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Shared and Distinct Genetic Influences Among Different Measures of Pulmonary Function

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Abstract

We examined shared and distinct genetic influences among standard measures of pulmonary functions: ratio of forced expiratory volume at 1 s to forced vital capacity (FEV1/FVC) and percent predicted values for forced expiratory volume at 1 s (FEV1%p), forced expiratory flow (FEFmax%p), and maximal voluntary ventilation (MVV%p) in 978–1,048 middle-aged (mean age = 55 years) male–male twins from the Vietnam Era Twin Study of Aging. A common latent factor ($h^2 = 0.30$) accounted for the correlations among these measures. This factor accounted for 54–81

% of the heritability of FEV1%p, FEFmax%p and MVV%p, but only explained 16 % of the heritability of FEV1/FVC. The remaining heritability of FEV1/FVC was explained by genetic influences independent of the common factor. Our findings suggest that while a common latent phenotype accounts for the relationships among different pulmonary function measures, the majority of genetic influences underlying FEV1/FVC—an index of pulmonary obstruction—are distinct from those underlying other pulmonary function measures.

Keywords

Lung; Heritability; Twins; Genes; Middle-age

Introduction

Pulmonary function is associated with many age-related outcomes, including coronary heart disease, lung cancer, dementia, cognitive function, and mortality (Kaseda et al. 2000; Marcus et al. 1989; Schünemann et al. 2000; Pathan et al. 2011; Chyou et al. 1996). Pulmonary function peaks in early adulthood and undergoes normative age-related decline that is influenced by both biological and environmental factors. Forced vital capacity (FVC) is the basic maneuver in pulmonary testing, measuring the total volume of air that can be expelled after a full inspiration. FEV1 is forced expiratory volume in the first second of an FVC trial. FEV1 and FVC and their ratio, FEV1/FVC, are clinically-relevant pulmonary function measures that are indicators of both restrictive and obstructive disease and disease progression (Pellegrino et al. 2005; Rabe et al. 2007).

In restrictive disease, such as pulmonary fibrosis, FEV1 and FVC are diminished proportionally, with values for FEV1/FVC appearing normal or even slightly increased (Pellegrino et al. 2005). In obstructive disease, such as asthma and chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, FEV1 and FVC are diminished disproportionately, resulting in reduced FEV1/FVC values (Pellegrino et al. 2005; Mannino et al. 2002). The Global Initiative for Chronic Obstructive Lung Disease suggests a FEV1/FVC ratio <70 % as the diagnostic cutoff for COPD (Rabe et al. 2007). Additionally, along with FEV1, FEV1/FVC is an indicator of obstruction severity (Balfe et al. 2002). Forced expiratory flow (FEF) is also measured during the FVC trial, measuring airflow (speed) during expiration. Studies have suggested that FEF may provide additional clinically-relevant information about obstructive disease, specifically that FEF may be a more sensitive indicator of asthma (Simon et al. 2010; Lebecque et al. 1993) and is an indicator of small airway disease (McFadden and Linden 1972). The maximum airflow during the FVC maneuver is termed FEF max and can also be reported as peak expiratory flow (PEF); PEF is one of the primary indices used in asthma management (Miller et al. 2005). Other spirometry measures are also sensitive to restrictive and obstructive disease, such as maximal voluntary ventilation (MVV), which measures the maximum volume of air inspired and expired over a specified period of time (Barreiro and Perillo 2004; Miller et al. 2005). MVV can be used to estimate breathing reserve during exercise and is an indicator of inspiratory muscle strength (Pellegrino et al. 2005; Aldrich et al. 1982).

Several studies have reported moderate to high heritabilities for pulmonary function, particularly in middle-aged and older adults. In a sample of 4,314 middle-aged Danish twins (mean age = 57 years), the heritability for FEV1 was estimated at $h^2 = 0.61$ (Ingebrigtsen et al. 2011). Similar heritability estimates for FEV1 ($h^2 = 0.67$ and $h^2 = 0.52$) have been found in the Swedish Adoption/Twin Study of Aging (mean age = 65 years) and the National Heart, Lung and Blood Institute Family Heart Study (mean age = 52 years) (McCleary et al. 1994; Wilk et al. 2000). However, heritability estimates for FEV1 were lower ($h^2 = 0.32$) in a sample of 374 twins from the Finnish Twin Study of Aging (mean age = 69 years) (Hukkinen et al. 2011). This study included only female twins while the Ingebrigtsen et al. and McCleary et al. studies included both genders. Thus, the lower heritability estimate from the Hukkinen et al. study may be due to sex differences in the genetic influences underlying pulmonary function. Two other studies of pulmonary function have found higher heritability estimates in men. Ingebrigtsen et al. (2011) reported a heritability estimate of 0.43 for PEF in men, but no significant genetic influences on PEF in women. Similarly, in a study of octogenarian Swedish twins from the OCTO-Twin study, heritability estimates for PEF in men and women were 0.54 and 0.34, respectively (Vasilopoulos et al. 2010). In addition to FEV1 and PEF, moderate heritabilities for FVC ($h^2 = 0.41$ – 0.54) and FEV1/FVC ($h^2 = 0.45$ – 0.46) have also been reported (Hukkinen et al. 2011; Wilk et al. 2000). To the best of our knowledge, no study of older adults has examined the heritability of MVV. One study reported heritability estimates >0.90 in a sample of 10–27 year old Indian twins; however, this study only included 54 twin pairs (Chatterjee and Das 1995).

Given the differential importance of various pulmonary function measures for clinical and functional assessments and the evidence for genetic influences on pulmonary function, researchers have postulated putative differential genetic effects on various pulmonary phenotypes (Chen 1999). Behavioral genetic methodologies can be used to assess the extent to which multiple phenotypes share common genes and, conversely, the extent to which they have distinct genetic influences. However, no study has extensively examined the genetic overlap among multiple spirometry measures. Thus, in the present study we examined the extent to which four measures of pulmonary function (FEV1, FEV1/FVC, FEFmax, and MVV) have shared or distinct genetic influences in middle-aged male twins.

Materials and methods

Sample

Data were obtained from Wave 1 of the Vietnam Era Twin Study of Aging (VETSA), a longitudinal study of cognition and aging beginning in midlife (Kremen et al. 2006). Participants in VETSA are from the Vietnam Era Twin Registry, a nationally representative sample of male–male twin pairs who served in the US military sometime between 1965 and 1975. Detailed descriptions of the Registry and ascertainment methods have been previously reported (Eisen et al. 1987; Henderson et al. 1990). VETSA twins resemble those of the larger Registry sample and are representative of the general population of similarly-aged adult males in terms of demographic and health characteristics (Center for Disease Control and Prevention 2003; National Center for Disease Statistics 2003). VETSA twins had the option to travel to Boston University or to the University of California, San Diego for a day-

long session that included physical and psychosocial assessments and an extensive neurocognitive battery. The VETSA Wave 1 sample includes 1,237 individuals (349 monozygotic twin (MZ) pairs and 265 dizygotic (DZ) twin pairs). The average age was 55.4 years (range: 51–60).

Spirometry

Pulmonary function was obtained during the FVC and the MVV procedures, and data were recorded using commercially available software (Breeze Suite; Med-Graphics, St. Paul, Minnesota). Measures obtained from spirometry included the percent predicted value for total forced expiratory volume (FVC%p), the percent predicted value for forced expiratory volume at 1 s (FEV1%p), the ratio of forced expiratory volume at 1 s to forced vital capacity (FEV1/FVC), the percent predicted value for maximum forced expiratory flow (FEFmax %p), and the percent predicted value for maximum voluntary ventilation (MVV%p). Percent predicted values were calculated using existing reference equations, which include measures of body size and age (Knudson et al. 1976; Bass 1973; Boren et al. 1966). FEV1/FVC was adjusted for height and age to closely match the percent predicted values for the other four measures. The pulmonary function values used for analysis represent the “best effort” from multiple trails (typically three trials). Percent predicted values <10 % or >200 % were assumed to be errors resulting from incorrect attempts during the tasks. Due to errors in the data recording equipment or failed/non-attempts by participants, between 100 and 170 participants had invalid pulmonary function data for each measure. After recoding invalid data as missing, values 3SD above or below the mean of any given measure were considered outliers and were also coded as missing. Each pulmonary measure was adjusted for smoking, diagnosis of pulmonary-related diseases (asthma, chronic bronchitis, and emphysema) and race/ethnicity. Smoking was indexed by pack years, which was calculated by multiplying number of cigarettes smoked per day/20 (estimate of packs per day) by the number of years smoked. Finally, each pulmonary function measure was standardized (z-scored). The final sample for any given measure, after controlling for covariates, ranged from $N = 978$ – 1048 (Table 1). Twins with valid data on at least one pulmonary function measure were included in the analyses.

Statistical analysis

Descriptive statistics and phenotypic analyses were conducted in SPSS for Windows (Version 18). Twin modeling was conducted in the structural equation modeling program, Mx (Neale et al. 2004). In the twin design the phenotypic variance of a trait can be decomposed into additive genetic (A), common or shared environmental (C; non-genetic factors that make twins similar) and non-shared environmental (E; non-genetic factors the make twins dissimilar plus measurement error) effects. Heritability (h^2) is defined as the proportion of total variation in a trait due to genetic influences. More detailed information on the twin design can be found elsewhere (Plomin et al. 2001).

The twin design can also be used to examine how genes and the environment influence the relationships among variables. The saturated model that perfectly recaptures the observed means and variances of all pulmonary measures served as a baseline comparison for subsequent models. The Cholesky Decomposition model was then fit to estimate the

underlying genetic and environmental variance/covariance matrix (Fig. 1a). Cholesky models can estimate the heritability (h^2 for each variable as well as the genetic correlations (r_g) between variables, i.e. extent to which two variables share the same genes). Shared (r_c) and non-shared environmental (r_e) correlations are analogous. Submodels were compared to the full Cholesky ACE model to determine: (1) if the effects of additive genetic influences (A) were significant (CE model) and (2) if the effects of shared environmental influences (C) were significant (AE model).

The Common Pathways model and Measurement model were then fit to determine the genetic and environmental factor structure underlying the relationships among the pulmonary function measures. The Common Pathways model (Fig. 1b) assumes that a single underlying latent phenotype is solely responsible for the covariation among the pulmonary measures. The variance of this latent phenotype is further partitioned into common genetic and environmental factors (A_c , C_c and E_c). The Common Pathways model allows for residual genetic and environmental influences specific to each individual measure (A_{s1} – A_{s4} , etc.). The Measurement model (Fig. 1c) is a nested submodel of the Common Pathways model. In this model, the residual variance for each measure that is not explained by the latent phenotype is assumed to be measurement error and is, therefore, modeled as specific non-shared environmental (E_s) factors.

Model fit was assessed by the difference in two times the log likelihood ($-2LL$) between models using the Likelihood Ratio Chi Square (χ^2) Test with degrees of freedom equal to the difference in the number of parameters between the two models. A significant ($p < 0.05$) increase in the χ^2 statistic indicates significantly poorer model fit. Akaike's information criterion (AIC) was also utilized to select the final model; lower AIC scores indicate greater parsimony, i.e. maximization of goodness-of-fit while minimizing the number of parameters required.

Results

Phenotypic analyses

Descriptive statistics are reported in Table 1. In the total sample, 7.1 % reported receiving a diagnosis for chronic bronchitis and emphysema and 7.5 % reported receiving diagnosis for asthma. Furthermore, 16.5 % of the total sample had FEV1/FVC values <70 %, the standard cutoff indicator for obstruction. For age, pack years, pulmonary disease diagnosis, and obstruction indication there were no differences between MZ and DZ twins. DZ twins were significantly taller than MZ twins; however, this difference is unlikely to bias the analyses because each pulmonary function measured was adjusted for body size. MZ and DZ twins did not significantly differ for any pulmonary function measure. FEV1%p, FEFmax%p and MVV%p were moderately correlated, with correlations ranging from 0.58 to 0.61 (Table 2). The correlations between FEV1/FVC and these pulmonary function measures were lower, although still statistically significant ($r = 0.31$ – 0.36). While FVC%p was moderately correlated with FEFmax%p and MVV%p ($r = 0.48$), because of how the FEV1/FVC ratio is constructed, FVC%p and FEV1/FVC had a small, negative correlation ($r = -0.12$). In contrast, FEV1%p was positively correlated with FEV1/FVC ($r = 0.36$). Statistically, it is inappropriate to model both FEV1%p and FVC%p in the same analyses, as FEV1%p is a

part of the total FVC%p score, as evidenced by the high correlation between FEV1%p and FVC%p ($r = 0.88$). Given that FVC%p was positively correlated with FEFmax%p and MVV%p, but negatively correlated with FEV1/FVC, we chose to include FEV1%p instead of FVC%p because all of the correlations between FEV1%p with other pulmonary function measures were positive. For comparisons with other studies, the univariate heritability of FVC%p was $h^2 = 0.37$ (95 % CI = 0.27–0.47).

Genetic analyses

Model fitting results are presented in Table 3. The Cholesky model that dropped all shared environmental effects (AE) fit the data well and had a lower AIC value compared to the full Cholesky ACE model, indicating that the Cholesky AE model was more parsimonious. Additionally, the Cholesky model that dropped all additive genetic effects (CE) had a significantly poorer model fit and had a higher AIC value compared to the full Cholesky ACE model. However, while shared environment (C) was estimated at <5 % for MVV%p and FEV1/FVC in the Cholesky ACE model; for FEV%p and FEFmax%p, $C = 0.13$ – 0.14 . Thus, we note that subsequent heritability estimates for FEV1%p and FEFmax%p calculated from the AE models could be inflated. Genetic correlations (Table 4), calculated from Cholesky AE model, between all the pulmonary measures were significant ($r_g = 0.42$ – 0.70), with the highest genetic correlation being between FEV1%p and MVV%p. FEV1/FVC ratio had the lowest genetic correlations with the other variables ($r_g = 0.42$ – 0.44). Likewise, the lowest non-shared environmental correlations were between FEV1/FVC and the other pulmonary function measures ($r_e = 0.28$ – 0.35).

The Common Pathways AE model did not fit the data significantly more poorly than the Cholesky AE model ($p = 0.32$); moreover, the Common Pathways AE model had a lower AIC value compared to the Cholesky AE model (Table 3). The Measurement model, however, fit the data significantly more poorly than the Common pathways model ($p < 0.01$). Thus, the Common Pathways AE model was chosen as the most parsimonious model. These results indicated that a single common latent factor accounted for the relationships among the pulmonary function measures; however, there were also significant measure-specific genetic and environmental factors that were separate from the common latent factor. The underlying latent factor in the Common Pathways model was moderately heritable, $h^2 = 0.30$ (from Fig. 2, $h^2 = 0.55 \times 0.55 = 0.30$), with the remaining variance explained by non-shared environmental factors. Table 5 presents total heritabilities of each measure. Heritabilities ranged from 0.22 for MVV%p to 0.37 for FEV1/FVC. For FEV1%p, FEFmax%p and MVV%p the majority of the heritability in each measure (54–81 %) was explained by the common factor. For FEV1/FVC, on the other hand, only a small amount of genetic variability (16 %) was explained by the common latent factor, with the majority of its heritability (84 %) explained by specific genetic factors distinct from the common factor. This result indicated that most of the genetic influences on FEV1/FVC were separate from those of other pulmonary measures. Likewise, whereas substantial portions of the non-shared environmental variance of FEV1%p, FEFmax%p and MVV%p were accounted for by the common factor, a majority (79 %) of the non-shared environmental variance in FEV1/FVC was due to specific non-shared environmental factors.

To confirm that our findings were not due to the relatively broad range of pulmonary function values included in our sample, we re-ran the analyses using a more conservative method of defining the pulmonary phenotypes by coding any values above 150 % and below 30 % as missing. The final sample sizes (after controlling for covariates) were reduced using this method, ranging from 885–977. Despite the smaller sample, results from these follow-up analyses were nearly identical to the analyses above. Again, a Common Pathways AE model provided no worse of a fit to the data compared to the Cholesky AE model ($X^2 = 11.62$, $df = 7$, $p = 0.11$). The common latent factor from this model showed a heritability of $h^2 = 0.37$ and accounted for the majority of the heritability in FEV1%p, FEFmax%p and MVV%p (62–87 %) but not for FEV1/FVC (17 %), consistent with the results from the larger sample. Full results from these analyses are available from the authors.

Discussion

This study is the first to examine the extent to which genetic influences on different pulmonary measures are shared and, likewise, the extent to which these influences are distinct. Our results indicated that a single, moderately heritable ($h^2 = 0.30$) common latent factor, as modeled in a Common Pathways model, explained the covariance among these pulmonary function measures. The common factor accounted for a substantial portion of the genetic and environmental influences of FEV1%p, FEFmax%p and MVV%p, but not FEV1/FVC. Additionally, our findings revealed that FEV1%p, FEFmax%p and MVV%p were moderately phenotypically correlated. Furthermore, as calculated from the Cholesky AE model, the genetic and environmental correlations (i.e. degree to which measures share the same genetic and environment influences) between these three measures were moderate to high ($r_g = 0.56$ – 0.71). While FEV1%p, FEFmax%p and MVV%p are indices of different lung functions, they are all dependent, to a degree, on lung volume. Furthermore, nearly all the genetic influences of MVV%p were accounted for by this common factor. Thus, these findings suggest that common latent factor from the Common Pathways model may be highly influenced by lung volume and/or total ventilatory capacity.

In contrast, our findings revealed that the majority of the genetic and environmental influences on FEV1/FVC were explained by distinct genetic and environmental factors separate from the common factor in the Common Pathways Model. As stated above, our results suggest that the common latent factor from the Common Pathways Model is highly influenced by lung volume and/or ventilatory capacity. FEV1/FVC, however, is an index of lung obstruction that is independent of lung volume due to the way the ratio is calculated. Thus, this unique quality of FEV1/FVC could, in part, explain why the majority of the variance in FEV1/FVC was not explained by the common latent factor. Moreover, the genetic and non-shared environmental correlations between FEV1/FVC and other measures, estimated from the Cholesky AE model, were much lower than those among FEV1%p, FEFmax%p and MVV%p. In comparison with previous research, our estimated genetic and non-shared environmental correlations between FEV1/FVC and FEV1%p ($r_g = 0.44$, $r_e = 0.35$) were somewhat lower than the genetic and non-shared environmental correlations between FEV1/FVC and FEV1 found in another study from the Netherlands Twin Registry ($r_g = 0.52$, $r_e = 0.43$) (Wu et al. 2010), although the confidence intervals in our study overlap with these prior estimates. We note that there are several differences between the present

study and that of Wu et al. that might account for this discrepancy. The Wu et al. sample was younger (mean age = 22 years), included both men and women, was based on a clinical sample in which at least one twin reported asthma, and also used absolute FEV1 rather than percent predicted FEV1. Overall, however, both studies support the hypothesis that there are significant genetic and environmental influences on FEV1/FVC that do not overlap with the genetic and environmental influences on other measures of pulmonary function.

Because FEV1/FVC is used as the diagnostic indicator of COPD and overall obstruction, genes specific to FEV1/FVC may be related to COPD itself or to the severity of pulmonary obstruction. Our results support findings from recent linkage and genome-wide association studies of different pulmonary function indices. For example, there is evidence for linkage on chromosome 18 for both FEV1 and FVC, but not for FEV1/FVC (Wilk et al. 2003), while the same study found evidence for linkage on chromosome 4 for FEV1/FVC, but not for FEV1 and FVC. In a recent large-scale meta-analysis, Artigas et al. reported 12 loci with genome-wide significant associations for FEV1/FVC that were different from the 3 loci identified for FEV1; there was only one identified locus that was associated with both measures (Soler Artigas et al. 2012). It should be noted, however, there may be limitations in using these studies of genetic variants, particularly for complex human phenotypes (Boomsma et al. 2002). One issue is the idea “missing heritability”; i.e. substantial portions of the heritabilities of complex disease remain unexplained by currently known genetic variants (So et al. 2011). Twin studies, on the other hand, can provide insight not only into the overall importance of genetic factors for one phenotype but also into how genetic factors influence relationships among traits and the degree to which different traits share a common set of genes.

Interestingly, there was a high degree of genetic overlap between FEV1%p and MVV%p ($r_g = 0.70$). In clinical practice, the use of MVV has largely been superseded by FEV1, with some studies utilizing equations to approximate MVV from FEV1 instead of measuring MVV directly (Pellegrino et al. 2005; Miller et al. 2005). The substantial degree of shared genes between these measures supports the assumption that they may index similar constructs. However, MVV%p had significant specific non-shared environmental effects separate from the common factor and its genetic and environmental influences did not completely overlap with those of FEV1%p, indicating some specificity in the genetic and environmental influences for MVV%p. While FEV1 and MVV index an aspect of lung volume, FEV1 only measures expiratory volume while MVV measures the volume both expired and inspired and is a direct measure of ventilatory capacity. Thus, MVV may still be a unique indicator of several physiological processes, including neuromuscular function and exercise capacity, and mechanisms underlying ventilatory capacity may differ from those underlying FEV1 (Pellegrino et al. 2005; Miller et al. 2005; Aldrich et al. 1982).

In reviewing our findings, several limitations should be considered. First, our sample consisted of all-male, mostly Caucasian participants, limiting the ability to generalize our findings to women and to men from other racial and ethnic groups. Similarly, because this study focused on late middle-age (age range = 51–60 years), future studies are needed to determine if the genetic architecture underlying relationships among pulmonary function measures differs across development. A third limitation is that our study did not obtain a

direct report of COPD diagnosis from participants, although 7.1 % of the sample reported bronchitis and/or emphysema diagnoses, which are parts of the COPD diagnosis. Likewise, nearly 17 % of our sample had FEV1/FVC below 70 %, which is an indicator for obstruction, particularly in COPD. However, we note that FEV1/FVC may also be diminished in other pulmonary disease, such as asthma; thus, this measure cannot be used to directly infer the proportion of our sample with COPD. The degree of overlap between COPD and asthma is still being evaluated and studies have provided evidence of differing etiologies of these diseases (Tzortzaki et al. 2011; Gibson and Simpson 2009). Of the participants in our sample reporting any pulmonary disease diagnosis, 23 % reported having both asthma and bronchitis/emphysema. Additionally, of participants with FEV1/FVC <70 %, 16.3 % reported having bronchitis/emphysema and 12.6 % reported having asthma. In general, while spirometry metrics are useful objective measures, they still should be considered supplementary to clinical evaluations for the diagnosis of pulmonary disease (Pauwels 2000). As noted previously, a fourth limitation is that the heritability estimates for FEV1%p and FEFmax%p obtained from the use of AE models were most likely slightly inflated because shared environmental influences were estimated as accounting for 13–14 % of the variance in these measures from the Cholesky ACE model. However, we did not believe this biased our primary multivariate results from the Common Pathways Model because C was estimated at less than 5 % for the other pulmonary measures; thus, covariance between pulmonary measures as indexed by the underlying latent phenotype would not be substantially influenced by shared environmental factors. Finally, because of the statistical properties of the relationships between FEV1%p, FVC%p, and FEV1/FVC, we could not include FVC%p in the multivariate analyses, although we report that the heritability of FVC%p ($h^2 = 0.37$) was within the range of heritabilities reported for the pulmonary function measures used in the multivariate analyses ($h^2 = 0.22–0.37$). Although we were unable to examine associations between FVC%p with other pulmonary function measures, our analyses did include several important measures of pulmonary function that indexed a range of pulmonary phenotypes, including lung volume, airflow, ventilatory capacity, and obstruction; thus, our results provide unique insight into the relationships among these different pulmonary indices.

The major strength of this study was the use of the twin design to elucidate shared and distinct genetic and environmental influences across several clinically relevant pulmonary function measures. We were able to determine that a common latent factor underlies relationships among these pulmonary measures and that both genes and non-shared environment influence individual differences in this common factor. Furthermore, the twin design allowed us to determine that FEV1 and MVV share a substantial portion of the same genes; however, each measure also had distinct influences. Finally, we found that FEV1/FVC, an important index of pulmonary obstruction, had specific genetic and environmental influences separate from the other pulmonary function measures, supporting the hypothesis that FEV1/FVC is an index of a clinically relevant, and distinct, pulmonary phenotype.

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Fig. 1. Multivariate genetic models. For ease of presentation, only one twin is represented in each figure. **A** (additive genetic), **C** (shared environment) and **E** (non-shared environment) pathways are depicted. **a** Depicts the Cholesky Decomposition model, including all source of variance: additive genetic influences (A_1 – A_4), shared environmental influences (C_1 – C_4) and non-shared environmental influences (E_1 – E_4). **b** Depicts the common pathways model and **c** Depicts the measurement model. A_C additive genetic influences, C_C shared environmental and E_C non-shared environmental influences common to all pulmonary

measures. A_s additive genetic influences, C_s shared environmental and E_s non-shared environmental influences specific to each pulmonary measure. $FEV1\%p$ percent predicted value forced expiratory flow in 1 s; $FEFmax\%p$ percent predicted value of maximum forced expiratory flow; $MVV\%p$ percent predicted value of maximal voluntary ventilations; $FEV1/FVC$ = ratio for forced expiratory volume in 1 s to forced vital capacity

Fig. 2.

Common pathways model for FEV1 %p, FEFmax %p, MVV%p, and FEV1/FVC including standardized parameter estimates. Squaring the path estimate from the common factor to each measure (i.e. factor loading) yields the amount of variance in each factor explained by the common factor. Heritabilities for individual pulmonary measures are calculated by first squaring the product of the A_C and the factor loading for any given measure, then adding this product to the squared specific genetic path estimate (A_S). Similar calculations can be performed to estimate the proportion of variance in each measure explained by non-shared environmental factors (E). *FEV1%p* percent predicted value forced expiratory flow in 1 s; *FEFmax%p* percent predicted value of maximum forced expiratory flow; *MVV%p* = percent predicted value of maximal voluntary ventilations; *FEV1/FVC* ratio for forced expiratory volume in 1 s to forced vital capacity

Table 1

Means and standard deviations for pulmonary function and related measures

Variables	Total sample ^a	MZ ^b	DZ ^b	p ^c
Age (year)	55.4 (2.5)	55.4 (2.5)	55.5 (2.4)	0.20
Height (in.)	69.5 (2.9)	69.3 (2.6)	69.8 (3.2)	0.00
Weight (pounds)	201.7 (36.5)	201.2 (36.8)	202.3 (36.0)	0.60
Pack years	19.7 (23.3)	20.0 (23.2)	19.3 (23.4)	0.59
Percent (%) with asthma diagnosis	7.5	8.1	6.7	0.35
Percent (%) with chronic bronchitis and/or emphysema diagnosis	7.1	7.3	6.9	0.67
Forced vital capacity, % of predicted (FVC %p)	106.2 (21.1)	106.7 (21.5)	105.6 (20.7)	0.43
Forced expiratory volume in 1 s, % of predicted (FEV1 %p)	100.9 (21.9)	101.3 (22.3)	100.4 (21.0)	0.54
Forced expiratory flow, % of maximum predicted (FEFmax %p)	112.2 (29.1)	112.1 (29.0)	112.3 (29.4)	0.90
Maximal voluntary ventilation, % of predicted (MVV %p)	111.6 (28.7)	110.3 (29.5)	113.3 (27.7)	0.10
Forced expiratory volume in 1 s, % of forced vital capacity (FEV1/FVC)	76.6 (8.2)	76.5 (8.3)	76.7 (8.1)	0.68
Percent (%) with FEV1/FVC <70 % (obstruction indicator)	16.5	17.1	15.7	0.61

^aThe final total sample ranged across measures. $N = 1,007$ for FVC%p, $N = 1,009$ for FEV1%p, $N = 1,048$ for FEFmax%p, $N = 978$ for MVV%p and $N = 1,001$ for FEV1/FVC

^bThe number of twin pairs in which both twins had complete pulmonary function data was $N = 232$ (MZ)/189 (DZ) for FEV1%p, $N = 248$ (MZ)/206 (DZ) for FEFmax%p, $N = 237$ (MZ)/166 (DZ) for MVV%p and $N = 230$ (MZ)/184(DZ) for FEV1/FVC

^cp values for age, height, weight, pack years and each pulmonary measure were calculated from T test between MZ and DZ twins. P-values for pulmonary disease diagnoses and obstruction indication were calculated from Chi-square test between MZ and DZ twins

Table 2

Phenotypic (pearson) correlations among pulmonary function variables

	FVC%p	FEV1%p	FEFmax%p	MVV%p	FEV1/FVC
Force vital capacity, % of predicted (FVC %p)	1.00				
Forced expiratory volume in 1 s, % of predicted (FEV1 %p)	0.88**	1.00			
Forced expiratory flow, % of maximum predicted (FEFmax %p)	0.48**	0.61**	1.00		
Maximal voluntary ventilation, % of predicted (MVV %p)	0.48**	0.58**	0.60**	1.00	
Forced expiratory volume in 1 s, % of forced vital capacity (FEV1/FVC)	-0.12**	0.36**	0.34**	0.31**	1.00

**
 $p < 0.01$

Table 3

Model fitting results for multivariate genetic models of FEV1%p, FEFmax%p, MVV%p and FEV1/FVC

	Absolute fit			Relative fit		
	-2LL	df	AIC	Model comparison	Likelihood ratio χ^2 test	df p
1. Saturated model	10065.23	3956	2153.23	–		
2. Cholesky ACE	10127.59	4002	2123.59	1	62.36	54 0.20
3. Cholesky AE	10131.39	4012	2107.39	2	3.80	10 0.95
4. Cholesky CE	10150.45	4012	2126.45	2	22.86	10 0.01
5. Common pathways AE	10139.59	4019	2101.59	3	8.20	7 0.32
6. Measurement model AE	10233.36	4023	2187.36	5	101.97	4 0.00

–2LL negative 2 times the log likelihood, df degrees of freedom, AIC Akaike's information criteria, χ^2 test-difference in –2LL between the two models being compared, FEV1%p percent predicted value forced expiratory flow in 1 s, FEFmax%p percent predicted value of maximum forced expiratory flow, MVV%p percent predicted value of maximal voluntary ventilations, FEV1/FVC ratio for forced expiratory volume in 1 s to forced vital capacity

Table 4

Genetic (r_g ; below diagonal) and non-shared environmental (r_e ; above diagonal) correlations among pulmonary function measures calculated from the AE Cholesky model, with 95 % confidence intervals

	FEV1%p	FEFmax%p	MVV %p	FEV1/FVC
Forced expiratory volume in 1 s, % of predicted (FEV1%p)		0.67 0.60–0.73	0.59 0.51–0.67	0.35 0.25–0.45
Forced expiratory flow, % of maximum predicted (FEFmax%p)	0.56 0.37–0.71		0.60 0.52–0.67	0.32 0.21–0.42
Maximal voluntary ventilation, % of predicted (MVV%p)	0.70 0.45–0.89	0.69 0.51–0.85		0.28 0.17–0.38
Forced expiratory volume in 1 s, % of forced vital capacity (FEV1/FVC)	0.44 0.22–0.64	0.42 0.24–0.56	0.42 0.17–0.66	

Table 5

Proportion of genetic (h^2) and non-shared environmental (e^2) variance for each pulmonary function measure explained by common and specific factors (from common pathways model)

	h^2 Total	h^2 Common ^d	h^2 Specific ^b	e^2 Total	e^2 Common ^c	e^2 Specific ^b
Forced expiratory volume in 1 s, % of predicted (FEV1%p)	0.30	0.20	0.10	0.70	0.44	0.26
		67 %	33 %		63 %	37 %
Forced expiratory flow, % of maximum predicted (FEFmax%p)	0.36	0.20	0.16	0.64	0.44	0.19
		54 %	46 %		69 %	31 %
Maximal voluntary ventilation, % of predicted (MVV%p)	0.22	0.18	0.04	0.78	0.41	0.37
		81 %	19 %		52 %	48 %
Forced expiratory volume in 1 s, % of forced vital capacity (FEV1/FVC)	0.37	0.06	0.31	0.63	0.13	0.50
		16 %	84 %		21 %	79 %

Because we used standardized variables in our analyses, actual estimates for each variance component translate into the proportion of total variance (genetic + environmental) explained

^a Estimate from common factor and % total genetic variance explained

^b Estimate from specific genetic factor and % total genetic variance explained

^c Estimate from common factor and % total non-shared environmental variance explained

^d Estimate from specific non-shared environmental factor and % total non-shared environmental variance explained