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Estimating Genetic Influences on the Age-at-Menarche: A Survival Analysis Approach

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A survival analysis regression model is described for analyzing twin data on the age-at-menarche. The model includes latent genetic and environmental covariates and allows one to test hypotheses regarding the nature of familial aggregation for age-at-onset. Additionally, the model accommodates a variety of baseline survival distributions and therefore may be used to test different developmental hypotheses. Model-fitting results indicate that a survival model with a baseline gamma distribution gives an adequate fit to recalled age-at-menarche of 1,888 pairs of Australian female monozygotic and dizygotic twins. Further, results show that additive genetic and dominance genetic effects contribute to shared variation in age-at-menarche. If there are common environmental influences on the timing of menarche, they are completely obscured by nonadditivity in genetic factors, and information from other relationships would be required to detect their effect.

KEY WORDS: twins, gamma distribution, correlated ages-of-onset

INTRODUCTION

Two approaches have been used previously to study genetic influences on the age-at-menarche. The first has been to test the significance and compare the magnitude of intrapair similarity measures (intraclass correlations, product-moment correlations, or intrapair mean-differences) computed from mother-daughter or twin data sets [Popenoe, 1928; Kantero and Widholm, 1971; Gedda and Brenci, 1975; Fishbein, 1977; Garn and Bailey, 1978]. Results from these studies have indicated a familial aggregation of pubertal timing, which, to some extent, is attributable to genetic effects. However, the magnitude of these effects remains unknown. Although in some cases Holzinger's [1929] heritability estimate has been derived from monozygotic (MZ) and dizygotic (DZ) twin correlations [Gedda and Brenci, 1975], the estimator may be biased due to its insensitivity to sampling variance and between family environmental influences [Nichols, 1965; Jinks and Fulker, 1970]. As a consequence, this heritability estimate offers little in its predictive power.

The second approach to studying genetic influences on menarche has been to use maximum likelihood model-fitting methods [Eaves et al., 1978] on twin data sets to estimate and test the significance of genetic and environmental components of phenotypic variance [van den Akker et al., 1987; Treloar and Martin, 1990]. Because it yields unbiased heritability estimates and allows the testing of specific inheritance hypotheses, this method is to be preferred over similarity comparisons. However, current approaches to model-fitting have limitations: they assume normality of age-at-menarche, and they are not easily applied to data sets with censored observations (i.e., individuals who have not yet begun to menstruate). Moreover, the methods do not allow the testing of developmental hypotheses regarding the mechanisms through which the familial age-at-onset correlation arises.

With the shortcomings of the previous methods in mind, we suggest a new approach to the analysis of twin data on the age-at-menarche. Here, survival analysis methods, introduced by Meyer and Eaves [1988], are used to model the age-at-menarche as a failure-time. Twin correlations between failure-times are parameterized by including latent genetic and environmental effects in a failure-time regression model. Additionally, a developmental hypothesis is tested by adopting the gamma distribution as the baseline distribution of the regression model. This age-at-onset model is then applied to the recalled age-at-menarche of 1,888 pairs of Australian female twins.

MATERIALS AND METHODS

Subjects and Items

The Australian National Health and Medical Research Council (NH&MRC) twin data base has been

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described in detail by others [Jardine et al., 1984; Martin and Jardine, 1986]. Briefly, between November 1980 and March 1982, questionnaires were mailed to 5,967 adult (ages 18 to 88 years) twin pairs from the volunteer Australian NH&MRC Twin Register. After reminders were sent to non-respondents, questionnaires were returned by 3,810 complete twin pairs, representing a 64% pairwise response rate. Of the respondents, 1,984 were female-female pairs.

Zygosity was diagnosed through questionnaire items regarding physical similarity and confusion in recognition by others [Jardine et al., 1984]. When compared to blood-typing, this method of zygosity determination has been found to be approximately 95% accurate in other twin populations [Nichols and Bilbro, 1966; Kasriel and Eaves, 1976]. From the questionnaire responses, 1,233 female-female pairs were diagnosed as MZ twins, while 751 were determined to be DZ.

The female twins were asked to complete several items regarding their reproductive history. These included items on menstrual history, contraceptive use, pregnancy, and childbearing. One of the menstrual items was "How old were you when you had your FIRST menstrual period?" The twins were asked to give both the year and month at menarche; 1,178 complete MZ and 711 complete DZ pairs noted *at least* the year in which their periods began. A genetic analysis of the covariance structure of these items has been described by Treloar and Martin [1990].

A subset of 67 individuals who had responded to the main questionnaire had previously (about 3 months earlier) completed a pilot questionnaire. A test-retest correlation of 0.91 ± 0.13 ($P < 0.001$) indicates that the self-reports of age-at-menarche are quite reliable over the 3 month interval. Unfortunately, we had no means of assessing the validity of the responses.

A Survival Analysis Model for Correlated Ages-at-onset

The failure-time regression model. A survival model for the analysis of familial age-at-onset data has been described previously by Meyer and Eaves [1988] and Meyer [1989]. In essence, the accelerated failure-time model (a regression model commonly used in survival analysis) is modified to include *latent* genetic and environmental covariates. The basic accelerated failure-time model makes use of the fact that parametric survival models are linear in $Y = \log T$, where T is a non-negative random variable representing an individual's time to failure [Kalbfleisch and Prentice, 1980]. Specifically, a general linear model for Y is

$$Y = -\log \mu + \sigma^{-1} W \qquad (1)$$

where μ and σ are parameters of the survival distribution of interest (e.g., the log-normal, exponential, Weibull, or gamma) and W is a random error term, with density defined by the parameters of the baseline distribution. To include covariates in this model, $\log\mu$ is replaced with $\alpha + z\beta'$, with α being a scaling parameter for the population, z, a row vector of s covariates [$z = (z_1, \ldots, z_s)$] and β the corresponding vector of regression coefficients. As a consequence, the covariates act additively on log failure-time or multiplicatively on the failure-time itself. They effectively accelerate or decelerate an individual's progression along the time axis by increasing or decreasing the value of $\log\mu$.

To introduce latent heterogeneity in an accelerated failure-time model, the existence of a latent "aging" covariate, z, is postulated. For a multifactorial age-at-onset model, it is assumed that z is influenced by a large number of genetic and environmental effects. If these effects act additively and independently, and if there is random mating for factors that influence pubertal timing, then quantitative genetic theory predicts that the distribution of z will tend towards normality as the number of influencing factors approaches infinity [Fisher, 1918]. For convenience, we assume that the latent aging covariate is $N(0, 1)$.

In a pair of relatives, latent aging covariates z_1 and z_2 follow a bivariate normal distribution with correlation r [denoted $\phi(z_1, z_2; r)$]. The correlation reflects familial aggregation for age-at-onset. If ages-at-onset are available from informative pairs of relatives, then r may be partitioned into genetic and environmental sources of shared variation. As an example, the path diagram [Wright, 1934] in Fig. 1 indicates additive genetic (A), dominance genetic (D), shared environmental (CE), and specific environmental (SE) effects on z in MZ and DZ twins. Assuming there is no genotype-environment interaction, genotype-environment covariation or assortative mating, then, from Fig. 1, expected MZ and DZ, twin correlations for the latent aging covariates are easily derived. By the rules of path analysis, $r_{mz} = h^2 + c^2 + d^2$ and $r_{dz} = 1/2h^2 + c^2 + 1/4d^2$, while var $z = h^2 + c^2 + d^2 + e^2$. Since estimates of d^2 and c^2 are confounded in data from twins reared together [Eaves, 1970; Martin et al., 1978], the MZ and DZ age-at-onset correlations may be parameterized in terms of h^2 and c^2 *or* h^2 and d^2. In either case, the difference between a variance of unity and the expected MZ correlation yields an estimate of e^2.

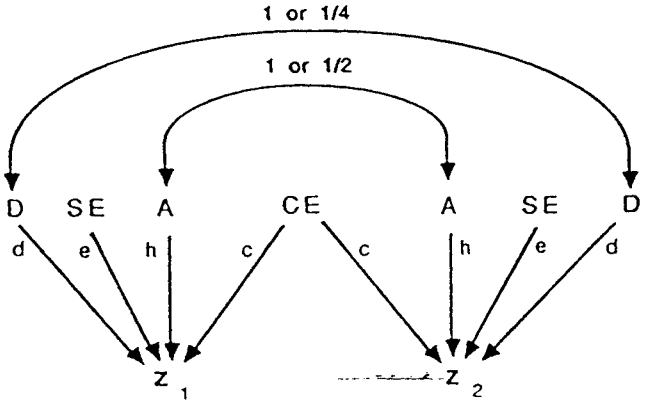

Fig. 1. Path diagram indicating dominance genetic (D), specific environmental (SE), additive genetic (A), and common environmental (CE) effects on latent aging covariates in twin pairs. *d*, *e*, *h*, and *c* are the corresponding path coefficients for these effects. The MZ additive and dominance genetic correlations are both equal to 1.0, while the DZ additive and dominance genetic correlations are equal to 0.5 and 0.25, respectively.

Baseline distribution and likelihood formulations. The method of maximum likelihood may be used to estimate the parameters of the accelerated failure-time model with latent covariates once a baseline distribution has been chosen. Although any one of a number of survival distributions could be used for this purpose, we have hypothesized [Meyer and Eaves, 1988; Meyer, 1989] that age-at-onset is determined by a gamma or multiple hit process. The reasons for choosing this distribution are threefold: it has been used previously by geneticists to describe the age-at-onset of mitral valve prolapse [Strahan et al., 1983], Alzheimer disease [Chase et al., 1983; Breitner et al., 1986], and death [Murphy, 1978; Murphy et al., 1987]; the parameters which define the distribution are heuristically appealing; and the distribution provides a flexible, positively skewed density function over a positive range of values. The latter two of these reasons are detailed below.

In a gamma process, a number of insults or "hits" (γ) must occur prior to the "failure" of an organism or product of interest. These hits occur independently, with the inverse of the mean waiting-time between hits given by μ, the distribution's rate parameter. The gamma distribution is thus equivalent to the convolution of γ identical exponential processes [Murphy, 1978].

When a gamma distribution is specified in the accelerated failure-time model (equation 1), σ is fixed to 1.0, μ is simply the inverse of the mean waiting-time between the hits of the process, and the value of γ determines the mean and variance of the random error term W [Kalbfleisch and Prentice, 1980]. Specifically, as γ increases, the mean of W increases while the variance decreases due to an individual's age-at-onset becoming a better index of the rate prameter.

Given μ and the number of hits, γ, the gamma probability density function (p.d.f.) at time t is

$$f(t) = \frac{\mu(\mu t)^{\gamma-1}\exp(-\mu t)}{\Gamma(\gamma)} \tag{2}$$

where the gamma function, $\Gamma(\gamma)$, is equal to $\int_0^\infty v^{\gamma-1}\exp(-v)dv$, which is equivalent to $(\gamma - 1)!$ for integer values of γ [Kalbfleisch and Prentice, 1980]. The skewness of the distribution decreases with increasing γ: when $\gamma = 1$, the distribution is exponential, as $\gamma \to \infty$, it approaches normality [Bartlett and Kendall, 1946]. Because of this relationship between γ and skewness, γ is termed the shape parameter of the distribution. On the other hand, μ is a scaling parameter. Decreases in μ result in increases in the mean and variance of the distribution but do not affect its higher moments.

In this application, an individual's failure-time is equivalent to her age-at-menarche. Hits of the gamma distribution, then, may be thought of as biological events that occur prior to menarche, such as hormonal or steroidal changes. The parameter μ, on the other hand, is hypothesized to reflect the rate at which these events occur. One possible determinant of μ is an individual's metabolic rate [Cameron et al., 1985]. If individual differences exist in metabolic rate or any other factor that contributes to the production of hormones or steroids, then the rate parameter μ will vary in the population and, using the accelerated failure-time model discussed previously, may be parameterized in terms of $\exp(\alpha + z\beta)$.

With the introduction of a covariate, equation 2 is rewritten as

$$f(t;z) = \frac{\exp(\alpha + z\beta)(\exp(\alpha + z\beta)t)^{\gamma-1}\exp(-\exp(\alpha + z\beta)t)}{\Gamma(\gamma)} \tag{3}$$

From this, the likelihood of observing N ages-at-onset or ages-at-observation (i.e., censored observations) (t_i, $i = 1, \ldots, N$), each with latent aging covariate z_i, may be formulated. As noted previously, we use a multifactorial model for the latent covariate z and assume that z is $N(0, 1)$. Additionally we assume independent censoring, or censoring that does not depend upon the value of the covariate or the individual's time to failure [Kalbfleisch and Prentice, 1980]. The likelihood (with respect to γ, α, and β) is then

$$L(\gamma, \alpha, \beta) = \prod_{i=1}^{N}\int_{-\infty}^{\infty}\phi(z_i)f(t_i;z_i)^{k_i}S(t_i;z_i)^{1-k_i}dz_i \tag{4}$$

where $\phi(z_i)$ is given by the standard normal p.d.f., k_i is an indicator variable [$k_i = 1$ if t_i is a failure-time; $k_i = 0$ if t_i is a (censored) survival time], and $S(t_i; z_i)$ is the gamma survival function, or the probability that an individual will survive longer than t_i. $S(t_i; z_i)$ is equivalent to 1 minus the cumulative probability of failure by time t_i or

$$1 - \frac{\int_0^s x^{\gamma-1}\exp(-x)\,dx}{\Gamma(\gamma)}$$

where $s = (\exp(\alpha + z_i\beta)t_i)$ [Kalbfleisch and Prentice, 1980].

Similarly, the joint likelihood of observing N pairs of related individuals with correlated latent aging covariates z_{1i} and z_{2i}; ages-at-onset or ages at observations t_{1i} and t_{2i}; and indicator variables k_{1i} and k_{2i} ($i = 1, \ldots, N$) is

$$L = \prod_{i=1}^{N}\int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\phi(z_{1i}, z_{2i}; r)f(t_{1i};z_{1i})^{k_{1i}}S(t_{1i};z_{1i})^{1-k_{1i}} f(t_{2i};z_{2i})^{k_{2i}}S(t_{2i};z_{2i})^{1-k_{2i}}dz_{2i}\,dz_{1i} \tag{5}$$

Equation 5 may be maximized with respect to α, β, γ, and r or, alternatively, with informative data sets, r may be parameterized in terms of shared genetic and environmental components of variance and the likelihood maximized with respect to these parameters.

Computation

A FORTRAN program (GAMEST) was written to minimize the negative logarithm of the marginal and joint likelihoods in equations 4 and 5. GAMEST utilizes

subroutines from the Numerical Algorithms Group (N.A.G.) [1988] software library for integration and minimization purposes. Subroutine D01FBF evaluates the integrals with Gauss-Hermite quadrature, while subroutine E04JBF uses a quasi-Newton algorithm for minimization. We have used GAMEST on simulated data sets with and without censored observations and have found it to yield fairly accurate and precise parameter estimates [Meyer and Eaves, 1988; Meyer, 1989].

GAMEST computes the matrix of information realized at the final solution with a numerical procedure outlined by Davis and Polonsky [1965]. The matrix may then be inverted, resulting in approximate variances and covariance for the parameter estimates. Standard errors derived from these variances may be used in the standard normal test statistic for hypothesis testing about $\hat{\alpha}$ and $\hat{\beta}$; however, the asymmetries of the likelihood surfaces with respect to $\hat{r}$ and $\hat{\gamma}$ indicate that the likelihood ratio statistic is more appropriate for hypothesis testing about these parameters [Meyer, 1989].

Data Analysis

For the analyses described below, it was assumed that the twins, who were all at least 18 years old at the time of questionnaire completion, had passed through the normal population's "risk period" for the onset of menstruation. Non-responses to the menarche item were therefore assumed to be due either to: 1) a true (but abnormal) absence of menarche; or 2) a failure to respond, even though menstruation had begun. Both cases were considered to be contaminants of the data set and were thus discarded rather than treated as censored observations. Further, in all analyses, age-at-onset was treated as a continuous variable, given in decimal years. This treatment, however, was not strictly correct since many individuals (1,400 MZ and 851 DZ) only noted the year, and not the month, at menarche. Properly, when only age in years is available, it should be treated as a discrete variable, and the marginal and joint likelihoods in equations 4 and 5 should be adjusted accordingly to integrate over all possible ages in an age category. However, this adjustment would have greatly increased computing time, which was already at a maximum. Thus, we assumed that age-at-onset was continuously distributed, while noting that specific environmental effects on age-at-onset (error variance) may increase and twin correlations, decrease, due to the failure to account for the discrete nature of the data.

Comparing MZ and DZ marginal distributions. One prediction under the multifactorial model described above is that MZ and DZ marginal age-at-onset distributions will not differ. Failure of this prediction would indicate that the simple genetic and environmental model used to account for within and between pair variation is not appropriate, and an alternative hypothesis must be considered. In order to test the equivalency of MZ and DZ age-at-onset distributions, the FORTRAN program GAMEST was used to maximize the logarithm of the marginal likelihood in equation 4 for the zygosity groups separately and jointly. A likelihood ratio chi-square test was then used to compare the two models. This test statistic has 3 degrees of freedom and is equal to twice the difference of the sum of the log-likelihoods for the separate zygosity groups (a six parameter model) and the log-likelihood for the combined groups (a three parameter model). It should be noted that this comparison will lead to more type I errors than expected from a chosen significance level. This is due to the fact that the correlation between observations has not been modeled and, as a result, the standard errors for the parameter estimates will actually be greater than those computed [Cox and Oakes, 1984]. Consequently, the test for an MZ/DZ distributional differences is liberal.

The goodness-of-fit of the more appropriate marginal model (i.e., the model with either separate or joint zygosity parameters) was assessed with a chi-square test by comparing observed and expected frequencies of ages-at-onset for each of nine age-at-onset categories. Expected frequencies were calculated by integrating the likelihood in equation 4 (with maximum likelihood estimates of α, β, and γ) between age-at-onset categories. Chi-square tests were then carried out separately on the marginal distributions of the first and second born twins, since a test on the combined marginal distributions may lead to an erroneous rejection of the gamma model due to the correlation between observations.

Fitting bivariate models and testing inheritance hypotheses. Using the program GAMEST, the logarithm of the likelihood in equation 5 was first maximized with respect to γ, α, β, r_{mz}, and r_{dz}. A second model was then fit that again included γ, α, and β but parameterized r_{mz} and r_{dz} in terms of genetic and environmental variance components. As pointed out previously, these parameterizations may include *either* additive genetic (A) and dominance genetic (D) effects *or* additive genetic and common environmental effects (CE), but may not include all three variance components. The choice of an A, D model or an A, CE model was guided by the estimates of the latent aging correlations. Specifically, if $\hat{r}_{dz}$ was less than $0.5\hat{r}_{mz}$, the correlations were parameterized in terms of additive genetic and dominance genetic effects, while if $\hat{r}_{dz}$ was greater than $0.5\hat{r}_{mz}$, an additive genetic and common environmental model was fit. (The reverse parameterizations were not considered since they would yield negative estimates of variance components.) One of the alternative models then served as a full model against which reduced models (with only additive genetic or common environmental effects) were compared by likelihood ratio chi-square tests. If the reduced model did not give a significantly worse fit to the data than the full model, it was chosen as the best model; otherwise, the full model was accepted. Since it is very unlikely biologically [Eaves, 1988], we did not consider a reduced model with only dominance genetic effects.

RESULTS

Summary statistics for both zygosity groups are given in Table I. Of note is the significant positive skewness in all marginal distributions. The Kolmogorov D statistic indicates that none of these distributions are normal, with $P < 0.01$ in all cases.

When gamma accelerated failure-time models were fitted to the marginal distributions of responses from

TABLE I. Summary Statistics for the Age-at-Menarche of Australian Twins*

	Monozygotic		Dizygotic	
	Twin 1	Twin 2	Twin 1	Twin 2
N	1178	1178	711	711
Mean	13.13 (1.43)	13.14 (1.43)	13.14 (1.37)	13.10 (1.42)
Skewness	0.46 (0.07)	0.40 (0.07)	0.15 (0.09)	0.26 (0.09)
Kurtosis	3.99 (0.15)	3.45 (0.15)	3.15 (0.18)	3.06 (0.18)
$Corr_{T1\text{-}T2}$[a]	0.65		0.18	

* Twins 1 and 2 denote first and second born twins. For means, standard deviations are in parentheses; for coefficients of skewness and kurtosis, standard errors are in parentheses.
[a] The twin product-moment correlation.

MZ and DZ twins jointly and separately, a likelihood ratio chi-square test indicated that the distributions for the two zygosity groups did not differ significantly ($\chi^2_3 = 1.49, P = 0.68$). Therefore, a basic assumption of the hypothesized multifactorial inheritance model has not been violated. For the model fitted to data from both zygosity groups, maximum likelihood estimates of γ, α, and β were 461.3 ± 10.0, 3.54 ± 0.01, and 0.0936 ± 0.0014, respectively. The standard normal test statistic indicates that β is significant ($Z = 66.8$; $P < 0.001$), suggesting that there are individual differences in the rate parameter of the gamma distribution.

Goodness-of-fit tests indicated that the gamma accelerated failure-time model provides a marginal fit to the data from first born twins ($\chi^2_5 = 11.25, P = 0.047$) and an adequate fit to the data from second born twins ($\chi^2_5 = 6.64, P = 0.25$). Observed and expected cell frequencies for each of nine age-at-onset categories are shown in Table II. Of note is the overestimate of twins with ages-at-menarche between 15 and 16 years, and the underestimate of twins with ages-at-menarche between 16 and 17 years.

The bivariate model-fitting results are shown in Table III. In model I, we have estimated r_{mz} and r_{dz} as well as the parameters of the gamma log-linear model. The estimates of α, β, and γ are quite similar to those obtained from the marginal analysis, and using the standard normal test statistic, are all significant ($P < 0.001$). Noteworthy is the fact that the latent aging correlations ($\hat{r}_{mz}$ and $\hat{r}_{dz}$) are both greater than the observed age-at-onset correlations. This is expected since, in the log-linear model (equation 1), Y, the logarithm of time to failure, is a function of the shared aging effect as well as a random effect, W.

TABLE II. Observed and Expected Cell Frequencies for Age-at-Menarche Under the Gamma Accelerated Failure-Time Model

Age-at-menarche (t, in years)	Expected	Observed	
		Twin 1[a]	Twin 2[b]
$t < 10$	6	7	8
$10 \le t < 11$	53	49	49
$11 \le t < 12$	225	218	223
$12 \le t < 13$	460	459	467
$13 \le t < 14$	522	545	528
$14 \le t < 15$	368	372	361
$15 \le t < 16$	174	146	157
$16 \le t < 17$	61	77	76
$t > 17$	20	16	20

[a] $\chi^2_5 = 11.25, P = 0.047$.
[b] $\chi^2_5 = 6.64, P = 0.25$.

TABLE III. Gamma Associated Failure-Time Model-Fitting Results for the Age-at-Menarche of Australian Twins†

Parameters	Maximum likelihood estimates		
	Model I	Model II	Model III
r_{mz}	0.71 (0.01)	—	—
r_{dz}	0.22 (0.04)	—	—
h^2	—	0.17 (0.11)	0.71 (0.01)
d^2	—	0.54 (0.18)	—
e^2	—	0.29	0.29
α	3.56 (0.02)	3.56 (0.02)	3.54 (0.04)
β	0.097 (0.002)	0.097 (0.002)	0.097 (0.001)
γ	459 (13)	459 (13)	449 (12)
$-2LR$[a]	—	—	10.3[b]

† Standard errors are given in parentheses.
[a] $-2LR$ is the likelihood ratio criterion against the full model.
[b] $P < 0.01$.

In considering an inheritance model for the latent aging correlations, we noted that $\hat{r}_{dz}$ was less than $0.5\hat{r}_{mz}$. It was therefore more appropriate to parameterize the correlations in terms of additive and dominance genetic effects rather than additive genetic and common environmental effects. The parameter estimates under this full genetic model (model II, Table III) indicate that dominance genetic effects account for 54% of the total variance of z, while additive genetic effects account for only 17%. An estimate of the specific environmental variance component is obtained by subtracting the total genetic variance from 1, yielding an estimate of 29%. When a reduced model with only additive genetic effects (model III) is compared to the full model by a likelihood ratio chi-square test, the statistic indicates that the reduced model provides a significantly worse fit to the data ($\chi^2_1 = 10.31, P < 0.001$). Consequently, we accept the full genetic model as the best model.

DISCUSSION

The survival model we have described allows for individual differences in developmental mechanisms and provides a framework for testing hypotheses regarding the nature of these differences. Certainly, parameter estimates of the gamma distribution, or any other baseline distribution, will not have a strict biological interpretation due to the complexity of the physiological changes occurring prior to menarche and the relative simplicity of the parametric processes. However, the estimates may provide some insight into development and

allow us to make distributional and correlational predictions for other data sets.

Not surprisingly, our model-fitting results suggest that a large number of events (γ) occurs prior to menarche. Attempting to account for each of these hits would certainly be a formidable, and unreasonable, task. Instead, insight into the appropriateness of the gamma distribution could be gained by estimating γ from additional data sets to determine whether the *complexity* of the developmental process, rather than the *speed*, is a replicable phenomenon. Further, other developmental milestones, highly correlated with the age-at-menarche, could be modeled to determine whether the relative timing of these events is paralleled in the relative estimates of γ.

Additional model-fitting results from both the marginal and bivariate analyses yield a significant estimate of β, suggesting that individual differences do exist in the inverse of the *mean* waiting-time between the hits of the gamma process. However, it is the extent to which these differences contribute to variability in Y (the logarithm of age-at-onset), versus the extent to which variability in Y is due to *within individual variability* in the waiting time between hits, which is perhaps of greater interest to the geneticist. This contribution of the latent aging covariate to total variation in Y is derived from equation 1 and given by the ratio $\beta^2/(\beta^2 + \text{var}(W))$. (As noted in our discussion of the baseline gamma distribution, var(W) depends upon γ, decreasing with increasing values of the parameter.) For the maximum likelihood parameter estimates of model I (Table III), the ratio above is equal to 0.81. Thus, under the gamma model, most of the variation in age-at-onset can, in fact, be ascribed to individual differences in μ.

After detecting significant individual differences in the rate parameter of the gamma model, we set out to determine the nature of these differences. The genetic and environmental model-fitting results indicated that a model including additive genetic, dominance genetic, and specific environmental effects was more appropriate than one with additive gene action and specific environmental effects alone. From the parameter estimates under the full model, we calculate that 71% of the variation in the latent aging covariate is due to dominance and additive genetic effects, while only 29% is due to individual environmental influences. Further, using the estimated variation in Y due to the latent aging covariate (81%), we find that dominance genetic effects contribute to 43% of the total variation in Y, while additive genetic effects contribute to only 14%.

The detection of dominance for age-at-menarche is especially intriguing since directional dominance effects are often found for fitness traits [Wimer and Wimer, 1985; Treloar and Martin, 1990], and the age at which a female begins to menstruate would certainly affect her reproductive fitness. However, it is important to mention that alternative hypotheses may be invoked to explain the small DZ twin correlation, which we have taken as evidence for dominance. These alternative explanations include sibling interaction effects, i.e., the onset of menstruation in one twin affecting the onset in her co-twin [Eaves, 1976; Carey, 1986; Treloar and Martin, 1990] or epistatic effects, i.e., interactions between different loci involved in a trait [Mather, 1974; Eaves, 1988]. In their analysis of the covariance structure of the menarche data, Treloar and Martin [1990] test the hypothesis of sibling interaction and conclude that it does not provide a better explanation of the data than the alternative genetic hypotheses. However, they point out that a dominance versus epistatic model cannot be resolved without additional data from mothers and daughters. When available, these data must be interpreted with care, given the noted secular trend in the menarcheal age of Australian twins [Treloar and Martin, 1990].

The absence of a common environmental influence on age-at-menarche is somewhat surprising. Other investigators [Cameron et al., 1985; Belmaker, 1982; Bielicki et al., 1986] have shown that diet and social class influence age-at-menarche and these factors would presumedly be shared as equally by DZ twins as by MZ twins living in the same household. However, it may be that the variability in diet or social class in this volunteer twin sample is so low that a common environmental influence is not detectable. Alternatively, common environmental influences may be obscured by the large amount of genetic nonadditivity. Data from other relationships (e.g., unrelated girls reared together) would be required to explore this latter possibility.

In conclusion, our results suggest that genes play a substantial role in determining the age at which Australian females begin to menstruate. This finding agrees with previous work that has yielded Holzinger's heritability estimates ranging from 0.70 to 0.80 [Gedda and Brenci, 1975; Fishbein, 1977] and mean pair differences typically less than 4 months in MZ twins, but 6–12 months in DZ twins [Fishbein, 1977; Sklad, 1977]. However, since the gamma accelerated failure-time model has allowed us to test specific developmental and inheritance hypotheses, it is more informative and has greater predictive power than the methods that have been used previously to study genetic effects on the timing of menarche.

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