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Multiple Regression Analysis of Twin Data: A Model-Fitting Approach

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The multiple regression methodology proposed by DeFries and Fulker (DF; 1985, 1988) for the analysis of twin data is compared with maximum-likelihood estimation of genetic and environmental parameters from covariance structure. Expectations for the regression coefficients from submodels omitting the h^2 *and* c^2 *terms are derived. Model comparisons similar to those conducted using maximum-likelihood estimation procedures are illustrated using multiple regression. Submodels of the augmented DF model are shown to yield parameter estimates highly similar to those obtained from the traditional latent variable model. While maximum-likelihood estimation of covariance structure may be the optimal statistical method of estimating genetic and environmental parameters, the model-fitting approach we propose is a useful extension to the highly flexible and conceptually simple DF methodology.*

KEY WORDS: multiple regression; twins; model-fitting; heritability.

INTRODUCTION

DeFries and Fulker (DF; 1985, 1988) proposed a multiple regression analysis of twin data that is very simple to employ, but also highly

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flexible. The basic model in which a cotwin's score is regressed on that of the proband's and the coefficient of relationship [1.0 for monozygotic (MZ) and 0.5 for dizygotic (DZ) twin pairs] provides a powerful test for genetic etiology in samples where the proband was ascertained because of a deviant score on a particular measure. The augmented model, in which the interaction term between the proband's score and the coefficient of relationship is added to the basic model, yields direct estimates of heritability (h^2) and shared environmental variance (c^2). With the addition of other interaction terms, this multiple regression model can be easily extended to test for differential heritability as a function of various independent variables such as age (Wadsworth *et al.*, 1989), gender (DeFries *et al.*, in press), and level of the phenotype (Detterman *et al.*, 1990; Cherny *et al.*, 1992). Using restriction fragment length polymorphism (RFLP) markers, the model has also been extended to detect linkage to quantitative trait loci (Fulker *et al.*, 1991). Due to its simplicity, ease of application, and flexibility, the DF method is now frequently employed as an alternative analysis of twin data (Plomin and Rende, 1991).

One apparent advantage to using conventional model-fitting procedures over DF analysis is that the estimates of h^2 and c^2 are constrained to be sensible; i.e., all proportion of variance components will not be negative or exceed unity. The DF method does not guarantee this to be the case. If, for example, the MZ correlation is more than twice the DZ correlation, the estimate of c^2 will be negative and that of h^2 may exceed unity. Conversely, if the DZ correlation exceeds the MZ correlation, the h^2 estimate will be negative. However, the DF methodology can be used to constrain estimates of h^2 and c^2 in a manner similar to the maximum-likelihood (ML) structural equations approach. Such constrained estimation of genetic and environmental parameters using the DF method was first reported by Cyphers *et al.* (1990).

The primary objectives of the present short report are threefold: (1) to derive expected regression coefficients when either h^2 or c^2 is constrained to be zero; (2) to compare estimates obtained using the DF method with those obtained from ML estimation of genetic and environmental parameters; and (3) to illustrate how the DF method can be used in a manner similar to the more conventional model-fitting procedures. Tests of h^2 and c^2 are available with both methods. We show that if either h^2 or c^2 is not significant, that parameter can be omitted from the model and the other parameter can be estimated under the constraint that the former is not present. This results in parameter estimates similar to those obtained from ML estimation under a similarly constrained model.

MODEL

The augmented DF regression model for estimating h^2 and c^2 is

$$C = b_3P + b_4R + b_5PR + A \tag{1}$$

where

C = cotwin's score
P = proband's score
R = coefficient of relationship (1.0 for MZ twins and 0.5 for DZ twins)
A = intercept

LaBuda *et al.* (1986) derived the expectations for the partial regression coefficients and showed that b_3 and b_5 yield unbiased estimates of c^2 and h^2, respectively. They formulated the regression equation in terms of the expected variances and covariances as

$$\mathbf{S}_X\mathbf{B} = \mathbf{S}_{XY} \tag{2}$$

where $\mathbf{S}_X$ is the expected covariance matrix among the independent variables and $\mathbf{S}_{XY}$ is the vector of expected covariances of the independent variables with the dependent variable. The expected regression coefficients, **B**, were derived by solution of Eq. (2):

$$\mathbf{B} = \mathbf{S}_X^{-1}\mathbf{S}_{XY} \tag{3}$$

The means of the MZ probands and DZ probands are expected to be equal and the MZ and DZ cotwin means are expected to equal those of the probands in an unselected sample. Under the assumption of equal means, the expected variances and covariances which LaBuda *et al.* derived for the augmented model reduce to

$$\mathbf{S}_X = \begin{array}{c} \\ P \\ R \\ PR \end{array} \begin{array}{c} \begin{array}{ccc} P & R & PR \end{array} \\ \left(\begin{array}{ccc} V_P & 0 & \dfrac{n_1 + n_2/2}{N} V_P \\ & 1/16 & 0 \\ & & \dfrac{n_1 + n_2/4}{N} V_P \end{array} \right) \end{array} \tag{4}$$

and

$$\mathbf{S}_{XY} = \begin{array}{c} \\ P \\ R \\ PR \end{array} \left(\begin{array}{c} C \\ \frac{n_1 + n_2/2}{N} V_A + V_C \\ 0 \\ \frac{n_1 + n_2/4}{N} V_A + \frac{n_1 + n_2/2}{N} V_C \end{array} \right) \tag{5}$$

where n_1 and n_2 are the number of MZ and DZ pairs, respectively, and $N = n_1 + n_2$.

If the interaction term is omitted from Eq. (1), the following equation results:

$$C = b_3 P + b_4 R + A \tag{6}$$

Omitting the last row and column from $\mathbf{S}_X$ and the last element of $\mathbf{S}_{XY}$ gives the expected covariance matrices of the variables in this model. Substituting these matrices into Eq. (2) and solving for **B** yields the following expectations for b_3 and b_4:

$$\mathbf{B} = \begin{array}{c} b_3 \\ b_4 \end{array} \left(\begin{array}{c} \frac{n_1 + n_2/2}{N} \frac{V_A}{V_P} + \frac{V_C}{V_P} \\ 0 \end{array} \right) \tag{7}$$

In the absence of genetic variance, the expectation for b_3 reduces to $V_C/V_P = c^2$.

Similarly, the b_3 term can be omitted from Eq. (1), resulting in the equation

$$C = b_4 R + b_5 PR + A \tag{8}$$

The expectations for b_4 and b_5 are derived in the same manner as the expectations for b_3 and b_4 in Eq. (6). Omitting the first row and column from $\mathbf{S}_X$ and the first element of $\mathbf{S}_{XY}$ gives the expected covariance matrices of the variables in this model. Substituting these matrices into Eq. (2) and solving for **B** yield the following expectations for b_4 and b_5:

$$\mathbf{B} = \begin{array}{c} b_4 \\ b_5 \end{array} \begin{pmatrix} 0 \\ \dfrac{V_A}{V_P} + \dfrac{n_1 + n_2/2}{n_1 + n_2/4} \dfrac{V_C}{V_P} \end{pmatrix} \tag{9}$$

In the absence of shared environmental variance, the expectation for b_5 reduces to $V_A/V_P = h^2$.

METHOD

Subjects were 110 MZ and 75 same-sex DZ twin pairs constituting the control sample from the Colorado Reading Project (DeFries *et al.*, 1991). Equations (1), (6), and (8) were fitted to Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974) Full-Scale IQ data and to data from the Reading Comprehension and Reading Recognition subscales of the Peabody Individual Achievement Test (PIAT; Dunn and Markwardt, 1970). Each twin's score was entered twice—once as proband and once as cotwin. In an unselected population such as this, either member of the pair could be designated the proband. In such a situation, parameter estimates using the DF models with double-entered data are unbiased. Of course, standard errors must then be adjusted for the correct degrees of freedom by multiplying them by $\sqrt{(df \text{ double-entered}/df \text{ single-entered})}$.

ML estimates of h^2, c^2, and e^2 were also obtained by fitting the standard G, C, E model (see, e.g., Heath *et al.*, 1989; Neale *et al.*, 1989) to the observed twin variance/covariance matrices (from single-entered data) using the structural equations program LISREL (Jöreskog and Sörbom, 1989). Models omitting, and therefore testing for, h^2 and c^2, corresponding to the models estimated using Eqs. (6) and (8), were also fitted to the data.

RESULTS AND DISCUSSION

The MZ and DZ variance/covariance matrices for all three measures, along with the correlations, are presented in Table I.

The results from both the DF and the ML model-fitting procedures for the WISC-R and PIAT Reading Comprehension (RC) and Reading Recognition (RR) data are presented in Tables II, III, and IV, respec-

Table I. Variance/Covariance Matrices with Correlations Above the Diagonals

	WISC-R		Reading comprehension		Reading recognition	
	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2
MZ						
Twin 1	140.0	.80	56.1	.47	38.1	.60
Twin 2	103.9	119.7	26.5	56.2	23.7	41.5
DZ						
Twin 1	109.0	.54	60.3	.39	36.0	.25
Twin 2	58.5	107.6	22.4	54.9	8.6	32.7

Table II. Model Comparisons Using the Two Methods: Full-Scale IQ

Model	h^2	c^2	e^2	NPAR	R^2/χ^2	$F/\Delta\chi^2$	df	p
Full								
DF	.52	.28	.20	3	.518			
ML	.43	.36	.21	3	2.87			
Drop h^2								
DF	.00	.70	.30	2	.502	5.83	1,181	$<.02$
ML	.00	.71	.29	2	13.92	11.05	1	$<.001$
Drop c^2								
DF	.83	.00	.17	2	.512	2.26	1,181	$>.10$
ML	.79	.00	.21	2	6.81	3.94	1	$<.05$

Table III. Model Comparisons Using the Two Methods: Reading Comprehension

Model	h^2	c^2	e^2	NPAR	R^2/χ^2	$F/\Delta\chi^2$	df	p
Full								
DF	.15	.31	.54	3	.190			
ML	.18	.29	.52	3	0.22			
Drop h^2								
DF	.00	.43	.57	2	.189	0.32	1,181	$> .55$
ML	.00	.44	.56	2	0.88	0.66	1	$> .40$
Drop c^2								
DF	.51	.00	.49	2	.182	1.87	1,181	$> .15$
ML	.50	.00	.50	2	2.15	1.93	1	$> .15$

tively. Estimates of h^2, c^2, and e^2 are similar using both methods of estimation, except for RR, where the MZ correlation exceeds twice the DZ correlation, resulting in a negative estimate of c^2 using the DF method.

Table IV. Model Comparisons Using the Two Methods: Reading Recognition

Model	h^2	c^2	e^2	NPAR	R^2/χ^2	$F/\Delta\chi^2$	df	p
Full								
DF	.73	−.13	.40	3	.249			
ML	.58	.00	.42	3	1.34			
Drop h^2								
DF	.00	.46	.54	2	.219	7.42	1,181	$< .01$
ML	.00	.47	.53	2	8.75	7.41	1	$< .01$
Drop c^2								
DF	.58	.00	.42	2	.248	0.34	1,181	$> .55$
ML	.58	.00	.42	2	1.34	0.00	1	1.00

The differences in parameter estimates may be attributed to differences in the ways the two estimation procedures pool, or equate, MZ, DZ, Twin 1, and Twin 2 variances. As expected, the two methods yield virtually identical parameter estimates (except for the RR data) when the ML models are fit to correlations rather than covariances.

Tests of h^2 and c^2 using the DF method were conducted via F test of the difference in squared multiple correlations (R^2) between the full model and the model without the h^2 or c^2 term in the equation. This is analogous to the difference chi-square test of ML model-fitting. These F statistics were computed using the true (single-entered) sample size rather than the double-entered sample size. The DF and ML tests yielded the same conclusions in all but one instance.

For the WISC-R data, the tests of dropping h^2 from the model, using both procedures, yielded the same conclusion: there is significant genetic variance. It appears that the ML method yields a more powerful test, since the significance level for h^2 is $p < .001$ using ML but only $p < .02$ using the DF method. The estimates of c^2 from the model omitting h^2, using both methods, were virtually identical (.70 vs. .71).

The DF and ML procedures also yielded highly similar estimates of h^2 (.83 vs. .79) when c^2 was dropped from the augmented model of the WISC-R data. However, the significance tests for c^2 were again somewhat different. The DF method yielded the conclusion that the shared environmental component did not account for a significant proportion of variance. In contrast, dropping c^2 from the model resulted in a significant change in chi-square when the ML procedure was employed. Again, ML appears to result in a statistically more powerful test.

That the ML tests are more powerful than those of the DF method, thereby making the DF method more conservative, appears to be a function of the size of the MZ and DZ correlations. For relatively high correlations, ML tends to result in a more powerful test. This difference in power is negligible when the MZ and DZ correlations are smaller, as illustrated by the results from the PIAT data.

The DF and ML tests of dropping h^2 from the model for the PIAT RC data again yielded the same conclusion. In this case, there is no significant genetic variance to these data. The significance levels were somewhat similar ($p > .55$ vs. $p > .40$), but with the ML test again being more powerful. The DF and ML estimates of c^2 from the models omitting h^2 were again highly similar (.43 vs. .44).

Tests of dropping c^2 from the model of the RC data also yielded the same conclusion from both the DF and the ML methods. There was no significant c^2 in these data and the significance levels were highly similar for both methods ($p > .15$). The estimates of h^2 from the models omitting c^2 were again highly similar (.51 and .50).

The DF and ML tests of dropping h^2 for the PIAT RR data were also consistent in their conclusions: significant genetic variance is present. The significance levels were highly similar in this case ($p < .01$ for both methods). The estimates of c^2 for the DF and ML models omitting h^2 were also virtually identical (.46 vs. .47).

Because the MZ correlation for the RR data is greater than twice the DZ correlation, fitting the full DF model results in a negative estimate of c^2, whereas the full ML model constrains this estimate to equal zero. Thus, in this case, the change in chi-square due to dropping c^2 from the full model is zero. Nevertheless, when the c^2 term is omitted from the model, the DF and ML methods yield identical estimates of h^2 (.58).

A primary objective of the present report was to illustrate how the multiple regression analysis of twin data can be employed to test more parsimonious alternative models. When initial tests of genetic and shared environmental parameters suggest that either h^2 or c^2 is not significant, that term can be omitted from the augmented model equation and the other parameter can be estimated under the constraint that the omitted component does not account for any of the phenotypic variance. It has been shown that these constrained estimates of h^2 and c^2 are unbiased. Furthermore, results obtained from analyses of several different data sets suggest that estimates obtained from constrained DF multiple regression models are similar to those obtained from conventional model-fitting procedures and tests of the resulting parameter estimates yield similar conclusions in most instances.

REFERENCES

Cherny, S. S., Cardon, L. R., Fulker, D. W., and DeFries, J. C. (1992). Differential heritability across levels of cognitive ability. *Behav. Genet.* **22**:153–162.

Cyphers, L. H., Phillips, K., Fulker, D. W., and Mrazek, D. A. (1990). Twin temperament during the transition from infancy to early childhood. *J. Am. Acad. Child Adoles. Psychiat.* **29**:392–397.

DeFries, J. C., and Fulker, D. W. (1985). Multiple regression analysis of twin data. *Behav. Genet.* **15**:467–473.

DeFries, J. C., and Fulker, D. W. (1988). Multiple regression analysis of twin data: Etiology of deviant scores versus individual differences. *Acta Genet. Med. Gemellol.* **37**:205–216.

DeFries, J. C., Olson, R. K., Pennington, B. F., and Smith, S. D. (1991). Colorado Reading Project: An update. In Duane, D. D., and Gray, D. B. (eds.), *The Reading Brain: The Biological Basis of Dyslexia*, York Press, Parkton, MD, pp. 53–87.

DeFries, J. C., Gillis, J. J., and Wadsworth, S. J. (in press). Genes and genders: A twin study of reading disability. In Galaburda, A. M. (ed.), *The Extraordinary Brain: Neurobiologic Issues in Developmental Dyslexia*, Harvard University Press, Cambridge, MA.

Detterman, D. K., Thompson, L. A., and Plomin, R. (1990). Differences in heritability across groups differing in ability. *Behav. Genet.* **20**:369–384.

Dunn, L. M., and Markwardt, F. C. (1970). *Examiner's Manual: Peabody Individual Achievement Test*, American Guidance Service, Circle Pines, MN.

Fulker, D. W., Cardon, L. R., DeFries, J. C., Kimberling, W. J., Pennington, B. F., and Smith, S. D. (1991). Multiple regression analysis of sib-pair data on reading to detect quantitative trait loci. *Read. Writ. Interdisciplin. J.* **4**:107–121.

Heath, A. C., Neale, M. C., Hewitt, J. K., Eaves, L. J., and Fulker, D. W. (1989). Testing structural equation models for twin data using LISREL. *Behav. Genet.* **19**:9–35.

Jöreskog, K. G., and Sörbom, D. (1989). *LISREL 7: A Guide to the Program and Applications*, 2nd ed., SPSS, Inc., Chicago.

LaBuda, M. C., DeFries, J. C., and Fulker, D. W. (1986). Multiple regression analysis of twin data obtained from selected samples. *Genet. Epidemiol.* **3**:425–433.

Neale, M. C., Heath, A. C., Hewitt, J. K., Eaves, L. J., and Fulker, D. W. (1989). Fitting genetic models with LISREL: Hypothesis testing. *Behav. Genet.* **19**:37–49.

Plomin, R., and Rende, R. (1991). Human behavioral genetics. *Annu. Rev. Psychol.* **42**:161–190.

Wadsworth, S. J., Gillis, J. J., DeFries, J. C., and Fulker, D. W. (1989). Differential genetic aetiology of reading disability as a function of age. *Irish J. Psychol.* **10**:509–520.

Wechsler, D. (1974). *Manual for the Wechsler Intelligence Scale for Children—Revised*, Psychological Corp., New York.

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