Onset of Psychopathology in Offspring by Developmental Phase and Parental Depression

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ABSTRACT

Objective: To determine the differential effects of parental major depression (MDD) on psychopathology of childhood, adolescent, and early-adult onset in offspring. **Method:** One hundred eighty-two offspring from 91 families in which one or more parents or neither parent had MDD were followed for more than 10 years and blindly reassessed by means of a structured diagnostic instrument. **Results:** Parental MDD is associated with increased risk in offspring of childhood-onset MDD (eightfold), anxiety disorder (threefold), conduct disorder (fivefold), and early-adult-onset MDD (fivefold) but not adolescent-onset MDD, where there is a marked increase in risk, particularly in girls, regardless of parental diagnosis. These findings were not explained by parental comorbidity, but the association with MDD was explained by parental age at onset of MDD—there was a 13-fold increase in childhood-onset MDD and a 7-fold increase in adult-onset MDD in offspring of parents with MDD of early (before age 30 years) onset. **Conclusion:** Childhood- and early-adult-onset MDD may be etiologically homogeneous and familial subtypes. The reason for the high incidence of adolescent-onset MDD, particularly in girls, regardless of parental diagnosis, needs to be determined. The childhood offspring of depressed parents are a potential target for evaluation, especially when the parent had an early-onset depression. *J. Am. Acad. Child Adolesc. Psychiatry,* 1998, 37(9):933–942. **Key Words:** child and adolescent psychopathology, major depressive disorder, family study, development phase, age at onset.

The association of parental major depression (MDD) with offspring psychopathology has been well documented in studies selecting the depressed parent as the proband and assessing the offspring (top-down design). In all of these studies a strong association has been found between parental MDD and childhood-onset psychopathology (Orvaschel et al., 1988; Weissman et al., 1987). In addition, Beardslee et al. (1993) found that depression and other parental affective disorders, as they occur in the community in parents who often are neither recognized nor treated, are associated with serious affective disorder in offspring. Whether the association with parental MDD continues with adolescent- and adult-onset psychopathology is less clear because these offspring have not been assessed through the full age period of risk.

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Family studies of adult relatives of depressed patients show a relationship between early-onset (<30 years) MDD and risk of MDD in first-degree relatives with some specificity of transmission (Weissman et al., 1984, 1987). However, the probands have not included the full range of onset ages, particularly childhood onsets, and information obtained from adult relatives on the earliest ages at onset is subject to recall bias.

Several family studies in which the depressed proband is a child or adolescent (bottom-up design) also show a strong relationship between childhood or adolescent depression and relative's psychopathology (Hammen et al., 1990; Harrington et al., 1997; Kovacs et al., 1997; Mitchell et al., 1989; Neuman et al., 1997; Puig-Antich et al., 1989; Williamson et al., 1995). These studies are limited, however, in that only relatives of depressed children in treatment are included and not all studies include both child and adolescent probands.

A high-risk longitudinal study of offspring and their parents is a suitable design for observing over time the association of parental MDD and the onset of offspring psychopathology. No previous high-risk study has had a sufficiently long follow-up period to determine the differential risk to offspring by the developmental phases

corresponding to childhood, adolescence, and early adulthood. We present results from a longitudinal study of offspring at high and low risk for MDD by virtue of their parental MDD status. Previously we showed (Weissman et al., 1997) that offspring of high-risk parents had significantly higher *lifetime* rates of MDD, phobias, panic disorder, and alcohol dependence when compared with those of low-risk parents. In this article we study parental MDD as a risk factor for onset of offspring psychopathology, particularly offspring MDD, by developmental phase of offspring. Does the positive association observed between parental MDD and childhood-onset psychopathology continue into adolescence and early adulthood onsets? Do patterns of association by developmental phase between parental MDD and a specific disorder vary by type of disorder? Do other comorbid disorders in parents or age at onset of parental MDD influence patterns of association between parental MDD and offspring psychopathology by developmental phase? This information has heuristic and clinical implications for determining the risk periods when interventions should be introduced and for identifying potentially homogeneous subtypes for genetic studies of depression.

METHOD

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

Sample and Assessments

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

At the initial interview (time 1), the sample consisted of 220 offspring, aged 6 to 23 years, from 91 families. Approximately 2 years after the initial interview (time 2), 85 (93%) of the original 91 families consented to participate. At time 2, 174 (79%) of the offspring were interviewed again. Approximately 10 years after the initiation of the study (time 10), the 91 original families were recontacted and reassessed. There were 4 deaths among the 91 probands, and 73 (84%) were interviewed again. Sixty-six spouses of probands were eligible to be interviewed. There were 5 deaths and of the remaining 61 living spouses, 52 (85%) were interviewed. Among the 220 offspring interviewed at time 1, there were 2 deaths (none by suicide) and 1 offspring was found to have Down syndrome. Eighty-four percent (182/217) of the offspring interviewed at time 1 were interviewed again at time 10. There were no significant differences in attrition rate of probands, spouses, or offspring by parental diagnostic status. Attrition for the probands and spouses did not vary significantly by sex or age. Although attrition of offspring did not differ by sex, older offspring were more likely to be interviewed than their younger counterparts (mean: 28.5 versus 26.4 years; $t = -2.09$, df 54.9, $p = .04$). There were two first onsets of MDD (determined by independent best-estimate diagnosis made blind to initial proband and offspring data [Leckman et al., 1982]) in the spouses of the nondepressed probands between times 2 and 10. These two families had four offspring and were reassigned to the depressed-parent group.

At time 10, probands, spouses of probands, and offspring were independently interviewed with the SADS-LA modified to include RDC, *DSM-III,* AND *DSM-III-R* criteria (Mannuzza et al., 1986). In the previous interviews, offspring younger than 18 years were interviewed with the child revision of the SADS and an informant, usually the mother, was also independently interviewed about the offspring (Weissman et al., 1987). All interviews of offspring were conducted blind to the parents' status and the offsprings' previous assessments. The interviews at times 2 and 10 covered an assessment period from the last interview until the present. Life charts were used to record all episodes of illness that occurred during the assessment period.

Interviewers and Best-Estimate Procedures

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

Data Analysis

Rates of disorder for each developmental phase were computed for high- and low-risk groups as follows: Childhood rates were computed by dividing the number of cases with first onset before age 13 years by the total number of male/female offspring. Adolescence rates were computed by dividing the number of cases with first onset between age 13 and 19 years by the number at risk for adolescent-onset MDD, i.e., by the number who at last interview were 13 years or younger and who had not had a first onset before age 13 (19 years was selected as the cutoff for adolescence for consistency with our previous studies, in which age at onset before 20 years appeared to be a specific subtype of depression). Adult rates were computed similarly to adolescence rates, except using age 20 instead of 13. The adult group consisted of offspring aged 20 to 36 years at time of last assessment (maximum age at onset of MDD in this group was 30 years; median age at onset was approximately 24 years). Odds ratios comparing rates between high- and low-risk groups, and associated confidence intervals (CIs), were computed using standard methods (Bishop et al., 1975).

How the association between parental MDD and offspring psychopathology varied with developmental phase was investigated as follows: For the prepubescent phase, a Cox proportional hazards model was fitted in which the incidence of disorder occurring before age 13 was considered the outcome and offspring who developed the disorder after age 13 were considered free of prepubescent-onset disorder; the risk set consisted of all offspring. Similar analyses were conducted (see Weissman et al., 1988, for details) for the other two

developmental phases. Potential confounding variables such as sex of offspring and other comorbid disorders of parents were controlled for by including them as independent variables (along with parental depression status) for each of the three models corresponding to the three developmental phases.

The relative risk (hazards ratio) corresponding to parental MDD indicates the association between parental MDD and offspring psychopathology and can be obtained for the three developmental phases. Comparison of these three relative risks indicates the variation of the association between parental MDD and offspring psychopathology by developmental phase. Formal test for the variation of this was performed by testing for nonproportionality of the hazard function (Cox and Oakes, 1984; Kleinbaum, 1997). Patterns of association with age at onset of parental MDD were analyzed by including two dummy variables representing (1) early-onset (<30 years) MDD in parent and (2) late-onset (≥30 years) MDD in parent, simultaneously, as independent variables in proportional hazards models fitted separately for each of the three developmental phases. Offspring were categorized into early/late-onset groups if the minimum age of one or both parents met the criterion for early or late onset, respectively. Early-onset MDD in parents was defined as before age 30 years, rather than before age 20 years (Weissman et al., 1984), to have sufficient cases among early-adult-onset offspring.

The fact that the disorder status of offspring from the same family may not be independent may violate the assumption of independence of the outcome variable implicit in the use of the proportional hazards model. Although attempts have been made to modify these models to accommodate correlated outcome variables, these models can be applied only under limited circumstances, and the software to run these models is not yet readily available. We expect that parameters obtained assuming independence will give unbiased estimates of the relative risk but that possibly the variances of these estimates will be underestimated.

RESULTS

Demographic Characteristics of Probands and Offspring

The probands did not differ by diagnostic groups on sex (60% females); age (mean years [SD]: 55.4 [7.8]); current marital status (78% married); religion (66% Catholic); employment status (44% full time); or household income (mean [SD]: $52,521 [$25,581]).

The offspring did not differ by parental diagnostic group on sex (55% female); age distribution at the end of the 10-year follow-up period (mean years [SD]: 27.71 [4.74]); current marital status (44% single, 47% married); religion (63% Catholic); education (50% with at least some college or trade school); employment (62.4% full-time); or annual income (mean [SD]: $23,736 [$18,840]), but they did differ on number of children. The high-risk offspring had significantly fewer children than the low-risk offspring (mean [SD]: 1.6 [0.7] versus 2.3 [1.1]; $p = .02$).

Incidence Rates of Offspring Psychopathology

Major Depression. For all developmental phases and for both sexes, the incidence of MDD in offspring was greater in the high- than the low-risk group. These differences reached significance in female childhood onset and in female and male adult onset. Adolescent girls had the highest rates of MDD, regardless of parental diagnosis. Almost all incidence cases in the low-risk offspring occurred in adolescents, particularly in females.

The sex difference in incidence rates of MDD emerged in adolescence, where a striking increase in rates in adolescent girls is observed in the high- and low-risk groups. There was little difference by sex in incidence rates of childhood- or adult-onset depression in high- or low-risk offspring. All of these rates are of first onset rather than lifetime or current prevalence.

Dysthymia. In contrast to the patterns found for MDD, the rates of adolescent-onset dysthymia were no higher than those of childhood-onset dysthymia in female offspring, but lower than rates of childhood-onset dysthymia in high-risk male offspring. Rates of adult-onset dysthymia were much lower than both childhood- and adolescent-onset dysthymia in high- and low-risk female offspring and high-risk male offspring. With the exception of childhood-onset dysthymia in male offspring, there was no increased risk for dysthymia in offspring of depressed parents by developmental phase.

Anxiety Disorders. The anxiety disorders presented in the lower half of Table 1 are those that occur most frequently in childhood. With the exception of overanxious disorder, which occurs most frequently in adolescence, in both high- and low-risk females the highest rates of these anxiety disorders are observed before puberty in male and female offspring. Indeed, all the anxiety disorders in the low-risk group, with the exception of overanxious disorder in females, had a childhood onset. Higher rates of every type of anxiety disorder were observed in the high-risk offspring, regardless of developmental phase or sex of offspring.

Conduct Disorder. Among male offspring, onset of conduct disorder (CD) occurred most frequently before puberty in the high-risk group and most frequently during adolescence in the low-risk group (Table 2). A fourfold increase in risk of childhood-onset CD was observed in high-risk males, while in adolescence the risk was approximately the same in males from high- and low-risk groups. Among female offspring, all cases of childhood-onset CD occurred in the high-risk group. However, the highest rates of CD were observed in adolescence for both the high- and low-risk groups.

TABLE 1
Incidence Rate of Mood and Anxiety Disorder in Offspring by Parental Depression Status, Offspring Sex, and Offspring Developmental Phase

DSM-III Diagnoses in Offspring	Offspring Sex	Offspring Developmental Phase [N_1, N_2]	Rate/100 of Disorder (n) One or Both Parents Depressed	Rate/100 of Disorder (n) Neither Parent Depressed	OR (95% CI)
Mood disorder					
Major depression	Male	Childhood [58, 24]	15.5 (9)	0 (0)	∞
		Adolescent [49, 24]	16.3 (8)	12.5 (3)	1.37 (0.33, 5.69)
		Adult [35, 20]	22.9 (8)	5.0 (1)	5.63† (0.65, 48.8)
	Female	Childhood [71, 29]	15.5 (11)	3.5 (1)	5.13† (0.63, 41.7)
		Adolescent [60, 28]	43.3 (26)	28.6 (8)	1.91 (0.73, 5.02)
		Adult [32, 20]	21.9 (7)	5.0 (1)	5.32 (0.60, 47.0)
Dysthymia	Male	Childhood [58, 24]	19.0 (11)	4.2 (1)	5.38† (0.66, 44.3)
		Adolescent [47, 23]	10.6 (5)	13.0 (3)	0.79 (0.17, 3.66)
		Adult [36, 19]	2.8 (1)	0 (0)	∞
	Female	Childhood [71, 29]	14.1 (10)	13.8 (4)	1.03 (0.29, 3.57)
		Adolescent [61, 25]	14.8 (9)	16.0 (4)	0.91 (0.25, 3.28)
		Adult [50, 21]	4.0 (2)	4.8 (1)	0.83 (0.07, 9.72)
Anxiety disorder					
Overanxious disorder	Male	Childhood [58, 24]	6.9 (4)	0 (0)	∞
		Adolescent [54, 24]	3.7 (2)	0 (0)	∞
		Adult [45, 23]	2.2 (1)	0 (0)	∞
	Female	Childhood [71, 29]	2.8 (2)	0 (0)	∞
		Adolescent [69, 29]	10.1 (7)	6.9 (2)	1.52 (0.30, 7.82)
		Adult [59, 26]	3.4 (2)	0 (0)	∞
Separation anxiety disorder	Male	Childhood [58, 24]	19.0 (11)	8.3 (2)	2.57 (0.53, 12.62)
		Adolescent [47, 22]	0 (0)	0 (0)	—
		Adult [43, 21]	0 (0)	0 (0)	—
	Female	Childhood [71, 29]	18.3 (13)	17.2 (5)	1.08 (0.35, 3.35)
		Adolescent [58, 24]	3.5 (2)	0 (0)	∞
		Adult [55, 24]	0 (0)	0 (0)	—
Phobia	Male	Childhood [58, 24]	10.3 (6)	4.2 (1)	2.65 (0.30, 23.32)
		Adolescent [52, 23]	0 (0)	0 (0)	—
		Adult [45, 22]	0 (0)	0 (0)	—
	Female	Childhood [71, 29]	23.9 (17)	10.3 (3)	2.73 (0.73, 10.15)
		Adolescent [54, 26]	5.6 (3)	0 (0)	∞
		Adult [49, 25]	2.0 (1)	0 (0)	∞

Note: N_1 = number at risk in high-risk group (one or both parents depressed); N_2 = number at risk in low-risk group (neither parent depressed); n = number of cases; OR = odds ratio; CI = confidence interval.
† $p < .01$.

There was no difference in risk for adolescent-onset CD in the high- and low-risk groups, which is similar to the pattern observed in male offspring.

Attention Deficit Disorder. All cases of attention deficit disorder (ADD), by diagnostic criterion, had a childhood onset (Table 2). Rates of ADD were highest in high-risk male offspring. Overall, the rates of ADD were higher in males than females for both high- and low-risk groups. There were no cases of ADD in low-risk female offspring.

Alcohol Abuse. It is not surprising that all cases of alcohol abuse, regardless of offspring sex and parental MDD, had either adolescent or adult onset (Table 2). Rates were higher in male than in female offspring. There was a twofold increase in risk during adolescence among high-risk males and a threefold increase in risk during adulthood.

Drug Abuse. With the exception of high-risk female offspring, all cases of drug abuse had their onset in adolescence or adulthood (Table 2). Few differences were observed between rates in high- and low-risk groups during adolescence, in either sex. However, high-risk females had an approximately twofold increase in risk of drug abuse in adulthood.

Relative Risks

Table 3 presents relative risks associated with parental MDD for each of the diagnoses by developmental phase of offspring. These relative risks were computed on the combined sample of male and female offspring to obtain greater statistical power. In addition, for diagnostic categories in which the number of cases observed was too small to perform meaningful analyses, we combined subcategories. There is a significant increase in risk due to parental MDD for offspring childhood-onset MDD, anxiety disorder, and CD. The increase in risk by parental MDD is not significant in adolescence for any of the diagnoses examined, while a significant increase in risk is observed for adult-onset MDD. Results of tests for nonproportionality, presented in the right-most column, indicate that differences in risk observed between the three developmental phases for MDD are statistically significant and that there is a trend for the relative risk of childhood-onset CD to be greater than that for adolescent-onset CD.

Effect of Parental Comorbidity and Age at Onset

To determine whether or not the relative risk of disorder due to parental MDD was confounded by the presence of other comorbid disorders in the parents, we controlled for the effect of the most frequently occurring comorbid disorders, i.e., anxiety, alcohol and drug abuse, and antisocial personality disorder (not shown here). The variations in the patterns of association with parental depression by developmental phase of offspring remained virtually unchanged, although there were slight changes in the relative risks for some of the offspring disorders.

TABLE 2
Incidence Rate of Disruptive and Substance Abuse Disorder in Offspring by Parental Depression Status, Offspring Sex, and Offspring Developmental Phase

DSM-III Diagnoses in Offspring	Offspring Sex	Offspring Developmental Phase [N_1, N_2]	Rate/100 of Disorder (n) One or Both Parents Depressed	Rate/100 of Disorder (n) Neither Parent Depressed	OR (95% CI)
Disruptive disorder					
Conduct disorder	Male	Childhood [58, 24]	29.3 (17)	8.3 (2)	4.56* (0.96, 21.6)
		Adolescent [41, 22]	19.5 (8)	18.2 (4)	1.09 (0.29, 4.13)
		Adult [26, 17]	0 (0)	0 (0)	—
	Female	Childhood [71, 29]	7.0 (5)	0 (0)	∞
		Adolescent [66, 29]	21.2 (14)	17.2 (5)	1.29 (0.42, 4.00)
		Adult [49, 23]	0 (0)	0 (0)	—
Attention deficit disorder	Male	Childhood [58, 24]	15.5 (9)	8.3 (2)	2.02 (0.40, 10.13)
		Adolescent [49, 22]	0 (0)	0 (0)	—
		Adult [41, 21]	0 (0)	0 (0)	—
	Female	Childhood [71, 29]	4.2 (3)	0 (0)	∞
		Adolescent [68, 29]	0 (0)	0 (0)	—
		Adult [65, 28]	0 0	0 (0)	—
Substance abuse disorder					
Alcohol abuse	Male	Childhood [58, 24]	0 (0)	0 (0)	—
		Adolescent [58, 24]	8.6 (5)	4.2 (1)	2.17 (0.24, 19.62)
		Adult [46, 22]	15.2 (7)	13.6 (3)	1.14 (0.26, 4.89)
	Female	Childhood [71, 29]	0 0	(0) (0)	—
		Adolescent [71, 29]	5.6 (4)	3.5 (1)	1.67 (0.18, 15.63)
		Adult [64, 28]	10.9 (7)	3.6 (1)	3.32 (0.39, 28.32)
Drug abuse	Male	Childhood [58, 24]	0 (0)	0 (0)	—
		Adolescent [58, 24]	13.8 (8)	12.5 (3)	1.12 (0.27, 4.64)
		Adult [43, 20]	7.0 (3)	10.0 (2)	0.68 (0.10, 4.40)
	Female	Childhood [71, 29]	1.4 (1)	0 (0)	∞
		Adolescent [70, 29]	10.0 (7)	10.3 (3)	0.96 (0.23, 4.01)
		Adult [60, 26]	6.7 (4)	3.9 (1)	1.79 (0.19, 16.80)

Note: N_1 = number at risk in high-risk group (one or both parents depressed); N_2 = number at risk in low-risk group (neither parent depressed); n = number of cases; OR = odds ratio; CI = confidence interval.
* $p < .05$.

TABLE 3
Relative Risk of Onset of Disorder in Offspring by Parental Depression, Controlling for Sex of Offspring

	Age First Onset in Offspring			*p* Value for Test of Nonproportionality
	Childhood	Adolescent	Adult	
MDD				
Parental depression	8.80* (1.18, 65.6)	1.72 (0.87, 3.39)	4.61* (1.05, 20.2)	.02
Dysthymia				
Parental depression	1.80 (0.68, 4.76)	0.90 (0.36, 2.23)	1.33 (0.14, 12.8)	NS
Anxiety disorder				
Parental depression	2.52* (1.19, 5.35)	3.96 (0.49, 32.2)	∞	NS
Conduct disorder				
Parental depression	4.86* (1.14, 20.6)	1.16 (0.53, 2.52)	—	.098
ADD				
Parental depression	2.53 (0.57, 11.3)	—	—	
Substance abuse				
Parental depression	∞	1.28 (0.54, 3.00)	0.75 (0.30, 1.92)	NS

Note: Values in parentheses represent 95% confidence intervals. MDD = major depression; ADD = attention deficit disorder; NS = not significant.
* $p < .05$.

We examined the effect of age at onset of parental MDD on rate of MDD in offspring by offspring developmental phase. Table 4 gives relative risks for selected disorders in offspring by early (<30 years) onset MDD and late (≥30 years) onset MDD in parents; offspring of nondepressed parents (low-risk) are used as the reference group. Early-onset MDD in parents significantly increased the risk of childhood (13-fold) and early-adult-onset (7-fold increase) MDD in offspring. However, there was no significant increase in risk, in childhood- or early-adult-onset MDD offspring, associated with late-onset MDD in parent. Furthermore, there was no significant association between onset of parental MDD (either early or late) and adolescent-onset MDD in off-

TABLE 4
Relative Risk of Selected Disorders in Offspring by Age at Onset of Depression in Parent and Developmental Phase of Offspring

Age at Onset of MDD in Parent[a]	Relative Risk for Disorder by Developmental Phase		
	Childhood	Adolescent	Adult
Major depression			
<30 years	13.10* (1.71, 100.6)	1.56 (0.72, 3.37)	6.82* (1.47, 31.72)
30+ years	4.13 (0.48, 35.37)	1.84 (0.86, 3.91)	2.38 (0.45, 12.57)
Dysthymia			
<30 years	1.81 (0.62, 5.30)	1.03 (0.37, 2.86)	1.06 (0.09, 12.83)
30+ years	1.43 (0.48, 4.27)	0.79 (0.26, 2.35)	0.73 (0.04, 14.58)
Any anxiety disorder			
<30 years	2.03† (0.88, 4.71)	3.04 (0.34, 27.28)	∞
30+ years	3.16** (1.43, 7.00)	3.51 (0.31, 40.48)	∞
Conduct disorder			
<30 years	6.29* (1.40, 28.20)	1.08 (0.44, 2.62)	—
30+ years	4.06† (0.89, 18.57)	1.18 (0.49, 2.84)	—

Note: Controlling for age and sex of child and year of birth of parent. Relative risks are based on comparison between offspring with at least one parent in relevant age-at-onset category and offspring of nondepressed parents. Values in parentheses represent 95% confidence intervals. MDD = major depressive disorder.
[a] Minimum age at onset in either depressed parent.
† $p < .1$; * $p < .05$; ** $p < .01$.

spring. With the exception of childhood- and early-adult-onset MDD, none of the other diagnoses in offspring (dysthymia, conduct, or anxiety disorders) were found to be associated with a significant differential effect of age at onset (when comparing early versus late) of MDD in parents.

DISCUSSION

This is the first study to examine the variation in onset of psychopathology in offspring associated with parental MDD by the developmental phase of offspring. Our results show that the association with parental MDD is strongest for childhood-onset psychopathology and particularly childhood-onset MDD. The diminished association with parental MDD was found in the offspring at adolescence because, with the exception of anxiety disorders, much of the psychopathology in offspring of nondepressed parents occurred in adolescence. This results in a dilution of the effect of parental depression on adolescent-onset psychopathology. In contrast, childhood-onset psychopathology was rarely observed in low-risk offspring. These findings could not be explained by parental comorbidity but were associated with early-onset MDD in parents. There was a 13-fold increased risk of childhood-onset MDD in offspring of early-onset MDD parents. It is noted that these patterns of association do not hold for mood disorders in general but are specific to MDD. There is no variation in onset of dysthymia in offspring associated with parental MDD, by developmental phase of offspring.

Patterns of Association Between Parental MDD and Offspring MDD

The association of early-onset MDD in one or more parents with childhood-onset MDD in offspring could be due to the fact that these offspring are exposed to parental MDD at a very young age, and, as a consequence, vulnerable offspring are likely to become depressed at an early age. Alternatively, childhood-onset MDD may be a genetically homogeneous subtype. Several studies have shown that second-degree relatives of depressed children have higher rates of depression than depressed adolescents or normal children (Kovacs et al., 1997; Orvaschel, 1990; Williamson et al., 1995), suggesting that the association between parental MDD and childhood depression is not wholly due to environmental factors. That the differential effect of early-onset MDD in a parent is observed only for childhood-onset MDD and not for other psychiatric diagnoses in offspring strengthens the argument that childhood-onset MDD represents a specific subtype. The lack of a significant association between early- or late-onset MDD in parents with adolescent-onset depression in offspring implies that adolescent-onset depression is etiologically heterogeneous. Mechanisms and processes such as alteration of social experiences, changes in self-perception, elevations in hormonal levels, alteration in the size and function of the brain, or a combination of these could be implicated (Goodyer, 1995).

The association of early-onset parental MDD with early-adult-onset MDD in offspring also strengthens the hypothesis that the association between parental MDD and offspring MDD may not be solely due to the environment created by the depressed parent. It suggests that after being blunted in adolescence, the effect of parental MDD emerges as a strong risk factor for offspring MDD in early adulthood, implying biological rather than environmental factors. The association of early-onset parental MDD with early-adult-onset MDD in offspring is consistent with our previous findings that early-onset MDD appears to be a subtype with high familial loading (Weissman et al., 1984, 1992).

Top-Down Studies

The Orvaschel et al. (1988) study is closest to ours in initial design and assessment, and the results are quite similar. Orvaschel et al. also found that all cases of childhood MDD occurred in offspring of high-risk probands, the rates of childhood MDD were of comparable magnitude (14.8%), and there were no cases of childhood-onset MDD in offspring of nondepressed probands. Furthermore, a twofold increase in rates of childhood anxiety disorders in high- compared with low-risk offspring was also observed in their study. Since 60% of these offspring were between the ages of 6 and 12 years, and the follow-up was only 18 months, comparisons in adolescents were not possible.

In a 3-year longitudinal study of psychiatric diagnoses in offspring of women with unipolar or bipolar affective disorder, compared with offspring of medically ill or normal controls, Hammen et al. (1990) found high rates of psychiatric disorder in offspring of unipolar women, with most onsets in childhood. They also found that the onset of MDD in offspring of unipolar women increased with age from childhood to adoles-

cence. In addition, there was a marked increase in rates of adolescent MDD (age 15–19) in offspring of medically ill controls but not in offspring of normal controls. Although the sample sizes were small and only proband mothers were considered, the trends are consistent with those observed in our study. Direct comparisons, however, are not possible because, with the exception of MDD, individual diagnoses were not presented by age at onset of offspring.

Beardslee et al. (1996) found that prior parental affective disorder (as it occurs in the community in parents who often are not treated) and prior childhood-onset psychopathology predicted adolescent affective disorder. However, they did not differentiate between incident and recurrent cases, making it difficult to make direct comparisons with our findings, which pertain only to incident cases.

Bottom-Up Studies

In bottom-up studies, children and adolescents selected from treatment settings are considered probands, and rates of psychopathology are determined in their first- and/or second-degree relatives. These rates are compared with rates of psychopathology in first- and/or second-degree relatives of control children. While this design differs in fundamental ways from the top-down design and does not permit a direct comparison of rates, it is possible to compare patterns of association.

Family studies of relatives of childhood- and adolescent-onset MDD probands consistently show higher familial rates of MDD in first- and second-degree relatives than in relatives of normal controls or controls with nonaffective disorder (Harrington et al., 1997; Kovacs et al., 1997; Orvaschel, 1990; Puig-Antich et al., 1989; Todd et al., 1993; Williamson et al., 1995). However, where direct comparisons are made between relatives of childhood-, adolescent-, and adult-onset MDD probands, the findings are less consistent. Mitchell et al. (1989) found that mothers of depressed child (7–12 years) probands compared with depressed adolescent (onset 13–17 years) probands had higher rates of drug abuse and suicidality, were younger at MDD onset (22.9 years versus 27.5 years), and sought treatment at an earlier age. Neuman et al. (1997) found a twofold increased risk of MDD among first-degree relatives of childhood- versus adult-onset probands with mood disorders. Taken together, these findings suggest that not only is childhood-onset MDD familial, but it may have higher familial loading than adolescent- and adult-onset MDD, which is generally consistent with the patterns observed in our study. In agreement with Todd et al. (1993) and Kovacs et al. (1997), pedigrees ascertained through children with childhood-onset depression may be candidates for genetic studies.

In contrast to these findings, Harrington et al. (1997), in a follow-up study into adulthood (on average 18 years after initial contact) of child and adolescent patients, found that there were no significant differences in rates of MDD in relatives of childhood-onset depressed probands compared with relatives of either adolescent- or early-adult-onset MDD probands. Differences in these findings could be due in part to the fact that Harrington et al. used pubertal status rather than chronological age. This resulted in some overlap in chronological age between the prepubertal and postpubertal onset groups. In addition, their study relied on medical records for selecting child and adolescent probands, who were then rediagnosed as adults. Although patterns of association with MDD in relatives differed between our study and that of Harrington et al. (1997), the general pattern of association between criminality in relatives and MDD probands by developmental phase of proband reported by Harrington et al. (1997) is also observed in our study. We found significant variation in the relative risk of MDD in offspring due to parental antisocial personality by developmental phase. Among high-risk offspring, the relative risk for childhood-onset MDD was 4.2 (95% CI: 1.52, 11.6), the relative risk for adult-onset MDD was 1.1 (95% CI: 0.27, 4.77), and the relative risk for early-adult-onset MDD was 8.75 (95% CI: 1.69, 45.4).

Associations between other psychopathology in children and adolescents and MDD in relatives have also been studied. Last et al. (1991), in a study of anxiety disorders in children and their families, showed a trend for children with anxiety disorders compared with children who were never psychiatrically ill to have higher rates of MDD in their first- and second-degree relatives. These results are consistent with our findings of an increased risk of childhood-onset anxiety in their offspring.

Consistent with our findings that the association was greater between parental MDD and childhood compared with adolescent CD onset, Simonoff et al. (1994) have found that the role of shared environment (parental MDD can be regarded as the shared environment in the context of our study) in CD decreases with age. Peer

influences in adolescence as noted by Kazdin (1995) have been implicated in the onset of antisocial behavior, such as substance use and abuse and delinquency.

Lewinsohn et al. (1993), in a randomly selected sample of high school students, found high rates of MDD in adolescence, which is consistent with our finding regarding the high rates of adolescent-onset MDD in offspring of nondepressed parents.

Limitations

Because the offspring in our study were between 6 and 23 years of age at time of first interview, it is possible that there is some recall bias associated with the reporting of age at onset of disorder, especially childhood onset, by those subjects who were adolescents or young adults at time of their first interview. However, the finding that rates of MDD in high- and low-risk offspring showed the familiar sharp increase in adolescence and changes in sex ratio at around the time of puberty suggests it is unlikely that recall bias plays a major role in the observed patterns of MDD (Angold, 1988; Christie et al., 1988). Moreover, that the childhood rates of disorder observed in our study are similar in magnitude to those observed by Orvaschel et al. (1988), where a majority of subjects were between ages 6 and 12 years at the time of interview, further supports the view that these patterns are not primarily a result of inaccurate recall. It is also possible that the depression status of the parent (the mother was usually the informant in the assessment of the youngest children) could bias the results. However, the offspring were interviewed at three points in time over the 10-year period, so self-report information was available as they matured.

Because of the small number of offspring in the low-risk group with any psychopathology, our power to detect significant differences in patterns was limited. As a result of the low rates of some of the childhood- and adult-onset disorders in the low-risk group estimates of relative risk, some of these estimates were unstable. We could not differentiate between the effects of having one parent versus both parents with MDD because there are too few families in which both parents are depressed for this analysis to be feasible. Furthermore, the generalizability of these findings may be limited because all of these families are white and 66% of them are Catholic.

Clinical Implications

Our findings suggest that the offspring of depressed parents are at high risk for childhood-onset psychopathology. Early age at onset (<30 years) MDD in parents markedly increases the risk of childhood- and early-adult-onset MDD but not of other childhood-onset diagnoses. Adolescence, particularly for girls, is a period of high risk for MDD regardless of parental history. Clinically this suggests that children (younger than age 13) of depressed parents, especially young parents with an onset of MDD before age 30, are a potential target for clinical evaluation. Alternatively, the parents of children with childhood-onset depression are at high risk for depression and should be considered for evaluation; a parent's request for an evaluation of a child's clinical state may in fact be also a request for treatment for himself/herself. The clinical significance of the high rates of MDD in adolescent girls is unclear. We suspect that the adolescent MDD that is nonfamilial compared with the familial type may have a lower rate of recurrence and morbidity.

Our future research will attempt to identify risk factors other than parental MDD, such as shared environments and other familial factors that may contribute to the onset of these disorders. In addition, we will investigate the differential course of mood and other mental disorders in these offspring. These findings may provide further guides to treatment.

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Tobacco Industry Promotion of Cigarettes and Adolescent Smoking. John P. Pierce, PhD, Won S. Choi, PhD, Elizabeth A. Gilpin, MS, Arthur J. Farkas, PhD, Charles C. Berry, PhD

Context: Whether tobacco advertising and promotion increases the likelihood that youths will begin smoking has important public policy implications. *Objective:* To evaluate the association between receptivity to tobacco advertising and promotional activities and progress in the smoking uptake process, defined sequentially as never smokers who would not consider experimenting with smoking, never smokers who would consider experimenting, experimenters (smoked at least once but fewer than 100 cigarettes), or established smokers (smoked at least 100 cigarettes). *Design:* Prospective cohort study with a 3-year follow-up through November 1996. *Setting and Participants:* A total of 1752 adolescent never smokers who were not susceptible to smoking when first interviewed in 1993 in a population-based random-digit dial telephone survey in California were reinterviewed in 1996. *Main Outcome Measure:* Becoming susceptible to smoking or experimenting by 1996. *Results:* More than half the sample (n = 979) named a favorite cigarette advertisement in 1993 and Joe Camel advertisements were the most popular. Less than 5% (n = 92) at baseline possessed a promotional item but a further 10% (n = 172) were willing to use an item. While having a favorite advertisement in 1993 predicted which adolescents would progress by 1996 (odds ratio [OR] = 1.82; 95% confidence interval [CI], 1.04–3.20), possession or willingness to use a promotional item was even more strongly associated with future progression (OR = 2.89; 95% CI, 1.47–5.68). From these data, we estimate that 34% of all experimentation in California between 1993 and 1996 can be attributed to tobacco promotional activities. Nationally, this would be over 700 000 adolescents each year. *Conclusion:* These findings provide the first longitudinal evidence to our knowledge that tobacco promotional activities are causally related to the onset of smoking. **JAMA** February 18, 1998;279:511–515. Copyright 1998, American Medical Association