ORIGINAL ARTICLE

Children With Prepubertal-Onset Major Depressive Disorder and Anxiety Grown Up

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Background: The continuity in adulthood of major depressive disorder (MDD) first arising before puberty is largely unknown. This information could guide early treatment and clarify the appropriateness of including children with MDD in genetic studies.

Methods: Eighty-three subjects with onset of MDD, 44 subjects with anxiety disorder and no MDD, and 91 subjects with no evidence of past or current psychiatric disorders were assessed by two psychiatrists before puberty (Tanner stage <III) and were evaluated 10 to 15 years later as adults by an independent team without knowledge of the initial diagnosis.

Results: The clinical outcome of children with prepubertal-onset MDD in adulthood includes a high risk of suicide attempts (nearly 3-fold compared with normal controls and 2-fold compared with children with anxiety) and bipolar disorder. Compared with controls, both the children with MDD and those with anxiety went on to have increased risk of substance abuse and conduct disorder but not other disorders, increased use of long-term psychiatric and medical services, and overall impaired functioning. Children with prepubertal-onset MDD with a recurrence of MDD during follow-up had higher rates of MDD in their first-degree relatives.

Conclusions: There is high morbidity in clinically referred children with prepubertal-onset MDD and anxiety, but continuity and specificity of MDD or anxiety disorder in adulthood is less clear. Caution is warranted in selecting clinically referred children with prepubertal-onset MDD for inclusion in genetic studies unless they have a family history of MDD and recurrence of MDD over time.

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NUMEROUS studies now show that the rate of major depressive disorder (MDD) begins to rise in adolescents with the onset of puberty,[1] particularly in girls.[2] While prepubertal-onset MDD does occur, the rates are low and the sex ratios are equal.[3-5] The few follow-up studies examining adolescent-onset MDD in young adulthood show that MDD is continuous, specific, and associated with high morbidity and potential mortality through suicide.[6-10] With the exception of the study by Harrington et al,[8] the continuity of prepubertal-onset MDD in adulthood is unknown. Even the important longitudinal studies of children with MDD by Kovacs et al[11-13] have not yet evaluated the children beyond adolescence. Harrington et al,[8] using a longitudinal design to assess the adult psychiatric status of depressed subjects compared with matched controls with other psychiatric disorders, found strong continuity and specificity of adolescent-onset MDD, but not prepubertal-onset MDD in adulthood. The childhood diagnoses were made retrospectively from medical records. Pubertal status was not determined by Tanner staging and only 18 subjects were studied. Information on continuity in adulthood is important to guide early treatment and to clarify the appropriateness of including children with MDD in genetic studies. We describe the continuity in adulthood of subjects first studied as children with prepubertal-onset MDD, anxiety disorder without MDD, and normal controls. All subjects were ascertained in the same period, studied using identical methods, and assessed in adulthood without knowledge of the original childhood diagnosis.

RESULTS

FOLLOW-UP RATES

Two hundred thirty-six (79%) of the original 300 probands with prepubertal onset

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SUBJECTS AND METHODS

The overall design was clinical follow-up conducted between 1992 and 1996 after the initial assessment between 1977 and 1985. Three hundred subjects with an original diagnosis of prepubertal-onset MDD (n = 108) or anxiety (n = 59) or normal controls (n = 133) were in the potential sample eligible for follow-up. The initial evaluation is described elsewhere,[14-16] and details of the follow-up of a separate sample of 134 subjects with adolescent-onset MDD and controls are described elsewhere.[10]

SELECTION OF CHILDREN WITH DEPRESSION OR ANXIETY DISORDERS

Children aged 6 years and older were screened for mental illness when they came to the Child and Adolescent Depression Clinic of New York State Psychiatric Institute New York, if they seemed sad, said they felt sad, had suicidal ideation or behavior, refused to attend school, were nervous or afraid, or displayed ritualistic behavior. If the screening indicated that the diagnosis of MDD or anxiety disorder was likely, the child entered a 2-week diagnostic evaluation (time 1) that included the Schedule for Affective Disorders for School-Aged Children (K-SADS) administered by a psychiatrist,[16] a pediatric examination that included Tanner staging to determine pubertal status (Tanner stages I and II),[17] and intelligence testing. The K-SADS was administered for a second time 2 weeks later to ensure the stability of the initial diagnosis. These dual assessments were carried out blindly, and the examiners reached independent diagnoses using the K-SADS.

All of the children with depression met the Research Diagnostic Criteria for MDD at time 1.[18] Of these, 61% had 2 or more anxiety disorders. Only one child had obsessive-compulsive disorder without comorbidity.

Subjects medically cleared by a pediatrician were accepted into the original research protocol only if they met the Research Diagnostic Criteria for MDD or an anxiety disorder without MDD[18] in both evaluations. Children were excluded from the original sample if they had been taking medication that could produce depressive symptoms (eg, amphetamines, phenothiazines) or other medication that could interfere with brain hypothalamic or pituitary function. A 2-week washout period determined if the child's affective symptoms were primary or secondary to drug intake. Other exclusion criteria included severe medical illness (especially endocrinopathy or heart disease); obesity (weight-to-height ratio greater than the 95th percentile); height or weight under the third percentile; clinical seizures or other major neurological illness; IQ lower than 70; or a diagnosis of anorexia nervosa, autism, or schizophrenia. Diagnostic information on the child was obtained first from the parent and then the child.

SELECTION OF CONTROLS

The normal controls were randomly selected from grades 3, 4, and 5 at an urban school in the neighborhood of the hospital.[14,15] Parents of every eighth child on the rolls of these grades were mailed a letter from the school administration soliciting their cooperation in a study of the development of thoughts, feelings, and behavior in children and their families. All assessments took place in the school outside of school hours. Only children who met criteria for none of the childhood psychiatric diagnoses in their lifetime, using the same diagnostic procedures, and who fit none of the exclusion criteria for the patient groups were accepted as normal controls.

FOLLOW-UP PROCEDURES

Mean follow-up time was 11.9 years (SD, 2.4 years). All data were collected by clinical interviewers blind to the original diagnosis and without access to the original clinical records. At follow-up, lifetime diagnostic information was collected separately from the subject and from an informant,

Continued on next page

of illness were located and 218 (73%) were assessed. Included are 1 subject with prepubertal-onset MDD, 2 with anxiety, and 5 normal controls who received only brief interviews consisting of demographics and diagnostic information because of refusal to continue with the complete interview (**Table 1**). Response rates by the 3 proband groups were marginally different ($P = .09$). There was no difference in sex and race between assessed and unassessed subjects within each group.

Table 1. Location and Follow-up Rates by Prepubertal-Onset Diagnosis*

Potential Sample	Prepubertal-Onset Diagnosis, No. MDD (n = 108)	Anxiety (n = 59)	Normal (n = 133)	Total, No. (%) (N = 300)
Located	91	48	97	**236** (79)
Assessed	83	44	91	**218** (73)
Refused	8	4	6	**18** (6)
Unlocated†	17	11	36	**64** (21)

*MDD indicates major depressive disorder.
†The differences in the percentages of subjects with unlocated MDD (16%) and anxiety disorder (19%) and normal controls (27%) were marginally significant (χ^2_2, 4.9; P = .08).

DEMOGRAPHIC CHARACTERISTICS

There were no significant group differences by sex, religion, education, or current employment status (**Table 2**). The groups differed by age at time 1 (subjects with anxiety were about 6 months younger than the other 2 groups), follow-up age (both ill groups were about 1 year older than the normal controls), follow-up interval (follow-up was about 2 years longer in the ill groups), race (more whites in the MDD group and more Hispanics in the anxiety group), and marital status (more were married, separated, or divorced in the ill groups). These differences were adjusted for in subsequent analyses. While the children were supposed to be aged 18 years or older at follow-up, 3 included subjects were several months short of this age, but were interviewed because

usually a parent, to augment the subject's report. Detailed information on sociodemographic status and psychiatric and medical treatment was obtained using standardized questions. Lifetime psychiatric status was obtained by direct interview using a revised Schedule for Affective Disorders and Schizophrenia for Lifetime Disorders (SADS-LA).[19,20] Information covering the past 2 months of functioning was obtained by direct interview using the Social Adjustment Scale, scored on a 5-point scale, with higher scores indicating more impairment.[21] Medical records were obtained and used to supplement the interview data, with the exception that initial medical records were not used in making follow-up diagnoses to preserve blindness. Family psychiatric status was assessed for all available adult first-degree relatives by direct interview using the SADS-LA and/or by family history from multiple informants using the Family History Screen.[22] Interviews of relatives were conducted blind to subjects' childhood diagnoses. Direct interviews were obtained for at least one relative per family and the rest by family history.

Assessments were completed by 18 clinically trained and experienced interviewers (social workers, psychologists, and nurses) who underwent a 5-day training program followed by 2 supervised interviews. Interviewers were assigned to cases only after completing both supervised interviews and achieving reliability as assessed by the clinical supervisor. Every 2 months, interviewers administered the SADS-LA and all other interview instruments with a second interviewer present; each interviewer rated the interview independently. Final psychiatric diagnoses were based on a best estimate procedure.[23] To derive best estimate procedure diagnoses, an experienced psychiatrist or psychologist who was not involved in data collection reviewed all available information, including direct and informant interviews, blind to the initial diagnostic status of the subject, and assigned lifetime *DSM-III-R* diagnoses. Eight clinicians completed the best estimate diagnosis procedure (see Weissman et al[2] for reliability studies).

Informed consent was obtained for all subjects at time 1 from the parent or legal guardian and at follow-up from all subjects and a parent or informant. The study at both times was approved by the combined Institutional Review Board of the New York State Psychiatric Institute and Columbia University Department of Psychiatry, New York, NY.

DATA ANALYSIS

Group differences among subjects with MDD, subjects with anxiety disorder, and normal controls were determined as follows. When the risk of the outcome considered did not vary with age and was dichotomous, χ^2 analyses[24] were used for direct comparisons, and logistic regression was used when controlling for potential confounders.[25] Continuous outcomes that were 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 continuous outcomes were not normally distributed, the Mann-Whitney and Kruskal-Wallis nonparametric procedures were used.[24]

For outcomes for which the risk was believed to vary with age, differences between groups were examined using survival analysis techniques. Specifically, the proportional hazards model[26] was used to determine the relative risk ratio of the outcome under consideration among the 3 groups, controlling for the effects of confounding variables. Plots comparing the cumulative probability of remaining free from substance abuse during the follow-up period among the 3 groups were made using the Kaplan-Meier method.[27] Because of the well-established link between the risk of psychopathology and the age of the child, to facilitate interpretation, the graph of these cumulative probabilities was plotted against age at time of follow-up rather than years since ascertainment. For all of the analyses, the follow-up period considered was 1 year since the time of initial ascertainment to ensure that episodes of disorder occurring in the follow-up period were new episodes and not a continuation of the index episode. A level of .05 was chosen a priori to infer statistical inference. All analyses were conducted using SAS software (SAS Inc, Cary, NC).[28]

of their availability. There were no significant differences between groups in follow-up income, social class,[29] time out of work because of psychopathology, number of pregnancies or miscarriages, number of abortions (low in all groups), or age at first pregnancy (data not shown). No children were given up for adoption.

SUICIDE ATTEMPTS

There were no suicides in the follow-up period. Seventeen children with MDD and 4 with anxiety had made a suicide attempt by time 1. Excluding subjects with a history of suicide attempts by time 1, 12 children with MDD (18%), 5 children with anxiety (12%), and 8 normal controls (9%) made their first suicide attempt during the follow-up period. Prepubertal-onset MDD carried nearly a 3-fold adjusted increased risk of suicide attempts compared with normal controls during the follow-up period and more than a 4-fold adjusted increase in lifetime risk (**Table 3**).

PSYCHIATRIC DISORDERS AT 1 YEAR AFTER ASCERTAINMENT

Rates of psychiatric disorders were calculated from 1 year after the initial ascertainment to the time of follow-up to avoid including the index episode. Similar analyses were done for the 2-year postascertainment period. Since the results were generally similar, only 1-year postascertainment rates are presented (**Table 4**). There were significantly higher rates of bipolar I disorder in the children with prepubertal-onset MDD compared with normal controls, a 3-fold adjusted increased risk of alcohol abuse/dependence in the children with prepubertal-onset MDD vs normal controls, a more than 2-fold adjusted increased risk of alcohol abuse/dependence in the children with prepubertal-onset anxiety vs normal controls, a 4-fold adjusted increased risk of conduct disorder (CD) in the children with prepubertal-onset MDD vs normal controls, and a more than 4-fold adjusted increased risk of CD in the children with prepubertal-onset anxi-

Table 2. Demographics at Follow-up by Prepubertal-Onset Diagnosis*

Characteristic	Prepubertal-Onset Diagnosis			*P*†		
	MDD (n = 83)	Anxiety (n = 44)	Normal (n = 91)	MDD vs Normal	Anxiety vs Normal	MDD vs Anxiety
Age at time 1, y‡	9.3 (1.9) [6-15]	8.6 (15) [6-12]	9.2 (1.2) [6-12]	.89	.02	.05
Age at follow-up, y‡	22.9 (2.6) [17.5-28.2]	22.3 (2.5) [17.2-28.6]	21.1 (2.2) [16.4-29.1]	<.001	.005	.15
Follow-up, y§	12.6 (2.4)	12.7 (2.2)	10.9 (2.1)	<.001	<.001	.70
Female, No. (%)	32 (38.5)	18 (40.9)	40 (52.7)	.06	.20	.80
Race, No. (%)						
White	36 (43.4)	13 (29.5)	23 (25.3)	.08	.02	.03
Black	24 (28.9)	8 (18.2)	38 (41.8)			
Hispanic	22 (26.5)	23 (52.3)	28 (30.8)			
Other	1 (1.2)	0 (0)	5 (2.2)			
Current religion, No. (%)						
Protestant	11 (15.9)	4 (11.4)	12 (16.9)	.80	.59	.81
Catholic	33 (47.8)	20 (57.1)	31 (43.6)			
Jewish	8 (11.6)	3 (8.6)	6 (8.4)			
Other	17 (24.6)	8 (22.9)	22 (31.0)			
Higher education, No. (%)						
≥College	22 (26.8)	17 (40.5)	36 (41.9)	.11	.97	.30
High school graduate	51 (62.2)	21 (50.0)	41 (47.7)			
<High school	9 (11.0)	4 (9.5)	9 (10.5)			
Current employment, No. (%)						
Full time	30 (37.5)	17 (41.5)	32 (39.0)	.58	.97	.76
Part time	18 (22.6)	11 (26.2)	23 (28.0)			
Unemployed	32 (40.0)	14 (33.3)	27 (32.9)			
Marital status, No. (%)						
Single	67 (81.7)	36 (85.7)	82 (97.6)	.002	.03	.51
Married	13 (15.9)	4 (9.5)	1 (1.2)			
Separated/divorced/widowed	2 (2.4)	2 (4.8)	1 (1.2)			

*Eight probands with partial interviews excluded from the demographic data, except for sex, age, race, and follow-up interval. MDD indicates major depressive disorder.

†Calculated using χ^2 comparisons for discrete outcomes and the Mann-Whitney test for continuous outcomes, each with df = 1.

‡Values are mean (SD) [range]. For an explanation of time 1, see the "Selection of Children With Depression or Anxiety Disorders" subsection of the "Subjects and Methods" section.

§Values are mean (SD).

Table 3. Completed Suicide and Suicide Attempts by Prepubertal-Onset Diagnosis*

	Prepubertal-Onset Probands, No. (%)			Relative Risk (95% CI)		
	MDD (n = 83)	Anxiety (n = 44)	Normal (n = 91)	MDD vs Normal	Anxiety vs Normal	MDD vs Anxiety
Suicides	0	0	0			
First suicide attempt after ascertainment†‡	12/66 (18)	5/41 (12.2)	8/9 (9)	2.8 (1.0-7.5)	1.5 (0.5-4.6)	1.8 (0.6-5.2)
Lifetime suicide attempts§	23 (27)	5 (11)	8 (9)	4.4 (1.7-11.6)	1.4 (0.4-4.8)	3.0 (1.0-8.7)

*MDD indicates major depressive disorder; CI, confidence interval.

†Persons with a reported suicide attempt before time 1 (see "Selection of Children With Depression or Anxiety Disorders" subsection of the"Subjects and Methods" section for explanation of time 1) were removed from these analyses.

‡The relative risk was derived from a proportional hazards model to control for unequal follow-up time adjusted for age (as a continuous variable), race (white vs nonwhite), and marital status (single vs married, separated, divorced, or widowed).

§The odds ratio for group comparisons was derived from logistic regression and adjusted for age (as a continuous variable), race (white vs nonwhite), and marital status (single vs married, separated, divorced, or widowed).

ety vs normal controls. The rates for the other psychiatric disorders did not differ among the 3 groups. There were no sex differences in survival rates among the subjects with prepubertal-onset MDD or anxiety or normal controls (data not shown). However, the rates of substance abuse during the follow-up period were increased in boys in all groups but did not reach significance in the normal controls because of the low frequency of occurrence.

The **Figure** illustrates the age of onset of substance abuse/dependence, including alcohol and other drugs, by showing cumulative survival rates during the observation period. The survival period without substance abuse/dependence begins to decrease around age 14 years in both ill groups. By the end of the observation period, at approximately age 28 years, 49% of the subjects with prepubertal-onset MDD (95% CI, 37%-60%) and 46% of the subjects with prepubertal-onset anxi-

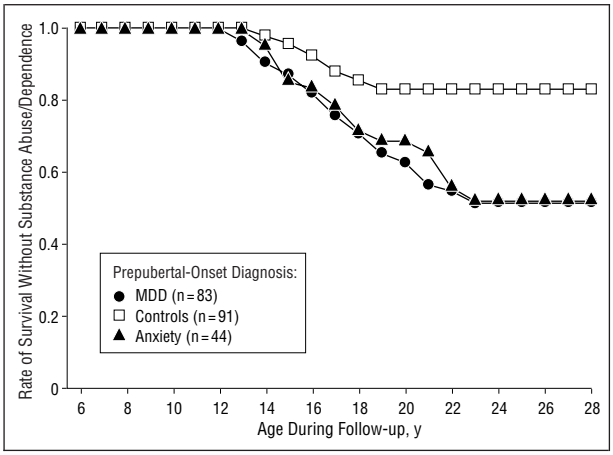
Table 4. Rates of Psychiatric Disorders 1 Year After Ascertainment by Prepubertal-Onset Diagnosis*

Disorders	Prepubertal-Onset Diagnosis, No. (%)			Relative Risk (95% CI)†		
	MDD (n = 83)	Anxiety (n = 44)	Normal (n = 91)	MDD vs Normal	Anxiety vs Normal	MDD vs Anxiety
Mood						
Major depression	27 (32.5)	20 (45.4)	32 (35.2)	0.8 (0.4-1.4)	1.1 (0.6-2.1)	0.6 (0.4-1.2)
Dysthymia	5 (6.0)	2 (4.5)	5 (5.5)	0.6 (0.2-2.5)	0.6 (0.1-3.4)	0.8 (0.2-4.4)
Bipolar I	4 (4.8)	1 (2.3)	0 (0.0)	*P* = .05‡	*P* = .33	2.2 (0.2-20.3)
Bipolar II	1 (1.2)	0 (0.0)	3 (3.3)	0.6 (0.04-8.5)	*P* = .55‡	*P* = .65‡
Anxiety						
Any anxiety disorder	14 (16.9)	13 (29.5)	20 (22.2)	0.5 (0.3-1.2)	1.0 (0.5-2.0)	0.5 (0.2-1.1)
Social phobia	2 (2.4)	2 (4.5)	5 (5.5)	0.5 (0.1-2.7)	0.8 (0.1-4.3)	0.6 (0.1-4.4)
Simple phobia	2 (2.4)	4 (9.1)	5 (5.6)	0.3 (0.1-2.0)	1.4 (0.3-5.5)	0.2 (0.04-1.2)
Panic disorder/attacks	6 (7.2)	5 (11.4)	8 (8.8)	0.5 (0.2-1.7)	1.0 (0.3-3.1)	0.5 (0.2-1.8)
Generalized anxiety	0 (0.0)	1 (2.3)	0 (0.0)	. . .	*P* = .33‡	*P* = .35‡
OCD	1 (1.2)	0 (0.0)	0 (0.0)	*P* = .48‡	. . .	*P* = .65‡
PSTD	2 (2.4)	3 (6.8)	5 (5.5)	0.3 (0.05-1.7)	0.8 (0.2-3.6)	0.4 (0.06-2.4)
Substance abuse/dependence						
Any	37 (44.6)	17 (38.6)	16 (17.6)	2.3 (1.2-4.5)	2.1 (1.0-4.3)	1.1 (0.6-1.9)
Alcohol	31 (37.3)	12 (27.3)	11 (12.1)	3.0 (1.3-6.6)	2.3 (1.0-5.6)	1.2 (0.6-2.4)
Drug	24 (28.9)	10 (22.7)	12 (13.2)	1.8 (0.8-3.9)	1.5 (0.6-3.5)	1.2 (0.5-2.5)
Other						
Schizophrenia	2 (2.4)	0 (0.0)	0 (0.0)	*P* = .23‡	. . .	*P* = .54‡
Eating disorder	2 (2.4)	3 (6.8)	2 (2.2)	0.7 (0.1-6.6)	2.4 (0.4-15.5)	0.3 (0.05-2.1)
Conduct disorder	12 (14.5)	7 (15.9)	3 (2.2)	3.9 (1.0-15.0)	4.7 (1.2-18.8)	0.8 (0.3-2.0)
Antisocial personality disorder	11 (13.2)	4 (9.1)	3 (3.3)	2.1 (0.5-8.6)	1.5 (0.3-7.1)	1.4 (0.4-4.4)

**Refers to probable/definite* DSM-III-R *psychiatric diagnoses from 1 year after ascertainment to the follow-up interview. MDD indicates major depressive disorder; CI, confidence interval; OCD, obsessive-compulsive disorder; and PTSD, posttraumatic stress disorder.*

†*The relative risk was derived from a proportional hazards model to control for unequal follow-up time adjusted for age (as a continuous variable), race (white vs nonwhite), and marital status (single vs married, separated, divorced, or widowed). Ellipses indicate that the relative risk was not calculable.*

‡*Fisher exact test.*



Survival free from substance abuse/dependence by age during follow-up and prepubertal-onset diagnosis. MDD indicates major depressive disorder.

ety (95% CI, 29%-64%) had experienced onset of substance abuse/dependence, compared with 19% in the normal group (95% CI, 11%-28%) (Wilcoxon test: χ^2_2, 10.47; $P = .005$).

Since comorbid CD may have explained the substance abuse/dependence findings in the prepubertal-onset group, we subdivided the sample into subjects with MDD with comorbid CD at time 1 (n = 13) and subjects with MDD without CD at time 1 (n = 69) and compared the rates of psychiatric disorders 1 year after ascertainment. The number of subjects with both anxiety disorder and CD (n = 3) was too small to make a comparison. If comorbid CD explained the findings, we would have expected subjects with comorbid CD to have the highest rate at follow-up of substance abuse and antisocial personality disorder (ASPD) and the lowest rate of MDD. There was no significant difference in diagnoses between groups, with the following exception: there was a significantly higher rate of adult ASPD in the children with prepubertal-onset MDD with comorbid CD vs those without CD (58.8% vs 6.3%; $P<.001$, $df = 1$). We also ran proportional hazards models, fitting CD at time 1 as a covariate (data available from the authors on request). Controlling for CD did not depreciate the relative risk to any significant degree, except for the comparison between children with MDD and normal controls for ASPD, for which the relative risk was reduced from 2.1 to 1.2. The comparison between children with anxiety and normal controls for any substance abuse and dependence lost significance when controlling for CD (relative risk, 1.9; 95% CI, 0.9-3.9), although the lower bound estimate of the relative risk was right at 1.0 before adjustment for CD.

TREATMENT AND SOCIAL ADJUSTMENT

A substantial percentage of subjects in all groups received brief mental health treatment. However, both of the ill groups were significantly more likely to have continuous outpatient treatment (≥6 months), psychiatric hospitalization, and inpatient surgery over the follow-up period. During the 2 months prior to the fol-

Table 5. Treatment and Social Adjustment During Follow-up by Prepubertal-Onset Diagnosis*

	Prepubertal-Onset Diagnosis			*P*†		
	MDD	Anxiety	Normal	MDD vs Normal	Anxiety vs Normal	MDD vs Anxiety
Outpatient treatment, No. (%)						
None	7 (9.1)	9 (21.4)	56 (65.1)	.001	.001	.06
Consulation/brief period	16 (20.8)	7 (16.7)	14 (16.3)	.46	.96	.59
Continuous treatment	54 (70.1)	26 (61.9)	16 (18.6)	.001	.001	.36
Psychiatric hospitalization, No. (%)	31 (40.3)	11 (27.5)	1 (1.2)	.001	.001	.17
Medical hospitalization, No. (%)	30 (39.5)	18 (42.9)	29 (33.7)	.45	.31	.72
Inpatient surgery, No. (%)	29 (38.1)	18 (42.9)	19 (22.1)	.02	.01	.69
Impairment in past 2 mo, No. (mean [SD])‡						
Work	54 (2.3 [1.3])	35 (2.5 [1.5])	71 (1.8 [1.1])	.008	.01	.77
Social/leisure	65 (2.4 [1.3])	37 (2.6 [1.5])	78 (1.9 [0.8])	.04	.09	.89
Extended family	62 (2.4 [1.2])	38 (2.6 [1.4])	76 (2.1 [0.9])	.21	.19	.78
Marital relations	19 (3.4 [2.0])	7 (3.4 [2.6])	11 (2.3 [1.7])	.11	.32	.95
Parental role	19 (2.1 [1.2])	5 (1.6 [0.9])	12 (1.5 [0.9])	.07	.80	.38
Overall	63 (2.7 [1.2])	37 (2.8 [1.4])	77 (2.1 [1.0])	.002	.006	.88

*MDD indicates major depressive disorder.
†Bivariate outcomes were measured by χ^2 or Fisher exact comparisons and continuous outcomes by Mann-Whitney comparisons, each with df = 1.
‡Based on the 5-point Social Adjustment Scale. A higher value signifies greater impairment.

low-up interview, both the ill groups reported significantly more impairment in work and overall functioning than the normal controls (**Table 5**).

RECURRENT DEPRESSION AND FAMILY HISTORY

We examined the rates of psychiatric disorders in the first-degree relatives, stratified by recurrence of MDD in the children with prepubertal-onset MDD (probands) and by incidence of MDD in both children with anxiety and normal controls (probands) during the follow-up period. The purpose was to determine if recurrence or onset of MDD in the children during the follow-up period was related to a family history of MDD. Recurrence or incidence in the children was defined as a full episode of MDD meeting diagnostic criteria over the follow-up period. For the probands with prepubertal-onset MDD, recurrence was estimated 1 year after ascertainment.

The rates of any mood disorder were significantly higher in the first-degree relatives of children with prepubertal-onset MDD with recurrence (59.7%) vs no recurrence of MDD (34.1%) (adjusted odds ratio, 3.1; $P = .002$) (**Table 6**). First incidence of MDD as compared with no occurrence MDD in the normal controls was also related to increased rates of any mood disorder in first-degree relatives (41.2% vs 23.6%; adjusted odds ratio, 2.4; $P = .003$). No other psychiatric disorder varied in relatives by recurrence or by incidence of MDD in the children.

COMMENT

Our study indicates that there is a poor adult outcome for both childhood-onset MDD and childhood-onset anxiety disorders (high suicide attempt rates, treatment utilization, and social impairment) as well as a lack of diagnostic specificity in adulthood for either disorder. Children with MDD and anxiety went on to have high rates of substance abuse and CD but not other disorders, with the exception of an increase in adult bipolar I disorder in the children with prepubertal-onset MDD. The subjects with prepubertal-onset MDD who had a recurrence of MDD over the follow-up period had higher rates of MDD in their first-degree relatives, suggesting that there is a subgroup of children with prepubertal-onset MDD with recurrent MDD that is familial. As noted by Rutter et al,[30] there are many curious features associated with MDD beginning in childhood, among them the low rates and equal sex ratio before puberty as well as the rapid increase in rates during adolescence, particularly in girls. Based on these findings and the data of Harrington et al[8] (discussed below), there is a differing clinical course between childhood-onset and adolescent-onset MDD in adulthood. There is also heterogeneity based on family history, with the recurrent form of prepubertal-onset MDD being familial.

Our findings are consistent with those of Harrington et al,[8] who also found a significantly lower risk of MDD during follow-up in the children with prepubertal-onset vs adolescent-onset MDD and no difference in risk of MDD in adulthood compared with controls. These findings were not anticipated by Harrington et al.[8] Since family data had suggested that early-onset MDD has the highest familial loading, they had argued that patients with prepubertal-onset MDD should have a recurrent course of MDD.[31] They noted that their unexpected findings could be the result of unreliable measures of MDD among prepubertal children or inaccurate documentation of puberty from medical records. However, inaccurate documentation of puberty, with more adolescent-onset MDD inadvertently included in the prepubertal-onset group, would have served to increase, not decrease, the rates of MDD in the prepubertal-onset MDD group as these children matured.

Findings regarding the clinical course of MDD also seem at variance with reports of an increased risk of prepubertal-onset MDD in the offspring of parents with

Table 6. Lifetime Rate of Psychiatric Disorders in First-Degree Relatives by Prepubertal-Onset Diagnosis and Recurrence or Incidence of Major Depressive Disorders (MDD) in the Proband During the Follow-up Period*

	Prepubertal-Onset Diagnosis in Proband								
	MDD			Anxiety			Normal		
	Recurrence of MDD in Proband During Follow-up†	No Recurrence	OR (95% CI)‡	Incidence of MDD in Proband During Follow-up†	No Incidence	OR (95% CI)‡	Incidence of MDD in Proband During Follow-up†	No Incidence	OR (95% CI)‡
Probands, No.	25	51		21	18		28	53	
Relatives, No.	77	179		69	54		85	157	
Diagnosis in relatives, No. (%)									
Mood disorder	46 (59.7)	61 (34.1)	3.1 (1.7-5.5)	32 (46.4)	23 (42.6)	1.3 (0.6-2.9)	35 (41.2)	38 (23.6)	2.4 (1.3-4.3)
Mania	2 (2.6)	7 (3.9)	0.3 (0.04-2.6)	8 (11.6)	4 (7.4)	1.8 (0.5-7.2)	2 (2.3)	8 (5.1)	0.4 (0.1-2.1)
Any anxiety	27 (35.1)	51 (28.5)	1.4 (0.7-2.5)	26 (37.7)	17 (31.5)	1.3 (0.6-3.0)	25 (29.4)	42 (26.7)	1.2 (0.6-2.2)
Alcohol abuse/dependence	16 (20.8)	31 (18.4)	1.3 (0.7-2.6)	15 (21.7)	5 (9.3)	2.1 (0.6-7.2)	15 (16.5)	26 (16.6)	1.0 (0.5-2.2)
Drug abuse/dependence	14 (18.2)	19 (10.6)	1.7 (0.8-3.7)	12 (17.4)	5 (9.3)	1.6 (0.5-5.3)	5 (5.9)	13 (8.3)	0.8 (0.3-2.4)
Schizophrenia	4 (5.2)	7 (3.9)	1.4 (0.4-5.0)	3 (4.3)	3 (5.6)	0.8 (0.1-4.2)	1 (1.2)	5 (3.1)	0.3 (0.03-2.5)
Conduct disorder	15 (19.5)	23 (13.4)	1.5 (0.7-3.2)	16 (23.2)	8 (14.8)	2.1 (0.7-6.3)	15 (17.6)	20 (12.7)	1.6 (0.7-3.5)
Antisocial personality disorder	9 (11.7)	15 (8.4)	1.1 (0.4-2.9)	13 (18.8)	9 (16.7)	0.9 (0.3-2.6)	10 (11.7)	14 (8.9)	1.4 (0.6-3.5)

*OR indicates odds ratio; CI, confidence interval.
†For probands with MDD, recurrence 1 year after ascertainment; for other probands, incidence any time during the follow-up period.
‡The odds ratio compares the rates of psychiatric disorders in relatives of probands who had a recurrence (incidence) vs no recurrence (no incidence) of MDD adjusted for age and sex of the relative.

MDD.[32,33] Because of these findings, we also expected that children with prepubertal-onset MDD would have high rates of MDD as they matured. However, a major difference in the study design could explain the differences in findings. For a top-down study design, the offspring of parents with MDD are selected by sampling their parents, not because they are brought for treatment. In this study, the subjects were children brought in for treatment (a bottom-up study design). It is also likely that only the children with MDD or anxiety who are the most disruptive are brought to treatment. This may have been especially true in the early 1980s when the sample was first identified and the conventional view was that depression rarely occurs in children. There was some suggestion of this—the rates of adult ASPD were highest in our sample of children with prepubertal-onset MDD with comorbid CD. However, even when we controlled for comorbid CD we did not find an increased rate of adult-onset MDD in the prepubertal-onset MDD probands. It is possible but not likely that treatment of MDD during follow-up reduced the recurrence of MDD. Medication and psychotherapy shown to be efficacious in these age groups were not widely available during much of the follow-up period. Our results can only be generalized to samples of children being brought to treatment and may not be representative of childhood-onset MDD and anxiety disorder sampled from community or high-risk studies.

Both Kovacs et al[13] and Todd et al[34] have suggested using children with prepubertal-onset MDD as probands in genetic studies. However, both of these studies used family history, not interview methods, which could have introduced informant bias. Our findings that subjects with prepubertal-onset MDD generally do not go on to have MDD in adulthood and that only those with recurrent MDD have a familial form of the disorder suggest that caution should be exercised in selecting for genetic studies children with MDD who are brought for treatment before puberty. A more conservative strategy might be to select children with MDD who have MDD or anxiety whose parents have MDD, which would eliminate the bias of who is brought to treatment,[32] or to select children with prepubertal-onset MDD and a family history of MDD and reassess those in the treated sample as they mature to determine whether they go on to have MDD in adulthood.

A substantial number of normal controls had first-onset MDD, anxiety disorders, and suicide attempts in the follow-up period, which covered adolescence and young adulthood. Epidemiological studies show that rates of MDD and anxiety disorders are high in this age group. The lifetime suicide attempt rate (9%) we found in the controls is close to the rate (7%) reported in a survey of 1710 high school students with an average age of 16 years.[35] The high rate of treatment utilization is consistent with findings in other studies of adolescents with MDD and anxiety.[36,37] The increased risk of surgery in ill probands was curious. We could not find any particular pattern of procedures. The course of prepubertal-onset MDD in adulthood is quite different from that found in long-term follow-up of adolescent-onset MDD, for which recent studies have found increased rates of MDD and not other disorders in adulthood.[6,8-10]

Study limitations include the sample size. While this is the largest sample of children with MDD evaluated in adulthood, it is still small for finer analysis of subgroups. Detailed data on the parental characteristics were not collected at time 1. The group with anxiety disorders was heterogeneous, and findings on clinical course by specific anxiety disorder are unstable. There was a lack of frequent follow-up assessment, possibly leading to biased retrospective recall. We attempted to minimize this by using multiple sources of information and best esti-

mates. We used Tanner stage less than III to define prepubertal status. This seemed reasonable at the time of the initial study, and recent data support this choice.[1]

The findings from this follow-up study suggest that clinically referred children with prepubertal-onset MDD or anxiety disorders have high morbidity and poor outcome, but the continuity and specificity of MDD or anxiety in adulthood are less clear. These findings argue for early identification and follow-up of children with prepubertal-onset MDD and anxiety, but the nature of the treatment based on these follow-up data is unclear.

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This article is dedicated to the late Joaquim Puig-Antich, MD, who, against the conventional wisdom of his day, had the vision to study young children with depression.

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