

# A Family Study of Major Depressive Disorder in a Community Sample of Adolescents

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**Background:** Family studies provide a useful approach to exploring the continuities and discontinuities between major depressive disorder (MDD) in children and adolescents and MDD in adults. We report a family study of MDD in a large community sample of adolescents.

**Methods:** Probands included 268 adolescents with a history of MDD, 110 adolescents with a history of non-mood disorders but no history of MDD through age 18 years, and 291 adolescents with no history of psychopathology through age 18 years. Psychopathology in their 2202 first-degree relatives was assessed with semistructured direct and family history interviews, and best-estimate diagnoses were derived with the use of all available data.

**Results:** The relatives of adolescents with MDD exhibited significantly elevated rates of MDD (hazard ratio [HR], 1.77; 95% confidence interval [CI], 1.46-2.31), dysthy-

mia (HR, 1.79; 95% CI, 1.11-2.87), and alcohol abuse or dependence (HR, 1.29; 95% CI, 1.05-1.53), but not anxiety disorders, drug abuse or dependence, or antisocial and borderline personality disorder. In contrast, anxiety, substance use, and disruptive behavior disorders in adolescents were not associated with elevated rates of MDD in relatives. However, the relatives of probands with anxiety and substance use disorders exhibited elevated rates of anxiety and substance use disorders, respectively.

**Conclusions:** The results provide evidence of the familial aggregation of adolescent MDD, and also indicate that there is a considerable specificity in the pattern of familial transmission. In addition, we found preliminary evidence of the familial aggregation of adolescent anxiety and substance use disorders.

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**D**URING THE past 2 decades, there has been increasing recognition of mood disorders in children and adolescents.<sup>1-4</sup> Much of the research in this area has focused on the continuities and discontinuities between depression in juveniles and adults.

The clinical manifestation of major depressive disorder (MDD) in children and adolescents tends to be similar to that of MDD in adults.<sup>5-7</sup> Few studies have followed up youths with MDD into adulthood, but the existing data indicate that many depressed adolescents experience episodes of MDD as adults.<sup>8-12</sup> In contrast, recent studies suggest that children with MDD may not be at increased risk for MDD as adults.<sup>9,13</sup> Data on the continuity between juvenile and adult MDD with respect to neurobiological correlates and medication response is still inconclusive.<sup>1,2,14,15</sup>

Family studies provide another means of exploring this issue. The familial transmission of MDD can be examined by means

of a top-down approach, which focuses on the offspring of parents with MDD, or a bottom-up approach, which focuses on the relatives of children and adolescents with MDD.<sup>16,17</sup> Most top-down studies have reported an increased rate of MDD in the offspring of parents with MDD.<sup>18-20</sup> However, these offspring also have elevated rates of a variety of nonmood disorders.

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The generalizability of top-down studies is limited, as most youths with MDD do not have parents with MDD. Unfortunately, there have been fewer bottom-up studies of juvenile MDD. These studies indicate that there is a higher rate of MDD in the relatives of children and adolescents with MDD than the relatives of normal control subjects.<sup>21-25</sup> Several studies have also reported a higher rate of MDD in the relatives of children and adolescents with MDD than in the relatives of juveniles with nonmood disorders,<sup>25-27</sup> but oth-

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## SUBJECTS AND METHODS

### SUBJECTS

#### Probands

Probands were selected in 3 cohorts from 9 high schools in western Oregon. Sampling fractions of 10%, 18.5%, and 20% were used for each cohort; sampling within each school was proportional to the size of the school, the size of the grade within the school, and the proportion of male and female students within grade. A total of 1709 adolescents (aged 14-18 years; mean age, 16.6 years; SD, 1.2 years) completed the initial (T1) assessment between 1987 and 1989. Approximately 1 year later, 1507 of the adolescents (88%) had a second evaluation (T2). Differences between the sample and the larger population from which it was selected, and between participants and those who declined to participate or dropped out before T2, were small.<sup>33</sup>

At age 24 years, all probands with a history of MDD (n=360) or nonmood disorders (n=284) through T2, and an approximately equal number of adolescents with no history of psychopathology through T2 (n=457), were invited to participate in a T3 evaluation. Of the 1101 T2 participants selected for a T3 interview, 940 (85%) completed the evaluation. The T2 diagnostic groups did not differ on the rate of participation at T3.

#### Relatives

We assessed lifetime psychopathology in the first-degree relatives (older than 13 years) of the T3 participants. To supplement the direct interviews and ensure that at least some data were available for relatives who could not be interviewed, informant data on relatives were collected from probands and/or other relatives. We sought to collect at least 2 sources of diagnostic data for each family member. Of the 1101 probands selected for a T3 interview, family diagnostic information was available for 840 (76%). Of the 940 probands with T3 data, family data were available for 802 (85%). Family data were also available for 38 probands who were selected for, but did not complete, the T3 evaluation. Of the 2750 relatives with diagnostic data, direct interviews were obtained from 1744 (63%). At least 2 sources of data were available for all but 440 relatives (16%).

For this report, we excluded probands with a history of psychotic disorder (n=2), bipolar disorder (n=19), and dysthymic disorder or adjustment disorder with depressed mood but no history of MDD (n=9 and 87, respectively) through T3. In addition, to maintain pure comparison groups, we excluded 46 subjects with nonmood disorders and 8 subjects with no history of psychopathology who developed a mood disorder for the first time between T2 and age 18 years. This report focuses on the remaining groups of 268 adolescents with a history of MDD, 110 adolescents with a history of nonmood disorders but no history of mood disorders, 291 adolescents with no history of psychopathology through age 18 years, and their 2202 first-degree relatives. The mean number of relatives per proband was 3.29 (SD, 1.17; median, 3.00).

### DIAGNOSTIC INTERVIEWS

#### Probands

At T1, probands were interviewed with a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children,<sup>34</sup> which included additional items to derive *DSM-III-R*<sup>35</sup> diagnoses. Modified 14-item Hamilton Rating Scale for Depression<sup>36</sup> scores for current or past depressive episodes were extracted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children.<sup>37</sup>

At T2 and T3, probands were interviewed by means of the Longitudinal Interval Follow-up Evaluation,<sup>38</sup> which elicited information about the course of psychopathology since the previous evaluation. In addition, antisocial and borderline personality disorder were assessed at T3 by means of the Personality Disorder Examination.<sup>39</sup> Because of low prevalence rates, we used dimensional scores (the sum of the scores for each criterion, rated on a 0-2 scale) in analyses of the personality disorders.<sup>40</sup> Interrater reliability of our T1, T2, and T3 diagnoses was generally excellent, as reported in detail elsewhere.<sup>10,33,40</sup>

#### Relatives

Parents and siblings older than 18 years were interviewed with the Structured Clinical Interview for *DSM-IV*, nonpatient version,<sup>41</sup> and the antisocial and borderline personality disorder sections of the Structured Clinical Interview

ers have found no differences.<sup>22,28,29</sup> These studies have also differed on whether the relatives of youths with MDD have elevated rates of nonmood disorders. All of these studies used clinical samples, and most relied on family history data rather than interviewing relatives directly.

This article presents the major findings from the Oregon Adolescent Depression Project family study, which used direct interviews to assess psychopathology in the first-degree relatives of a large community sample of adolescents with a history of MDD, a history of nonmood disorders, and no lifetime history of psychopathology. This study has 2 important methodologic features. First, the use of a community sample increases the generalizability of the findings, as clinical samples of children and adolescents are not representative of cases in the com-

munity,<sup>30</sup> and studies of adult MDD indicate that patient samples can bias the results of family studies.<sup>31,32</sup> Second, we used a longitudinal approach to diagnosis, examining the probands twice in adolescence and a third time in young adulthood.

We addressed 4 questions: (1) Is there a higher rate of MDD in the relatives of adolescents with a history of MDD than in the relatives of adolescents with no history of psychopathology? (2) Do the relatives of adolescents with a history of nonmood disorders also have elevated rates of MDD? (3) Are the rates of nonmood disorders higher in the relatives of adolescents with MDD than in the relatives of never-depressed adolescents? (4) Does the familial aggregation of MDD vary according to the sex of probands and relatives?

for DSM-IV for Axis II Personality Disorders.<sup>42</sup> Siblings between the ages of 14 and 18 years were interviewed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children, modified for DSM-IV.<sup>43</sup> All interviews were conducted blind to proband diagnoses. To guard against interviewers being biased by patterns of psychopathology within a family, no interviewer examined more than 2 members of the same family. Interrater reliability was assessed by having a second rater independently rate audiotapes of a randomly selected sample (n=157) of interviews. Interrater reliability was excellent for lifetime diagnoses of MDD ( $\kappa=0.94$ ), anxiety disorders ( $\kappa=0.90$ ), alcohol abuse or dependence ( $\kappa=0.86$ ), and drug abuse or dependence ( $\kappa=0.89$ ). There were too few cases to calculate interrater reliability for antisocial and borderline personality disorder.

Family history data were collected by means of the revised Family Informant Schedule and Criteria,<sup>44</sup> modified to derive DSM-IV diagnoses. In addition, we assessed borderline personality disorder by means of the relevant section from the Family History Interview for Personality Disorders.<sup>45</sup> On the basis of a random sample of informant interviews (n=242), interrater reliability ranged from fair to excellent for lifetime diagnoses of MDD ( $\kappa=0.90$ ), anxiety disorders ( $\kappa=0.77$ ), alcohol abuse or dependence ( $\kappa=0.90$ ), drug abuse or dependence ( $\kappa=0.82$ ), antisocial personality disorder ( $\kappa=0.56$ ), and borderline personality disorder ( $\kappa=1.00$ ).

## PROCEDURE

After a thorough description of the study, written informed consent was obtained from the probands and relatives.

Proband interviews at T3 and interviews with relatives and informants were conducted by telephone, which generally yields results comparable with those of face-to-face interviews.<sup>46-48</sup> Most of the interviewers had advanced degrees in clinical or counseling psychology or social work, and several years of clinical experience. All interviewers were trained in the use of the Structured Clinical Interview for DSM-IV and the Family Informant Schedule and Criteria and completed at least 2 supervised training interviews, achieving  $\kappa>0.80$  for concordance between their symptom ratings and those of the supervisor.

Best-estimate diagnoses<sup>49</sup> were derived for all relatives by means of DSM-IV criteria by 4 senior diagnosticians. Two diagnosticians, blind to proband diagnoses, independently derived diagnoses for each relative with the use of all available data. Disagreements were resolved by consensus. Interrater reliability for best-estimate diagnoses was good to excellent: MDD ( $\kappa=0.91$ ), anxiety disorders ( $\kappa=0.94$ ), alcohol abuse or dependence ( $\kappa=0.97$ ), drug abuse or dependence ( $\kappa=0.96$ ), antisocial personality disorder ( $\kappa=0.80$ ), and borderline personality disorder ( $\kappa=0.72$ ).

## DATA ANALYSIS

Descriptive characteristics were compared between groups by means of  $\chi^2$  tests for categorical variables and analysis of variance for continuous variables. Rates of lifetime best-estimate Axis I disorders in relatives were analyzed by means of Cox proportional hazards (PH) models. The dependent variable was time to onset of disorder; relatives without the disorder were considered censored. Best-estimate Axis II disorders in relatives were analyzed by means of multiple logistic regression (LR) models. As relatives were clustered within families rather than comprising independent observations, the use of standard PH and LR models would underestimate the SEs, increasing the chance of type I errors. Therefore, we estimated the PH and LR models by means of Taylor series linearization (or generalized estimating equations), which takes the clustered structure of the data into account.<sup>50</sup> The major independent variables were lifetime diagnoses of MDD, anxiety disorders, disruptive behavior disorders, and substance use disorders in the probands. All proband diagnoses were entered into the models simultaneously to control for proband comorbidity. Therefore, the effect for any particular proband diagnosis was over and above the effects of the other proband diagnoses. The models were adjusted for sex of the proband, sex of the relative, generation of the relative (parent or sibling of the proband), education of the relative (college graduate vs not), whether the relative had received a direct interview, and number of family history interviews on the relative. In addition, in analyses of antisocial and borderline personality disorders in relatives, the corresponding proband Personality Disorder Examination dimensional scores at T3 were included as covariates. In all analyses,  $\alpha$  was set at .05 and tests were 2 tailed.

## RESULTS

### CHARACTERISTICS OF PROBANDS AND RELATIVES

For descriptive purposes, the probands were divided into 3 groups: probands with a history of MDD; probands with a history of nonmood disorders but no lifetime MDD (NMD); and probands with no history of mental illness through age 18 years (NMI). The groups were similar with respect to age and race (**Table 1**). Probands with MDD were significantly more likely to be female and had significantly higher scores on the Hamilton Rating Scale for Depression than did the NMD and NMI probands, while

probands with NMD had significantly higher Hamilton Rating Scale for Depression scores than did NMI probands.

The MDD probands had a mean age at onset of 14.9 years; 26% had a history of recurrent major depressive episodes; and the mean duration of their longest episode was 6 months. More than 40% of the NMD probands had substance use and disruptive behavior disorders, and 30% had anxiety disorders. Although the rates of nonmood diagnoses were significantly lower among the MDD probands, many of them also had a history of nonmood disorders.

The relatives of the MDD, NMD, and NMI probands were similar with respect to age, sex, generation (parent or sibling), and number of informant interviews (**Table 2**). However, compared with the relatives of NMI probands, the relatives of probands with MDD were sig-

**Table 1. Descriptive Characteristics of the Proband Diagnostic Groups\***

Characteristics	Proband Diagnostic Group			Test Statistics
	NMI (n = 291)	NMD (n = 110)	MDD (n = 268)	
<b>Demographics</b>				
Age, mean (SD), y	16.6 (1.3)	16.7 (1.1)	16.7 (1.1)	$F_{2,666} = 1.02, P = .36$
Sex, % F	49.8 <sub>a</sub>	42.7 <sub>a</sub>	72.0 <sub>b</sub>	$\chi^2_2 = 39.95, P < .001$
Race, % white	88.3	89.1	90.3	$\chi^2_2 = 0.57, P = .75$
<b>Characteristics of depressive episodes</b>				
Worst HDRS score, mean (SD)	2.4 <sub>a</sub> (3.4)	4.0 <sub>b</sub> (4.7)	11.4 <sub>c</sub> (5.8)	$F_{2,666} = 273.39, P < .001$
MDD onset age, mean (SD), y	NA	NA	14.9 (2.8)	NA
MDD duration, mean (SD), wk	NA	NA	26.5 (60.3)	NA
No. of MDD episodes, %				
1	NA	NA	73.9	NA
2	NA	NA	17.9	NA
≥3	NA	NA	8.2	NA
<b>Other diagnoses, %</b>				
Dysthymia	NA	NA	5.2	NA
Anxiety disorder	NA	30.0	19.0	$\chi^2_1 = 5.43, P = .02$
Substance use	NA	42.7	21.6	$\chi^2_1 = 17.28, P < .001$
Disruptive behavior	NA	40.9	12.7	$\chi^2_1 = 37.57, P < .001$

\*NMI indicates not mentally ill; NMD, nonmood disorder; MDD, major depressive disorder; HDRS, 14-item Hamilton Depression Rating Scale (extracted from the Schedule for Affective Disorders and Schizophrenia for School-Age Children); and NA, not applicable. Means or percentages with different subscript letters differ significantly at  $P < .05$ .

**Table 2. Descriptive Characteristics of First-Degree Relatives by Proband Diagnostic Group\***

Characteristics	Proband Diagnostic Group			Test Statistics
	NMI (n = 988)	NMD (n = 350)	MDD (n = 864)	
Age, mean (SD), y	39.8 (13.6)	40.2 (13.5)	39.9 (13.4)	$F_{2,2198} = .015, P = .86$
Sex, % F	50.9	47.7	50.0	$\chi^2_2 = 1.06, P = .61$
Race, % white	91.2	93.2	93.7	$\chi^2_2 = 3.04, P = .22$
Education, mean (SD), y	14.0 <sub>a</sub> (2.1)	14.0 <sub>ab</sub> (2.1)	13.7 <sub>b</sub> (2.1)	$F_{2,1419} = 4.80, P = .008$
Bachelor's degree or higher, %	31.7 <sub>a</sub>	28.4 <sub>ab</sub>	25.0 <sub>b</sub>	$\chi^2_2 = 10.00, P = .006$
<b>Relationship, %</b>				
Mothers	29.4	31.1	30.9	$\chi^2_4 = 2.29, P = .68$
Fathers	28.6	30.6	30.0	NA
Siblings	42.0	38.3	39.1	NA
<b>Interview information</b>				
SCID, %	66.1 <sub>a</sub>	70.0 <sub>a</sub>	57.9 <sub>b</sub>	$\chi^2_2 = 21.06, P < .001$
No. of FISCs, mean (SD)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	$F_{2,2199} = 1.80, P = .17$

\*NMI indicates not mentally ill; NMD, nonmood disorder; MDD, major depressive disorder; NA, not applicable; SCID, Structured Clinical Interview for DSM-IV; and FISC, Family Informant Schedule and Criteria. Means or percentages with different subscript letters differ significantly at  $P < .05$ .

nificantly less likely to have completed college. In addition, a significantly greater proportion of relatives of probands with NMD and NMI than relatives of probands with MDD received direct interviews.

#### RATES OF MOOD AND NONMOOD DISORDERS IN RELATIVES

The rates of mood disorders, particularly MDD and dysthymic disorder, were moderately and significantly elevated in the relatives of adolescent probands with a history of MDD (**Table 3**). In contrast, the relatives of adolescents with MDD generally did not exhibit elevated rates of nonmood disorders, with the exception of a small, but significant, increase in the rate of alcohol

abuse or dependence. To explore this finding further, we examined whether the increased rate of alcohol abuse or dependence in the relatives of adolescents with MDD could be attributed to comorbid MDD in the same relatives. Indeed, when comorbid MDD in the relative was included as an additional covariate in the PH model, it was significantly associated with alcohol abuse or dependence in the same relative (hazard ratio [HR], 1.45; 95% confidence interval [CI], 1.21-1.74). However, the association between MDD in probands and alcohol abuse or dependence in relatives was no longer significant (HR, 1.19; 95% CI, 0.99-1.43), suggesting that the increased rate of alcoholism in the relatives of adolescents with MDD may be due to MDD-alcohol abuse or dependence comorbidity in those relatives.

**Table 3. Lifetime Best-Estimate Rates of Psychiatric Disorders Among First-Degree Relatives by Proband Diagnostic Group\***

Disorder in Relatives	Proband Diagnostic Group, No. (%)			Adjusted Hazard Ratios (95% CI) for Proband Disorders†			
	NMI (n = 988)	NMD (n = 350)	MDD (n = 864)	MDD	Anxiety Disorders	DIS	SUB
Mood	235 (23.8)	98 (28.0)	321 (37.2)	<b>1.71 (1.42-2.07)</b>	0.94 (0.72-1.22)	1.30 (1.00-1.70)	1.09 (0.89-1.34)
MDD	209 (21.2)	85 (24.3)	293 (33.9)	<b>1.77 (1.46-2.31)</b>	0.97 (0.74-1.26)	1.24 (0.97-1.59)	1.10 (0.89-1.36)
Dysthymia	29 (2.9)	13 (3.7)	44 (5.1)	<b>1.79 (1.11-2.87)</b>	0.62 (0.30-1.26)	1.09 (0.55-2.15)	1.14 (0.63-2.04)
Bipolar	13 (1.3)	6 (1.7)	11 (1.3)	0.87 (0.35-2.16)	1.11 (0.35-3.55)	2.00 (0.77-5.14)	0.36 (0.09-1.49)
Anxiety	102 (10.3)	50 (14.3)	114 (13.2)	1.10 (0.83-1.47)	<b>1.57 (1.12-2.20)</b>	<b>1.62 (1.11-2.36)</b>	1.21 (0.86-1.70)
Alcohol abuse	240 (24.3)	115 (32.9)	285 (33.0)	<b>1.29 (1.05-1.53)</b>	<b>1.27 (1.01-1.60)</b>	1.08 (0.84-1.38)	<b>1.32 (1.04-1.68)</b>
Drug use	134 (13.6)	85 (24.3)	167 (19.3)	1.10 (0.85-1.43)	0.94 (0.67-1.33)	<b>1.44 (1.07-1.95)</b>	<b>1.60 (1.20-2.14)</b>
Antisocial personality/conduct‡	31 (3.1)	20 (5.7)	41 (4.7)	1.07 (0.67-1.72)	0.99 (0.52-1.87)	1.03 (0.55-1.92)	1.35 (0.69-2.64)
Borderline personality‡	20 (2.0)	12 (3.4)	26 (3.0)	0.78 (0.45-1.35)	1.12 (0.56-2.24)	1.73 (0.89-3.36)	1.45 (0.75-2.80)

\*CI indicates confidence interval; NMI, not mentally ill; NMD, nonmood disorder; MDD, major depressive disorder; DIS, disruptive behavior disorders; and SUB, substance use disorders. Hazard or odds ratios presented in boldface are significant at  $P < .05$ . Hazard and odds ratios have similar interpretations as measures of the strength of an effect. A hazard or odds ratio of 1 indicates no effect, while a hazard or odds ratio of 10 indicates that the index group has 10 times the risk of the comparison group.

†Adjusted for sex of proband, sex of relative, relationship to proband, education of relative, direct interview participation, number of informant interviews, and other proband disorders.

‡Odds ratios via logistic regression are presented. Proband Personality Disorder Examination dimensional scores for antisocial and borderline personality disorders were included as covariates for the corresponding family disorder models.

**Table 4. Lifetime Best-Estimate Rates of MDD by Family Member as a Function of Proband Sex\***

Family Member	Proband Group								
	MDD (n = 864)			NMD (n = 350)			NMI (n = 988)		
	%	SE	95% CI	%	SE	95% CI	%	SE	95% CI
Female proband sample									
Mother (n = 384)	44.3	3.6	37.4-51.3	29.8	6.7	18.7-44.0	29.0	3.8	22.2-36.8
Father (n = 375)	28.9	3.3	22.9-35.8	10.9	4.6	4.7-23.0	14.1	2.9	9.3-20.8
Female sibling (n = 234)	43.6	4.9	33.5-54.4	34.6	8.0	17.5-56.9	24.5	4.5	16.0-35.6
Male sibling (n = 267)	23.5	3.6	16.5-32.3	24.2	6.9	12.1-42.6	8.8	2.8	4.3-17.1
Male proband sample									
Mother (n = 282)	36.0	5.6	26.1-47.3	27.4	5.7	17.9-39.6	24.8	3.6	18.5-32.5
Father (n = 274)	37.5	5.7	27.2-49.1	24.6	5.5	15.5-36.7	14.2	2.9	9.4-20.9
Female sibling (n = 199)	18.9	7.2	9.5-33.9	25.0	10.0	12.4-44.1	29.8	4.4	21.1-40.3
Male sibling (n = 187)	25.6	6.4	13.7-42.7	20.9	5.4	10.1-38.3	23.8	4.2	15.6-34.4

\*MDD indicates major depressive disorder; NMD, nonmood disorder; NMI, not mentally ill; and CI, confidence interval.

The specificity of familial aggregation of MDD was further supported by the data on rates of mood disorders in the relatives of adolescents with nonmood diagnoses. The relatives of probands with anxiety, disruptive behavior, and substance use disorders did not have significantly elevated rates of mood disorders.

Both the anxiety and substance use disorders exhibited significant familial aggregation. There was a moderately elevated rate of anxiety disorders in the relatives of adolescents with a history of anxiety disorders, and small to moderate, but significant, increases in the rates of alcohol abuse or dependence and drug abuse or dependence in the relatives of adolescents with a history of substance use disorders. The relatives of adolescents with a history of disruptive behavior disorders also had a significantly elevated rate of drug abuse or dependence; however, they did not exhibit increased rates of alcohol abuse or dependence or antisocial personality disorder.

There was a high degree of specificity in the familial aggregation of substance use disorders, as the rela-

tives of adolescents with substance use conditions did not exhibit increased rates of any nonsubstance disorder. There was somewhat less specificity in the familial aggregation of anxiety and disruptive behavior disorders. The rate of alcohol abuse or dependence was elevated in the relatives of adolescents with anxiety disorders, and the rate of anxiety disorders was elevated in the relatives of probands with disruptive behavior disorders.

#### IMPACT OF SEX ON FAMILIAL TRANSMISSION OF MDD

The rate of MDD in relatives did not differ as a function of proband sex (**Table 4**). However, female relatives had a significantly higher rate of MDD than male relatives (HR, 1.41; 95% CI, 1.12-1.78). Although parents and siblings had similar uncorrected rates of MDD, there was a significant effect for generation of relatives in the Cox PH model because of the earlier age at onset of MDD in the siblings (mean, 17.2 years; SD, 6.0 years) than the par-

ents (mean, 30.8 years; SD, 11.3 years) (HR, 2.27; 95% CI, 1.72-3.03). Finally, there was a significant interaction between proband sex and relative sex ( $\chi^2_1=6.21$ ;  $P=.01$ ). In the relatives of female probands, the rate of MDD was significantly higher in females than males (HR, 1.79; 95% CI, 1.37-2.34). In contrast, among the relatives of male probands, the rates of MDD were similar for males and females (HR, 0.69; 95% CI, 0.41-1.15). No other interactions were significant.

#### INFORMANT REPORT AS A POTENTIAL SOURCE OF BIAS

Psychopathology in informants can bias reports of psychopathology in their relatives,<sup>51,52</sup> producing spurious evidence of familial aggregation. We addressed this possibility in 2 ways. First, we included interactions between each of the proband diagnoses and whether relatives were directly interviewed in the PH and LR models. None of the interaction terms was significantly associated with any of the diagnoses in relatives. Second, we reanalyzed the data by using only Structured Clinical Interview for *DSM-IV*, rather than best-estimate, diagnoses of relatives. The findings were generally similar to the results with best-estimate diagnoses. The adjusted HRs (95% CIs) for MDD in relatives were 1.64 (1.30-2.07) for proband MDD, 1.11 (0.81-1.53) for proband anxiety disorders, 1.38 (1.01-1.88) for proband disruptive disorders, and 0.80 (0.60-1.08) for proband substance use disorders.

#### COMMENT

These results are consistent with previous evidence of the familial aggregation of adolescent MDD from both bottom-up and top-down studies<sup>16-29</sup> and extend these earlier findings to a community sample.

The magnitude of the familial aggregation of MDD was somewhat smaller than in previous family studies of adult MDD.<sup>53,54</sup> This may be due to the use of a community sample, as clinical samples appear to overestimate the degree of familial aggregation.<sup>31,32</sup> Alternatively, Wickramaratne and Weissman<sup>55</sup> suggested that familial transmission plays a smaller role in adolescent-onset MDD than childhood- or adult-onset MDD. Although 13% of our MDD probands had a childhood (before age 12 years) onset, most had an onset in adolescence.

We also found that dysthymia aggregated in the families of adolescents with MDD. This is consistent with family studies of adult probands that have reported a familial relationship between dysthymia and MDD.<sup>56,57</sup>

Previous studies, from both the bottom-up and top-down perspectives, have reported conflicting findings regarding the specificity of familial aggregation of juvenile MDD.<sup>18-20,22,25,26,29</sup> The present study examined this issue from 2 directions and in both cases found evidence of specificity. First, after controlling for proband comorbidity, the only nonmood disorder that was significantly elevated in the relatives of adolescents with MDD was alcohol abuse or dependence. The relatives of adolescents with MDD did not exhibit increased rates of anxiety disorders, drug abuse or dependence, or antiso-

cial and borderline personality disorders. Second, the relatives of adolescents with anxiety, disruptive behavior, and substance abuse disorders did not exhibit significantly elevated rates of any mood disorders.

Claims of specificity must be qualified in several respects, however. First, although we tested the significance of the associations between probands' and relatives' diagnoses, we did not formally test the significance of the differences in the magnitude of these associations between different diagnoses. This can be assessed informally by inspecting the 95% CIs for the hazard and odds ratios in Table 3. There is some overlap between the CI for the association between MDD in probands and MDD in relatives and the CIs for the associations between MDD in probands and alcohol abuse or dependence, anxiety disorders, and antisocial personality disorders in relatives. In addition, the CI for the association between proband MDD and relative MDD overlaps with the CI for the association between disruptive behavior disorders in probands and MDD in relatives. Finally, when the analyses were restricted to relatives with direct interviews, there was a small but significant association between proband disruptive behavior disorders and MDD in relatives. Nonetheless, the overall pattern of results suggests that the familial transmission of mood disorders is largely independent of the transmission of anxiety, disruptive behavior, and substance use disorders.

Although this article focused on the familial aggregation of adolescent MDD, we also presented data on the familial transmission of several groups of nonmood disorders. Although conclusions must remain tentative until these groups are broken down into more specific conditions, the data suggest that there are significant, and fairly specific, patterns of familial aggregation for adolescent anxiety and substance use disorders. Previous family and offspring studies of juvenile anxiety<sup>58-60</sup> and substance use disorders<sup>60,61</sup> have also reported significant familial aggregation, although the findings on specificity of transmission have been mixed.

Consistent with previous studies, adolescents with disruptive behavior disorders had a significantly elevated rate of drug abuse or dependence in their relatives.<sup>62</sup> The finding of an increased rate of anxiety disorders in the relatives of adolescents with disruptive behavior disorders was unexpected, although it is consistent with at least 1 previous study.<sup>63</sup> The lack of associations between proband disruptive behavior disorder and alcohol abuse or dependence and antisocial personality disorder in relatives was also surprising.<sup>64</sup> However, it is consistent with a previous study that also failed to find an increased rate of alcoholism in the relatives of youths with attention deficit disorder.<sup>65</sup>

We also explored the role of sex in the familial transmission of adolescent MDD. Previous studies of adult MDD have differed on whether female probands have a similar<sup>66,67</sup> or greater<sup>68,69</sup> familial liability to MDD. In our sample of adolescents, there was a significant interaction between sex of the proband and sex of the relative. The expected female preponderance of MDD was observed in the relatives of female probands. Among the relatives of male probands, however, males exhibited a nonsignificantly higher rate of MDD than females. To our

knowledge, this effect has not been reported before. However, in a review and reanalysis of earlier family studies of adult mood disorders, Faraone et al<sup>70</sup> found a pattern of greater proband-relative concordance in same-sex than opposite-sex sibling pairs. These data suggest that the factors involved in the etiology of MDD may differ, at least in part, between males and females.<sup>66</sup> Alternatively, these results may be due to cultural transmission, with same-sex relatives having a greater impact than opposite-sex relatives through identification or modeling.

The lifetime prevalence of most disorders in the relatives of NMI probands were comparable with findings of the National Comorbidity Survey.<sup>71</sup> The sole exception was the lower rate of anxiety disorders in the present study, possibly caused by differences in diagnostic instruments and procedures.

This study had several limitations. The diagnoses of the probands and relatives were based on retrospective data (although the probands had 3 diagnostic evaluations), and the long-term test-retest reliability of lifetime diagnoses in community samples is only moderate.<sup>72,73</sup> Although we were able to conduct direct interviews with 63% of the relatives, we were forced to rely on informant data for the remaining 37%. Our assessment of Axis II disorders in relatives was limited to antisocial and borderline personality, and, when using Axis II psychopathology in probands as a covariate, we used assessments conducted in young adulthood rather than adolescence. Finally, diagnoses in probands were based on *DSM-III-R*, while diagnoses in relatives were based on *DSM-IV*, possibly attenuating estimates of the degree of familial aggregation.

In conclusion, this study indicates that adolescent MDD exhibits both significant familial aggregation and a high degree of specificity of transmission. These data support the validity of the diagnosis of MDD in adolescents, and the continuity between adolescent and adult MDD. In addition, we observed a significant and relatively specific pattern of familial aggregation for most broad categories of nonmood disorders, supporting the validity and distinctiveness of these other forms of psychopathology in adolescents.

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## REFERENCES

- Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J, Dahl RE, Perel J, Nelson B. Childhood and adolescent depression: a review of the past 10 years, part I. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1427-1439.
- Birmaher B, Ryan ND, Williamson DE, Brent DA, Kaufman J. Childhood and adolescent depression: a review of the past 10 years, part II. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1575-1583.
- Goodyer IM. *The Depressed Child and Adolescent: Developmental and Clinical Perspectives*. Cambridge, England: Cambridge University Press; 1995.
- Kovacs M. Depressive disorders in childhood: an impressionistic landscape. *J Child Psychol Psychiatry*. 1997;38:287-298.
- Carlson GA, Kashani JH. Phenomenology of major depression from childhood through adulthood: analysis of three studies. *Am J Psychiatry*. 1988;145:1222-1225.
- Mitchell J, McCauley E, Burke P. Phenomenology of depression in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1988;27:12-20.
- Ryan ND, Puig-Antich J, Ambrosini P, Rabinovich H, Robinson D, Nelson B, Iyengar S, Twomey J. The clinical picture of major depression in children and adolescents. *Arch Gen Psychiatry*. 1987;44:854-861.
- Garber J, Kriss MR, Koch M, Lindholm L. Recurrent depression in adolescents: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1988;27:49-54.
- Harrington RC, Fudge H, Rutter M, Pickles A, Hill J. Adult outcomes of childhood and adolescent depression, I: psychiatric status. *Arch Gen Psychiatry*. 1990;47:465-473.
- Lewinsohn PM, Rohde P, Klein DN, Seeley JR. The natural course of adolescent major depressive disorder, I: continuity into young adulthood. *J Am Acad Child Adolesc Psychiatry*. 1999;38:56-63.
- Rao U, Ryan ND, Birmaher B, Dahl RE, Williamson DE, Kaufman J, Rao R, Nelson B. Unipolar depression in adolescents: clinical outcome in adulthood. *J Am Acad Child Adolesc Psychiatry*. 1995;34:566-578.
- Weissman MM, Wolk S, Goldstein RB, Moreau D, Adams P, Greenwald S, Klier CM, Ryan ND, Dahl RE, Wickramaratne P. Depressed adolescents grown up. *JAMA*. 1999;281:1707-1713.
- Weissman MM, Wolk S, Wickramaratne P, Goldstein RB, Adams P, Greenwald J, Ryan ND, Dahl RE, Steinberg D. Children with prepubertal-onset major depressive disorder and anxiety grown up. *Arch Gen Psychiatry*. 1999;56:794-801.
- Emstie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. Double-blind placebo-controlled trial of fluoxetine in depressed children and adolescents. *Arch Gen Psychiatry*. 1997;54:1031-1037.
- Ryan ND, Varma D. Child and adolescent mood disorders: experience with serotonin-based therapies. *Biol Psychiatry*. 1998;44:336-340.
- Essau CA, Merikangas KR. Familial and genetic factors. In: Essau CA, Petermann U, eds. *Depressive Disorders in Children and Adolescents*. Northvale, NJ: Jason Aronson; 1999:261-285.
- Strober M. Family-genetic aspects of juvenile affective disorders. In: Goodyer IM, ed. *The Depressed Child and Adolescent: Developmental and Clinical Perspectives*. Cambridge, England: Cambridge University Press; 1995:149-170.
- Downey G, Coyne JC. Children of depressed parents: an integrative review. *Psychol Bull*. 1990;108:50-76.
- Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model of understanding mechanisms of transmission. *Psychol Rev*. 1999;106:458-490.
- Weissman MM. Psychopathology in the offspring of depressed parents: direct interview studies. In: Dunner DL, Gerson ES, Barrett JB, eds. *Relatives at Risk for Mental Disorder*. New York, NY: Raven Press; 1988:143-159.
- Kutcher S, Marton P. Affective disorders in first-degree relatives of adolescent onset bipolars, unipolars, and normal controls. *J Am Acad Child Adolesc Psychiatry*. 1991;30:75-78.
- Puig-Antich J, Goetz D, Davies M, Kaplan T, Davies S, Ostrow L, Asnis L, Twomey J, Iyengar S, Ryan ND. A controlled family history study of prepubertal major depressive disorder. *Arch Gen Psychiatry*. 1989;46:406-418.
- Todd RD, Neuman R, Geller B, Fox LW, Hickok J. Genetic studies of affective disorders: should we be starting with childhood onset probands? *J Am Acad Child Adolesc Psychiatry*. 1993;32:1164-1171.
- Williamson DE, Ryan ND, Birmaher B, Dahl RE, Kaufman J, Rao U, Puig-Antich J. A case-control family history study of depression in adolescents. *J Am Acad Child Adolesc Psychiatry*. 1995;34:1596-1607.
- Harrington RC, Fudge H, Rutter ML, Bredenkamp D, Groothues C, Pridham J. Child and adult depression: a test of continuities with data from a family study. *Br J Psychiatry*. 1993;162:627-633.
- Kovacs M, Devlin B, Pollock M, Richards C, Mukerji P. A controlled family history study of childhood-onset depressive disorder. *Arch Gen Psychiatry*. 1997;54:613-623.
- Weller RA, Kapadia P, Weller EB, Fristad M, Lazaroff LB, Preskorn SH. Psychopathology in families of children with major depressive disorders. *J Affect Disord*. 1994;31:247-252.
- Livingston R, Nugent H, Rader L, Smith GR. Family histories of depressed and severely anxious children. *Am J Psychiatry*. 1985;142:1497-1499.
- Mitchell J, McCauley E, Burke P, Calderon R, Schloredt K. Psychopathology in parents of depressed children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1989;28:352-357.
- Goodman SH, Lahey BB, Fielding B, Dulcan M, Narrow W, Regier D. Representativeness of clinical samples of youth with mental disorders: a preliminary population-based study. *J Abnorm Psychol*. 1997;107:3-14.
- Kendler KS. Is seeking treatment for depression predicted by a history of depression in relatives? implications for family studies of affective disorder. *Psychol Med*. 1995;25:807-814.

32. Sullivan PF, Wells JE, Joyce PR, Bushness JA, Mulder RT, Oakley-Browne MA. Family history of depression in clinic and community samples. *J Affect Disord*. 1996;40:159-168.
33. Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. Adolescent psychopathology, I: prevalence and incidence of depression and other DSM-III-R disorders in high school students. *J Abnorm Psychol*. 1993;102:133-144.
34. Orvaschel H, Puig-Antich J, Chambers WJ, Tabrizi MA, Johnson R. Retrospective assessment of prepubertal major depression with the Kiddie-SADS-E. *J Am Acad Child Adolesc Psychiatry*. 1995;34:1596-1607.
35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
36. Hamilton M. A rating scale for depression. *J Neurol Neurosurg*. 1960;23:56-61.
37. Endicott J, Cohen J, Nee J, Fleiss J, Sarantakos S. Hamilton Depression Rating Scale: extracted from Regular and Change Versions of the Schedule for the Affective Disorders and Schizophrenia. *Arch Gen Psychiatry*. 1981;38:98-103.
38. Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott PA. The Longitudinal Interval Follow-up Examination: a comprehensive method for assessing outcome in retrospective longitudinal studies. *Arch Gen Psychiatry*. 1987;44:540-548.
39. Loranger AW. *Personality Disorder Examination (PDE) Manual*. Yonkers, NY: DV Communications; 1988.
40. Lewinsohn PM, Rohde P, Seeley JR, Klein DN. Axis II psychopathology as a function of Axis I disorders in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry*. 1997;36:1752-1759.
41. First MB, Gibbon M, Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders: Nonpatient Edition (SCID-I/NP)*. New York: Biometrics Research Dept, New York State Psychiatric Institute; 1996.
42. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press; 1997.
43. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
44. Mannuzza S, Fyer AJ. *Family Informant Schedule and Criteria (FISC)*. New York, NY: New York State Psychiatric Institute; 1990.
45. Ferro T, Klein DN, Norden K, Donaldson SK, Lizardi H. Development and reliability of the Family History Interview for Personality Disorders. *J Personal Disord*. 1995;9:169-177.
46. Rohde P, Lewinsohn PM, Seeley JR. Comparability of telephone and face-to-face interviews in assessing axis I and II disorders. *Am J Psychiatry*. 1997;154:1593-1598.
47. Sobin E, Weissman MM, Goldstein RB, Adams P. Diagnostic interviewing for family studies: comparing telephone and face-to-face methods for the diagnosis of lifetime psychiatric disorders. *Psychiatr Genet*. 1993;3:227-233.
48. Wells KB, Burnham MA, Leake B, Robins LN. Agreement between face-to-face and telephone-administered versions of the depression section of NIMH Diagnostic Interview Schedule. *J Psychiatr Res*. 1988;22:207-220.
49. Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM. Best-estimate of lifetime psychiatric diagnoses. *Arch Gen Psychiatry*. 1982;39:879-883.
50. King TM, Beaty TH, Liang K-Y. Comparison of methods for survival analysis of dependent data. *Genet Epidemiol*. 1996;13:139-158.
51. Chapman TF, Mannuzza S, Klein DF, Fyer AJ. Effects of informant mental disorder on psychiatric family history data. *Am J Psychiatry*. 1994;151:574-579.
52. Kendler KS, Silberg JL, Neale MC, Kessler RC, Heath AC, Eaves LJ. The family history method: whose psychiatric history is measured? *Am J Psychiatry*. 1991;148:1501-1504.
53. Goldstein RB, Weissman MM, Adams PB, Horwath E, Lish JD, Charney D, Woods SW, Sobin C, Wickramaratne PJ. Psychiatric disorders in relatives of probands with panic disorder and/or major depression. *Arch Gen Psychiatry*. 1994;51:383-394.
54. Weissman MM, Gerson ES, Kidd KK, Prusoff BA, Leckman JF, Dibble E, Hamovit J, Thompson WD, Pauls DL, Guroff JJ. Psychiatric disorders in the relatives of probands with affective disorder. *Arch Gen Psychiatry*. 1984;41:13-21.
55. Wickramaratne PJ, Weissman MM. Onset of psychopathology in offspring by developmental phase and parental depression. *J Am Acad Child Adolesc Psychiatry*. 1998;37:933-942.
56. Goodman DW, Goldstein RB, Adams PB, Horwath E, Sobin C, Wickramaratne P, Weissman MM. Relationship between dysthymia and major depression: an analysis of family study data. *Depression*. 1994/1995;2:252-258.
57. Klein DN, Riso LP, Donaldson SK, Schwartz JE, Anderson RL, Ouimette PC, Lizardi H, Aronson TA. Family study of early-onset dysthymia: mood and personality disorders in relatives of outpatients with dysthymia and episodic major depression and normal controls. *Arch Gen Psychiatry*. 1995;52:487-496.
58. Beidel DC, Turner SM. At risk for anxiety, I: psychopathology in the offspring of anxious parents. *J Am Acad Child Adolesc Psychiatry*. 1997;36:918-924.
59. Last CG, Hersen M, Kazdin A, Orvaschel H, Perrin S. Anxiety disorders in children and their families. *Arch Gen Psychiatry*. 1991;48:928-934.
60. Merikangas KR, Dierker LC, Szatmari P. Psychopathology among offspring of parents with substance abuse and/or anxiety disorders: a high-risk study. *J Child Psychol Psychiatry*. 1998;39:711-720.
61. West MO, Prinz RJ. Parental alcoholism and childhood psychopathology. *Psychol Bull*. 1987;102:204-218.
62. Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT. Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. *J Am Acad Child Adolesc Psychiatry*. 1990;29:526-533.
63. Biederman J, Faraone SV, Keenan K, Steingard R, Tsuang MT. Familial association between attention deficit disorder and anxiety disorders. *Am J Psychiatry*. 1991;148:251-256.
64. Pfiffner LJ, McBurnett K, Lahey BB, Loeber R, Green S, Frick PJ, Rathouz PJ. Association of parental psychopathology to the comorbid disorders of boys with attention deficit-hyperactivity disorder. *J Consult Clin Psychol*. 1999;67:881-893.
65. Faraone SV, Biederman J, Keenan K, Tsuang MT. Separation of DSM-III attention deficit disorder and conduct disorder: evidence from a family-genetic study of American child psychiatric patients. *Psychol Med*. 1991;21:109-121.
66. Kendler KS, Prescott CA. A population-based twin study of lifetime major depression in men and women. *Arch Gen Psychiatry*. 1999;56:39-44.
67. Merikangas KR, Weissman MM, Pauls DF. Genetic factors in the sex ratio of major depression. *Psychol Med*. 1995;15:63-69.
68. Bierut LJ, Heath AC, Bucholz KK, Dinwiddie SH, Madden PAF, Statham DJ, Dunne MP, Martin NG. Major depressive disorder in a community-based twin sample: are there different genetic and environmental contributions for men and women? *Arch Gen Psychiatry*. 1999;56:557-563.
69. Reich T, Van Eerdewegh P, Rice J, Mullaney J, Endicott J, Klerman GL. The familial transmission of primary major depressive disorder. *J Psychiatr Res*. 1987;21:613-624.
70. Faraone SV, Lyons MJ, Tsuang MT. Sex differences in affective disorder: genetic transmission. *Genet Epidemiol*. 1987;4:331-343.
71. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51:8-19.
72. Bromet EJ, Dunn LO, Connell MM, Dew MA, Schulberg HC. Long-term reliability of diagnosing lifetime major depression in a community sample. *Arch Gen Psychiatry*. 1986;43:435-440.
73. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women: reliability of diagnosis and heritability. *Arch Gen Psychiatry*. 1993;50:863-870.