Selecting Early Onset MDD Probands for Genetic Studies: Results From a Longitudinal High-Risk Study

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Recent studies have found high rates of familial aggregation of major depression (MDD) in relatives of depressed children coming for treatment, leading investigators to suggest that probands for genetic studies of MDD should be selected from samples of depressed children being brought for treatment. Implicit in this recommendation is the assumption that childhood and adult depression are similar disorders. This assumption in turn implies that children with prepubertal or adolescent onset depression are at high risk for having recurrent episodes of MDD that continue into adulthood. The data supporting this latter hypothesis, however, is limited and contradictory. In this article we report results from a high-risk longitudinal family study in which we explored the recurrence and continuity into adulthood of prepubertal or adolescent onset MDD in offspring who were at high or low risk for MDD, by virtue of their parental depression status. One hundred eighteen offspring from 55 families in which one or more parents had MDD and 50 offspring from 21 families in which neither parent had MDD were followed for more than 10 years (all offspring were 20 years or older at the end of follow-up time) and blindly reassessed using a semistructured diagnostic instrument. Offspring with childhood/adolescent onset MDD were at significantly greater risk for recurrence in adulthood (after age 25) as compared with offspring without an onset of childhood/adolescent MDD, if they had a history of parental MDD. In contrast, among offspring without a history of parental MDD, those with childhood/adolescent onset MDD were at no greater risk for continuing to have MDD in adulthood (after age 25) than those without childhood/adolescent onset MDD. Moreover, there was a trend for offspring with childhood/adolescent onset MDD to be at greater risk for recurrence after age 25 if they had a history of parental MDD, as compared with offspring without a history of parental MDD (60 vs. 18%). We conclude that childhood/adolescent onset MDD is a heterogeneous disorder, with family history of MDD appearing to define a subtype of childhood/adolescent onset MDD that is recurrent and continues into adulthood. Our findings suggest that caution should be exercised in selecting depressed children and adolescents brought for treatment as probands in genetic studies of early onset MDD. A conservative strategy would be to select only those depressed children and adolescents with a family history of MDD and reassess the treated sample as they mature, ensuring that they go on to have MDD in adulthood. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 96:93–101, 2000
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INTRODUCTION

The recent National Institute of Mental Health Genetics workgroup was convened to address research priorities for determining genetic influences on mental disorders [Genetics and Mental Disorders: Report of the National Institute of Mental Health's Genetic Workshop. NIH, 1998]. Among the recommendations

were large-scale molecular genetic studies of schizophrenia and bipolar disorder as well as early onset depression (defined as onset before the age of 20 years) that is also recurrent. The latter was based partially on the observation that the familial nature of major depression (MDD) is strongest for early onset (< 20 or < 30 years) [Mendlewicz and Baron, 1981; Weissman et al., 1984, 1988] and for recurrent MDD [Bland et al., 1986, Kupfer et al., 1989]. These latter observations have led some investigators, based on their studies of families of depressed children, to argue that probands for genetic studies could be selected from samples of depressed children coming for treatment [Kovacs et al., 1997; Todd et al., 1993]. This assumption rests on the belief that childhood and adult depression are similar disorders, implying that children with prepubertal and adolescent onset depression will go on to have recurrent episodes in adulthood. The data supporting this assumption is limited and contradictory. Several independent studies [Harrington et al., 1990; Lewinsohn et al., 1999; Pine et al., 1998; Rao et al., 1995; Weissman et al., 1999a] have shown that subjects with adolescent onset MDD have a high risk of recurrence and continuity into adulthood. In contrast, Harrington et al. [1990] and Weissman et al. [1999b] have shown in independent studies that prepubertal children with MDD are less likely to continue to have MDD in adulthood, although Weissman et al. [1999b] have shown that recurrence and continuity into adulthood is more likely if the prepubertal depressed child has a family history of MDD. Most of these studies include depressed children and adolescents being brought to treatment who were sampled from clinics. Thus, the data on continuity (or the lack thereof) into adulthood, in these studies, may be biased by selection factors that determine the treatment-seeking processes for depressed children. For example, in Weissman's study the findings on continuity into adulthood suggest that children with prepubertal onset MDD being brought for treatment may include a preponderance of disruptive children who later develop alcoholism and conduct disorder as they mature.

In this article we present data on the continuity and recurrence of MDD between childhood (defined as <13 years)/adolescent (defined as 13–19 years) onset MDD and MDD in adulthood (≥20 years) in the offspring of depressed and nondepressed parents. The advantages of this design are threefold: (1) The children are not selected from treatment settings; (2) the study is longitudinal (including three assessments over 10 years) so that the clinical course could be studied more directly as the children matured into adulthood; (3) since both high- and low-risk samples (as defined by a history of parental MDD) were included, the association between parental MDD and the recurrence and continuity into adulthood of offspring MDD can be directly examined. The question that we attempt to answer here is whether children or adolescents who have experienced an episode of MDD should be selected as probands in genetic studies of early onset recurrent MDD. Specifically, we explore the following issues: (a) are offspring with childhood/adolescent onset MDD more likely to have MDD in adulthood if they have a history of parental MDD, and (b) does the risk of continuity into adulthood of MDD vary with whether the first onset was in childhood or adolescence?

MATERIALS AND METHODS

See Weissman et al. [1997] for a full description of the overall methods, which are briefly described below.

Sample and Assessments

Offspring were initially selected for the presence or absence of a lifetime history of MDD based on Research Diagnostic Criteria (RDC) in their parents who were receiving ambulatory treatment. The normal controls came from a New Haven, Conn., community survey and had no history of psychiatric illness as judged from at least four direct interviews (the last two using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version modified for the study of anxiety disorders (SADS-LA) during a 10-year period [Mannuzza et al., 1986]. All probands were white and group matched for age and sex.

At the initial interview (time 1), the sample consisted of 220 offspring, aged 6 to 23 years, from 91 families. Approximately two years after the initial interview (time 2), 85 (93%) of the 91 original families consented to participate. At time 2, 174 (79%) of the offspring were interviewed again. Approximately 10 years after the initiation of the study (time 10), the 91 original families were contacted and reassessed. There were four deaths among the 91 probands and 73 (84%) were interviewed again. Sixty-six spouses of probands were eligible to be interviewed. There were five deaths and of the remaining 61 living spouses; 52 (84%) were interviewed. Among the 220 offspring interviewed at time 1, there were two deaths (neither by suicide) and one offspring was found to have Down syndrome. Eighty-four percent (182/217) of the offspring interviewed at time 1 were interviewed again at time 10. There were no significant differences in attrition rates of probands' spouses or offspring by parental diagnostic status. Attrition for the probands and spouses did not vary significantly by sex or age. Although attrition of offspring did not differ by sex, older offspring were more likely to be interviewed than their younger counterparts (mean:28.5 versus 26.4 years; t = −2.09, df 54.9, $p = 0.04$). There were two first onsets of MDD (determined by independent best-estimate diagnosis made blind to initial proband and offspring data [Leckman et al., 1982] in the spouses of the nondepressed probands between times 2 and 10. These two families had four offspring and were reassigned to the depressed-parent group.

At time 10, probands, spouses of probands, and offspring were independently interviewed with the SADS-LA modified to include RDC, *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) criteria [Mannuzza et al., 1986]. In the previous interviews offspring younger than 18 years were interviewed with the child revision of the SADS and an informant, usually the mother, was also independently interviewed

about the offspring [Weissman et al., 1987]. All interviews of offspring were conducted blind to the parents' status and the offspring' previous assessments. The interviews at time 2 covered the period from birth to the last interview and at time 10 covered an assessment period from the last interview until the present. Life charts were used to record all episodes of illness that occurred during the assessment period.

Interviewers and Best-Estimate Procedures

Interviewers and best estimators were MD, PhD, or master's level clinically experienced mental health professionals. See Weissman et al. [1997] for information on training, monitoring, and interrater reliability described elsewhere. Best-estimate diagnoses of offspring were based on all available information collected for the time period of assessment and were conducted blind to the proband diagnosis, independent of the previous offspring diagnosis, and by at least two clinicians.

Data Analysis

Group differences among offspring with childhood onset MDD, adolescent onset MDD, and controls who had neither childhood nor adolescent onset MDD were determined as follows: when the risk of the outcome considered did not vary with age and was dichotomous, chi-square analyses or Fisher's exact tests (when cell sizes were extremely small) were used for direct comparisons, and logistic regression was used when controlling for potential confounders. Continuous outcomes that were assumed to be normally distributed were tested using t-tests and analysis of variance for direct comparisons and analysis of covariance to adjust for the effect of covariates. When the continuous outcomes were not normally distributed, or when the outcome was ordinal, the Mann-Whitney and Kruskal-Wallis nonparametric procedures were used [Siegel, 1956].

For dichotomous outcomes where the risk was believed to vary with age, differences between groups were examined using survival analysis techniques. Specifically, plots comparing the cumulative probability of developing an episode of MDD after a specified age among groups was made using the Kaplan Meier method [Kaplan and Meier, 1958]. The proportional hazards model [Cox and Oakes, 1984] was used to determine the relative risk of the outcome under consideration among the groups of interest, while controlling for the effects of confounding variables. Because the disorder status of offspring from the same family may not be independent, the assumption of independence of the outcome variable implicit in the use of the proportional hazards model may be violated. To overcome this problem we used the methods of Binder [1992], which extend the methods of Lin and Wei [1989], who proposed a method of estimating the covariance matrix of the estimated parameters when the model is misspecified, to those situations where there is correlation among sample units. SUDAAN [Shah et al., 1996] was used to obtain the appropriate adjusted variances for the relevant parameters. All other analyses were performed using SAS statistical analysis software, version 6.04 (SAS Institute Inc., Cary, N.C.).

RESULTS
Sample Characteristics

Table I shows the sociodemographic characteristics of offspring with and without childhood/adolescent onset depression in both high-risk (one or more parents depressed) and low-risk (neither parent depressed) groups. The sample studied was restricted to those offspring who were over 20 years of age when last interviewed (time 10). Fifty-three male offspring and 65 female offspring from a total of 55 families in the high-risk group were greater than age 20 at the end of follow-up time. Of these, 15 (28%) males and 36 (55%) females had a first onset of MDD in childhood or adolescence. The low-risk group consisted of 24 male and 26 female offspring from a total of 21 families, who were greater than age 20 years at end of follow-up. Of these, three (14%) male offspring and seven (27%) female offspring had a first onset of MDD in adolescence. Only one female offspring and no male offspring had an episode of MDD in childhood. Consequently, the analysis in the low-risk group was restricted to only those offspring with a first onset of MDD in adolescence and those with neither childhood nor adolescent onset MDD.

A significantly greater proportion of females was found in offspring with adolescent onset MDD as compared with offspring without childhood/adolescent onset MDD. There were no statistically significant differences in socioeconomic status across the three groups. Overall, at the end of the follow-up period, offspring with adolescent onset MDD tended to be somewhat older, and offspring with childhood onset MDD tended to be somewhat younger, than offspring who did not have either childhood or adolescent onset MDD. However, these age differences were found to be statistically significant only in the low-risk group, in which offspring with adolescent onset MDD were found to be, on average, three years older than those without childhood/adolescent onset MDD.

Relative Risk of MDD in Adulthood

To help illustrate whether offspring with childhood or adolescent onset MDD were more likely than offspring without MDD in childhood or adolescence to have an episode of MDD in adulthood, the proportions of offspring with an episode of MDD occurring in adulthood among offspring with and without childhood/adolescent MDD is presented in Table II. The rightmost columns of this table show the corresponding relative risk for having an episode of MDD in this time period (adjusted for varying ages of offspring and offspring gender using proportional hazards models). Following suggestions by Harrington et al. [1990], the risk of MDD in adulthood was examined using two criteria for onset in adulthood to determine how far into adulthood recurrent episodes of MDD occur: (1) onset of MDD after 20 years of age and (2) onset of MDD after 25 years of age. The second age threshold of 25 years was selected for the following reasons because the

TABLE I. Sociodemographic Characteristics of Offspring With and Without Childhood/Adolescent Major Depression (MDD) by Parental Depression Status

	Depression status of offspring		
	Childhood onset MDD	Adolescent onset MDD	No childhood/ adolescent MDD
One or both parents depressed			
Number of offspring	[18]	[33]	[67]
Gender			
Male	38.9 (7)	24.2[a] (8)	56.7[a] (38)
Female	61.1 (11)	75.8 (25)	43.3 (29)
Age at follow up (yrs)			
Mean (s.d.)	27.0 (3.64)	29.8 (3.92)	28.3 (4.41)
(range)	(21.2–32.6)	(21.9–38.0)	(20.1–35.9)
Socioeconomic status			
I, II, and III	33.3 (6)	66.7 (22)	53.9 (35)
IV and V	66.7 (12)	33.3 (11)	46.1 (30)
Neither parent depressed			
Number of offspring		[10]	[40]
Gender			
Male		30.0 (3)	52.5 (21)
Female		70.0 (7)	47.5 (19)
Age at follow up (yrs)			
Mean (s.d.)		30.7[b] (2.61)	27.7[b] (3.69)
(range)		(24.9–34.3)	(20.1–34)
Socioeconomic status			
I, II, and III		50.0 (5)	50.0 (20)
IV and V		50.0 (5)	50.0 (20)

[a]$p = .002$.
[b]$p = 0.085$.

mean age of offspring at the end of the follow-up period was approximately 30 years of age, and we have defined the beginning of adulthood as 20 years; therefore, we determined that the midpoint of the range 20–30 years was an appropriate second threshold for adulthood in the context of this study. The findings varied considerably with these different age criteria for adult onset.

Relative Risk of MDD in Adulthood by Childhood/Adolescent and Parental MDD Status

Relative Risk of MDD After Age 20. When adulthood was defined as greater than 20 years of age, results showed that both childhood-onset and adolescent onset MDD increased the risk for MDD in adulthood as compared with those without childhood/adolescent onset MDD in high-risk offspring (Table II). This risk did not vary by development phase of offspring: both offspring with childhood-onset MDD and offspring with adolescent onset MDD were approximately three times more likely to have an episode of MDD after age 20 than offspring without childhood/ adolescent MDD. Among low-risk offspring, those with adolescent onset MDD were approximately 11 times more likely to experience an episode of MDD in adulthood as compared with offspring without MDD in childhood/adolescence. Although the relative risk of MDD in adulthood is greater in low-risk offspring than in high-risk offspring, this difference was not statistically significant. It is of interest to note that these differences appear to occur because high-risk offspring without childhood/ adolescent MDD are more likely to have an onset of MDD in adulthood (22%) as compared with low-risk offspring without childhood onset MDD (5%). Because

of the significantly higher rates of anxiety disorders that were found in offspring with childhood/adolescent onset MDD, these analyses were repeated with anxiety disorder included as a covariate. The results remained virtually unchanged.

Relative Risk of MDD After Age 25. When the outcome was defined as the occurrence of an episode of MDD after age 25, only one of the nine offspring in the low-risk group with adolescent onset MDD and none of those without childhood/adolescent onset MDD had an episode of MDD after age 25 (Table II). In contrast, offspring in the high-risk group continued to have episodes of MDD after age 25. Moreover, there was still a significantly increased risk of an episode of MDD in adulthood for offspring with childhood onset MDD as well as those with adolescent MDD when compared with those offspring without childhood/adolescent onset MDD when the threshold age for adulthood was increased from 20 to 25.

Effect of Parental MDD Status on Cumulative Risk of MDD in Adulthood

While the previous set of analyses allowed us to determine whether offspring with childhood or adolescent MDD are at higher risk for MDD in adulthood and whether this relative risk varied with parental depression status, it does not directly answer the question of whether offspring with childhood or adolescent MDD are more likely to have recurrent episodes of MDD in adulthood if they have a history of parental MDD. In this section we report results of survival analyses performed to answer this question.

In Figures 1 and 2 we present the results of compar-

TABLE II. Rates of Major Depression (MDD) and Relative Risk of MDD in Adulthood for Offspring With Childhood or Adolescent Onset MDD Compared With Offspring Without Childhood/Adolescent Onset MDD

MDD in adulthood	Depression status of offspring			Relative risk[a]	
	Childhood onset MDD	Adolescent onset MDD	No childhood/ adolescent MDD	A	B
One or both parents depressed				A	B
MDD after age 20	[18]	[33]	[67]	2.275†	3.20***
	38.9 (7)	60.0 (20)	22.4 (15)	(0.9, 5.745)	(1.63, 6.3)
MDD after age 25	[12]	[29]	[50]	4.01*	3.60*
	50.0 (6)	37.9 (11)	12.0 (6)	(1.07, 15.1)	(1.32, 9.84)
Neither parent depressed					
MDD after age 20		[10]	[40]		10.78**
		60.0 (6)	5.0 (2)		(2.07, 56.2)
MDD after age 25		[9]	[31]		(0.225)[b]
		11.1 (1)	0.0 (0)		

†: p < 0.1; *: p < 0.05; **: p < 0.01; ***: p < 0.001.
[a]Results from Proportional Hazard Model (adjusting for correlation between family members) controlling for sex and age at last interview. A: Relative Risk of childhood Onset MDD and no childhood/adolescent onset MDD. B: Relative Risk of adolescent onset MDD and no childhood/adolescent onset MDD.
[b]Fischer's exact probability.

ing the cumulative risk of experiencing an episode of MDD after ages 20 and 25, respectively, for offspring with childhood/adolescent MDD, by the depression status of their parents. Results shown in Figure 1 indicate that among offspring with childhood/adolescent onset MDD, 89% with a history of parental MDD, as compared with 75% without a history of parental MDD, experienced a subsequent episode of MDD after age 20. This difference in risk was not statistically significant. Because survival analysis removes a subject from the sample once the subject has experienced a single episode of depression after age 20 the plots in Figure 1 provide little information about the risk for MDD further into the follow-up period, for example, after age 25. Therefore, we examined the risk of depression occurring after age 25, results of which are presented in Figure 2. We observed a trend ($p = 0.08$) overall for offspring with childhood/adolescent MDD to be at far greater risk for having an episode of MDD after age 25 if they had at least one depressed parent as compared with those offspring with neither parent depressed. For example, Figure 1 shows that although 60% of offspring in the high-risk group had an episode of MDD between the ages of 25–35 years, only 18% of offspring in the low-risk group did so. The results in Figures 1

and 2 taken together imply that almost all of the recurrent episodes of MDD experienced by low-risk offspring occurred between the ages of 20–25 years.

Relative Risk of MDD in Adulthood by Gender of Offspring

We found (results not shown) that among offspring with a history of childhood/adolescent onset MDD, female offspring of depressed parents were significantly more likely than male offspring to have an episode of MDD after age 20 (relative risk = 4.7, 95% confidence interval [CI]: 1.41, 15.6). In contrast, among offspring with a history of adolescent onset MDD, but without a parental history of MDD, females were no more likely to have an episode of MDD after age 20 than males. Although the risk of MDD after age 25 for offspring with childhood/adolescent onset MDD and a history of parental depression was higher for females than males, this difference was no longer found to be statistically significant (relative risk = 2.302, 95% CI: 0.518, 10.24).
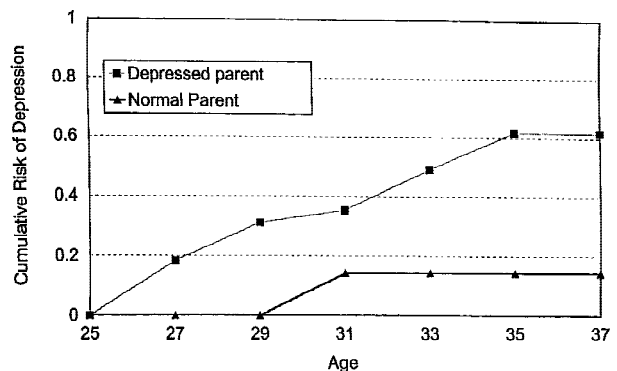
Course of MDD

In an effort to understand the varying patterns of risk for MDD in adulthood by parental depression sta-
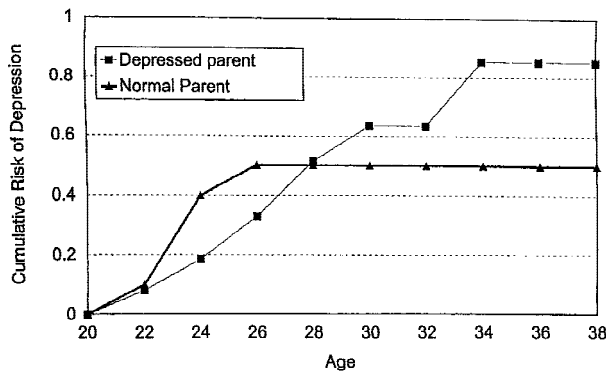
Fig. 1. Cumulative risk of MDD after age 20 in offspring with childhood/adolescent onset MDD by parental depression status.

Fig. 2. Cumulative risk of MDD after age 25 in offspring with childhood/adolescent onset MDD by parental depression status.

TABLE III. Characteristics of Course of MDD during Follow-Up Time Interval in Offspring With Childhood or Adolescent Onset MDD

	One or both parents depressed				Neither parent depressed	
	Childhood onset MDD		Adolescent onset MDD		Adolescent onset MDD	
Characteristic	Male (N = 7)	Female (N = 11)	Male (N = 8)	Female (N = 25)	Male (N = 3)	Female (N = 7)
Age of onset (yrs)						
Mean	9.71	9.82	16.38	15.42[a]	17.33	17.43[a]
(SD)	(1.70)	(2.36)	(2.00)	(1.85)	(1.15)	(1.81)
(range)	(7–12)	(6–12)	(13–19)	(13–19)	(16–18)	(14–19)
number of episodes, %						
1	0.0[b]	18.2	75.0[b,c]	20.0[c]	0.0	14.3
2+	100.0	81.8	25.0	80.0	100.0	85.7
Median number of episodes (range)	4 (2–4)[d]	4 (1–8)	1 (1–2)[d,e]	3 (1–7)[a]	2 (2–3)	3 (1–5)
Average duration of MDD episode (weeks)						
Median	17.5	31	12	23.14	52	11.67
(range)	(5–71.5)	(9.3–104.7)	(7–390)	(2–104)	(5.5–82.7)	(1.5–124)
Number of episodes per year of follow-up time (median)	0.22[f]	0.21	0.09[5,g]	0.23[g]	0.16	0.21
Percentage of follow-up time spent in episode of MDD (median)	0.03	0.10	0.02	0.10	0.13	0.06

[a]Significant differences ($p = 0.0155$) between mean age of MDD in female offspring with depressed parents and normal parents.
[b]Significant differences ($p = 0.00699$).
[c]Significant differences ($p = 0.00822$).
[d]Significant differences ($p = 0.0026$) between median number of episodes in male offspring of depressed parents with childhood and adolescent onset MDD.
[e]Significant differences ($p = 0.0065$) between median number of episodes in male and female offspring of depressed parents with adolescent onset MDD.
[f]Significant differences ($p = 0.0008$) between median of average number of episodes in male offspring of depressed parents with childhood and adolescent onset MDD.
[g]Significant differences ($p = 0.0008$) between median of average number of episodes in male and female offspring with adolescent onset.

tus and offspring gender, we examined the characteristics of the course of MDD in offspring with childhood or adolescent onset major depression. These characteristics are presented in Table III by gender and parental depression status of offspring. There were significant variations in the course of major depression by gender for both prepubertal and adolescent onset major depression in offspring of depressed parents.

Results show that, for offspring with adolescent onset MDD and a history of parental MDD, females tended to have more frequent episodes of longer duration than males. However, only the median number of episodes was found to be significantly greater. Significant differences in frequency or duration of episode were not observed by gender among offspring with childhood onset MDD. There were no statistically significant variations in the course of MDD by gender in offspring of nondepressed parents although this could be due to the small number of males with MDD in this group.

When female offspring in the high-risk group were compared with those in the low-risk group, we found that although the median number and range of episodes were very similar for adolescent onset depression in female offspring of both depressed and nondepressed parents, the average duration of these episodes appeared to be shorter in the female offspring of nondepressed parents, although this difference was not found to be statistically significant. In addition, the mean age of onset for MDD among high-risk females was significantly earlier (15.4 years) than the mean age of onset of MDD (17.4 years) in the low-risk group. The lower half of Table III shows characteristics of course of MDD adjusted for unequal lengths of follow-up time in off-spring. The findings obtained after adjusting for unequal lengths of follow-up time remained essentially unchanged.

Rates of Other Adult Psychiatric Disorders

To determine whether the increase in risk of depression in adulthood among offspring with childhood/adolescent onset MDD was accompanied by an increase in risk for other adult psychiatric disorders, we compared rates of psychiatric disorders with onset after age 20 in offspring by childhood/adolescent onset MDD status (results not shown). With the exception of MDD, there were no statistically significant differences in risk, for any of the psychiatric disorders we examined, among offspring with childhood/adolescent onset MDD compared with those without childhood/adolescent onset MDD for either the high- or low-risk offspring.

DISCUSSION

The primary findings of this study suggest the following.

(1) For offspring without a parental history of MDD, a history of childhood/adolescent MDD placed them at significantly increased risk for developing an episode of MDD after age 20 when compared with those without a history of childhood/adolescent MDD. This increased risk, however, did not persist after age 25.

(2) For offspring with a history of parental MDD (a) there was a significantly increased risk of MDD after age 20 for those with a history of childhood/adolescent MDD when compared with those with-

out a history of childhood/adolescent MDD. Moreover, this increased risk for MDD persisted even after the age of 25. (b) Offspring with childhood onset MDD were not significantly different from those with adolescent onset MDD with respect to their risk of MDD in adulthood. (c) Female offspring with childhood/adolescent onset MDD were more likely than male offspring to continue to have recurrent episodes in adulthood.

(3) Overall, there was a trend for a history of parental depression to increase the risk for depression in adult life, after age 25, among individuals with childhood or adolescent onset MDD.

In both high- and low-risk groups offspring with childhood/adolescent MDD were found to have significantly higher rates of anxiety disorders in childhood (prior to the onset of MDD) when compared with offspring without childhood/adolescent onset MDD. However, when the presence of a prior anxiety disorder was controlled for in the analyses, the results remained virtually unchanged.

Our findings appear to support the hypothesis that offspring with an onset of MDD in childhood or adolescence are more likely to continue to have subsequent episodes of MDD in adult life (>25 years) if they had a history of parental MDD. Although we found that both male and female offspring with adolescent onset MDD who did not have a history of parental MDD had subsequent episodes of MDD in the first five years of adult life, the majority of these offspring did not continue to have them thereafter. Because the number of females with childhood/adolescent MDD far outnumber the number of males with childhood adolescent onset MDD in both high- and low-risk groups, a possible contribution to the difference in patterns of risk in offspring by parental MDD status is the difference in course of adolescent-onset MDD observed in female offspring by their parental depression status. We found that female offspring of nondepressed parents had, on average, an onset of MDD two years later than that of those with a depressed parent, and that although both groups on average had multiple episodes of MDD, those with no history of parental depression tended to have episodes of shorter duration. There were too few male offspring in the low-risk group to make meaningful comparisons among male offspring by parental depression status.

Comparison With Other Studies

To our knowledge this is the only study to examine the continuity between childhood/adolescent depression and depression in young adulthood in the context of a high-risk design. Consequently, our findings regarding the differential effect of parental MDD on the risk of MDD in adulthood, in offspring with childhood/adolescent MDD, cannot be directly compared with results from other studies. However, overall findings that are independent of parental depression can be compared with these other studies.

Although several studies have examined the longitudinal course of childhood and adolescent MDD in clinical [e.g., Garber et al., 1988; Harrington et al., 1990;

Kovacs et al., 1984] as well as community [e.g., Cohen et al., 1993; Feehan et al., 1993, Garrison et al., 1990; Kandel and Davies 1986; Reinherz et al., 1993] samples, few have followed these subjects into adulthood. Of the handful of studies that have followed children and adolescents with MDD into adulthood [Garber et al., 1988; Harrington et al., 1990; Lewinsohn et al., 1999; Rao et al., 1995; Weissman et al., 1999a,b], with the exception of the Harrington et al. [1990] study and the Weissman et al. [1999a,b] study, which included prepubertal as well as adolescent subjects with MDD, these studies were restricted to subjects with adolescent MDD. Findings from the studies on subjects with adolescent onset MDD were consistent with ours, in that all of these studies found that subjects who had MDD in adolescence were more likely to have MDD in young adulthood also than study participants without adolescent MDD, and that in general the increased risk of disorder in adulthood was specific to MDD and not to other adult psychopathology. However, in contrast to our findings, Harrington et al. [1990] found that subjects with prepubertal MDD were at no greater risk for MDD in adulthood than subjects without prepubertal or adolescent onset MDD. In addition, they found that subjects with adolescent MDD were significantly more likely to continue to have MDD in adulthood when compared with those with prepubertal MDD. Differences in study design (children and adolescents with MDD were selected from a treatment setting) as well as the fact that all but one of the offspring with prepubertal onset MDD in our study had a history of parental depression may account for this discrepancy. Weissman et al. [1999b] found that although subjects with prepubertal onset MDD were at no greater risk than controls for MDD in adulthood, those who had recurrent episodes during the follow-up time were more likely to have a family history of affective disorder. This observation is consistent with our finding that for offspring with a parental history of MDD, having an onset of MDD in childhood increased the risk of having recurrent episodes of MDD that continue into adulthood.

Limitations

The number of male offspring with childhood onset MDD and a history of parental MDD and the total number of offspring with childhood/adolescent onset MDD and no history of parental MDD was small and consequently we lacked the statistical power needed to perform formal tests of interaction. Nevertheless, given the paucity of high-risk longitudinal studies, we believe that even those results with marginal significance are worth reporting and may suggest important factors for discriminating between familial and nonfamilial forms of childhood and adolescent onset MDD. A further limitation is that our categorization of prepubescence and adolescence was based on age and not on Tanner staging [Tanner, 1962]. Moreover, the age-of-onset of MDD in childhood/adolescence was in some cases based on retrospective recall. It is unlikely, however, that the patterns of risk of MDD in adulthood that we have reported here can be solely or even mostly due to bias in recalling age-at-onset. Additionally, the depressed par-

ents were selected from a treatment facility for depression; whether these findings could be similar for offspring in an untreated sample of depressed parents is not known.

Implications for Selecting Depressed Children for Genetic Studies

Our findings indicate that offspring with an onset of MDD in childhood or early adolescence and a history of parental MDD are at high risk for continuing to have episodes of MDD well into adult life. Our findings also suggest that continuity into adulthood, rather than recurrence alone, may be the factor that characterizes familial from nonfamilial subtypes of MDD. We note that our findings were based on offspring of depressed parents where the majority of depressed parents had been selected from a treatment setting. In contrast, findings based on a sample of prepubertal onset depressed children brought for treatment [Weissman et al., 1999b] show that prepubertal onset MDD subjects are no more likely to go on to have MDD in adulthood than normal control children. Consistent with the finding of Weissman et al. [1999b], and based on a sample of prepubertal onset and postpubertal onset depressed children and adolescents brought for treatment, Harrington et al. [1990] found that the continuity to major depression in adulthood was significantly lower in prepubertal probands than in postpubertal probands, leading them to argue that prepubertal onset cases may be mainly due to adverse family environments, whereas postpubertal onset cases may be mainly due to genetic influences [Harrington et al., 1997]. Discrepancies between our findings and those of Weissman et al. [1999b] and Harrington et al. [1990] may occur, at least in part, because factors that influence adults to seek treatment for themselves differ considerably from those that may cause them to seek treatment for their children, as noted by Verhulst [1995]. However, consistent with our findings, Weissman et al. [1999b] also showed that only those prepubertal onset children with recurrent onset MDD have a familial form of the disorder. Our findings taken together with the findings of Weissman et al. [1999b] strengthen and lead us to extend the conclusions they made regarding potential prepubertal onset depressed probands, to both prepubertal and early adolescent onset MDD probands, namely that in selecting depressed children as probands for genetic studies a conservative strategy would be to either (a) select offspring of depressed parents, where the offspring had an onset of MDD in childhood or early adolescence, so that bias due to factors that influence treatment seeking for depressed children [Verhulst, 1995] is reduced ; or (b) to select depressed children brought for treatment with a family history of MDD and reassess the treated sample as they mature, to ensure that they go on to have MDD in adulthood.

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