Parental Major Depression and the Risk of Depression and Other Mental Disorders in Offspring

A Prospective-Longitudinal Community Study

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Background: This article examines associations between *DSM-IV* depressive disorders, their natural course, other psychopathology, and parental major depression in a community sample of adolescents and young adults.

Methods: Baseline and 4-year follow-up data were used from the Early Developmental Stages of Psychopathology Study, a prospective-longitudinal community study of adolescents and young adults. Results are based on 2427 subjects who completed the follow-up and for whom diagnostic information for both parents was available. *DSM-IV* mental disorders in respondents were assessed using the Munich-Composite International Diagnostic Interview. Information on depression in parents was collected as family history information from the respondents and from diagnostic interviews with parents of the younger cohort.

Results: Offspring with 1 (odds ratio [OR], 2.7; 95% confidence interval [CI], 2.1-3.5) or 2 affected parents (OR, 3.0; 95% CI, 2.2-4.1) had an increased risk for depression. They also had a higher risk for substance use (1 parent affected: OR, 1.4; 95% CI, 1.1-1.7; both parents affected: OR, 1.4; 95% CI, 1.0-1.8) and anxiety disorders (1 parent affected: OR, 1.6; 95% CI, 1.3-1.9; both parents affected: OR, 2.1; 95% CI, 1.6-2.8). There were no differences whether mother or father was affected. Parental depression was associated with an earlier onset and a more malignant course (severity, impairment, recurrence) of depressive disorders in offspring.

Conclusions: Major depression in parents increases the overall risk in offspring for onset of depressive and other mental disorders and influences patterns of the natural course of depression in the early stages of manifestation.

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A VAST NUMBER of studies have investigated the association between depression in parents and psychopathology in their offspring. Studies using the "top-down" approach have consistently shown that offspring of depressed parents have a substantially increased risk for experiencing not only depressive disorders, but also other psychopathology, such as anxiety or substance-use disorders.[1-17] From another perspective, "bottom-up" studies examining clinically referred depressed children and adolescents have reported increased rates of depression and other forms of psychopathology in their adult relatives.[18-25]

Although the association between parental depression and offspring psychopathology seems to be sufficiently studied, there are several weaknesses of previous research. Thus, with 2 exceptions,[14,15] all studies have included affected individuals (either parent or child) in treatment as index probands. Because of the effects of self-selection, treatment, and help-seeking bias, these results may not be representative of depressive disorders in general.[26] Further, most studies have failed to consider diagnostic comorbidity within the affected parents, so it is often not clear whether the reported associations are unique for parental depression or whether the associations may also be explained by confounding comorbid disorders in parents.[15,27] Additionally, most studies have focused on diagnostic status in the mother or in either parent, and only a few have evaluated associations separately for affected mothers and fathers or different levels of parental loading.[2,3,7,17]

A final, understudied issue is the natural course of depressive disorders in offspring of affected parents in terms of onset, severity, persistence, and risk of recurrence. A precise picture of the natural course of depressive disorders in these offspring requires prospective-longitudinal designs. Although during the past decade there have been methodologically

SUBJECTS AND METHODS

SAMPLE

Data come from the Early Development Stages of Psychopathology Study (EDSP), a prospective-longitudinal study designed to collect data on the prevalence, incidence, familial risk and other risk factors, comorbidity, and course of mental disorders in a representative sample of 3021 respondents aged 14 to 24 years at baseline. These respondents represent the offspring in this report. The EDSP consists of a baseline survey, 2 follow-up surveys, and a family supplement. Detailed descriptions of the study are reported elsewhere.[28,29] The baseline sample was drawn in 1994 from the government registries in Munich, Germany, of registrants expected to be 14 to 24 years of age at the time of the baseline interview in 1995. Details about the sampling and representativeness of the whole EDSP sample, along with its sociodemographic characteristics, have been previously presented.[28-30] A total of 3021 interviews were completed at baseline (T0; response rate, 71%). The first follow-up study (T1) was conducted only for respondents aged 14 to 17 years at baseline, whereas the second follow-up study was conducted for all respondents. In the first follow-up, which took place at an average of 20 months after baseline, a total of 1228 interviews were completed (response rate, 88%). From the 3021 respondents of the baseline study, a total of 2548 interviews were completed at the second follow-up (T2), which occured at an average of 42 months after baseline (response rate, 84%).

In the EDSP family supplement, direct diagnostic interviews were conducted with the parents of the younger cohort (the 14- to 17-year-olds at baseline).[29] As we were interested not only in familial psychopathology, but also in early developmental information about the respondents, primarily the mothers were interviewed. Fathers were interviewed only if the mother was not available (deceased or not locatable). The parents of 1053 adolescents were interviewed directly (in 1026 cases the mother, in 27 cases the father; response rate, 86%).

The results reported in this article are based on the 2427 respondents who completed the whole study period and for whom diagnostic information about psychopathology in both parents was available. Throughout the article, data are weighted by age, sex, geographic location, noncontact, and nonresponse to match the distribution of the sampling frame.[29]

DIAGNOSTIC ASSESSMENT OF OFFSPRING

Diagnoses of the offspring are based on the *DSM-IV*[31] and were assessed with the computer-assisted version of the Munich-Composite International Diagnostic Interview (M-CIDI[32]), an updated version of the World Health Organization's Composite International Diagnostic Interview version 1.2.[33] The reliability and validity of the M-CIDI have been reported.[34-36] Diagnostic findings were obtained by using the M-CIDI/*DSM-IV* diagnostic algorithms. In all assessments, interviews were administered by highly trained clinical interviewers—mostly graduate students in psychology. Most interviews were carried out in the homes of the respondents.

The diagnoses considered in this article include depressive disorders (major depression, dysthymia), bipolar disorders (bipolar I and bipolar II disorders), anxiety disorders (panic disorder with and without agoraphobia, agoraphobia without panic disorder, specific phobia, phobia not otherwise specified, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder), and substance use disorders (alcohol abuse and dependence, nicotine dependence, and illicit drug abuse and dependence). Descriptors of the severity of depression (eg, number of depressive episodes, impairment, treatment seeking) refer to the self-identified worst episode of depression. Overall impairment due to depression was assessed by asking the respondents how much their depression impaired daily life and activities during the worst period. Social role–specific impairment was assessed by questions in which respondents were asked how much during the 4 weeks preceding the interview depressive symptoms made them feel impaired in (1) daily activities such as work, house work, or studies; (2) leisure-time activities; and (3) social contact with family, friends, and colleagues.

At baseline, the lifetime version of the M-CIDI was used. At each of the follow-up assessments, we applied the M-CIDI interval version, which refers to the period of assessment from the last interview until the present. For those respondents aged 14 to 17 years at baseline, the complete follow-up status from baseline to second follow-up is assessed from the aggregation of information obtained from the first and second follow-up interviews. For respondents older than 17 years at baseline, the complete follow-up status is assessed from the second follow-up questions, which cover the time between baseline and second follow-up.

PARENTAL HISTORY

In a separate M-CIDI family history module administered at baseline and second follow-up, respondents provided family history information on all first-degree relatives. Family history items were designed using a modified version of the Family History Research Diagnostic Criteria[37] as a model. To obtain family history information about the same *DSM-IV* diagnoses that are in the M-CIDI, M-CIDI stem questions

sound longitudinal studies of offspring of depressed parents that suggest that parental depression leads to an earlier onset as well as a more complicated course of depression in the offspring,[7-10,13,14] none of them have used a representative community sample to evaluate such specific course characteristics.

The present study examines, on the basis of a representative community sample of adolescents and young adults, the association of a history of major depression in parents with depression and other mental disorders, along with the course of depression in offspring in terms of age of onset, severity, and impairment.

RESULTS

PREVALENCES

Study criteria for major depression were fulfilled by 42.1% of mothers and 23.4% of fathers (**Table 1**). In 33.7% and 16.0% of the sample, respectively, one (mother only,

were used at baseline. Questions to determine whether the relative sought professional help because of his or her respective symptoms were also asked. In the second follow-up, we used an extended version of the family history module, which contained fully structured sections covering *DSM-IV* criteria.

Parents of the younger cohort were independently assessed with the M-CIDI in the EDSP family supplement, providing direct diagnostic information about the interviewed parent. Interviewers were blinded to the diagnostic findings of the respective offspring. The parent M-CIDI contained a module that provided family history data for the noninterviewed parent and other family members of the respondent.[38,39]

Family history status of major depression was determined by using all available diagnostic information about the occurrence of any major depression episode in parents. Diagnostic estimates for the parents of the younger cohort took into account the family history data obtained from the respondent as informant, as well as the M-CIDI information and family history data obtained from the parent interview.[39] For the older cohort, for which no direct parent interviews were available, we used only family history information obtained from the respondent. The accuracy of family history information was examined by comparing the diagnostic information obtained from the respondents about their mothers, with the information obtained from the mothers themselves. This was also achieved by comparing the family history information obtained from the respondents about their fathers, with the family history information obtained from the mothers about the fathers. Overall, only moderate sensitivity (48% for the detection in mothers, 63% for the detection in fathers), but acceptable high specificity (68% for mothers, 85% for fathers), was found for major depression. For this article, any indication of a major depressive episode was accepted for a positive diagnosis in parents. Therefore, the diagnostic certainty should be interpreted on the "probable" level.[39]

STATISTICAL ANALYSES

As our goal was to examine the degree to which parental major depression is associated with diagnostic outcomes in children, parental major depression was the independent variable. Main diagnostic outcomes were the offspring's cumulative lifetime incidences of *DSM-IV* depressive and other mental disorders at second follow-up, which were calculated by adding baseline and follow-up incident cases.

For the analyses of associations between major depression in parents and psychopathology in offspring, logistic regressions for binary responses (odds ratio [OR]) were used. For the analysis of impairment variables, cumulative logistic regressions were used. Hereby, it is assumed that the covariates are related to a shift on a latent continuum that underlies the observed categories, and this overall association is described with cumulative ORs (CUMORs). This provides more statistical precision in estimates as compared with dichotomization.[40]

For quantitative outcomes of severity of depression that were count variables (values of 0, 1, 2, ...; eg, the number of depressive episodes), negative binomial regressions were used. Hereby, the skewness of these variables is taken into account, as well as overdispersion (when a variance is higher than expected under the Poisson model for the dependent variable conditional on the covariate values[41]). Associations are described by incidence rate ratios (ie, the factor by which the mean differs from the mean in the comparison group).

Age-specific cumulative lifetime incidences were estimated with the Kaplan-Meier-method[42] using age of onset information from the offspring. Statistical inferences are based on the stratified Cox model for discrete time (ie, before testing for differences, different curves in strata defined by birth year cohorts and sex of the offspring are calculated nonparametrically[42]). The interaction term parental major depression×age was added to the model when the proportional hazards assumption was violated. The latter was tested with Schoenfeld residuals.[43] This was done to see whether offspring with affected parents have an earlier onset of the disorder under consideration. Such a model provides hazard ratios (HRs) for the main effect of parental major depression and for the interaction effect with age. An HR less than 1 for the interaction term indicates that offspring with affected parents have an earlier onset than offspring without affected parents. The age-specific HR for the effect of parental major depression is given by the following:

$$HR\ (Age) = HR\ Main\ Effect \times HR\ Interaction\ Effect^{age}$$

When Cox analyses were conducted with multiple anxiety or substance use disorders, the age of onset of the chronologically earliest disorder was used.

Analyses were performed using the Stata software package[44] and applying the Huber-White sandwich matrix for weighted data.[45] Sex and age of offspring were controlled for by including them as independent variables in the respective model. $P < .05$ was considered statistically significant. All associations were tested for interaction with sex of offspring, and in cases of significant effects, associations were then separately determined for males and females. To protect for misleading results obtained by aggregating 2 cohorts with different ascertainment strategies, all associations were tested for an interaction effect with age cohort. In case of significance, analyses were run separately within each cohort.

26.2%; father only, 7.5%) or both parents were affected. Of the offspring, 19.5% reported at least 1 episode of major depression by the second follow-up, and 3.8% fulfilled criteria for lifetime dysthymia. Substance use disorders were reported by 43.1% of the offspring when nicotine dependence was included, and by 31.3% of the offspring when nicotine dependence was excluded. Bipolar disorders were reported by 3.1%; and any anxiety disorder, by 35.0% of the offspring. Depressive and anxiety disorders were more common in female offspring than in male offspring, while substance use disorders were more common in male offspring than in female offspring. No gender differences were found for bipolar disorders.

ASSOCIATIONS BETWEEN PARENTAL DEPRESSION AND PSYCHOPATHOLOGY IN OFFSPRING

Compared with the offspring of nondepressed parents, offspring of either 1 or 2 depressed parents reported

Table 1. Major Depression in Parents and Cumulative Lifetime Incidence Rates of *DSM-IV* Depressive and Other Disorders in Offspring*

	Frequency			
	No. of Subjects	N_W	$\%_W$	95% CI
Major depression in parents†				
Neither parent	1231	1214	50.4	48.2-52.6
Mother	1026	1015	42.1	40.0-44.4
Father	535	564	23.4	21.5-25.4
Mother only	661	631	26.2	24.3-28.2
Father only	170	180	7.5	6.4-8.8
Just one parent	831	811	33.7	31.6-35.8
Both parents	365	384	16.0	14.3-17.7
Depressive disorders and other psychopathology in study sample‡				
Depressive disorders				
Major depression (single or recurrent)				
Males	162	168	14.0	11.9-16.4
Females	281	302	25.0§	22.3-28.0
Total	**443**	**470**	19.5	17.7-21.4
Dysthymia				
Males	31	28	2.4	1.6-3.5
Females	64	63	5.2§	3.9-6.9
Total	**95**	**91**	3.8	3.0-4.8
Other *DSM-IV* disorders (main diagnostic groups)‖				
Substance use disorders				
Males	635	630	52.4§	49.2-55.5
Females	388	409	33.9	30.9-37.1
Total	**1023**	**1039**	43.1	40.9-45.4
Excluding nicotine dependence				
Males	547	543	45.1§	42.0-48.3
Females	202	211	17.5	15.2-20.1
Total	**749**	**754**	31.3	29.3-33.4
Bipolar disorders				
Males	29	34	2.8	1.8-4.1
Females	42	41	3.4	2.4-4.8
Total	**71**	**75**	3.1	2.4-4.1
Anxiety disorders				
Males	315	305	25.4	22.7-28.3
Females	530	537	44.5§	41.3-47.8
Total	**845**	**842**	35.0	32.8-37.2

*N_W indicates weighted number of subjects; $\%_W$, weighted percentage of subjects; and CI, confidence interval. Unweighted N total = 2427; weighted total N = 2409.

†"Mother" indicates the proportion of cases in which the mother was affected, irrespective of the diagnostic status of the father; "Father," the proportion of cases in which the father was affected, irrespective of the diagnostic status of the mother; "Mother only," the proportion of cases in which the mother, but not the father, was affected; "Father only," the proportion of cases in which the father, but not the mother, was affected.

‡Indicates the cumulative lifetime incidence at second follow-up.

§Indicates the group with the higher rate. The gender difference is significant at $P<.05$. Male vs female odds ratio was 2.0 (95% CI, 1.6-2.7) for a major depressive disorder; 2.3 (95% CI, 1.4-3.7) for dysthymia; 0.5 (95% CI, 0.3-0.6) for any substance use disorder including nicotine dependence; 0.3 (95% CI, 0.2-0.3) for any substance use disorder excluding nicotine dependence; and 2.4 (95% CI, 1.9-2.9) for any anxiety disorder.

‖Rates for specific disorders are available on request. Substance use disorders include alcohol abuse/dependence, illicit drug use/dependence, and nicotine dependence. Bipolar disorders include bipolar I and II. Anxiety disorders include panic disorder with or without agoraphobia, agoraphobia without panic disorder, phobia not otherwise specified, social phobia, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder. Since the $\%_W$ values have been rounded, the sum of the individual $\%_W$ does not always equal 100%.

higher rates of depression and almost all other disorders under consideration (**Table 2**). With few exceptions, risks were similar in offspring with 1 vs 2 affected parents. The exceptions were bipolar II, obsessive-compulsive disorder, posttraumatic stress disorder, and the aggregated category of anxiety disorders, for which risks were higher in offspring with 2 affected parents. In general, adjusting for parental comorbidity yielded similar results. Only the associations between parental depression and alcohol dependence, agoraphobia, phobia not otherwise specified, and social phobia in offspring failed to reach significance, suggesting that the

increased rates of these disorders in the offspring may be due to comorbid disorders in the parents. In an effort to exclude the hypothesis that the lack of differences between 1 and 2 depressed parents could be explained by coparental psychopathology in offspring with 1 affected parent, we additionally reran the analyses controlling for coparental psychopathology. These analyses yielded similar findings.

All parent-offspring associations were tested for differences between male and female offspring. In general, associations were comparable in size for sons and daughters. Interaction effects were found only as follows: among

Table 2. Lifetime Association of Parental Major Depression With *DSM-IV* Depressive and Other Mental Disorders in Their Offspring*

	Parental Loading of Major Depression						
	Neither Parent Affected (N_W = 1214)	One Parent Affected (N_W = 811)			Both Parents Affected (N_W = 384)		
DSM-IV Disorder in Offspring†	$\%_W$	$\%_W$	OR	95% CI	$\%_W$	OR	95% CI
Affective disorders							
Major depression	12.3	26.1	2.5‡	1.9-3.2	28.5	2.8‡	2.0-3.9
Dysthymia	1.8	5.3	2.9‡	1.7-5.1	6.8	3.9‡	2.1-7.5
Any depressive disorder	13.1	29.1	2.7‡	2.1-3.5	31.3	3.0‡	2.2-4.1
Bipolar I	1.0	3.2	3.2‡	1.4-7.1	5.7	5.7‡	2.6-12.8
Bipolar II	0.3	0.5	1.7§	0.3-7.7	2.5	8.6‡	1.9-38.0
Any affective disorder	14.2	31.9	2.8‡	2.2-3.6	35.3	3.3‡	2.4-4.4
Substance use disorders							
Alcohol abuse	19.0	21.7	1.3‡‖	0.9-1.7	18.2	1.1	0.8-1.5
Alcohol dependence	7.6	9.7	1.4	0.9-2.0	12.1	1.8‡‖	1.1-2.7
Nicotine dependence	20.7	26.8	1.4‡‖	1.1-1.8	31.2	1.7‡	1.3-2.3
Any illicit drug abuse/dependence	6.2	11.1	2.0‡	1.4-2.8	10.5	1.9‡	1.2-2.9
Any substance use disorder including nicotine dependence	39.8	46.4	1.4‡	1.1-1.7	46.6	1.4‡‖	1.0-1.8
Any substance use disorder excluding nicotine dependence	28.4	34.9	1.5‡	1.2-1.9	33.0	1.3‖	0.9-1.8
Anxiety disorders							
Panic disorder with or without agoraphobia	1.7	2.7	1.6¶	0.8-3.2	4.8	2.9‡	1.4-6.1
Agoraphobia without panic disorder	1.9	4.4	2.3‡‖	1.3-4.1	4.6	2.4‡‖	1.2-5.0#
Phobia not otherwise specified	5.9	8.5	1.4	0.9-2.1	10.7	1.9‡‖	1.2-3.0
Social phobia	7.5	11.8	1.6‡‖	1.1-2.3	13.0	1.8‡‖	1.1-2.7
Specific phobia	17.7	23.5	1.4‡‖	1.1-1.8	29.2	1.9‡¶	1.4-2.6
Generalized anxiety disorder	2.5	6.1	2.5‡	1.5-4.3	9.0	3.7‡	2.0-6.8
Obsessive-compulsive disorder	0.6	0.8	1.4§	0.5-3.8	4.0	6.9‡	2.7-17.8
Posttraumatic stress disorder	0.9	1.6	1.8§	0.7-4.8	5.3	6.1‡	2.5-14.9
Any anxiety disorder	28.6	39.1	1.6‡§	1.3-1.9	46.2	2.1‡¶	1.6-2.8

*N_W indicates weighted number of subjects; $\%_W$, weighted percentage of subjects; OR, odds ratio; and CI, confidence interval. Unweighted N total = 2427; weighted total N = 2409.

†Cumulative lifetime incidence at the time of the second follow-up.

‡The OR is significant at *P*<.05. All ORs are controlled for age and gender of the offspring. The reference group is "neither parent is affected."

§The difference in the ORs between "one parent affected" and "both parents affected" is significant at *P*<.05. The ORs for the differences are OR = 5.0 (95% CI, 1.6-15.7) for bipolar II; OR = 5.0 (95% CD, 1.9-13.4) for obsessive-compulsive disorder; OR = 3.4 (95% CI, 1.4-8.2) for posttraumatic stress disorder; and OR = 1.4 (95% CI, 1.0-1.8) for any anxiety disorder.

‖Values failed to reach significance when controlling for parental anxiety and alcohol use disorders.

¶Significant interaction effects were found for gender of offspring as follows: interaction of gender × one parent affected for panic disorder, OR = 0.2 (95% CI, 0.0-1.0); OR = 4.9 (95% CI, 1.2-19.1) for male offspring; OR = 1.0 (95% CI, 0.4-2.2) for female offspring; interaction of gender × both parents affected: OR for specific phobia = 2.6 (95% CI, 1.4-5.0); OR for male offspring = 1.0 (95% CI, 0.6-1.7); and OR for female offspring = 2.7 (95% CI, 1.8-4.0).

#A significant effect was found for the interaction of cohort × both parents: OR for interaction = 5.6 (95% CI, 1.0-28.2); OR for younger cohort = 0.7 (95% CI, 0.1-2.6); and OR for older cohort = 3.7 (95% CI, 1.5-9.3).

offspring of 1 affected parent, only males had a higher risk for panic disorder, while among offspring of 2 affected parents, only females had a higher risk for specific phobia as well as for any anxiety disorder. The examination of interaction with cohort revealed that among offspring of 2 affected parents, risk for agoraphobia was increased only in the older cohort.

SEX OF AFFECTED PARENT

To examine whether the pattern of associations differed by sex of the affected parent, analyses were conducted after dividing offspring into those with an affected mother only and those with an affected father only. Compared with the offspring of nonaffected parents, offspring of both groups had higher rates of depression and other mental disorders (**Table 3**). Associations were not different between maternal and paternal depression.

With the exception of male offspring of affected mothers having a higher risk for panic disorder, no notable differences in risks were found between male and female offspring. The examination of interaction with the cohort revealed only one effect: among the offspring of affected fathers, risk for any substance use disorder (including or excluding nicotine dependence) was increased only in the younger cohort.

MAJOR DEPRESSION IN PARENTS AND AGE OF ONSET

The **Figure** shows the offsprings' age-specific probability of developing any type of depression by number of affected parents. First onset of any depressive disorder was earlier in offspring with 2 affected parents when compared with offspring without affected parents (for interaction with age, HR=0.9, 95% confidence interval [CI]=0.8-0.9; for main effect from this model, HR=8.5,

Table 3. Cumulative Lifetime Rates of *DSM-IV* Mental Disorders by Gender of Affected Parent*

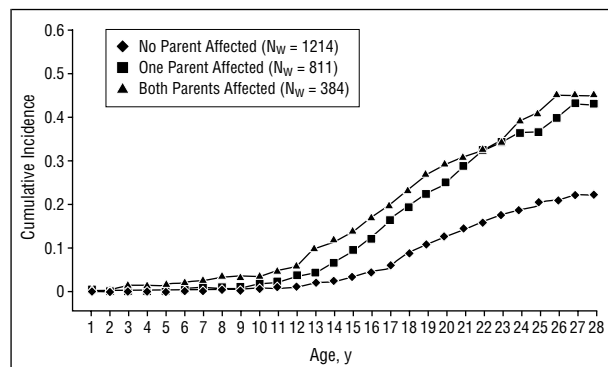| | Parental Loading of Major Depression | | | | | | |
| | Neither Parent Affected (N_W = 1214) | Only Mother Affected (N_W = 631) | | | Only Father Affected (N_W = 180) | | |
DSM-IV Disorder in Offspring†	%$_W$	%$_W$	OR	95% CI	%$_W$	OR	95% CI
Affective disorders							
Major depression	12.3	25.0	2.3‡	1.8-3.1	30.0	3.1‡	2.0-4.8
Dysthymia	1.8	5.4	2.9‡	1.6-5.1	5.2	3.0‡	1.2-7.2
Any depressive disorder	13.1	28.2	2.6‡	2.0-3.4	32.2	3.2‡	2.1-4.9
Bipolar I	1.0	3.3	3.4‡	1.4-7.8	2.5	2.5	0.7-8.5
Bipolar II	0.3	0.5	1.6	0.3-8.1	0.6	2.0	0.3-13.0
Any affective disorder	14.2	30.9	2.7‡	2.0-3.5	35.3	3.4‡	2.2-5.0
Substance use disorders							
Alcohol abuse	19.0	20.8	1.3	0.9-1.7	25.1	1.5	0.9-2.3
Alcohol dependence	7.6	10.3	1.6‡	1.0-2.3	7.5	1.0	0.5-1.9
Nicotine dependence	20.7	26.6	1.4‡	1.1-1.8	27.5	1.4	0.9-2.2
Any illicit drug abuse/dependence	6.2	11.5	2.1‡	1.5-3.1	9.5	1.6	0.9-3.1
Any substance use disorder including nicotine dependence	39.8	46.8	1.4‡	1.1-1.8	44.9	1.2	0.9-1.8‖
Any substance use disorder excluding nicotine dependence	28.4	34.8	1.5‡	1.2-2.0	35.1	1.4	0.9-2.1‖
Anxiety disorders							
Panic disorder with or without agoraphobia	1.7	3.1	1.8§	0.9-3.7	1.4	0.8	0.2-2.9
Agoraphobia without panic disorder	1.9	4.1	2.1‡	1.1-3.9	5.3	2.9‡	1.2-6.9
Phobia not otherwise specified	5.9	9.5	1.6‡	1.1-2.3	5.2	0.9	0.4-1.8
Social phobia	7.5	12.4	1.7‡	1.2-2.5	9.7	1.3	0.7-2.4
Specific phobia	17.7	23.0	1.3‡	1.0-1.7	25.1	1.6‡	1.0-2.5
Generalized anxiety disorder	2.5	5.7	2.3‡	1.3-4.1	7.5	3.1‡	1.4-7.1
Obsessive-compulsive disorder	0.6	0.6	0.9	0.3-3.1	1.7	2.9	0.8-11.1
Posttraumatic stress disorder	0.9	1.5	1.6	0.5-4.9	2.1	2.4	0.6-9.3
Any anxiety disorder	28.6	39.9	1.6‡	1.3-2.0	36.4	1.4	0.9-2.1

*N_W indicates weighted number of subjects; %$_W$, weighted percentage of subjects; OR, odds ratio; and CI, confidence interval.
†Cumulative lifetime incidence at the time of the second follow-up.
‡The OR is significant at $P<.05$. All ORs are controlled for age and gender of the offspring. The reference group is "neither parent is affected."
§Significant interaction effect was found for gender of offspring as follows: interaction of gender × only mother affected for panic disorder, OR = 0.2 (95% CI, 0.0-0.9); for male offspring, OR = 5.8 (95% CI, 1.5-23.5); for female offspring, OR = 1.1 (95% CI, 0.5-2.5).
‖Signficant interaction effect was found for the cohort as follows: interaction cohort × only father affected: for substance use disorder including nicotine dependence, OR = 0.5 (95% CI, 0.2-0.9); for younger cohort, OR = 2.1 (95% CI, 1.2-3.5); and for older cohort, OR = 0.9 (95% CI, 0.6-1.6). For the interaction cohort × only father affected, for substance use disorder (excluding, nicotine dependence): OR = 0.5 (95% CI, 0.2-0.9); for younger cohort, OR = 1.7 (95% CI, 1.1-2.8); and for older cohort, OR = 1.0 (95% CI, 0.5-2.0).

Age of onset of any depression in offspring, by parental history of major depression. N_w indicates number of subjects.

95% CI = 2.9-24.6), whereas there was no such finding when only 1 parent was affected (for interaction with age, HR = 1.0, 95% CI = 0.9-1.0; for main effect from this model, HR = 2.5, 95% CI = 0.6-9.5). Age of onset characteristics were also examined separately for major depression and dysthymia. Both disorders started earlier in offspring with 2 affected parents than in offspring without affected par-

ents (major depression: for interaction with age, HR = 0.9, 95% CI = 0.8-0.9; for main effect from this model, HR = 9.2, 95% CI = 2.7-31.3) (dysthymia: for interaction with age, HR = 0.9, 95% CI = 0.7-0.9; for main effect from this model, HR = 29.9, 95% CI = 5.0-176.1).

Because of restricted sample sizes in some specific anxiety disorders, age of onset characteristics were determined for the main diagnostic group of "any anxiety disorder." For anxiety disorders, no interactions between age of onset in offspring and parental depression were found. Concerning substance use disorders, age of onset characteristics were separately evaluated for nicotine dependence, alcohol dependence, and abuse or dependence of any illicit drugs. Offspring with 2 affected parents develop drug abuse or dependence earlier (for interaction with age, HR = 0.8, 95% CI = 0.6-0.9; for main effect from this model, HR = 34.8, 95% CI = 1.9-615.9) as compared with offspring without affected parents. By contrast, the age of onset for nicotine dependence and for alcohol use disorders did not vary by parental diagnostic status. All interaction effects proved similar when adjusting for parental comorbidity.

Table 4. Severity and Treatment Seeking for Parental Major Depression*

| | Parental Major Depression | | | | | |
| | Neither Parent Affected (N_w = 149) | | Either One or Both Parents Affected (N_w = 321) | | | |
	%$_w$ or Mean	SD	%$_w$ or Mean	SD	OR/IRR†	95% CI
Indicators of severity						
Suicidal attempts‡	6.5	. . .	8.2	. . .	1.3	0.6-2.9
Suicidal ideas§	0.7	1.2	0.9	1.3	1.3	0.9-1.8
Number of depressive symptoms‖	5.9	1.4	6.0	1.7	1.0	0.9-1.1
Number of periods with depressed mood, lack of energy or loss of interest	2.7	5.7	5.2	13.8	1.8¶	1.1-2.9
Persistence#	9.0	. . .	30.0	. . .	4.5¶	1.9-10.5
Treatment seeking because of depression**						
Hospitalization	3.7	. . .	7.6	. . .	2.0	0.6-6.2
Doctor	16.6	. . .	27.7	. . .	1.8¶	1.0-3.4
Any treatment	20.3	. . .	33.8	. . .	1.9¶	1.1-3.4

*N_w indicates the weighted number of subjects; %$_w$, weighted percentage of subjects; OR, odds ratio; IRR, incidence rate ratio; CI, confidence interval; and ellipses, not applicable.

†For binary variables (suicidal attempts, persistence, treatment seeking), ORs were calculated; for count variables (suicidal ideas, number of symptoms and periods), IRRs were calculated.

‡At least 1 suicide attempt vs no suicide attempt.

§Number of endorsed items from a total of 4 possibilities: frequent thoughts of death, desire for death, concrete suicidal plans, or suicidal attempts.

‖During the worst episode (range, 0-9).

¶The OR/IRR is significant at $P<.05$. All ORs/IRRs are controlled for age and gender of the offspring. Reference group is "neither parent affected."

#Proportion of offspring with any depressive disorder (major depression or dysthymia) at baseline that reported any depressive disorder again during follow-up (N_w = 72).

**With the exception of persistence, which was assessed for cases with major depression (N_w = 470) or with dysthymia (N_w = 91), parameters were assessed only for offspring with major depression (N_w = 470).

Table 5. Impairment by Parental Major Depression*

| | Offspring With Major Depression at Baseline or Follow-up (N_w = 470) | | | | | |
Impairment Due to Depressive Symptoms†	Not at All, %$_w$	Somewhat, %$_w$	A Lot, %$_w$	Very Much, %$_w$	CUMOR	95% CI
Overall impairment due to depressive symptoms‡						
No parent affected	0.0	17.9	53.9	28.3	1.0	
Either parent affected	1.3	10.2	48.2	40.3	1.6§	1.1-2.5
Impairment in daily activities (work/school/household)‖						
No parent affected	62.7	26.9	7.9	2.5	1.0	
Either parent affected	57.1	29.9	10.2	2.8	1.3	0.8-2.0
Impairment in leisure-time activities‖						
No parent affected	73.2	18.4	6.8	1.7	1.0	
Either parent affected	63.8	24.7	8.8	2.7	1.6	0.9-2.5
Impairment in social contacts‖						
No parent affected	75.8	17.7	5.6	1.0	1.0	
Either parent affected	62.3	28.5	7.5	1.8	1.9§	1.2-3.1

*N_w indicates weighted number of subjects; %$_w$, weighted percentage of subjects; CUMOR, cumulative odds ratio; and CI, confidence interval.

†Parameters were assessed for offspring with major depression.

‡During the worst period.

§$P<.05$.

‖Describes current impairment in the 4 weeks preceding the assessments. Since the %$_w$ values have been rounded, the sum of the individual %$_w$ does not always equal 100%.

CLINICAL CHARACTERISTICS BY PARENTAL MAJOR DEPRESSION

As indicated by several clinical characteristics, severity of depression was greater in offspring of affected parents than in offspring of nonaffected parents. Overall, offspring of depressed parents reported higher persistence, more depressive episodes, increased rates of treatment seeking (**Table 4**), and also higher impairments in social contacts and leisure activities (**Table 5**).

COMMENT

Consistent with most previous reports,* we found that parental major depression increases offspring risk for depression. Our results, however, are an extension of previous findings insofar as (1) parent-offspring associations were explored using *DSM-IV* criteria in a represen-

References 4, 8-10, 13-15, 19, 20, 23-25.

tative sample, (2) subjects were examined prospectively across the period of risk of initial onset of depressive disorders, and (3) the use of a large sample size promises power benefits for the statistical analyses.

Depression in parents was associated not only with offspring depression but also with other psychopathology (ie, anxiety or specific substance use disorders). These associations remained stable even after adjustment for parental comorbidity. The literature contains mixed findings regarding the specificity of the familial transmission of major depression.[10,15,18,19,23,24] We found that within-disorder associations (eg, parental depression with depression in offspring) were in most cases, considerably higher than cross-disorder associations (eg, parental depression with anxiety disorders in offspring), suggesting a certain specificity of the parent-offspring associations of depression. Nevertheless, our cross-disorder findings also deserve attention. The higher risk for nicotine dependence in offspring is especially interesting as it has never before been reported. Previous studies[46,47] found that early anxiety and depression predict later nicotine dependence. Thus, familial transmitted anxiety and depression in children might increase the risk for subsequent nicotine dependence, or the familial association might indicate shared etiologies[48,49] for these 2 disorders.

Unlike most studies, we additionally examined associations by sex of the affected parent. Although it is critical that the diagnostic procedures were not entirely comparable between mothers and fathers, our findings suggest that maternal and paternal depression affect male and female offspring similarly. These results are in line with those of other family genetic studies,[3-5,7,15,17,19,20,50] which found no compelling evidence for substantial sex-specific effects in the familial transmission of depression.

We also showed that the offspring of affected parents experience a more malignant course of depression, which that is manifested by a higher number of depressive episodes, higher persistence, and higher treatment seeking. These findings are consistent with observations in clinical studies[10,14] in which parental depression is associated with higher illness severity in offspring. Further, the literature provides some evidence that early-onset depression may constitute a "familial subtype" of depression.[10] Overall, our finding that offspring of 2 affected parents have an earlier onset of depression supports this hypothesis; however, our results also indicate a potentially differential influence of parental concordance on this outcome. To our knowledge, this effect has not been reported before, but it indicates that the diagnostic status of both parents should be considered in future studies.

In terms of parental loading, having 1 or 2 affected parents seems to equally influence the offspring's risk for depression. Although one might expect a monotonic relationship between the number of affected parents and the same disorder in the offspring, our findings, together with the findings of other clinical studies[7,17] do not support such a hypothesis. Whatever the explanation of this observation might be (eg, mobilization of protective factors when both parents are affected), this lack of systematic effect of different parental loading suggests that the familial transmission of depression does not follow simple patterns. Beardslee et al[51] and Rutter et al,[52] who reviewed the research on genetic and environmental factors in this field, concluded that parental depression probably exerts its influence on offspring through several genetic and environmental factors that most likely interact in very complex patterns. An important topic for future research would be to unravel these patterns of environmental and genetic influences that increase vulnerability[53] for depression.

Our findings should be interpreted with caution because the inclusion of family history information might have produced biased estimates of parental psychopathology. One concern in this respect is the rather low sensitivity of family history information.[54-57] To increase sensitivity, all available diagnostic information about probable major depression in parents was used. This might explain the relatively high rate of depressive disorders in parents. Another concern is whether family history information is influenced by the respondents' diagnostic status.[58,59] We examined whether respondents with mental disorders demonstrated higher sensitivity for parental psychopathology when compared with unaffected respondents, but we found no evidence for biased estimates. The use of family history information could also have caused an underestimation of comorbidity among depressed parents and, therefore, an attenuation of specificity. Further, different assessment stategies were used for ascertainment of parental psychopathology in the 2 age cohorts. To protect for misleading results obtained by aggregating both cohorts, all associations were tested for interaction with age cohort. As we found only 2 cohort effects, the different ascertainment strategies probably did not systematically bias our findings. Although the young age of our sample makes it rather unlikely that onset of depression in offspring preceded the onset of depression in parents, we cannot absolutely guarantee this temporal ordering in all cases. This issue could not be addressed in the analyses, as information about age of onset in parents was not assessed in the family history interviews. Finally, not all respondents have fully passed through the entire risk period for onset of mental disorders, but the inclusion of false-negative cases probably resulted in diminished, rather than overestimated, associations.

This study has once more demonstrated that offspring of depressed parents constitute an important high-risk group. Our findings argue for specific prevention and intervention efforts in those offspring. Specifically, the early detection of mental health problems in offspring of depressed parents seems to be crucial, as this would allow the treatment of early manifestations of mental problems before they cause clinical impairment.

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