21]. The model fitting procedure included an investigation of interaction or polynomial terms and examination of the effect of observations with high regression leverage. Definitive final models were shown to provide a valid summary of the observed data.

Phenotypic variance was partitioned into four components: 1) additive genetic effects (σ^2_A) (the additive effects of genes); 2) common family environment (σ^2_C) (environmental exposures shared by an entire family, *e.g.* ownership of a cat or dog or consumption of the same food); 3) common sibling environment (σ^2_{CS}) (environmental exposures unique to siblings over and above the common family environment, *e.g.* sharing a bed or a bedroom); and 4) the residual variance (σ^2_E) (which is assumed to arise from non-familial random factors, *e.g.* occupational exposure of a father to environmental pollutants).

The narrow-sense heritability (h^2_N) was defined as the ratio of variance due to additive genetic effects (σ^2_A) to the total phenotypic variance of each trait [26]:

$$h^2_N = \sigma^2_A/(\sigma^2_A + \sigma^2_C + \sigma^2_{CS} + \sigma^2_E) \qquad (1)$$

Asymptotic standard errors for h^2_N were obtained by reparameterizing the covariance model in terms of h^2_N rather than σ^2_A.

The statistical associations of covariates entered as fixed effects and the current response variable were assessed by removal of terms from the mean model and calculation of a likelihood ratio Chi-squared test statistic [26]. The same approach was used as an approximate guide to the "significance" of a departure of the value of a variance component from its null value (zero). Statistical significance was taken as the $p \leqslant 0.05$.

Standard goodness-of-fit tests to check overall validity of models were performed using the FISHER program [25].

Extended modelling. In order to investigate the extent to which additive genetic effects were shared with asthma and atopic rhinitis, the original mean model for each phenotype of interest (*e.g.* FEV1 levels) was extended by adding (one at a time) terms for these other outcomes of interest (*e.g.* asthmatic status). Under such circumstances, a large reduction in the magnitude of σ^2_A suggested a sharing of additive genetic factors, and therefore sharing of genetic determinants.

Because this was not a standard nested model problem, an approach based upon profile likelihoods [27] was used to assess the magnitude of any change in the estimate of the genetic component of variance (σ^2_A). σ^2_{Ao} was defined as the estimated value of σ^2_A in the original model and σ^2_{AE} as its equivalent in the extended model. The extended model was then refitted and the value of σ^2_A constrained so it was forced to take the value σ^2_{Ao}. The ratio of the likelihoods of the free and constrained models measured the plausibility of the hypothesis that the true value of σ^2_A was unchanged by extending the model. In a standard nested model problem, a likelihood ratio of 6.82 approximates to p=0.05. More generally, a likelihood ratio in excess of 10 is moderate evidence that the hypothesis of shared determinants is plausible, and one in excess of 100 is strong evidence.

Results

Characteristics of families

Table 1 shows the characteristics of the family members; data shown were collected at the survey when each individual was aged 25–60 yrs and was closest to age 45 yrs. The mean number of children per family was 2.0. The number of offspring ranged from 1–7 and there were a total of 938 offspring with available data. Males and females were equally represented in the study population.

Effects of age, sex, cigarette smoking and height

Average FEV1 and FVC levels were higher for males (fathers and sons) than females (mothers and daughters), and higher for offspring (sons and daughters) than parents (mothers and fathers). Conversely, average % predicted FEV1 and FVC levels were lower for males (fathers and sons) than females (mothers and daughters) (table 2). The prevalence of current smoking was higher in parents than offspring and higher in males than females. Asthma was more prevalent in offspring compared with parents. Both asthma and atopic rhinitis were more prevalent in females than males (table 1). Bivariate analysis by ANOVA indicated that both FEV1 % pred ($F_{3,1870}$=43.40, p<0.0001) and FVC % pred ($F_{3,1870}$=43.40, p<0.0001) were significantly lower in the group of heavy smokers (table 2). FEV1 % pred were significantly lower in asthmatics (T_{213}=7.10, p<0.0001) and in those with atopic rhinitis (T_{843}=2.63, p=0.01) (table 2). Similarly, FVC % pred were significantly lower in asthmatics (T_{216}=4.82, p< 0.0001) and in those with atopic rhinitis (T_{859}=2.06, p=0.04) (table 2).

The multivariate variance components modelling confirmed these relationships, and indicated that age had a significant effect on FEV1 levels in both males and females (Chi-squared$_1$=275.6, p<0.0001 and Chi-squared$_1$=204.2, p<0.0001, respectively) and on FVC levels (Chi-squared$_1$=95.2, p<0.0001 and Chi-squared$_1$=85.3, p<0.0001 respectively). FEV1 and FVC were lower in older males and females. Height also had a significant effect in both males and females on FEV1 levels (Chi-squared$_1$=275.5, p<0.0001 and Chi-squared$_1$=143.9, p<0.0001, respectively) and on FVC levels (Chi-squared$_1$=414.6, p<0.0001 and Chi-squared$_1$= 241.6, p<0.0001, respectively). Levels were higher in taller males and females. Cigarette smoking was closely associated in both males and females with reduced levels of FEV1 (Chi-squared$_3$=75.7, p<0.0001 and Chi-squared$_3$=28.3, p<0.0001, respectively) and FVC (Chi-squared$_3$=19.0, p=0.0001 and Chi-squared$_3$=12.5, p= 0.003, respectively). The overall sex effect (see mean model in appendices) was significant for both FEV1 (Chi-squared$_6$=225.9, p<0.0001) and FVC (Chi-squared$_6$=317.9, p<0.0001) levels.

Association with asthma and atopic rhinitis

Doctor diagnosed asthma was associated with decreased FEV1 (Chi-squared$_1$=77.7, p<0.0001) and FVC

Table 1. – Characteristics of family members

Variable	Mothers	Fathers	Daughters	Sons
Subjects n	468	468	483	455
Age yrs	47.2±4.8	48.0±4.9	37.4±5.9	37.3±6.5
Height m	1.61±0.06	1.73±0.06	1.64±0.06	1.76±0.06
FEV1 L	2.56±0.47	3.44±0.68	3.06±0.50	4.10±0.70
FVC L	3.36±0.55	4.73±0.74	3.81±0.61	5.22±0.77
FEV1 % pred	104.5±17.0	97.8±16.9	108.4±15.1	103.1±14.7
FVC % pred	107.6±15.7	105.6±14.2	108.6±14.6	104.4±12.7
Smoking				
Never	64.8	26.9	52.8	49.4
Exsmoker	12.8	24.4	29.4	22.6
Light	9.6	16.7	8.5	15.0
Heavy	12.8	32.0	9.3	13.0
Asthma	6.2	4.1	15.7	14.0
Atopic rhinitis	30.8	22.0	32.9	23.1

Data are presented as mean±SD or percentages. FEV1: forced expiratory volume in one second; FVC: forced vital capacity.

(Chi-squared$_1$=23.6, p<0.0001). Doctor diagnosed atopic rhinitis was also associated with decreased FEV1 (Chi-squared$_1$=13.3, p=0.0001) and FVC (Chi-squared$_1$=5.1, p=0.01). These associations were independent of age, sex, smoking status, height and familial correlations.

Variance components and heritability estimates

After adjustment for all covariates, h^2N of FEV1 was 38.9% (SE 9.1%), *i.e.* additive genetic effects (σ^2A) contributed around two fifths of the total variance (fig. 1 and model 1, table 3). σ^2A was significantly greater than zero (Chi-squared$_1$=17.4, p<0.0001). The remaining variance was largely the result of nonfamilial environmental effects (σ^2E). Familial environmental effects (σ^2CS and σ^2C) were not significantly different from zero.

The h^2N of FVC was estimated to be 40.6% (SE 8.9%), *i.e.* σ^2A contributed approximately two-fifths of the total variance (figure 2 and model 1, table 4. σ^2A was significantly greater than zero (Chi-squared$_1$=19.4, p<0.0001). Environmental effects common to families (σ^2C) were not significantly different from zero and contributed only minimally, if at all, to total phenotypic variance. Environmental effects common to siblings (σ^2CS) were significantly greater than zero (Chi-squared$_1$=5.9, p=0.009). The majority of phenotypic variance was attributable to nonfamilial environmental effects (σ^2E).

The extended modelling indicated that adjustment of the FEV1 for asthma status resulted in a small fall (to mean±SEM 0.086±0.022), 89.6% of baseline model, see model 2 in table 3) in the σ^2A estimate. This was consistent with an ~10% overlap in genetic (σ^2A) determinants, and was associated with a likelihood ratio of 1.23, consistent with little or no change in σ^2A. Adjustment of the FVC model for asthma status resulted in an estimated 0.8% fall (to 0.125±0.028), 99.2% of baseline model, see model 2 in table 4) in the estimate of σ^2A. The likelihood of the unconstrained model was only 1.12 times greater than that of the constrained model, consistent with little or no change in σ^2A.

Adjustment of the FEV1 for atopic rhinitis status resulted in a small fall (to 0.094±0.023), 97.9% of

Table 2. – Values for % predicted forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) levels in asthmatics and smokers

Group	FEV1 % pred	FVC % pred
Smoking		
Never	104.8±15.7	107.1±14.7
Exsmoker	104.1±16.9	107.2±14.1
Light	103.8±14.9	108.7±13.7
Heavy	94.1±15.4	102.7±14.0
Asthma	93.7±19.9	101.0±16.9
Nonasthma	104.3±15.6	107.2±14.0

Data are presented as mean±SD.

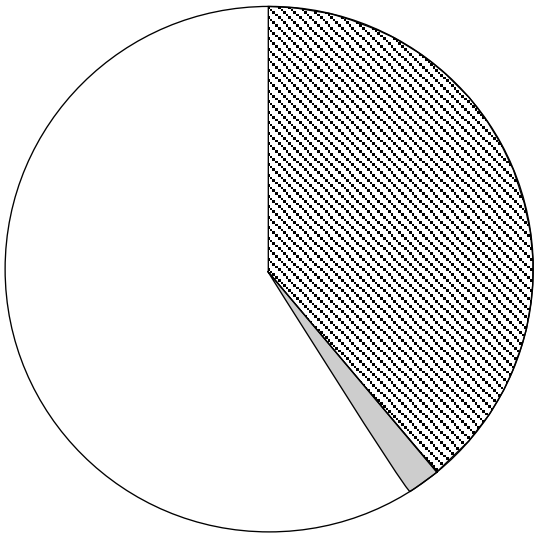

Fig. 1. – Components of total variance in forced expiratory volume in one second (FEV1). The following data are presented as estimated mean±SEM (% of total variance): □: residual error variance (σ^2E), 0.146±0.014 (59.1%); ▨: additive genetic variance (σ^2A), 0.096±0.023 (38.9%); ■: common family environmental variance (σ^2C), 0.005±0.011 (2.0%); note that common sibling environmental variance (σ^2CS) is zero.

Table 3. – Maximum likelihood models showing variance components estimates for forced expiratory volume in one second (FEV_1) at baseline and after sequential adjustment for covariates

Model	σ^2_A	σ^2_C	σ^2_{CS}	σ^2_E
Baseline	0.096±0.023	0.005±0.011	0.000	0.146±0.014
Baseline+doctor diagnosed asthma (ever)	0.086±0.022 (89.6%)	0.002±0.011 (40.0%)	0.000	0.132±0.013 (90.4%)
Baseline+doctor diagnosed atopic rhinitis (ever)	0.094±0.023 (97.9%)	0.004±0.011 (80.0%)	0.000	0.133±0.013 (91.1%)

Data are presented as mean±SEM (% of baseline). All models are adjusted for age, sex, height and smoking status. σ^2_A: additive genetic component of variance; σ^2_C: common family environmental component of variance; σ^2_{CS}: common sibling environmental component of variance; σ^2_E: residual error (random environmental) component of variance.

baseline model, see model 3 in table 3) in the σ^2_A estimate. This was consistent with an ~2% overlap in genetic (σ^2_A) determinants, and was associated with a likelihood ratio of 1.08, consistent with little or no change in σ^2_A. Adjustment of the FVC model for atopic rhinitis status resulted in an estimated 0.8% fall (to 0.125±0.028), 99.2% of baseline model, see model 3 in table 4) in the estimate of σ^2_A. The likelihood of the unconstrained model was only 1.10 times greater than that of the constrained model, consistent with little or no change in σ^2_A. The goodness-of-fit tests did not indicate any significant lack-of-fit problems for any of the models reported.

Discussion

The present study was designed to recruit a sample of families containing individuals assessed in adulthood and who were representative of a general Caucasian population. It has shown that adult FEV_1 and FVC levels are strongly heritable traits, each with genetic determinants that are distinct from asthma and atopic rhinitis.

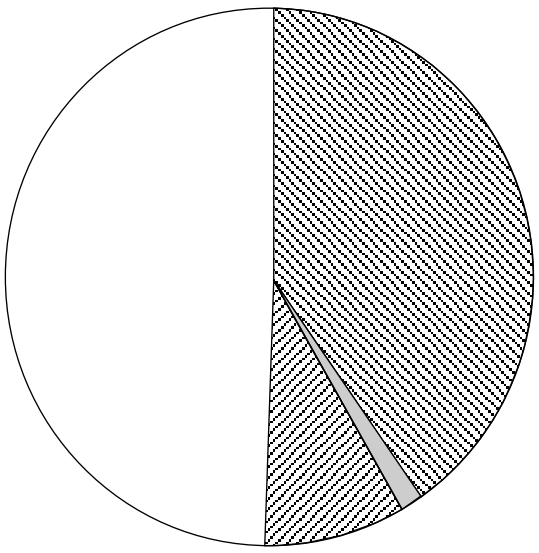

Fig. 2. – Components of total variance in forced vital capacity (FVC). The following data are presented as estimated mean± SEM (% of total variance): □: residual error variance (σ^2_E), 0.153±0.019 (49.4%); ▨: additive genetic variance (σ^2_A), 0.126± 0.028 (40.6%); ▩: common family environmental variance (σ^2_C), 0.004±0.014 (1.3%); ▨: common sibling environmental variance (σ^2_{CS}), 0.027±0.012 (8.7%).

The prevalence rates for self-reported asthma and wheeze for parents and children in this study are similar to those previously reported in other Australian studies [28, 29]. The higher prevalence of doctor diagnosed asthma in the offspring (table 1) reflects the widely observed rising prevalence rates of asthma over the past two decades in developed nations [30, 31]. Surveys of random samples have previously shown that the prevalence of wheeze and diagnosed asthma in the Busselton community increased substantially over the decade 1981–1990 [32]. The relationships of FEV_1 and FVC levels to age, sex and cigarette smoking in the Busselton population were consistent with previous population-based studies of Caucasians [28–31, 33]. The smoking rates for parents and offspring (table 1) were similar to those derived from relevant demographic estimates for the Australian population [34].

A problem with some previous studies of spirometric indices has been inadequate adjustment for the effects of the many factors which might bias a heritability estimate. Such factors include height, sex, age, race and tobacco smoke exposure [12]. Because these factors aggregate in families, it is important that they are adjusted for in genetic epidemiological analyses which attempt to define unique genetic determinants of the spirometric measures themselves. The current study adjusted for height, sex, age, and active tobacco smoke exposure. It was unnecessary to adjust for race, as all members of the Busselton population included in the current study were Caucasian. Thus, the present study provides evidence that FEV_1 and FVC levels may be under some degree of significant genetic control, independent of genetic factors influencing body size, sex-specific expression and susceptibility to environmental tobacco smoke.

In the nuclear family design, estimates of the effects of common sibling environment are completely confounded with the estimated effects of genetic dominance (nonadditive effects of alleles at the same locus) [26]. The heritability estimates presented in this paper are therefore conservative, as the numerator includes only additive genetic effects. However, scrutiny of tables 3 and 4 suggests that even the extreme assumption that all of the σ^2_{CS} estimate was in fact due to dominance genetic effects, would have made little or no difference to the substantive conclusions.

Both pedigree- and twin-based studies give consistent evidence of a genetic contribution to the variability

Table 4. – Maximum likelihood models showing variance components estimates for forced vital capacity (FVC) at baseline and after sequential adjustment for covariates

Model	σ^2_A	σ^2_C	σ^2_{CS}	σ^2_E
Baseline	0.126±0.028	0.004±0.014	0.027±0.012	0.153±0.019
Baseline+doctor diagnosed asthma (ever)	0.125±0.028 (99.2%)	0.001±0.014 (25.0%)	0.028±0.011 (103.7%)	0.126±0.017 (82.4%)
Baseline+doctor diagnosed atopic rhinitis (ever)	0.125±0.028 (99.2%)	0.003±0.014 (75.0%)	0.027±0.012 (100.0%)	0.131±0.019 (85.6%)

Data are presented as mean±SEM (% of baseline). All models are adjusted for age, sex, height and smoking status. σ^2_A: additive genetic component of variance; σ^2_C: common family environmental component of variance; σ^2_{CS}: common sibling environmental component of variance; σ^2_E: residual error (random environmental) component of variance.

of lung function [6–11, 13–16, 18, 35–37]. Estimates of the broad-sense heritabilities of FEV1 and FVC derived from twin studies that have adjusted for body size, have ranged 0–~75%. In agreement with previous studies reporting a substantial heritability of FEV1 and FVC levels [11, 18] the present results suggest substantial correlations in adult FEV1 and FVC levels between genetically related. Most of the observed familial correlation′s in adult FEV1 and FVC were attributable to genetic rather than environmental factors. However, the majority of the total variance in adult FEV1 and FVC levels was due to nonfamilial environmental factors.

In adults and children, FEV1 and FVC levels are strongly associated with asthma [1–3]. The present analysis allowed estimation of the overlap between genetic determinants of the spirometric measures studied and asthma and atopic rhinitis. In the present study, the observed close relationships of these spirometric measures to asthma were consistent with previous reports. However, little evidence was found that the association of asthma or atopic rhinitis with both FEV1 and FVC levels was due to the sharing of additive genetic determinants. Conversely, there was evidence of genetic and environmental determinants influencing FEV1 and FVC which were unshared with asthma and atopic rhinitis. The unshared genetic determinants suggest the existence of a distinct genetic pathway modulating FEV1 and FVC independently of asthma or other atopic disease (atopic rhinitis), age-, height- or sex-dependent expression or genetic susceptibility to tobacco smoke exposure. Independence of the genetic determinants of FEV1 and FVC from asthma has not been previously demonstrated.

The present study suggests the presence of important genetic determinants of two pathophysiological traits associated with asthma COPD and lower respiratory symptoms and further shows for the first time that FEV1 and FVC levels in adulthood are traits that are genetically distinct from asthma and atopic rhinitis. COPD is a disease that like asthma is currently the subject of intensive genetic investigation by many groups internationally and which makes extensive use of FEV1 as an intermediate phenotype [38, 39].

The results of this study, which suggest that immunoglobulin E mediated inflammatory processes are genetically distinct from spirometric indices, therefore also have important implications for genetic studies of chronic obstructive pulmonary disease. Programmes of gene identification in asthma will be facilitated by the recognition that forced expiratory volume in one second and forced vital capacity are not proxies for "asthma" in adults; different genetic mechanisms are likely to regulate these spirometric measures and susceptibility to asthma or atopy. The specific genes regulating these spirometric measures remain to be defined.

Appendices

1. The mean models were specified as follows:

$$\text{Mean} = \delta(\beta_1 + \beta_2\ (\text{age}) + \beta_3(\text{height}) + \beta_4(\text{exsmoker status}) + \beta_5(\text{light smoker status}) + \beta_6(\text{heavy smoker status})) + (1-\delta)(\beta_7 + \beta_8\ (\text{age})) + \beta_9(\text{height}) + \beta_{10}(\text{exsmoker status}) + \beta_{11}(\text{light smoker status}) + \beta_{12}(\text{heavy smoker status}) \quad (2)$$

Where βn with the nth fixed regression coefficient and δ is a binary indicator variable taking the value 1 in males and 0 in females. This model permitted independent covariate profiles for the phenotype of interest in males and females.

2. The total phenotypic variance (conditional on the mean model) was based on a conventional covariance structure [26] and was specified as:

$$(\sigma^2) = \sigma^2_A + \sigma^2_{CS} + \sigma^2_C + \sigma^2_E \quad (3)$$

3. The conditional covariances within a family were specified as:

(i) $0.5\sigma^2_A + \sigma^2_{CS} + \sigma^2_C$ between two siblings;
(ii) $0.5\sigma^2_A + \sigma^2_C$ between a parent and a child; and
(iii) σ^2_C between two parents.

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