Family resemblance for normal pulmonary function

E. J. DEVOR
Department of Psychiatry, Washington University School of Medicine and the Jewish Hospital of St Louis

and M. H. CRAWFORD
Department of Anthropology and Laboratory of Biological Anthropology, University of Kansas

Received 10 November 1983; revised 30 January 1984

Summary. Family resemblance for normal pulmonary function as measured by forced vital capacity and one second forced expiratory volume is assessed using a path analysis model which incorporates sex differences in transmissibility of the phenotype from parents to offspring as well as in the effect of a correlated shared-sibling environment. Application of this model, called XTAU, to familial correlations indicates that transmissible factors, which may be genetic or cultural, account for 20-30% of the variation in these measures. Further, a pronounced same-sex-specific effect of the sibling environment is indicated which enhanced the observed correlation between same-sex siblings and diminished the observed correlation between opposite-sex siblings. These results are consistent with findings of twin studies of pulmonary function indicating high heritability for both FVC and FEV₁₀. In addition, the complex multifactorial model of family resemblance for normal pulmonary function is shown to have implications for specifying causal models of pulmonary disorders such as asthma, bronchitis, allergic rhinitis, and chronic obstructive pulmonary disease.

1. Introduction

Genetic/family studies of human pulmonary function have concentrated primarily on abnormal function such as in chronic obstructive pulmonary disease (COPD) and bronchitis (e.g. Hurst 1959, Hole and Wasserman 1965, Larson and Barman 1965, Larson, Barman, Kueppers and Fudenberg 1970, Higgins and Keller 1975, Tager, Rosner, Tishler, Speizer and Kass 1976) or in the identification of genetic markers such as α₁-antitrypsin and the immunoglobulins in these disorders (e.g. Drew-Miller, Gleich, Offord and Dunnette 1979, Lelloch and Claude 1980, Kauffmann, Kleisbauer, Cambon-de-Muzon, Mercier, Constans, Blanc, Rouch and Feingold 1983). Apart from a few reports on the range of normal spirometric values in selected populations, however, investigations of ventilatory capacity in healthy individuals have only rarely addressed either familial correlations (Higgins and Keller 1975, Tager et al. 1976, Kauffmann 1980) or twin resemblance (Man and Zamel 1976, Hankins, Drage, Zamel and Kronenberg 1982, Hubert, Fabsitz, Feinleib and Gwinn 1982). Such investigations do suggest that a substantial amount of normal variation in pulmonary function may be accounted for by factors, either genetic or environmental, unique to individual families.

In order to determine the proportion of variation attributable to direct familial transmission as distinct from that attributable to shared familial environment we here present the results of an investigation of family resemblance for the pulmonary function measures forced vital capacity (FVC) and one-second forced expiratory volume (FEV₁₀) in a sample of healthy non-smoking individuals. The method employed to assess the components of family resemblance is the XTAU path analysis model of Rice, Cloninger and Reich (1978, 1980). Results indicate that from 20 to 30% of normal variation in these measures is accounted for by genetic and cultural factors transmitted directly from parents to their offspring. Further, an additional source of
resemblance between siblings is found in a same-sex-specific effect of the shared-sibling environment. These results are consistent with the findings from twin studies and, in addition, provide an explanation of observations of familial aggregation of abnormal pulmonary function independent of the distribution of putative genetic markers.

2. Materials and methods

Subjects and data
FVC and FEV$_{1.0}$ spirometric values were obtained on a sample of 305 men and 339 women volunteers participating in a study of ageing and longevity in the Mennonite brethren of Kansas and Nebraska (cf. Crawford and Rogers 1982). Three quarters of the subjects on whom data were obtained are members of the Goessel, Kansas Mennonite congregation and the remainder are residents of the nearby Meridian, Kansas Mennonite congregation. Genealogical information collected on these populations permitted us to group 307 (47.7%) individuals from the original sample into 96 nuclear family units composed of at least one pair of first-degree relatives. As the original data were not collected with a family-study orientation, these nuclear family units consist mostly of parents and one or two offspring, but some sib-only groups are included. The family groupings give a total of 360 first-degree relative-pair observations from which correlations could be computed.

For the purpose of comparison, a large set of familial correlations for FEV$_{1.0}$ was obtained from a published report (Higgins and Keller 1975). Unfortunately, no comparable correlation data for FVC could be found in the literature.

Methods
Comparison of raw data FVC and FEV$_{1.0}$ means and standard deviations in the Mennonite sample with those from the Tecumseh, Michigan study (Higgins and Keller 1973), showed that there were no significant differences between the two populations regardless of sex or age cohort. Because the Mennonite brethren proscribe the use of tobacco and alcohol, the Mennonite individuals in this study did present slightly better average FEV$_{1.0}$ values except in the oldest age groups where there were no differences. The FVC values of the two groups were nearly identical in all age and sex groups.

Several studies of ventilatory capacity suggest that stature, along with age and sex, is important in individual variation in both FVC and FEV$_{1.0}$ values (Cotes, Rossiter, Higgins and Gibson 1966, Higgins and Keller 1973, Morris, Temple and Koski 1973). For this reason the effects of sex, age and stature were simultaneously controlled for in the Mennonite raw data by a polynomial regression with stature, sex, age, age$^2$, age$^3$, age$^4$, and all four possible sex-by-age interactions. The best fit polynomial regression equations, containing only the significant ($P > 0.05$) terms, for the two traits were found to be similar to those reported by Cotes et al. (1966) and by Higgins and Keller (1973) for other populations.

Standardized residuals were computed from the best-fit polynomials and their distributional characteristics with regard to skewness and commingling were examined using the FORTRAN commingling analysis program SKUMIX (MacLean, Morton, Elston and Yee 1976). Under this routine the standardized residuals, $x$, are transformed via a scaled power transform.

$$y = \begin{cases} \frac{1}{P} \left[ \left( \frac{x}{r} + 1 \right)^P - 1 \right], & P > 0 \\ r \ln(x/r + 1), & P = 0 \end{cases}$$

(1)
where the scalar, \( r \), is chosen such that \( x/r + 1 \) is always positive. Note that this function is continuous at \( P = 0 \) by l'Hôpital's rule and is the identity transform at \( P = 1 \) (MacLean et al. 1976). Various hypotheses regarding the distribution of \( y \) are tested using likelihood ratio criteria.

Sex-specific familial correlations were computed for all first-degree relative pairs in the nuclear family sub-sample using the standardized residuals of FVC and FEV\(_{1.0}\) from the total sample. Family resemblance was then analysed using the FORTRAN path analysis program XTAU (Rice et al. 1980, Rice 1981). The XTAU model is an extension of the basic TAU model of family resemblance (Rice et al. 1978) in which an allowance is made for the possibility of sex differences in transmissibility from parent to offspring as well as in the effect of a correlated shared-sibling environment. The full XTAU model for a nuclear family with two children is shown in figure 1. A total of ten parameters will serve to specify fully the model, viz.: \( m \), assortative mating between spouses; \( \tau_1 \) and \( \tau_2 \) transmissibility of a phenotype from father and mother respectively; \( \tau_{11}, \tau_{12} \) and \( \tau_{22} \), the relative contribution made by each parent to the transmissible component of an offspring's phenotype according to the sex of the offspring; and \( c_{11}, c_{12} \) and \( c_{22} \), sex-specific shared sibling environmental effects. The two parameters \( e_i \) are derived from \( t_i \) according to the relationship \( e_i = \sqrt{1 - t_i^2} \).

![Path diagram](image)

Figure 1. Path diagram representing the sources of resemblance in a nuclear family composed of parents and two children. The quantities in boxes are observed phenotypes while those in circles are latent variables. All path parameters in the model are estimated from observed familial correlations except \( e_i \) and \( e_j \) which are derived as \( e_i = \sqrt{1 - t_i^2} \). The figure is by courtesy of Dr John Rice, and reproduced with permission.

Applying the rules of path analysis (Wright 1968, Li 1975) to the path diagram in figure 1, the parameters of the full XTAU model produce a total of eight equations for correlation among the members of an intact nuclear family. The equations produced are:

\[
\begin{align*}
    r_{P_{12}} &= m, \\
    r_{P_{01}} &= \tau_{11}t_1^2 + m\tau_{21}t_1t_2.
\end{align*}
\]
\[ r_{p_{12}} = \tau_{11}t_{12}^2 + m\tau_{22}t_{12}^2, \]  
\[ r_{p_{21}} = \tau_{21}t_{12}^2 + m\tau_{11}t_{12}^2, \]  
\[ r_{p_{22}} = \tau_{22}t_{12}^2 + m\tau_{22}t_{12}^2, \]  
\[ r_{oo_{11}} = (\tau_{11}t_{12}^2 + \tau_{21}t_{12}^2)t_{12}^2 + 2m\tau_{11}\tau_{21}t_{12}t_{12}^2 + c_{12}e_{12}, \]  
\[ r_{oo_{21}} = (\tau_{11}\tau_{22} + \tau_{21}\tau_{12})t_{12}t_{12}^3 + m(\tau_{11}\tau_{22} + \tau_{21}\tau_{12})t_{12}t_{12}^3 + c_{22}e_{22}. \]  

However, since the parameters of the model are unknown they must be estimated on the basis of observed familial correlations. With ten parameters and only eight possible observations the full XTAU model is under-determined. In order to obviate this problem we have followed the precedent of Rice et al. (1980) and Potter, Rice, Dahlberg and Dahlberg (1983) by imposing the constraint \( \tau_{ij} = \tau = 0.50 \). This constraint makes explicit an assumption that whatever transmissibility is present for a trait, its actual transmission from parent to offspring behaves in a polygenic, or more accurately, a multifactorial, manner. That is to say, if a certain percentage of the variation in a complex trait is found to be due to transmissible factors, that percentage is modelled as a multifactorial component. Such an assumption is a matter of convenience and cannot be disproved on the basis of nuclear family data alone (Potter et al. 1983). On the other hand, given the nature of the traits being studied by this method, it is not an unreasonable assumption to make.

In the context of the observed correlations \( r_1, r_2, \ldots, r_k \) and the specific constraints placed on the model, the path parameters \( \theta \) which maximize the likelihood function,

\[ L = \frac{1}{2} \sum_{i=1}^{k} \left( f(r_i) - f(r_i(\theta))^2 \right) (N_i - 3) \]  

are chosen by a numerical optimization routine (Rice 1981). The function \( f \) in (10) is Fisher’s Z-transformation. Tests of specific hypotheses regarding the presence or absence of transmissibility and the effect of the sibling environment are carried out using likelihood ratio criteria (Rice et al. 1978).

3. Results

Distribution of residuals

A commingling analysis of the standardized residuals of FVC and FEV\(_{1.0}\) in the Mennonite sample showed that the power transformation required to remove skewness was not significantly different from the identity transform, \( P = 1.0 \). The estimated skewness parameter for FVC of \( P = 1.147 \pm 0.120 \) is not different from \( P = 1.0 \) by the likelihood ratio chi-square (\( \chi_{1}^2 = 3.30, \text{ns} \)) nor is the estimate of \( P = 1.21 \pm 0.118 \) for FEV\(_{1.0}\) (\( \chi_{1}^2 = 3.19, \text{ns} \)). Consequently, there is no evidence of commingling in the distribution of the residuals in either trait. We therefore adopt a hypothesis that, within the limits of the present data, both ventilatory capacity measures may best be described by a single normal distribution.

Homogeneity of familial correlations

Familial correlations for FVC and FEV\(_{1.0}\) are presented in table 1. The first two sets of correlations were computed from the standardized residuals in the Mennonite sample and the third set is the FEV\(_{1.0}\) correlation data pooled from figures reported by Higgins and Keller (1975). Higgins and Keller present familial correlations by age.
groups which, after testing for between-age-group heterogeneity, could be pooled into
a single set for comparison. Pooling was accomplished by taking the weighted sum of
the corresponding Z-transformed correlations within relative-pair class and then the
inverse Z transform (Snedecor and Cochran 1980).

### Table 1. Observed familial correlations and sample sizes for the Mennonite FVC and FEV\(_{1.0}\) data and for the pooled Higgins and Keller (1975) FEV\(_{1.0}\) data.

<table>
<thead>
<tr>
<th>Correlation</th>
<th>FVC</th>
<th>FEV(_{1.0})†</th>
<th>FEV(_{1.0})‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>(n)</td>
<td>(r)</td>
</tr>
<tr>
<td>Marital (m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father-son ((r_{\text{F}s1}))</td>
<td>0.142</td>
<td>54</td>
<td>0.037</td>
</tr>
<tr>
<td>Father-daughter ((r_{\text{F}s2}))</td>
<td>0.095</td>
<td>48</td>
<td>0.013</td>
</tr>
<tr>
<td>Mother-son ((r_{\text{M}s1}))</td>
<td>0.124</td>
<td>37</td>
<td>0.157</td>
</tr>
<tr>
<td>Mother-daughter ((r_{\text{M}s2}))</td>
<td>0.129</td>
<td>59</td>
<td>0.130</td>
</tr>
<tr>
<td>Homogeneity (\chi^2)§</td>
<td>0.020</td>
<td></td>
<td>0.525</td>
</tr>
<tr>
<td>Brother-sister ((r_{\text{B}s1}))</td>
<td>0.633</td>
<td>24</td>
<td>0.610</td>
</tr>
<tr>
<td>Brother-sister ((r_{\text{B}s2}))</td>
<td>0.241</td>
<td>25</td>
<td>0.391</td>
</tr>
<tr>
<td>Sister-sister ((r_{\text{S}s2}))</td>
<td>0.472</td>
<td>21</td>
<td>0.490</td>
</tr>
</tbody>
</table>

* \(P<0.05\).

§ 'Effective' sample size, \((\Sigma n) - 3\).

‖ The chi-square statistic is computed as: \(\chi^2 = \Sigma(n_i - 3)z_i^2 - [\Sigma(n_i - 3)z_i] / \Sigma(n_i - 3)\), where \(z_i = [\ln(1 + r_i) - \ln(1 - r_i)]\).

Parent-offspring and sibling correlations within samples were also tested for
heterogeneity. None of the parent-offspring correlations were found to be significantly
heterogeneous and, among the sibling correlations, only the pooled values from the
Higgins and Keller report were significantly heterogeneous \((\chi^2 = 8.632, P < 0.05)\). Examination of the pattern of sibling correlation in the Mennonite sample leads us to
suspect that the failure to demonstrate significant heterogeneity in these data is due to
the small sample size rather than to a lack of true heterogeneity.

**Family resemblance**

The results of applying the XTAU path model to the observed familial correlations
for FVC and FEV\(_{1.0}\) from Table 1 are presented in Table 2. It can be seen that, under the
assumption \(\tau_{ij} = \tau = 0.50\), a general, otherwise unconstrained, XTAU model provides
an acceptable fit to the observed correlations in all cases. The goodness-of-fit statistic
for the general model and for all three alternative models in Table 2 is computed from
the sum of the squared differences between the observed and predicted Z-transformed
correlations (Rice *et al.* 1980). Degrees of freedom of the statistic are determined as the
number of correlations, in this study there are eight, minus the number of estimated
model parameters, in this case there are from three to six depending upon the con-
straints imposed on the model. Thus for FVC the goodness-of-fit of the general model
is \(\chi^2 = 3.27, 0.25 < P < 0.10\) and for the Mennonite FEV\(_{1.0}\) and the Higgins and Keller
FEV\(_{1.0}\) it is \(\chi^2 = 0.62, 0.75 < P < 0.50\) and \(\chi^2 = 4.56, 0.25 < P < 0.10\), respectively.
Table 2. Maximum likelihood parameter estimates and goodness-of-fit statistics for the Mennonite FVC and FEV$_{1.0}$ data and for the pooled Higgins and Keller (1975) FEV$_{1.0}$ data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No constraints§</th>
<th>$t_1 = t_2$</th>
<th>$c_{11} = c_{12} = c_{22}$</th>
<th>$t_1 = t_2$, $c_{11} = c_{12} = c_{22}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$m$</td>
<td>0.142</td>
<td>0.142</td>
<td>0.142</td>
<td>0.142</td>
</tr>
<tr>
<td>$t_1$</td>
<td>0.431</td>
<td>0.449</td>
<td>0.419</td>
<td>0.449</td>
</tr>
<tr>
<td>$t_2$</td>
<td>0.473</td>
<td>—</td>
<td>0.486</td>
<td>—</td>
</tr>
<tr>
<td>$c_{11}$</td>
<td>0.660</td>
<td>0.663</td>
<td>0.472</td>
<td>0.469</td>
</tr>
<tr>
<td>$c_{12}$</td>
<td>0.171</td>
<td>0.172</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$c_{22}$</td>
<td>0.460</td>
<td>0.461</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\chi^2_{(d.f.)}$</td>
<td>3.27(2)</td>
<td>4.25(3)</td>
<td>5.57(4)</td>
<td>5.58(5)</td>
</tr>
<tr>
<td>FEV$_{1.0}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$m$</td>
<td>0.037</td>
<td>0.037</td>
<td>0.037</td>
<td>0.037</td>
</tr>
<tr>
<td>$t_1$</td>
<td>0.368</td>
<td>0.411</td>
<td>0.501</td>
<td>0.411</td>
</tr>
<tr>
<td>$t_2$</td>
<td>0.471</td>
<td>—</td>
<td>0.500</td>
<td>—</td>
</tr>
<tr>
<td>$c_{11}$</td>
<td>0.627</td>
<td>0.632</td>
<td>0.517</td>
<td>0.510</td>
</tr>
<tr>
<td>$c_{12}$</td>
<td>0.370</td>
<td>0.368</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$c_{22}$</td>
<td>0.486</td>
<td>0.487</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\chi^2_{(d.f.)}$</td>
<td>0.62(2)</td>
<td>0.69(3)</td>
<td>1.50(4)</td>
<td>1.61(5)</td>
</tr>
<tr>
<td>FEV$_{1.0}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$m$</td>
<td>0.171</td>
<td>0.171</td>
<td>0.171</td>
<td>0.171</td>
</tr>
<tr>
<td>$t_1$</td>
<td>0.593</td>
<td>0.576</td>
<td>0.626</td>
<td>0.576</td>
</tr>
<tr>
<td>$t_2$</td>
<td>0.560</td>
<td>—</td>
<td>0.626</td>
<td>—</td>
</tr>
<tr>
<td>$c_{11}$</td>
<td>0.364</td>
<td>0.369</td>
<td>0.146</td>
<td>0.146</td>
</tr>
<tr>
<td>$c_{12}$</td>
<td>—0.004</td>
<td>—0.019</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$c_{22}$</td>
<td>0.256</td>
<td>0.255</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\chi^2_{(d.f.)}$</td>
<td>4.56(2)</td>
<td>4.73(3)</td>
<td>11.25(4)</td>
<td>13.00(5)</td>
</tr>
</tbody>
</table>

§ All models tested under the prior assumption $\tau_i = \tau = 0.50$.

Accepting that the general model of family resemblance fits the observed data, significance tests of nested alternative models in which various specific constraints are imposed are carried out by comparison to the general model. From equation (10) we see that $-2\ln(1) = \chi^2_{df}$ which is the goodness-of-fit statistic reported above. By likelihood ratio criteria $-2\ln(L_{Alt}/L_{Gen}) = -2(\ln(L_{Alt}) - \ln(L_{Gen}))$ is asymptotically distributed as $\chi^2_\nu$ where $\nu$ is the difference in the number of estimated parameters between the general model and any specific alternative. Therefore, $\chi^2_{Alt.} - \chi^2_{Gen.}$ is also distributed as $\chi^2_\nu$, where $\nu$ is now the difference in the degrees of freedom of two goodness-of-fit statistics. Using this scheme, the alternative model specifying that there is no sex-specific difference in the transmissibility of FVC ($t_1 = t_2$) cannot be rejected given the statistic $\chi^2_1 = 4.25 - 3.27 = 0.98$, ns (table 2). Moreover, accepting that $t_1 = t_2$, the alternative model further specifying that there is no sex-specific difference in the effect of the shared-sibling environment cannot be rejected ($\chi^2_3 = 5.58 - 3.27 = 2.31$, ns). Thus, we entertain a model of family resemblance for FVC based upon the present data in which there are no sex-specific effects in either transmissibility or sibling environment. The estimated parameters of this model from table 2 are $m = 0.142$, $t_1 = 0.449$ and $c_{ij} = 0.469$. The estimated 'heritability' of FVC under this model is $t_1^2 = 0.202$ indicating that 20-22% of the variation in this trait is due to genetic and cultural factors transmitted directly from parents to offspring.

The value $c_{ij} = 0.469$ estimated for FVC is a correction which permits the estimation of the relative importance of the shared-sibling environment in the overall sibling correlation observed. The parameters of the XTAU model in figure 1 can be used to produce a general expression for sibling correlation when there are no sex effects. This expression is $t_{oo} = (\tau_F + \tau_M + 2\tau_F \tau_M m t^2) t^2 + c e^2$. The relative importance of shared-
sibling environment is, therefore, $ce^2/r_{oo}$, where $r_{oo}$ is the overall sibling correlation observed. For FVC the estimated value of the relative importance of shared sibling environment in sibling correlation is $0.374/0.449 = 0.833$, which indicates that the majority of the resemblance between siblings for this trait is attributable to shared environment.

A model similar to the one proposed for FVC is indicated for the Mennonite FEV$_{1.0}$ as well. There is no evidence for sex effects in transmissibility ($\chi^2 = 0.69 - 0.62 = 0.07$, ns) or in the shared sibling environment ($\chi^2 = 1.61 - 0.62 = 0.99$, ns). Therefore, the model for family resemblance of FEV$_{1.0}$ among the Mennonites has the parameters $m = 0.037$, $t_1 = 0.411$ and $c_{ij} = 0.517$. The estimated ‘heritability’ for FEV$_{1.0}$ is $t_2^2 = 0.169$, or 16.9%. The relative influence of the shared-sibling environment in the observed sibling correlation is $0.424/0.497 = 0.853$. This larger influence is, of course due to the lower transmissibility of the trait.

The Higgins and Keller (1975) data present a different result for FEV$_{1.0}$ than do the Mennonite data. While the alternative model specifying no sex difference in transmissibility ($t_1 = t_2$) cannot be rejected ($\chi^2 = 4.73 - 4.56 = 0.17$, ns), the alternative model specifying no sex-specific difference in the shared-sibling environment when $t_1 = t_2$ is easily rejected ($\chi^2 = 13.00 - 4.56 = 8.44$, $P < 0.05$). Thus, in the larger Higgins and Keller sample a model of family resemblance for FEV$_{1.0}$ is indicated in which there is no sex effect in transmissibility, but there is a significant sex-specific effect of the shared-sibling environment. Parameter estimates for this model are $m = 0.171$, $t_1 = 0.576$, and $c_{11} = 0.369$, $c_{12} = -0.019$, $c_{22} = 0.255$. The corresponding estimated ‘heritability’ is $t_2^2 = 0.322$, or 32.2%. With a sex-specific effect of the shared-sibling environment indicated, the relative importance of the sibling environment must be estimated separately for each sex-specific sibling correlation. The estimated relative importance of the sibling environment when sibling are the same sex is $0.250/0.422 = 0.593$ for brothers, and $0.173/0.346 = 0.500$ for sisters. When siblings are of opposite sex the relative importance of their shared environment is $-0.019/0.163 = -0.079$. These estimates indicate that shared-sibling environment enhances sibling correlation when sibs are the same sex, but that there is actually a small diminishing effect when they are of opposite sex.

4. Discussion

A path analysis model (XTAU) which allows for sex differences in both the transmissibility of a trait and in the contribution of shared environment in the resemblance between siblings has been applied to familial correlations for the pulmonary function measures forced vital capacity (FVC) and one-second forced expiration volume (FEV$_{1.0}$). Results indicate that approximately 20-30% of the variation in these traits is attributable to factors, both genetic and cultural, transmitted directly from parents to their offspring. Further, the relative effect of shared-sibling environment is shown to account for the majority of the resemblance between siblings. When a larger comparative sample of FEV$_{1.0}$ familial correlations from the Tecumseh, Michigan study is analysed, it is shown that the sibling environmental effect is same-sex-specific. We believe that the failure to resolve this specificity in the Mennonite data is a consequence only of the smaller sample size and, therefore, we suggest that the model entertained for the Higgins and Keller sample data be regarded as the most likely model of family resemblance for both pulmonary function traits. Naturally, further study on a larger sample is required to verify this assertion. The larger sample should include not only nuclear families, but extended pedigrees and separation data, such as half-sibs and
full sibs reared apart. In this way more resolution of the transmissible component will be possible as well.

The source of the significant same-sex-specific effect of the shared sibling environment is comparatively easy to assess. Numerous studies of ventilatory capacity have shown that physical activity does have an effect on the measures used. Individuals who are more physically active tend to have FVC and FEV$_{1.0}$ values substantially different from individuals who are not active (e.g. Shapiro and Patterson 1962). It has been historically true that boys are encouraged to be physically active and to participate in athletics, while girls have not. In addition, traditional male occupations are generally more strenuous than are traditional female occupations. While these tendencies are less true today, they should nonetheless result in brothers having a higher correlation for ventilatory capacity than sisters and in a low or even negative cross-sex sibling correlation. In fact, part of the reason why we believe that there is a same-sex-specific sibling environmental effect in the Mennonite sample that was not resolved due to the small sample size, is that the Mennonite brethren have long maintained traditional occupation differences in which men perform the greatest part of the most physical activities associated with farming and women perform the greatest part of the less physical activities, as well as a majority of the household maintenance. These differences are established early in childhood in a Mennonite family and continue throughout life. Thus, a significant same-sex effect of the shared-sibling environment is expected in both populations. A similar phenomenon appears to be operating for similar reasons to produce a significant sex effect of the sibling environment with regard to spatial visualizing ability (Rice et al. 1980).

The combination of directly transmitted genetic and cultural factors and of shared and individual environmental effects operating to produce the observed variation in ventilatory capacity makes these traits true complex multifactorial phenomena. The degree of resemblance between any two individuals will depend upon a complex interaction of biological relatedness and shared environment, both in and out of the household. The multifactorial model presented here is, therefore, consistent with the results of twin studies of normal pulmonary function. Hubert et al. (1982) report an estimated heritability of $h^2 = 0.91$ for FVC and $h^2 = 0.77$ for FEV$_{1.0}$ from their study of MZ and DZ twins reared together. Man and Zamel (1976) report a similar finding from their twin study of maximum expiratory flow volume (MEFV). In both of these reports the authors subscribe to the hypothesis of Green, Mead and Turner (1974) that ventilatory capacity is determined in large part by the geometry of the large airways. This geometry has been shown to be under strong genetic influence and Green et al. suggest that subsequent variation in pulmonary function is non-genetic in nature. Our results tend to support further this contention, except in so far as we are unable to distinguish between genetic and cultural components of transmissibility using the XTAU model.

Finally, the results of the present study of family resemblance for normal pulmonary function, when viewed in the context of the multifactorial model, do shed some light on findings regarding pulmonary disorders that display strong familial patterns. Larson et al. (1970) reported that familial emphysema displayed a pattern of aggregation that could not be accounted for by the $\alpha_1$-antitrypsin deficiency. They suggest that both constitutional factors (i.e. inherited liability) and shared environmental factors (i.e. acquired liability) are operating independent of $\alpha_1$-antitrypsin deficiency to place relatives of affected individuals at higher risk. Similarly significant familial aggregations have been reported for chronic bronchitis, allergic rhinitis and
asthma (Higgins and Keller 1975, Tager et al. 1976). The pattern of allergic rhinitis, asthma and bronchitis noted by Higgins and Keller is congruent with that for FEV\(_{1.0}\) values in the same population. The true complex multifactorial model implicated for normal pulmonary function in this study translates directly into a multifactorial liability scale in which abnormal function represents one extreme. If genetic factors are responsible for normal large airway geometry, then variation in the same genetic factors will result in geometries which increase risk for pulmonary dysfunction. Such risk is then increased among those who share the abnormal geometry by descent as a consequence of the modifying effects of common familial environment.

Acknowledgements

This research was supported in part by grant No. AG01646-01 from the National Institutes of Health and by National Institute of Mental Health Post-Doctoral Training Grant No. MH-14677.

References


RICE, J., 1981, GENLIB: A Library of Computer Programs for the Genetic Analysis of Family Data (St Louis: Department of Psychiatry, Washington University School of Medicine and the Jewish Hospital of St Louis).


Address correspondence to: Dr E. J. Devor, Department of Psychiatry, The Jewish Hospital of St Louis, 216 S. Kingshighway Blvd., P.O. Box 14109, St Louis, Missouri 63178, USA.


Résumé. La ressemblance familiale pour la fonction pulmonaire normale telle que la Capacité Vitale Forcée et le Volume Expiratoire Forcé en une seconde est établie à l'aide d'un modèle d'analyse de piste qui incorpore les différences sexuelles de transmissibilité du phénotype des parents aux enfants ainsi que d'effet d'un milieu de fratrie corrélat et partagé. L'application de ce modèle, appelé XTAU, aux corrélations familiales indique que les facteurs transmissibles, qui peuvent être génétiques ou culturels, expliquent 20–30% de la variation de ces mesures. De plus, un effet prononcé spécifique de même sexe du milieu de fratrie est indiqué; il a élevé la corrélation observée entre germains de sexe opposé. Ces résultats sont cohérents avec les résultats d'études sur jumeaux de la fonction pulmonaire indiquant une héritabilité élevée pour chacune des FVC et FEV₁,₀. En outre, le modèle multifactoriel complexe de ressemblance familiale pour la fonction pulmonaire normale est montré avoir des implications pour spécifier des modèles causaux de désordres pulmonaires tels que l'asthme, la bronchite, la rhinite allergique et la maladie pulmonaire obstructive chronique.