ORIGINAL ARTICLE

The Influence of Genetic Factors and Life Stress on Depression Among Adolescent Girls

Judy Silberg, PhD; Andrew Pickles, PhD; Michael Rutter, MD; John Hewitt, PhD; Emily Simonoff, MD; Hermine Maes, PhD; Rene Carbonneau, PhD; Lenn Murrelle, PhD; Debra Foley, PhD; Lindon Eaves, PhD

Background: The possible causes of greater depression among adolescent girls were investigated by examining variation in the influence of genetic and environmental risk factors among 182 prepubertal female, 237 prepubertal male, 314 pubertal female, and 171 pubertal male twin pairs from the Virginia Twin Study of Adolescent Behavioral Development.

Objectives: To compare the trajectory of depressive symptoms among boys and girls from childhood to adolescence; to analyze the role of genetic, shared, and unique environmental factors in depression among prepubertal and pubertal male and female twins; and to investigate a possible link between liability to depression and one salient index of the child's environment: past-year life events.

Methods: Child-reported depression was assessed using the Child and Adolescent Psychiatric Interview and ratings of past-year life events and pubertal status obtained by maternal questionnaire and interview, respectively.

Results: The impact of life events on depression was particularly evident in the adolescent girls. The results from model fitting indicate increased heritability for depression in this group, and its long-term consistency was mediated primarily by latent genetic factors. Model fitting also showed that at least part of the liability to depression and to life events can be linked to a common set of genes in the adolescent girls, and there is a notable developmental increase in the genetic variance for life events.

Conclusions: The greater heritability for depression in pubertal girls, its genetic mediation over time, and the increase in genetic variance for life events may be one possible explanation for the emergence of increased depression among pubertal girls and its persistence through adolescence.

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From the Virginia Institute for Psychiatric and Behavioral Genetics, Virginia, Commonwealth University, Richmond (Drs Silberg, Maes, Carbonneau, Murrelle, Foley, and Eaves); School of Epidemiology and Health Sciences, University of Manchester, Manchester (Dr Pickles), Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, London (Dr Rutter), and the Section of Child and Adolescent Psychiatry and Psychology, Guy's Hospital, London (Dr Simonoff), England; and the Institute for Behavior Genetics, Boulder, Colo (Dr Hewitt).

ONE OF the more strikingly consistent findings in the epidemiology of depression is the greater prevalence of both depressive symptoms and diagnosable major depression in females compared with males.[1-6] Whereas the rates of depression are reported to be approximately the same in boys and girls before adolescence[7-9] or even slightly elevated in prepubescent boys,[10-12] by midadolescence the predominance of depression among women is well established,[13-17]—a trend that continues through young adulthood into middle age.[18,19]

Both biological and social factors have been implicated in explaining this rise in depressive symptoms among adolescent girls. Because the emergence of sex differences in depression occurs within the period of greatest pubertal change, investigators have focused on the role of reproductive hormones. Some support has been found for an association between hormonal concentrations and negative affect[20-24]; however, social factors, including negative life events and their interaction with pubertal status (but not hormonal status), account for more of the variance in negative affect than biological factors alone.[25] Early pubertal timing and its social implications have also been postulated as an important risk factor in girls.[26-31] Two recent studies, however, report that pubertal status has a greater influence in predicting female depression than age[32,33] or the timing of puberty.[32]

There is also some evidence for a familial influence on adolescent depression,[34-41] and several investigators have suggested that early-onset cases of depression (before age 20 years) are associated with increased familial risk,[42-46] particularly among the relatives of pubescent probands.[47] Eaves et al[48] report substantial genetic effects on depression among a large sample of 8- to 16-year-old twins. The re-

MATERIALS AND METHODS

DESIGN AND SAMPLE

The Virginia Twin Study of Adolescent Behavioral Development is a population-based, 4-wave, prospective study of more than 1400 male and female juvenile twin pairs. Founded on a longitudinal, cohort-sequential follow-up of a sample of 8- through 16-year-old twins and their parents, the study was designed to elucidate the influence of hereditary and environmental factors on the development of child and adolescent psychopathology. Details concerning the ascertainment, sample structure, and wave 1 cooperation rate have been provided elsewhere.[48,50-52] Of the 1302 families with twins still between the ages of 8 and 16 years at the second wave of assessment, 1022 (78%) completed a wave 2 home interview. Since we were interested in comparing depression in children prior to and after the onset of puberty, we wanted to include as many prepubescent and pubescent twins as possible. Hence, the data collected from both the first and second waves of the study were jointly analyzed. These included 338 monozygotic (MZ) and 156 dizygotic (DZ) female twin pairs and 252 MZ and 158 DZ male twin pairs from wave 1 and a subsample of 246 MZ and110 DZ female pairs and 194 MZ and108 DZ male pairs who participated in a second family interview when the twins were on average 1.5 years older.

MEASUREMENT PROTOCOL

The major source of clinical information for assessing psychopathology is provided by the Child and Adolescent Psychiatric Assessment (CAPA),[53] a semistructured, investigator-based psychiatric interview administered by separate skilled interviewers to both twins and at least one of the twins' parents. For the present analysis, a subscale score composed of the 9 child-rated CAPA symptoms that met criteria for a diagnosis of *DSM-III-R* Major Depressive Episode was used as an index of depression. Each symptom was scored 0 or 1 depending on its presence in at least 2 areas of children's lives and on the degree of control they had over its expression.

The occurrence of each of 39 past-year life events was included as part of a series of questionnaires that the parents and the twins were asked to complete during the home interview.[54,55] To help circumvent confounding the report of life stress with the rating of depression,[56] maternal reports of the twins' past-year life events were analyzed. Life events were categorized a priori as potentially within (eg, breaking up with someone) or beyond (eg, death of a close friend) the individual's control. Since we were interested in understanding the extent to which the genes for depression also increased the risk of experiencing negative life events, we analyzed only those events that could arise as much from the child's genotype as from his or her environment, such as failing a grade or losing a close friend through arguments. A life-events subscale was obtained by comparing those "behavior-dependent" events that were significantly associated with the ratings of depression, using a separate regression model for boys and girls.

The mothers' ratings of several pubertal items from the Pubertal Development Scale[57] obtained during the course of the psychiatric interview were used to assess the twins' pubertal status. The puberty measure used was composed of 3 items that showed a an age distribution similar to the Tanner stage III age distribution from the Great Smoky Mountain Study, a population-based, singleton study of children and adolescents.[58] These items concerned body hair, facial hair, and breaking voice in boys and body hair, breast development, and menarche in girls. The 3 items were scored as follows: 0, no; 1, yes barely; 2, yes definitely; or 3, development complete. To obtain a continuous measure, the 3 sex-specific items were added into a subscale score, and a score of 2 was used as the cutoff for characterizing twins as prepubertal or pubertal.

STATISTICAL ANALYSIS

Epidemiological Trends

In estimating the means for the different age groups in the sample, it is important to take account of the repeated-measures structure of the data. Because 2 waves of data are included, some twin pairs are informative about both ages, but the repeated measures introduce correlated errors of measurement that will lead to the underestimation of SEMs. We therefore used PROC MIXED program (SAS, version 6.12)[59] to generate maximum likelihood estimates of mean CAPA depression scores (by age and sex) that take account of the cross-wave and cross-twin covariances as part of the fitted model.

To evaluate the impact of life events on depression, the maximum likelihood estimates of depression symptom scores for each age were examined among both those

sults of 1 twin study of childhood and adolescent depression demonstrate increasing heritability with increasing age among 411 juvenile twins as assessed by questionnaire.[49]

To further explore the influence of genetic and environmental risk factors on adolescent depression, particularly among adolescent girls, data on depression in prepubertal and pubertal male and female same-sex twins from the Virginia Twin Study of Adolescent Behavioral Development were analyzed. Our goals were (1) to compare the trajectory of depressive symptoms among boys and girls from childhood into adolescence; (2) to analyze the role of genetic, shared, and unique environmental factors in depression among prepubertal and pubertal male and female twins; and (3) to investigate a possible common etiology between liability to depression and one salient index of the child's environment: past-year life events.

RESULTS

EPIDEMIOLOGICAL TRENDS

Life Events

The life events significantly associated with the twins' depression were, with slight exceptions, comparable in

boys and girls who had and those who had not experienced a significant life event in the past year.

The main and interactive effects of sex, pubertal status, age, and total number of past-year life events on depression scores were then assessed with a regression analysis that used both waves of data and allowed for the correlation between twins. The partial sums of squares for each variable that controlled for the effect of all the other variables in the model were estimated using the type III sums of squares procedure in SAS, version 6.12.[59] For all analyses, an α level of significance of .05 was used.

Univariate Genetic Analysis

The analysis of twin data represents a powerful method for quantifying genetic and environmental influences on behavioral variation.[60] To elucidate potential differences in the influence of genes on depression as a function of pubertal status and sex, the twin correlations for depression were estimated separately in prepubertal and pubertal male and female MZ and DZ twins. In estimating the twin correlations, to make the most efficient use of the available information, we allowed for the covariance structure of the twin observations across waves. Using the statistical program Mx,[61] the maximum likelihood estimates of the twin correlations using both wave 1 and 2 data were derived under a factor model in which the means, variances, and covariances were constrained to be the same twin for pairs and across the 2 data sources.

To obtain more precise estimates of the relative influence of genetic, shared, and nonshared environmental factors on depression, genetic and environmental structural equation models were then fitted to the raw data from wave 1 and 2 simultaneously by the method of maximum likelihood pedigree analysis[62] using Mx.[61] To obtain the best-fitting model, a series of submodels in which the genetic and/or shared environmental effects were fixed to 0 were compared with the full model by likelihood ratio χ^2 analysis.

BIVARIATE GENETIC ANALYSIS

Twin Correlations

An examination of the pattern of correlations between MZ and DZ twins allows us to infer the influence of genetic and environmental factors on variation in a single behavior. The cross-twin and cross-trait correlations (ie, the correlation between a twin's measure of trait A with the cotwin's measure of trait B and vice versa) allows us to decompose the causes of covariation between 2 behaviors, such as depression and life events.

Bivariate Structural Equation Modeling

To systematically test and resolve different etiological models regarding the causes of association between depression and life events, a bivariate common factor model was fitted to the twin data. This model can specifically test whether the genes that predispose to negative life events are those that increase risk of depression.

The bivariate common factor model (shown in **Figure 1** for an individual of a pair) includes 2 common genetic risk factors that are variable specific but common to both waves ($A_c$evts and $A_c$dep), unique environmental effects for each trait that are correlated across the 2 waves (Eevts and Edep), and a shared environmental factor specific to life events (Cevts) (the shared environmental parameter is a latent environmental construct, but life events is a measured variable that may be mediated by genetic or environmental factors). This model assumes that the association between depression and life events is due to a common genetic risk factor ($A_c$dep-evts) that influences both depression and life events at both waves 1 and 2.

Prior to model fitting, the data were normalized and standardized by age and sex using the PROC RANK and PROC STANDARD procedures (SAS, version 6.12),[59] setting the means and variances to be equivalent across each age. For the bivariate analysis, models were fitted to the 8×8 polyserial correlations matrices consisting of CAPA depression symptoms scores for twin 1 and twin 2 and maternal ratings of both twins' life events from waves 1 and 2. The correlation matrices were weighted with the asymptotic covariance matrices using Prelis 2,[63] and the models were fitted to the twin data by maximum likelihood using the statistical program Mx.[61] Since we were fitting to correlation matrices, the variance in each observed phenotype was constrained to be equal to 1. The overall goodness of fit of the models was evaluated using a likelihood ratio χ^2 analysis with an α level of .05. To obtain the best-fitting and most parsimonious model, Akaike information criteria[64] were computed as the χ^2 result minus 2 times the degrees of freedom.

boys and girls. These included increased quarreling between parents, parent becoming less interested or less loving, parent becoming more nagging, failing grades on a report card, and failing a grade. For girls, breaking up with a boyfriend proved depressogenic, whereas failing to make an athletic team or band or losing a close friend through arguments was associated with depression in boys.

Sex and Age Differences in the Prevalence of Depressive Symptoms

The age distribution of mean CAPA depression scale scores (**Figure 2**) indicated that boys and girls were quite similar in their level of depression before age 12 years, but the rates for girls show an increase over those for boys thereafter. Although the rates of depressive symptoms also increase for boys during adolescence, the rise is not as marked as for girls.

For both boys and girls who have experienced 1 or more life events, depression scores show a steady increase after age 11 years; however, the mean depression score is still higher for girls, particularly for the older girls (except for the oldest boys). For those boys who have not experienced a notable past-year life event, the age distribution of depression scores is nearly flat. For girls, the increase in depression is still evident (although not nearly as steep), implicating factors other

than life events to explain an age-related rise in these symptoms.

Regression Analysis

The regression of depression on age and sex indicates a significant difference in depression between boys and girls with increasing age ($P<.001$) (a sex × age interaction) consistent with the trends described above.

A regression analysis conducted separately on the boys and girls (results available on request) indicates a significant main effect of total number of life events for both boys and girls but a significant interaction between events and pubertal status and age only for girls.

Because of the marked collinearity between age and pubertal status, we were unable to estimate the effects of these 2 variables simultaneously. Separate regression models were therefore fitted using either puberty or age. Under 2 separate regression models (1 for pubertal status and 1 for age), each variable's partial sums of squares and associated probability were used to examine these effects in the 2 sexes together (**Table 1**). The results for pubertal status and age are strikingly similar, indicating that after controlling for the effect of all the other variables in the regression model, the impact of life events on depression is significantly greater in the pubertal girls (sex × pubertal status [age] × life events interaction).

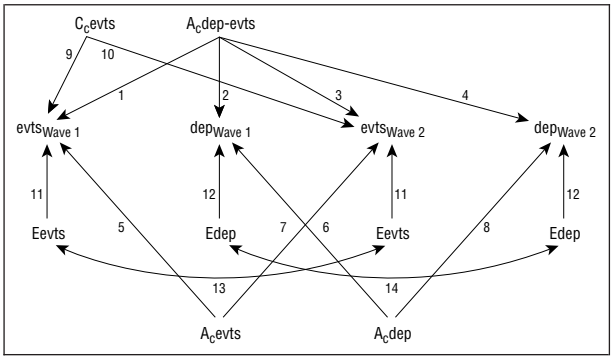

Figure 1. *The bivariate common factor model includes a common genetic risk factor that influences both depression and life events at both waves and 2 common genetic risk factors that are common to both waves but variable specific. Numbers are path numbers. $A_c$dep-evts indicates a common genetic factor for depression and life events; $C_c$evts, a shared environmental factor for life events; $A_c$dep, a common genetic factor for depression; $A_c$evts, a common genetic factor for life events; Eevts, a unique environmental factor influencing life events; and Edep, a unique environmental factor influencing depression.*

GENETIC ANALYSES

Genetic and Environmental Influences on Depression in Prepubertal and Pubertal Male and Female Twins

The maximum likelihood estimates of the MZ and DZ twin correlations and components of variance for depression (**Table 2**) indicate increased heritability only for pubertal girls (28%), consistent with a genotype × puberty × sex interaction. In all but the adolescent girls, the genetic parameter could be fixed to 0 without significant deterioration in the fit of the model.

To determine whether the same genetic factors influence risk for both depression and life events, we limited our analysis to the pubertal girls, given the evidence for genetic influences on depression only in this group.

Overall, the twin correlations (**Table 3**) for depression were nearly identical in the 2 waves (0.37 MZ vs 0.09 DZ) and indicate genetic influences. The pat-

Table 1. Regression Analysis of Child and Adolescent Psychiatric Assessment (CAPA) Depression Scores on Main and Interactive Effects of Sex, Pubertal Status (Age), and Past-Year Life Events (N = 3120)

	Sum of Squares*	
	Pubertal Status	Age
Sex	2.15	0.04
Pubertal status (age)	0.63	0.08
Life events	0.26	0.71
Sex × pubertal status (age)	0.03	0.10
Sex × life events	0.10	3.10
Life events × pubertal status (age)	2.15	1.35
Sex × pubertal status (age) × life events	7.87†	7.67†

**The type III sum of squares represents the contribution of the source after controlling for all other variables in the model.*
†P<.001.

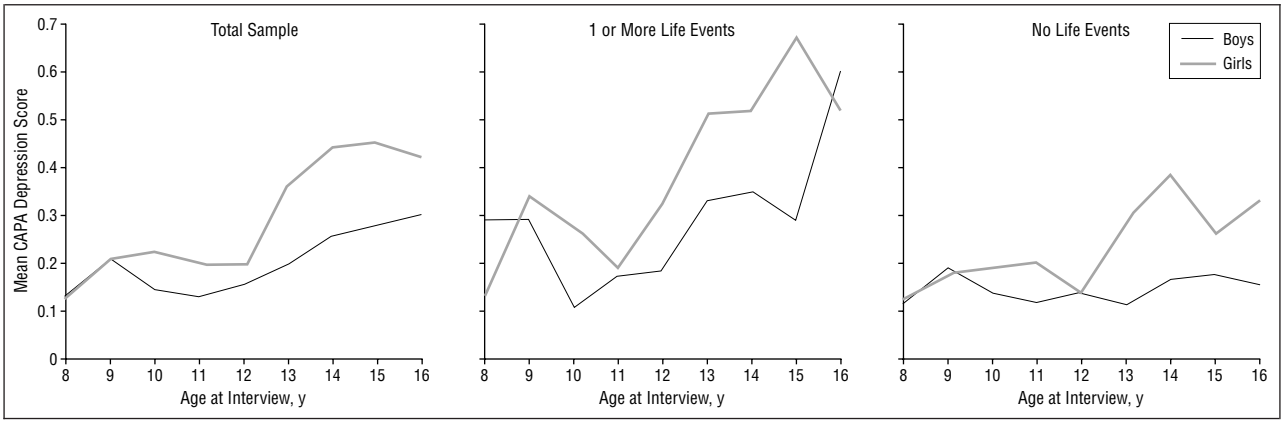

Figure 2. *The mean Child and Adolescent Psychiatric Assessment (CAPA) depression scores are given by age and sex for the total sample (1420 boys and 1700 girls), those with 1 or more life events (416 boys and 527 girls), and those without 1 or more life events (980 boys and 1138 girls).*

Table 2. Genetic Shared Environmental and Unique Environmental Components of Variance in Depression in Prepubertal and Pubertal Male and Female Monozygotic (MZ) and Dizygotic (DZ) Twins

	Maximum Likelihood Estimate				
	Twin Correlation (No.)		Component of Variance		
Pubertal Group	MZ	DZ	Genetic	Shared Environmental	Unique Environmental
Prepubertal males	0.14 (220)	0.00 (150)	0.00	0.00	1.00
Prepubertal females	0.13 (187)	0.00 (75)	0.00	0.00	1.00
Pubertal males	0.18 (226)	0.15 (114)	0.00	0.00	1.00
Pubertal females	0.35 (394)	0.13 (194)	0.28	0.00	0.72

Table 3. Twin Correlations for Depression and Life Events Among Monozygotic (MZ) and Dizygotic (DZ) Pubertal Female Twins

	MZ Twin Pairs (N = 185)			DZ Twin Pairs (N = 88)		
Variables	Wave 1	Wave 2	Cross-Wave*	Wave 1	Wave 2	Cross-Wave*
Twin 1 to twin 2, depression	0.374†	0.371†	0.113/0.292¶	0.093†	0.089†	0.027/0.000¶
Twin 1 to twin 2, events	0.906‡	0.890‡	0.415/0.515¶	0.749‡	0.522‡	0.196/0.271¶
Twin 1, depression to twin 2, events	0.252§	0.020§	0.046/0.157#	0.157§	0.095§	0.146/–0.103#
Twin 1, events to twin 2, depression	0.163§	0.192§	0.091/0.088#	–0.004§	–0.089§	–0.049/–0.146#
Twin 1, depression to twin 1, events	0.201‖	0.097‖	0.029/0.204**	0.141‖	0.190‖	0.041/–0.044**
Twin 2, depression to twin 2, events	0.136‖	0.174‖	0.059/0.098**	0.164‖	0.157‖	0.264/0.021**
Twin 1, depression to twin 1, depression			0.438††			0.218††
Twin 1, events to twin 1, events			0.390††			0.532††
Twin 2, depression to twin 2, depression			0.342††			0.300††
Twin 2, events to twin 2, events			0.555††			0.510††

**Cross-wave indicates wave I to wave II and wave II to wave I correlations.*
†*Twin correlations for depression.*
‡*Twin correlations for life events.*
§*Cross-twin, cross-variable, within wave.*
‖*Within twin, within wave, cross-variable.*
¶*Cross-twin, cross-wave, within variable.*
#*Cross-twin, cross-variable, cross-wave.*
***Within twin, cross-variable, cross-wave.*
††*Within twin, within variable, cross-wave.*

tern of twin correlations for life events at wave 1 (0.91 MZ vs 0.75 DZ) is consistent with shared environmental influences, whereas genetic effects predominate at the second wave of measurement (0.89 MZ vs 0.52 DZ). The average cross-twin and cross-variable correlations (0.16 MZ vs 0.04 DZ) provide information regarding the causes underlying the association between depression and life events. These indicate genetic influences, as do the average cross-twin and cross-wave correlations for the 2 variables separately (0.20 MZ vs 0.01 DZ for depression) and (0.46 MZ vs 0.23 DZ for life events) an index of the causes of persistence of depression and life events over time.

Bivariate Model-Fitting Results

The full bivariate common factor model provided an excellent fit to the twin data (χ^2_{62}=31.36, $P>.99$, Akaike information criteria= – 92.64). The best-fitting bivariate common factor model (**Figure 3**) (details on request) indicates that there is a common genetic factor ($A_c$depevts) that influences risk for depression and negative life events (within each wave and across time); however, the substantial genetic effects specific to depression (paths 7 and 8) and the specific genetic influence on the ratings of life events at wave 2 (path 6) indicate that the overlap is far from complete.

The paths from the common genetic factor to ratings of depression at the 2 times of measurement show that long-term stability of depression during adolescence is primarily accounted for by latent genetic factors. Consistent with the twin correlations, the shared environment had less influence on the ratings of life events at wave 2 than at wave 1. The genetic path to ratings of life events at wave 1 could be eliminated entirely, whereas there was significant genetic variance on life events at the second wave of measurement.

Overall, these results indicate notable genetic influences on both depression and life events; 30% of the variance in depression at the 2 waves of measurement is due to the genes and the remainder is due to unique environmental effects. Genetic factors account for a significant proportion of the variation in the reporting of life events, particularly at wave 2 (49% vs 91%).

COMMENT

The demonstrable increase in depression among girls during adolescence in our population sample of juvenile twins

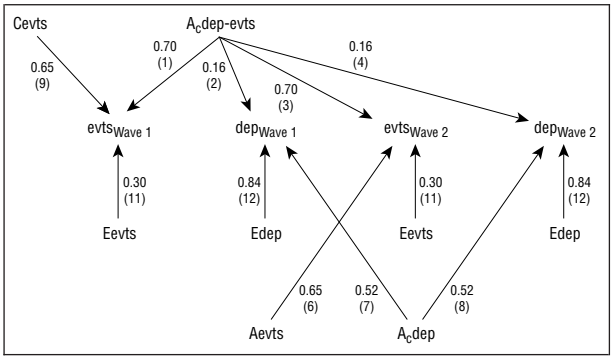

Figure 3. *Path coefficients from the best-fitting bivariate common factors model for the data on depression and life events for adolescent girls (185 monozygotic, 88 dizygotic). Path numbers are in parentheses. See the legend for Figure 1 for general abbreviations.*

is consistent with the findings from other epidemiological samples.[6,12,65] Our analysis showed a significant effect of life events in boys and girls, with a stronger effect in the pubertal girls.

For boys, depression appears to be largely attributable to the occurrence of negative life events, since any age-related increase in male depression is evidenced only among those who have experienced a life event in the past year. For girls, the rise in depressive symptoms is still evident (although to a lesser extent) among those who have not experienced a notable life event, implicating other putative risk factors. The estimates of the genetic and environmental influences on depression are also consistent with these age- and sex-related trends. The results from model fitting indicate a significant effect of the genes only in the adolescent girls that accounts for approximately 28% to 30% of the overall variance in depression.

Our results also indicate that the long-term stability of depression in pubertal girls is best explained by latent genetic factors. Furthermore, the influence of genes on the occurrence of life events is not stable; rather, our data support a developmentally related increase in genetic variance for life events. Whereas a "switching on of genes" for depression at wave 1 may be one explanation for the increase in depression among girls early in adolescence, their genetic mediation over time combined with the subsequent increase in genetic variance on life events at wave 2 may in part explain the persistence of these symptoms through adolescence.

In the final part of our analysis we attempted to resolve the cause of association between life events and depression in adolescent girls. The fit of a bivariate common factor model shows that part of the genetic risk for depression is attributable to a genetic predisposition to experiencing particular stressful life events. This is consistent with a recent study of depression among adult female twins[66] and growing literature[67-71] demonstrating "genetic control over exposure to the environment."[72]

The current findings should be interpreted within the context of many potentially important limitations. For example, if MZ twins have more similar environmental experiences than DZ twins, this could result in a spuriously high estimate of genetic influences. We did find a significant association between twin similarity in life events and similarity in depression among MZ twins, a clear violation of the equal environments assumption. This is not a surprising finding since one possible reason for MZ twins experiencing more similar life events is that the genes for life events may be correlated with depression. An alternative explanation is that MZ twins are more often in the same place at the same time; however, the correlations between depression and life events and a variety of indices of environmental similarity, including sharing the same room, having the same friends, dressing alike, or sharing the same class at school, were nonsignificant, providing support for a genetic explanation for greater similarity in life events among MZ twins.

Our measure of life events was based solely on a checklist, which may or may not completely and accurately index salient features of the child's environment. As with many studies of childhood psychopathology, our analysis may be influenced by rater effects that could lead to erroneous conclusions about causality. For example, although the maternal ratings of life events were selected to obtain a more objective measure of life stress independent of the child's depression, the mother's own history of psychopathology could influence her perception of her child's life.

Rather than a direct assessment, maternal ratings of pubertal status were used to assess the twins' pubertal development. The self-report version of this scale has been shown to have good reliability and validity,[5] with correlation values of 0.81 and 0.89 with maternal ratings of boys and girls, respectively.

Because of the low incidence of depressive disorder in the sample[51] we have analyzed self-reported depressive symptoms rather than depressive disorder; however, the depression scale used had a correlation value of 0.6 with overall incapacity to function assessed as part of the CAPA interview, indicating that it is a clinically relevant measure of psychopathology. Additionally, the endorsement of a particular depressive symptom in the CAPA interview is based on a relatively high threshold. The individual symptom must be somewhat uncontrollable, must intrude in 2 or more of the child's activities, and must last at least 1 hour during the course of the day. Because the CAPA has a threshold built in at the item level, it is likely that these symptoms are reflecting more than normal variation as assessed by questionnaires. An analysis of depressive symptoms obtained from the Recent Mood and Feelings Questionnaire[73] in this same population has demonstrated a very different pattern of twin correlations, specifically, a significant influence of the shared environment (J. Lessem, PhD, personal communication, February 12, 1998), suggesting that the CAPA is assessing a different depressive phenotype, perhaps one that is more extreme than that assessed solely by questionnaire.

Finally, the bivariate common factor model represents only 1 of many equally plausible genetic or psychosocial models for explaining these data. Furthermore, since our analyses were limited to those events that could arise from either the genotype of the child or his or her environment, our findings are not generalizable to understanding the association between depression and purely environmental events that are, by definition, beyond the child's control.

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Reprints: Judy L. Silberg, PhD, Virginia Commonwealth University, Department of Human Genetics, Virginia Institute for Psychiatric and Behavioral Genetics, PO Box 980003, Richmond, VA 23298-0003 (e-mail: Jsilberg@hsc.vcu.edu).

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