Am. J. Hum. Genet. 47:137–148, 1990

Age at Menarche as a Fitness Trait: Nonadditive Genetic Variance Detected in a Large Twin Sample

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Summary

The etiological role of genotype and environment in recalled age at menarche was examined using an unselected sample of 1,177 MZ and 711 DZ twin pairs aged 18 years and older. The correlation for onset of menarche between MZ twins was .65 ± .03, and that for DZ pairs was .18 ± .04, although these differed somewhat between four birth cohorts. Environmental factors were more important in the older cohorts (perhaps because of less reliable recall). Total genotypic variance (additive plus nonadditive) ranged from 61% in the oldest cohort to 68% in the youngest cohort. In the oldest birth cohort (born before 1939), there was evidence of greater influence of environmental factors on age at menarche in the second-born twin, although there was no other evidence in the data that birth trauma affected timing. The greater part of the genetic variance was nonadditive (dominance or epistasis), and this is typical of a fitness trait. It appears that genetic nonadditivity is in the decreasing direction, and this is consistent with selection for early menarche during human evolution. Breakdown of inbreeding depression as a possible explanation for the secular decline in age at menarche is discussed.

Introduction

Onset of menstruation is an important landmark in female development. Menarche is an identifiable event in the gradual course of pubertal development, following breast development and pubic hair growth. The age at which it occurs is highly variable, and although regular ovulatory cycles may not follow for some time, the causes and consequences of onset are of both biological and medical interest. Age at menarche is a significant risk factor for a number of important outcomes; early menarche increases risk of breast cancer (Pike et al. 1981; Drife 1986; Vihko and Apter 1986; Kampert et al. 1988; Negri et al. 1988), and both early and late menarche have been associated with risk of multiple miscarriage (Martin et al. 1983; Wyshak 1983; Bracken et al. 1985).

Covariates at Age of Menarche

Many investigators have acknowledged that genetic factors may be important in timing of menarche, and associations with a large number of biosocial variables have been reported, although frequently the causal relationship is not clear. Correlates include body-fat levels (Frisch 1987), skeletal maturity (Tanner 1978), number of younger brothers, and father's departure from the family home before daughter has reached 6 years of age (Jones et al. 1972). Suggestions that pheromones may influence menarche led to assessment of family composition and family size in the latter study. Certain illnesses and inherited conditions have also been associated with advancing (hyperthyroidism and encephalitis), delaying (uremia, congenital heart disease, cystic fibrosis, and diabetes mellitus), or completely inhibiting (Turner syndrome) menarche (Golub 1983). In a study of women aged 15–34 years who had sickle cell disease (all seen within 12 mo of reported menarche), late menarche was associated with low fetal and total hemoglobin, low mean cell volume, low weight and height, and lower social class (Graham et al. 1986).

Nutrition and environmental differences such as health and sanitation have often been suggested as the key factors responsible for population differences in age at menarche (Wyshak and Frisch 1982). Malnutrition

Received December 28, 1989; revision received March 12, 1990.

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0002-9297/90/4701-0019$02.00

both retards growth and delays menarche (Tanner 1978). Girls who engage in exercise and athletic training have later onset of menstruation, related either to lean:fat body ratio (Frisch 1987) or to direct effects on hormonal secretion and metabolism (Rebar and Cumming 1981, but also see Stager and Hatler 1988). Both slower rates of physical growth and delayed menarche have been associated with geographical residence, particularly higher altitude (Eveleth and Tanner 1976). Urban as opposed to rural residence has been related to earlier menarche (Kantero and Widholm 1971*a;* Tanner 1978). Racial differences in age at menarche have been dismissed as being relatively unimportant per se, since no significant differences in mean menarcheal age were observed between different racial groups living in homogeneous socioeconomic circumstances (Weir et al. 1971; Goodman et al. 1983). Immigrant subgroups within a country who are in heterogeneous circumstances have, however, shown mean differences (Jones et al. 1972). Significant variation with respect to month and season of menarche (Kantero and Widholm 1971*a;* Tanner 1978) and to season of birth (Burrell et al. 1961) has been observed both within and between studies. Climate per se has minimal effect on menarcheal age (Golub 1983), although hotter environmental temperature has been associated with earlier menarche (Saar et al. 1988).

Secular Trends

In Europe and the United States in the past century a secular trend toward earlier age at menarche has been documented (Tanner 1973), questioned (Zacharias and Wurtman 1969; Bullough 1981), and reaffirmed (Wyshak and Frisch 1982; Goodman 1983). In Europe, age at menarche declined by about 2–3 mo/decade in the past century and a half, compared with a decline in the United States of about 2 mo/decade in the past century (Wyshak and Frisch 1982). This trend has leveled off earlier in some countries than in others (Drife 1986) and has not been universal (Zacharias and Wurtman 1969). Correlating with reduction in the range of menarcheal ages has been a steady secular increase in height during this century in most Western industrial societies (Cavalli-Sforza and Bodmer 1971), and this may reflect a causal relationship between skeletal growth and menarche. Both trends have been attributed to improving environmental circumstances, based on more equitable socioeconomic conditions (Cavalli-Sforza and Bodmer 1971; Wyshak and Frisch 1982). Cameron (1979) has suggested that stabilization of the secular trend in height has been caused by the reaching of a genetically determined threshold rather than an environmental optimum.

Family and Twin Studies

Highly significant correlations between mothers' and daughters' ages at menarche have been reported and are summarized in table 1, along with results of other kin studies (also see Chern et al. 1980). Other significant mean menarcheal age differences between sisters compared with unrelated girls and between MZ and DZ twin pairs, have been reported, often without correlation coefficients (see table 1). The overall impression from previous studies is that there is a familial correlation for age at menarche and that this is, at least partly, genetically determined. However, family environment may also play a role; comparison between a group of 29 pairs of female MZ twins reared apart and a group of 29 female MZ pairs reared together led Shields (1962) to conclude that separated twins may have differed more in age at menarche than did those reared together (and that first-born twins were more likely to menstruate first).

Subjects and Methods

Subjects

In 1980–82, as part of a health survey by mailed questionnaire, information about menarche was obtained from 1,888 female twin pairs in a larger sample of 3,808 adult twin pairs from the Australian National Health and Medical Research Council (NH&MRC) Twin Register (Jardine et al. 1984; Martin and Jardine 1986; Eaves et al. 1989). Questionnaires were mailed to 5,967 twin pairs aged 18 years or older. Ages of respondents ranged from 18 to 88 years. After one or two reminders to nonrespondents, completed questionnaires were returned by both members of 3,808 twin pairs (64% pairwise response rate).

A two-item zygosity questionnaire was used to determine zygosity for same-sex pairs (Jardine et al. 1984). Such questionnaires have been shown to give at least 95% agreement with diagnosis based on extensive blood-typing (Cederlof et al. 1961; Nichols and Bilbro 1966; Martin and Martin 1975; Kasriel and Eaves 1976; Magnus et al. 1983).

Female twins were asked to answer, in years and months, the question, How old were you when you had your FIRST menstrual period? No response was given by 96 individuals from 95 twin pairs of the 1,983 MZ and DZ female pairs in the sample; the age distribution of these nonrespondents did not differ significantly from that of respondents. Sixty-five cases of reported late menarche (between 16 and 21 years of age) were checked for validity in various ways, and no reasonable grounds

Table 1

Earlier Kin Studies of Age at Menarche

A. Studies of Mothers and Daughters

Study	No. of Mothers	No. of Daughters	$r \pm SE$
Bolk 1923	45	71	.54 ± .08
Popenoe 1928	200	351	.40 ± .03
Israel 1959	1,053[a]		.28
Damon et al. 1969	66	78[b]	.24 ± .11
Behn and Treloar 1969	563[b]		.27
Kantero and Widholm 1971*b*	1,946[a]		.28
Chern et al. 1980	399	609[b]	.22[c] ± .04
Richter and Kern 1980	284[a]		Significant[d]
Kaur and Singh 1981	72	83	.39

B. Studies of Sisters

Study	No. of Sisters	$r \pm SE$
Popenoe 1928	351	.39 ± .03
Chern et al. 1980	403[b]	.25 ± .06[e]

C. Studies of Sisters and Unrelated Women

Study	No. of Sisters	No. of Unrelated Women	Mean Interval (mo)	
			Sisters	Unrelated Women
Petri 1935[f]	145	120	12.9	18.6
Reymert and Jost 1947[f]	72	200	10.6	13.9

D. Studies of MZ and DZ Twins

Study	No. of MZ Twins	No. of DZ Twins	Mean Interval (mo)	
			MZ Twins	DZ Twins
Petri 1935[f]	51	47	2.8	12.0
Tisserand-Perrier 1953[f]	46	39	2.2	8.2
Fischbein 1977	28	48	3.5 (r = .93)	8.5 (r = .62)

E. Study of Unspecified Twins

Study and Location	No. of Pairs	h^2
Van den Akker et al. 1987:		
London	364	.72
Birmingham	98	.54

[a] Mother-daughter pairs.
[b] Contains some prospective recording.
[c] Regression coefficient.
[d] Coefficient not given.
[e] ANOVA calculation.
[f] Cited by Zacharias and Wurtman (1969, p. 872).

could be found for excluding them. Effective numbers of female twin pairs for the analyses to be reported here are thus 1,177 MZ pairs and 711 DZ pairs.

To allow for the possible interaction of age with causes of variation in age at menarche (given both the secular trend reported since last century and possible effects of interval of recall), the total sample was subdivided into four age cohorts with intervals chosen to ensure

that each cohort contained roughly equal numbers: twin pairs born before 1939 (cohort 1), and those born during 1939–50 (cohort 2), 1951–58 (cohort 3), and 1959–64 (cohort 4).

Scaling

Menarche, reported retrospectively, is not a normally distributed variable (Zacharias et al. 1970). Excessive peaking around the mean has been noted, perhaps reflecting faulty memory or reluctance to be classified as abnormal, although prospective studies find similar skewness and kurtosis (Jones et al. 1972). We note that directional genetic nonadditivity (dominance or epistasis) resulting from directional selection would be expected to produce noncentrality (Fisher et al. 1932; Mather 1973).

Examination of the frequency distribution revealed that responses were clustered around whole and half years. In preliminary analysis we assessed the use of whole years compared with years and months combined to form decimal years. Pearson correlations (± standard errors [SEs]) for whole years were .64 ± .03 for the entire sample of MZ pairs and .19 ± .04 for DZ twins. The corresponding Pearson correlations for decimal years were .65 ± .03 and .18 ± .04. Polychoric correlations and their asymptotic SEs were also calculated by PRELIS (Jöreskog and Sörbom 1986) by using whole years as classes, and this produced estimates of .67 ± .01 and .19 ± .04. The estimates were unperturbed by differing assumptions about the distribution, so we chose to work with decimal years, since, in contrast to polychoric correlations, this has the advantage of allowing one to work with variances and covariances of the unscaled continuous measurements, rather than with a single correlation and variances standardized to unity.

The stability of the twin correlations under differing distributional assumptions also boosts confidence in the major inference that can be drawn from the data (see below), namely, that there is a large amount of nonadditive genetic variation for age at menarche. This inference rests on the fact that the DZ correlation is significantly less than half the MZ correlation. Extreme noncentrality of the raw distribution can sometimes generate scale-dependent evidence for genetic nonadditivity, which can be removed by an appropriate transformation of scale (Mather and Jinks 1982, chap. 3). Calculation of the polychoric correlation scales categories to minimize such noncentrality, and the fact that these estimates are so similar to the Pearson correlations suggests that artifactual evidence for nonadditivity is not being generated by noncentrality in the raw data. Furthermore, it is unlikely that false inferences will be drawn during the maximum-likelihood model-fitting process, despite departures from the assumption of multivariate normality on which the method rests.

Model Fitting

This analysis of cross-sectional twin data fitted univariate genetic models to covariance matrices for MZ and DZ twin groups (Heath et al. 1989) by using Lisrel 7.16 (Jöreskog and Sörbom 1989) for structural equation modeling. The path diagram in figure 1 depicts the sources of both variance and covariance for twins reared together. Models may allow for additive gene action (h), nonadditive gene action (d = dominance or epistasis), environmental influences specific to an individual (e), and environmental effects common to both cotwins (c). However, genetic nonadditivity and shared environment are completely confounded in data on twin pairs reared together (Eaves 1970; Martin et al. 1978; Grayson 1989; Heath et al. 1989; Hewitt 1989), and

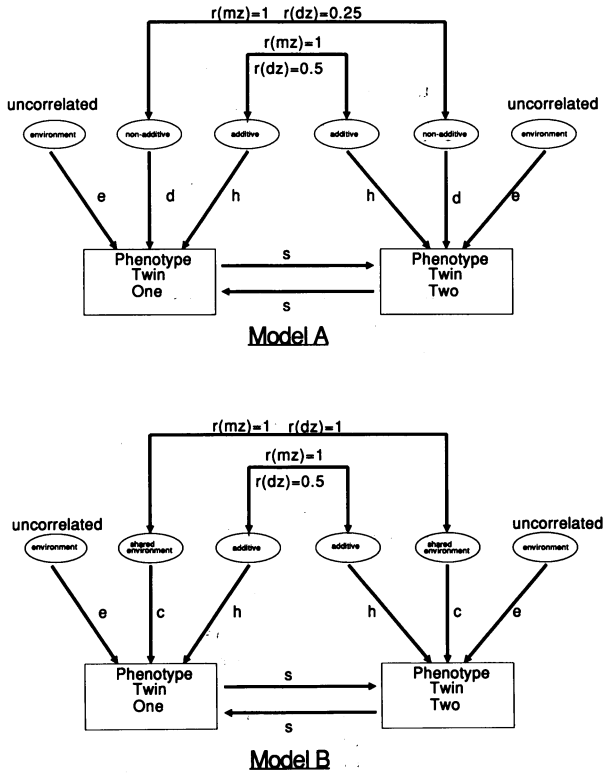

Figure 1 Path diagram of twin resemblance. Alternative sources of between-family variation are shared environmental effects (c) in Model B or nonadditive genetic effects (d) in Model A. Parameters common to both models are individual environmental effects (e), additive genetic effects (h), and reciprocal sibling interaction (s).

only one of them may be estimated. Specifically, if the DZ correlation is less than half the MZ correlation, genetic dominance (or epistasis) is indicated, while shared environment increases the DZ correlation to more than half the MZ correlation. A further parameter specifying reciprocal sibling interaction (s), which measures the effect of the first twin's phenotype on that of her cotwin and vice versa (Carey 1986; Heath et al. 1989) can be included, although there is little power to detect it in the presence of c or d.

Since we used covariance matrices, model-fitting was by maximum likelihood, and assessment of fit was by goodness-of-fit χ^2. The significance of a parameter was assessed by the change in χ^2 when it was either added to a simpler model or dropped from a more complex one. It has been argued that this is a less ambiguous test of significance of a source of variance than using the SE, which can indicate significance or not, depending on the exact parameterization used (Neale et al. 1989).

Results

Distribution of Age at Menarche

The cumulative distributions of age at menarche for the total sample are shown in figure 2. Within a cohort, with regard to mean recalled age at menarche there were no significant differences (1) between twin 1 and twin 2 within either MZ or DZ pairs or (2) between MZ and DZ twins. Descriptive statistics for each cohort are presented in table 2. Means for the first three cohorts conform to the reported secular trend in menarcheal age; mean recalled menarche was about 3 mo earlier in twins born in the 1950s (cohort 3) than in those born before 1939 (cohort 1) ($P < .01$). However, this trend is apparently reversed in the youngest cohort, which has mean age at onset approaching that of the oldest cohort and not significantly different from that of the second cohort. We have no explanation for this reversal. No associations were found between age at menarche and either father's occupational status or subject's own education level.

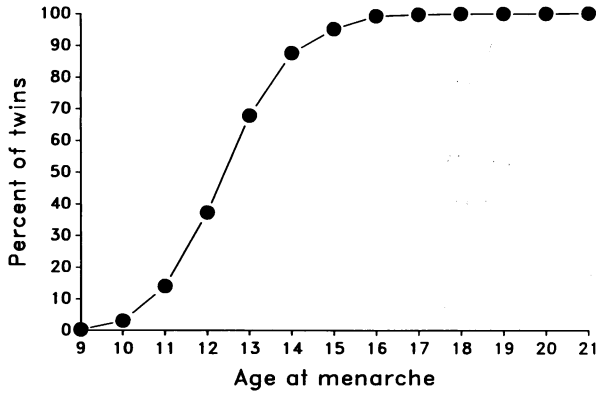

Figure 2 Cumulative distribution of age at menarche

Over all individuals, a significant positive correlation was found between age and age at menarche ($r = .05$, $n = 3{,}870$, $P < .001$), but the proportion of variance accounted for is trivial. Note that skewness is positive in each cohort, significantly so in each case, consistent with either nonadditive gene action toward earlier menarche or the predominance of alleles acting additively to decrease age at menarche (Martin et al. 1978).

Consistency of Recall

A pilot questionnaire was sent to 100 pairs of twins 3 mo before the main mailing. Replies to both the pilot and main questionnaire were received from 67 females, and their responses to the menarche item may be used to assess the consistency with which they recall the timing of this event. The correlation between responses on the first and second occasions (mean interval 100 d) was .91 ± .13 ($P < .001$). The age distribution of this pilot subsample was typical of that of the entire female sample, so we may be confident that females are highly

Table 2

Mean Age at Menarche, Skewness, and Kurtosis for All Twins, by Birth Cohort

Birth Cohort (period)	No. of Pairs	Mean ± SD Age at Menarche	Mean ± SE	
			Skewness	Kurtosis
1 (before 1939)	523	13.26 ± 1.23	.201 ± .107	2.773 ± .213
2 (1939–50)	492	13.05 ± 1.24	.236 ± .110	3.599 ± .220
3 (1951–58)	499	13.02 ± 1.26	.543 ± .109	4.053 ± .218
4 (1959–64)	374	13.19 ± 1.10	.345 ± .126	3.049 ± .252

consistent in their recall of the timing of menarche. The extent to which recall is consistent with the actual timing is another question—on which, unfortunately, we have no data (but see Discussion).

Correlates of MZ Discordance

Twins, particularly MZ pairs, provide a natural matched-pair design for testing the effect of certain treatment differences. First, the effect of birth order was tested to see whether being second born, with a higher risk of birth trauma (particularly anoxia), was related to later menarche (i.e., slower development), but the difference was trivial and not significant. Neither was there a correlation between birth interval (in the 899 MZ pairs where both twins agreed on that interval) and interval between twins' onsets of menstruation—either in the total sample (r = .07, NS) or in the separate birth cohorts (r = .05–.13, NS).

Heavier self-reported birthweight was not associated with earlier menarche for either first- (r = –.02) or second-born (.01) MZ twin (940 pairs). In 31 MZ pairs where birthweight difference exceeded 960 g, no significant association between menarche interval and birthweight difference was found (r = –.13). Given the hypothesized role for critical weight threshold and skeletal growth threshold in triggering menarche (Tanner 1978; Frisch 1981, 1987), we calculated the correlations between self-reported adult height and weight at the time of completion of the questionnaire and recalled age at menarche, but coefficients were small (.06–.09) and not significant. Thus, none of the variables selected could even partly explain observed discordance in timing of menarche in MZ twins.

Models Fitted

Models were fitted to the 2 × 2 covariance matrices for MZ and DZ twins in each cohort, shown in table 3 with corresponding twin correlations. Since, for each cohort, the DZ correlation was less than half the MZ correlation, shared environment (c) could not be an important source of sibling correlation relative to genetic nonadditivity (d), and so it was omitted from further consideration (but see Grayson 1989; Hewitt 1989). Models fitted were thus (1) a *full* model (model I; h, d, and e) containing additive and nonadditive (dominance or epistasis) genetic factors plus individual environmental influences, (2) an *additive* genetic model (model II, h and e) with no allowance for nonadditivity (d = 0), and (3) an "*unequal environments*" model with additive and nonadditive genetic effects but allowing environmental variance to be different for first- and second-born twins (model III, h, d, e_1, and e_2). The rationale of this model is that, although we have not detected significant effects of either birth order or birth

Table 3

Variances, Covariances, and Correlations of Age at Menarche for Twins, by Zygosity and Birth Cohort

	MZ			DZ		
Birth Cohort	No. of Pairs	First Born	Second Born	No. of Pairs	First Born	Second Born
1 (before 1939)	332	1.926	.662	191	1.980	.149
		1.278	2.188		.326	2.399
2 (1939–50)	303	2.152	.587	189	1.964	.155
		1.270	2.175		.335	2.362
3 (1951–58)	315	2.071	.727	184	1.777	.187
		1.570	2.248		.348	1.945
4 (1959–64)	227	1.771	.657	147	1.540	.294
		1.078	1.520		.433	1.415
All twins	1,177	2.000	.649	711	1.837	.183
		1.323	2.081		.357	2.076

Note.—In each matrix, variances are on the diagonal, covariance is in the bottom left, and correlation is in the upper right (underlined).

interval on the mean age at menarche, it is still possible that the second-born twin is subject to greater variance in perinatal trauma and that this is reflected in subsequently greater variance in menarcheal age.

For each cohort the full model (i.e., model I) gave a good fit to the data (table 4). Dropping d from the model (resulting in model II) caused a significant worsening of fit in the first three cohorts (χ^2_1 = 6.70 [P < .01], 4.05, and 4.70 [P < .05], respectively), although not in the youngest cohort (χ^2_1 = 0.03), suggesting that genetic nonadditivity is a major source of variation in age at menarche. Inspection of the variances for first- and second-born twins in table 3 revealed a tendency for the second-born twin to have greater variance (though it is interesting that this was not revealed in the youngest cohort). Next we fitted the full model but allowed unique environmental influences to be different for first- and second-born twins (model III) and found a just-significant improvement in fit for the first cohort (4.42 − 0.56 = χ^2_1 = 3.86 [P = .05]) but not for the other cohorts.

We may ask whether the parameters being estimated differ significantly between the four cohorts. To test this we fitted the full model jointly to data from all four cohorts (i.e., all eight covariance matrices) and obtained χ^2_{21} = 57.2. The sum of χ^2 values for the fit of the full model to each cohort separately is χ^2_{12} = 13.1, and if this is subtracted from the former figure we have χ^2_9 = 44.1, which is highly significant and indicates that the parameter estimates are heterogeneous across cohorts. Further analysis showed that results for the three older cohorts were heterogeneous inter se, so heterogeneity does not arise solely from differences between the youngest cohort and the others.

It is a reasonable expectation that absolute values of genetic variance for age at menarche will remain stable over the short period of evolutionary time encompassed by our study. Given evidence of secular trends toward earlier menarche, what is likely to change between cohorts is the amount of environmental variance. We therefore fitted a model in which we constrained the genetic parameters h and d to be equal in all four cohorts but allowed the environmental effect e to take a different value for each cohort (table 5, model 1). This gave both an adequate fit (χ^2_{18} = 25.4 [P = .12]) and a great improvement over the model which constrained all parameters to be equal across cohorts (χ^2_{21} = 57.2). We have previously shown greater environmental variance for the second-born twin in the oldest cohort, and adding this refinement to the model (table 5, model 2) produces χ^2_{17} = 21.5, confirming the significant improvement of χ^2_1 = 3.89 (P = .05). At this stage we reconfirmed the importance of genetic nonadditivity; dropping d from model 2 gave χ^2_{18} = 33.88 (table 5, model 3), a significant worsening of χ^2_1 = 12.41 (P < .001).

There is one other source of variation we need to consider, and that is the interaction between siblings. It is conceivable that if one twin starts menstruating, for pheromonal or other reasons this may influence the timing of menarche in her cotwin. If it tends to advance menarche in the cotwin, this is called a "cooperative" or "imitation" effect; if it retards the cotwin's menarche, this is a "competitive" or "contrast" effect (Eaves 1976; Carey 1986). This reciprocal interaction between the phenotypes of cotwins is indicated by the paths marked s in figure 1. If those phenotypes have a genetic component, then the sibling interaction itself will have both a genetic component and differential effects on the variances and covariances of MZ and DZ twins. In certain circumstances these effects will be difficult to distinguish from nonadditive genetic variation (Jardine 1985; Carey 1986). To see whether this is the case in our menarche data, we first added s to our model 2. The results (table 5, model 4) show a slight positive estimate of s, a reassigning of all genetic variance to d, and a slightly smaller χ^2 of χ^2_{16} = 20.67, a nonsig-

Table 4

Model Fitting to Covariances of Age at Menarche for All Twin Pairs and Individual Birth Cohorts of Twins

Birth Cohort and Model	h	d	$e_{(1)}$	e_2	df	χ^2
1: I	.000	1.153	.887		3	4.42
II[a]	1.145	. . .	.910		4	11.12
III[b]	.000	1.152	.797	.970	2	.56
2: I	.264	1.095	.945		3	1.65
II[a]	1.116	. . .	.967		4	5.70
III[b]	.275	1.091	.910	.981	2	1.02
3: I	.451	1.112	.763		3	3.60
II[a]	1.207	. . .	.776		4	8.30
III[b]	.451	1.112	.705	.817	2	2.10
4: I	.966	.276	.749		3	3.43
II[a]	1.004	. . .	.750		4	3.46
III[b]	.962	.290	.815	.674	2	.93
All twin pairs:						
I	.453	1.041	.845		3	4.18
II[a]	1.132	. . .	.861		4	19.06
III[b]	.456	1.039	.808	.880	2	1.61

[a] Without dominance.
[b] When e is allowed to differ between twin 1 and twin 2.

Table 5

Fitting Models Jointly to Data from All Four Cohorts

A. Model 1: Constrain Additive and Nonadditive Variance to Be Equal between All Cohorts; Constrain $e_1 = e_2$, But Allow e to Differ between Cohorts

Birth Cohort	h	d	e	
1	.529	.995	.898	
2	.529	.995	.947	
3	.529	.995	.782	$\chi^2_{18} = 25.36$
4	.529	.995	.719	$P = .12$

B. Model 2: As Model 1, But $e_{(1)} \neq e_2$ for Cohort 1

Birth Cohort	h	d	$e_{(1)}$	e_2
1	.530	.994	.810	.978
2	.530	.994	.947	
3	.530	.994	.782	$\chi^2_{17} = 21.47$
4	.530	.994	.719	$P = .20$

C. Model 3: Final Test for Nonadditivity; Set $d = 0$

Birth Cohort	h	d	$e_{(1)}$	e_2
1	1.123	0	.828	.997
2	1.123	0	.964	
3	1.123	0	.798	$\chi^2_{18} = 33.88$
4	1.123	0	.726	$P = .01$

D. Model 4: Test for Sibling Interaction; Add s to Model 2

Birth Cohort	h	d	s	$e_{(1)}$	e_2
1	.000	1.089	.025	.836	1.002
2	.000	1.089	.025	.972	
3	.000	1.089	.025	.805	$\chi^2_{16} = 20.67$
4	.000	1.089	.025	.738	

E. Model 5: Sibling Interaction or Nonadditivity? Model 4 But Set $d = 0$

Birth Cohort	h	d	s	$e_{(1)}$	e_2
1	1.219	...	−.065	.749	.925
2	1.219	...	−.065	.889	
3	1.219	...	−.065	.730	$\chi^2_{17} = 25.54$
4	1.219	...	−.065	.674	

NOTE.—χ^2_1 values are as follows: (model 1–model 2) = 3.89, (model 3–model 2) = 12.4, (model 2–model 4) = 0.8, and (model 5–model 4) = 4.87.

nificant decrease of $\chi^2_1 = 0.8$ from the fit of model 2. However, since there is a high degree of confounding between s and d, a more critical test is to add s to model 3, which has d fixed to zero—or, looked at another way, to drop d from model 4. Model 5 (table 5) now estimates a slight negative value of s and yields $\chi^2_{17} = 25.54$; this is an improvement over model 3, which has neither s nor d ($\chi^2_1 = 8.34$) but is worse than model 4 (both s and d) by $\chi^2_1 = 4.87$ ($P < .05$). These comparisons suggest strongly that the major source of nonadditivity in variance for menarcheal age is either genetic dominance or epistasis, rather than sibling interaction.

Table 6

Genetic and Environmental Components of Variance for Age at Menarche

	Genetic Component (%)			Environmental (%)
	Additive	Nonadditive	Total	
Cohort 1:				
Twin 1	22.71	42.59	65.30	34.70
Twin 2	21.18	39.73	60.91	39.09
Cohort 2.....	21.45	40.23	61.68	38.32
Cohort 3.....	22.98	43.11	66.09	33.91
Cohort 4.....	23.63	44.31	67.94	32.06

The proportions of genetic and environmental variance of age at menarche for each birth cohort are shown in table 6 and are based on the estimates of path coefficients from the fit of the most parsimonious model (model 2 in table 5).

Although we defend the sequence of model fitting executed above as an exploratory exercise to gain as much from our data as possible, it must be admitted that to some extent the models we have fitted have been influenced by inspection of the data and other post hoc considerations. This being so, it could be argued that the conventional significance levels we have used to judge biological interest are too liberal, particularly in view of the considerable power conferred by our large sample size. We must therefore urge caution in accepting some of our more borderline inferences, but nevertheless we let them stand, since the ultimate test is whether they can be replicated. We are currently conducting further extensive twin and family studies with the potential for such replication.

Discussion

Our analysis of causes of individual differences in recalled age at menarche in 1,888 pairs of twins has produced strong evidence for the importance of additive and nonadditive genetic variance in all age cohorts and for slightly greater environmental influences in older

than in younger twins. This may be due to greater error of recall in the older members of the sample. In the oldest birth cohort (born before 1939), there was evidence of greater influence of environmental factors on age at menarche (hence lower heritability) in the second-born twin than in the first-born twin, perhaps reflecting the greater risk of perinatal trauma to the second born, although no mean differences were evident. All environmental influences detected were specific to the individual and not shared with the cotwin; we cannot rule out the possibility that there are common environmental influences on timing of menarche in twins, but we can say that they must be small relative to nonadditive genetic effects (Grayson 1989; Hewitt 1989). It is interesting that in an early study Popenoe (1928) reported (see table 1) a higher sister-sister correlation (.39 ± .03) than we have found for DZ twins (.18 ± .10), and we speculate that in the early part of the century the sibling correlation might have been inflated by environmental influences on age at menarche which differed between families but were shared by sisters (e.g., nutrition) but that any such inequalities declined rapidly in importance as the century progressed.

In all cohorts genetic variance accounted for a much higher proportion of total variance than did environmental factors, ranging from 61% in the oldest cohort to 68% in the youngest cohort. Dominance or epistasis was the major component of genetic variance in the three older cohorts but was not significant in the youngest cohort. In view of the great difficulty in detecting even large amounts of genetic nonadditivity in the classical twin study (Martin et al. 1978), it is surprising that we obtained significant estimates of d in any cohort. It should be noted that the youngest cohort is also the smallest numerically and that the inability to detect significant dominance in this cohort more probably reflects lack of power and the high negative correlation of estimates of h and d than it reflects a genuine cohort difference in genetic architecture. It should also be noted that we have evidence that the source of nonadditivity we are calling genetic dominance or epistasis is not an artifact of reciprocal sibling interaction, even though it is known to be extremely difficult to distinguish between the two (Jardine 1985).

Reliability of Recalled Age at Menarche

We have relied entirely on self-reported age at menarche, although in many cases decades have passed since it actually occurred. Our results, therefore, are only as reliable as the accuracy of recall of this event. Our repeatability data have given considerable evidence of *consistency* of recall, but this does not mean that recall is accurate. Further evidence of consistency of recall comes from Treloar (1974), who found that memory of menarche was consistent for 20 years or more following original recording, within a few years of the event, by 2,700 college women. Evidence of *accuracy* comes from a study in which, after 19 years, recall of the prospectively recorded event correlated .75 with the actual timing; after 39 years this fell to .60 (Damon and Bajema 1974), and this increase in error of recall is consistent with the greater environmental variance estimated in our older cohorts.

Representativeness of the Sample

Normative data on age at menarche in Australia are available only from small studies (e.g., see Marlay 1971; Jones et al. 1972), none of which is based on representative community samples. Our sample has been shown to be representative of the Australian population on a number of variables, such as drinking behavior (Jardine and Martin 1984), personality factors, and anxiety and depression (Kendler 1983; Jardine et al. 1984). The sample is unselected for anything except volunteering to enroll on the Australian NH&MRC Twin Register and returning the questionnaire, so it may well be random with respect to age at menarche. We assume that, in relation to their population birth cohorts, responding women do not differ significantly in distribution of menarcheal ages and that, provided the fundamental assumptions of the twin method are valid, the inferences which we draw about causes of individual differences will be applicable to the population.

Interpretation of Twin Data

The conclusion that genetic differences have a significant effect on age at menarche rests ultimately upon the finding that, for this variable, the correlation between MZ twin pairs is greater than that for DZ pairs. It is commonly objected that this difference arises because of the greater "environmental" correlation of MZ pairs. What evidence exists suggests that any excess "environmental" correlation of MZ pairs, compared with DZ pairs, arises because MZ twin pairs, being genetically identical, behave more similarly and therefore create for themselves more similar environments (Kendler 1983; Heath et al. 1989; Morris-Yates et al., in press).

Since all but five twin pairs were living together when they experienced menarche, age at separation from cotwin could not have produced a greater environmental correlation for *actual* age at menarche in MZ than it did in DZ twins. However, it is possible that more fre-

quent cohabitation or social contact at the time of completion of the questionnaire might have influenced *recall* of menarche and that this may have differentially biased MZ and DZ correlations. Twins reported their degree of contact on a six-point scale from 1 ("we live together") to 6 ("we never see/contact each other"), and there was high agreement ($r = .89$) between twins on this scale. Although the degree of cohabitation and contact was greater in MZ than in DZ pairs, the correlation between degree of contact and interval between reported menarche of cotwins was .11 in MZ pairs ($P < .001$) and .03 (NS) in DZ pairs. While the correlations are in the expected direction, with those twins who see each other less often reporting greater discordance in timing of menarche, the proportion of variance accounted for is trivial, and there is no support for the notion that greater MZ similarity is due to greater personal contact, communication, or collaboration.

Genetic Nonadditivity and Biological Fitness

The most interesting feature of our results is the large amount of genetic nonadditivity detected for age at menarche. In twin data we are unable to tell whether this is due to genetic dominance or to additive × additive epistasis (Mather 1974), and parent-offspring data are needed to resolve this issue (Heath et al. 1984). Since dominance variance does not contribute to the parent-offspring correlation but epistasis does (in the same measure as to the sibling correlation), a lower parent-offspring than sibling correlation would tend to support dominance as the source of nonadditivity. However, the data from other studies collated in table 1 tend to suggest that the mother-daughter correlation is about the same as the sister-sister (or DZ) correlation, both being considerably less than half the MZ correlation. This points to epistasis rather than to dominance as the main source of genetic nonadditivity for timing of menarche, although it must be admitted that the power to make this discrimination by the data available is rather low.

A further point in favor of epistasis, rather than dominance, as an explanation has been made by Eaves (1988), who points out that for dominance effects to produce such a marked reduction in the sibling correlation requires very unequal gene frequencies, whereas even modest inequalities in gene frequencies in the presence of digenic interactions can lead to large reductions in the sibling correlation below the additive expectation. With hindsight, the idea that interactions between different loci might be important in governing the timing of so crucial an event is not surprising.

Positive skewness in the distribution of age at menarche would be consistent with genetic nonadditivity acting in the decreasing direction, i.e., toward earlier menarche. This is the pattern we would expect if over evolutionary time there had been natural selection toward earlier menarche (Mather 1973). It also raises the intriguing possibility that another explanation for the secular trend toward earlier menarche may be the breakdown of inbreeding depression. Although we have argued that MZ, DZ, and mother-daughter correlations are consistent with additive × additive epistasis, it is very likely that there are also both genetic nonadditivity due to dominance at single loci and epistatic interactions with dominant effects at multiple loci (Mather 1973, 1974). Inbreeding would reduce the effects on the mean of these interactions, and one would expect later menarche in the daughters of consanguineous matings (although we have been unable to find any data on this point). Conversely, breakdown of inbreeding in a population would be expected to regenerate these interactions and result in lowering the age at menarche.

This possibility has been raised in a Norwegian study (Liestøl 1982) but was discounted because mobility was high in Oslo in the last part of the nineteenth century when negligible changes were seen in menarcheal age (Liestøl 1982). Similarly, Cavalli-Sforza and Bodmer (1971, p. 610) dismiss breakdown of inbreeding depression as an explanation for secular changes in stature, arguing that estimates of the base rates of inbreeding are too low to account for the dramatic secular changes (e.g., see Hulse 1958; Tanner 1965). Good inbreeding data (e.g., see Bashi 1977) would help resolve this issue, but it appears likely that improved environmental conditions remain the most likely cause of secular trends.

Our study is currently being extended to include parents, siblings, and adult children of this twin sample, as well as a large new cohort of younger twins and their relatives. With this larger sample we shall be in a much stronger position to test our conclusions concerning genetic nonadditivity by comparing mother-daughter, twin, and sister correlations.

Acknowledgments

Data collection and analysis were supported by a grant from NH&MRC to N.G.M., Dr. J. D. Mathews, and Dr. J. B. Gibson. We thank Dr. Rosemary Jardine and Marilyn Olsen for assistance with data collection, David Duffy and Ulrich Kehren for help in preparing the manuscript, and Lindon Eaves for helpful remarks. S.A.T. holds an NH&MRC Biomedical Postgraduate Scholarship.

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