Article

Children of Depressed Mothers 1 Year After Remission of Maternal Depression: Findings From the STAR*D-Child Study

Priya Wickramaratne, Ph.D.
Marc J. Gameroff, Ph.D.
Daniel J. Pilowsky, M.D., M.P.H.
Carroll W. Hughes, Ph.D.
Judy Garber, Ph.D.
Erin Malloy, M.D.
Cheryl King, Ph.D.
Gabrielle Cerda, M.D.
A. Bela Sood, M.D.
Jonathan E. Alpert, M.D., Ph.D.
Madhukar H. Trivedi, M.D.
Maurizio Fava, M.D.
A. John Rush, M.D.
Stephen Wisniewski, Ph.D.
Myrna M. Weissman, Ph.D.

Objective: Maternal major depressive disorder is an established risk factor for child psychopathology. The authors previously reported that 1 year after initiation of treatment for maternal depression, children of mothers whose depression remitted had significantly improved functioning and psychiatric symptoms. This study extends these findings by examining changes in psychiatric symptoms, behavioral problems, and functioning among children of depressed mothers during the first year after the mothers' remission from depression.

Method: Children were assessed at baseline and at 3-month intervals with the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version, the Child Behavior Checklist, and the Children's Global Assessment Scale for 1 year after their mothers' remission or for 2 years if the mothers did not remit. The authors compared children of early remitters (0–3 months; N=36), late remitters (3–12 months; N=28), and nonremitters (N=16).

Results: During the postremission year, children of early-remitting mothers showed significant improvement on all outcomes. Externalizing behavioral problems decreased in children of early- and late-remitting mothers but increased in children of nonremitting mothers. Psychiatric symptoms decreased significantly only in children of mothers who remitted, and functioning improved only in children of early-remitting mothers.

Conclusions: Remission of mothers' depression, regardless of its timing, appears to be related to decreases in problem behaviors and symptoms in their children over the year after remission. The favorable effect of mothers' remission on children's functioning was observed only in children of early-remitting mothers.

(Am J Psychiatry 2011; 168:593–602)

One consistently replicated finding in psychiatry is the increased risk of psychiatric disorders, particularly major depression and anxiety disorders, in the offspring of parents with major depression (1–12). Major depression is likely a complex disorder (13, 14) with environmental stress acting as an episode trigger in vulnerable individuals (15, 16). Parents' acute depressive symptoms likely contribute to a stressful environment for children. Decreases in depressed parents' symptoms might be linked with reductions in children's symptoms and behavioral problems. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Child study was designed to examine the relation of maternal remission from depression to children's functioning and psychopathology (17) in mothers who were being treated in STAR*D (18, 19). When STAR*D began, only two published studies had shown that reducing parental symptoms provided some immediate benefit to children. One study's clinicians had not directly treated the parents' depression (20), and the other was a pilot study of 18 depressed mothers (21). Two additional studies have since reported findings consistent with a relationship between children's clinical state and parental depression (22, 23).

In the STAR*D-Child study, we hypothesized that remission of maternal depression would be linked with reduced offspring symptoms when the mothers remitted. At the initiation of the mother's treatment, about one-third of their children had a current psychiatric disorder and one-half had a history of psychiatric disorder (24). After 3 months of antidepressant treatment, maternal remission of major depression was significantly associated with reductions in the children's diagnoses and symptoms (17).

During the year after initiation of the mothers' treatment for depression, the outcomes for offspring of mothers who remitted early (during the first 3 months after treatment initiation), later (after 3 months of treatment), or not at all over the first year were examined separately (25). A statistically significant difference was observed

This article is featured in this month's AJP Audio, is discussed in an editorial by Dr. Birmaher (p. 563), and is an article that provides Clinical Guidance (p. 602).

between groups, with a decrease in symptoms evident in children of early and late remitters, but not in children of nonremitters. These findings were limited by the fact that children of mothers who remitted after 6 and 9 months were followed for only 1–6 months after maternal remission. Furthermore, we were not able to determine the effect of maternal remission on subsequent changes in child outcomes because the study period was 1 year from the mother's treatment initiation. Because the children were followed up every 3 months for 1 year after maternal remission, or for 2 years if the mother remained depressed, this study focuses on changes in psychiatric symptoms and functioning among children of depressed mothers during the year following remission of maternal depression to determine the longer-term effects of maternal remission on subsequent changes in child outcomes.

Method

*STAR*D and STAR*D-Child Studies*

STAR*D (www.star-d.org) was a multisite study designed to determine the comparative effectiveness of different treatment options for outpatients 18–75 years old with nonpsychotic major depression and without a lifetime diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder (19, 26). All study participants were initially treated with citalopram. Those intolerant of or not remitting when treated with citalopram were offered other treatments, including other antidepressants, cognitive-behavioral therapy (CBT), or a combination of these, using an equipoise randomized design (27).

The STAR*D-Child study recruited 824 women, ages 25–60 years old, at seven of the 14 regional centers participating in STAR*D. Of these, 808 women (98%) were screened to ascertain whether they had any children 7–17 years old; 177 of them (22%) had children in that age range, and of these, 174 (98%) met all eligibility criteria; 151 of those eligible (87%) agreed to enter the child study. If a mother had more than one child of eligible age, one was selected randomly (17). Mothers provided separate written informed consent for themselves and for their child.

The child assessors were not involved in the mothers' treatment, were blind to mothers' remission status, and were independent of the team that treated the mothers. The mothers' clinical assessments were completed by STAR*D staff members who were not involved in the children's assessments. Baseline assessments were conducted before or within 2 weeks after the start of treatment of the mothers' depression.

Sample

A total of 151 mother-child pairs were assessed at baseline, and 127 of these completed at least one follow-up assessment (Figure 1). Because the primary aim of the study was to examine the relation of the mother's remission to child outcomes during the year following her remission, our primary analysis was restricted to mothers who remitted in the course of the study and did not suffer a subsequent relapse while enrolled in the study. Early remitters were mothers who remitted in the first 3 months (N=36), and late remitters were those who remitted between months 3 and 12 (N=28). A comparison group of nonremitters (N=16) comprised mothers who did not remit in either the first or second year of the study. We excluded from the analyses 20 mothers who relapsed, three who were late remitters (two for whom data on child or mother were unavailable after remission and one because remission occurred during the second year of treatment), and 24 nonremitters (because data on child or mother were unavailable after the first 12 months of treatment).

Figure 2 shows the analytic design of the present study. Mothers and children were followed for varying lengths of time by design. Although children of late-remitting mothers were followed for longer periods than early-remitting mothers, the length of the study period that we analyzed is the same for all children regardless of the time of the mother's remission (i.e., the 1-year period after mother's remission).

Assessments and Measures

Maternal assessments were conducted as part of a comprehensive battery of assessments for all STAR*D participants. A diagnosis of a current maternal major depression was established by clinical interview and confirmed using a symptom checklist based on DSM-IV criteria (18). The severity of depressive symptoms over the previous 7 days was assessed by a clinician using the 17-item Hamilton Rating Scale for Depression (HAM-D; 28, 29). As in STAR*D, remission was defined as having a HAM-D score ≤7, and relapse was defined as a HAM-D score ≥14 any time after having remitted. Mothers who remitted by the first 3-month evaluation were considered early remitters; those who remitted after the first 3 months of follow-up were considered late remitters, provided that they remained in remission during the subsequent year. Not all remitted mothers were observed for the entire year of follow-up because some dropped out of the study during the follow-up period.

Remission was also assessed by self-report using the 16-item Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR). When follow-up HAM-D scores were unavailable, QIDS-SR scores were imputed based on an analysis of the relation between the HAM-D and the QIDS-SR used in the STAR*D study (30–32).

The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) was used to assess DSM-IV psychiatric diagnoses in the children (see online supplement of Kaufman et al. [33]). A clinical assessor interviewed mothers and children separately. To minimize time, sections of the K-SADS-PL focusing on disorders highly prevalent among children of depressed parents (i.e., mood, anxiety, and disruptive disorders [1, 34]) were used. The qualifications, training, and reliability of child assessments have been reported elsewhere (24). We examined symptoms derived from the K-SADS-PL interview with the mother (about the child) and separately with the child. We interviewed the children and scored their responses before we interviewed the mothers. A mother's interview followed immediately after the completion of the child interview. The variable "child symptoms" consists of a count of the symptoms included in the child's K-SADS-PL screening interview that were currently present at the threshold or subthreshold level. We created a similar variable based on the clinical interviews with mothers about their child.

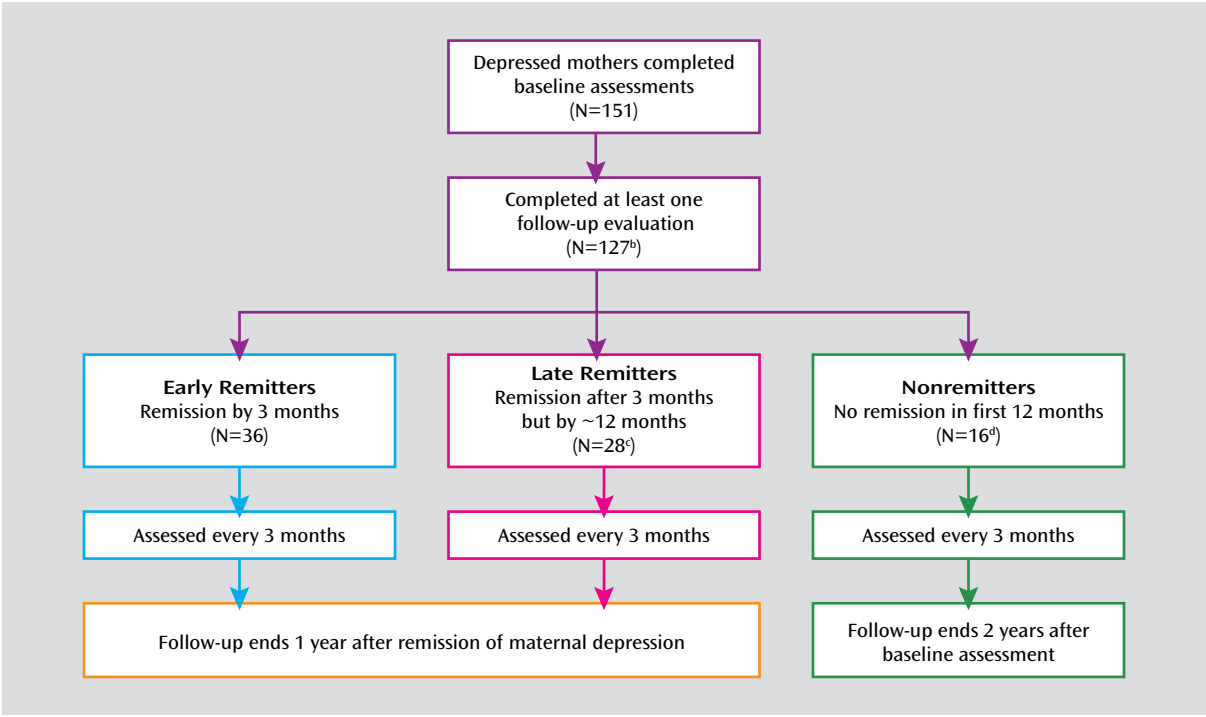
The Child Behavior Checklist (35) assessed total, internalizing, and externalizing symptoms as reported by mothers. Scores are presented as T scores ranging from 0 to 100, with higher scores indicating a greater number or severity of symptoms. Scores above 70 indicate clinical impairment.

The Children's Global Assessment Scale (36) is a clinician-based measure of global functioning with a scale range from 0 to 100. Scores above 90 indicate superior functioning, and scores below 70 indicate impaired functioning. We used a 2-week time frame based on all available child data.

Data Analysis

The relation of maternal remission status to child outcome in the year following remission was assessed with Poisson regression analysis when the outcome was the number of child

FIGURE 1. Participant Flow in the STAR*D-Child Study[a]



[a] Remission was defined as Hamilton Depression Rating Scale (HAM-D) score ≤7. Relapse was defined as HAM-D score ≥14 following remission.
[b] Number of mothers with follow-up data. Twenty of the 127 were early or late remitters but were excluded from the analysis because they subsequently relapsed.
[c] Excluded are three late remitters: two because of missing child or mother data after the remission date and one because remission occurred late during the second year of treatment.
[d] Excluded are 24 nonremitters because child and/or mother data were unavailable after the first 12 months of treatment.

symptoms at each time point, and was assessed with longitudinal mixed-effects regression when the child outcome was a continuous variable, such as the Children's Global Assessment Scale or Child Behavior Checklist score. Maternal remission status (early, late, or nonremitting) was included in the models as a three-level categorical predictor variable. All regressions were conducted within a generalized estimating equations framework to adjust for correlations between repeated observations over time. The Poisson regressions used an exchangeable correlation matrix (37), and the longitudinal mixed-effects regressions used an unstructured covariance matrix (38). We performed analyses using PROC GENMOD (for Poisson regression) and PROC MIXED (for linear regressions using longitudinal mixed-effects analysis) in SAS, version 9 (SAS Institute, Cary, N.C.). For all of the models described above, we included the following potential confounding variables in the analyses: child's age and gender; household income; mother's baseline HAM-D score, presence of an anxiety disorder or substance use disorder at baseline, and marital status; child's treatment status over the course of the study (any versus no treatment); and child's baseline score for the outcome under consideration. An interaction term representing time by maternal remission status was included in the regression analyses to formally test whether the rate of change in child symptom outcomes varied according to maternal remission status.

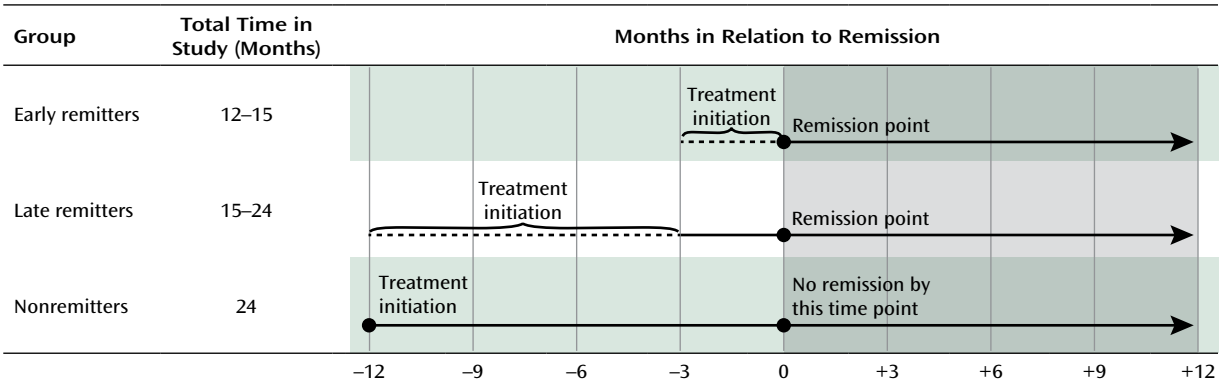
Missing outcome data were handled by initially assuming that the data were missing at random for the continuous variables analyzed using mixed-effects models, and missing completely at random when using Poisson regression analysis using generalized estimating equations. Under this assumption, valid analyses can be conducted using models such as the mixed-effects models based on maximum likelihood inference. Because of the large number of dropouts at the 12-month assessment in the late remission category, we performed a sensitivity analysis by rerunning all models after deleting the 12-month assessment for all participants and comparing patterns of change as represented by the beta coefficients for the 9-month period after maternal remission, and comparing results. Data on household income were missing for three mothers, and the average household income of all mothers in each maternal remission category was imputed.

Results

Baseline Characteristics of Depressed Mothers and Their Children

A significant association was observed between household income and maternal remission status (p=0.02), with early-remitting mothers having the highest household income (Table 1). Early-remitting mothers were more likely to be currently married than late- and nonremitting mothers (p<0.05). Not surprisingly, baseline HAM-D scores of depressed mothers varied significantly by maternal remission status, with early-remitting mothers having fewer symptoms (the lowest scores). A higher proportion of children of early-remitting mothers were boys, but the association fell short of statistical significance (p=0.09). Children of early-remitting mothers had significantly fewer symptoms at baseline by mothers' reports.

FIGURE 2. Analytic Design of the STAR*D-Child Study of Children's Outcomes in Relation to Illness Course of Mothers Treated for Depression[a]



[a] For each of the three groups, the horizontal timeline depicts the potential length of time (in months) spent in the study, zero-centered on the remission date (for remitters) or on the date 12 months after treatment initiation (for nonremitters). For remitters, the dotted portions of the lines signify time ranges in relation to the remission point during which treatment was initiated. The shaded area depicts the five potential assessments per participant that are analyzed in this study (at times 0, +3, +6, +9, and +12). For remitters, this covers the 12-month period following remission, and for nonremitters, it covers the 12-month period following the first 12 months of participation in the study, given the absence of remission during those first 12 months.

Child Outcomes and Maternal Remission Status

We compared child outcomes by time of remission of maternal depression adjusting for child's age and gender; household income; mother's baseline HAM-D score, presence of an anxiety disorder at baseline, presence of a substance use disorder at baseline, and marital status; and child's baseline score for the outcome under consideration and treatment status over the course of the study (Table 2). We first determined whether there were significant changes in children's outcomes among offspring of early-, late-, and nonremitting mothers separately during the year following maternal remission. Table 2 shows that there were statistically significant decreases over time in the number of symptoms among children of both early- and late-remitting mothers (as reflected in the negative beta coefficients and associated p values) but not in children of nonremitting mothers. However, formal tests of differences in the magnitude of the rate of change in child-reported symptoms (beta coefficients) among the three groups as reflected in the group-by-time of maternal remission interaction coefficient were not statistically significant. Similar patterns were observed for maternal reports of children's symptoms (Table 2).

Child Behavior Checklist total problem scores for children of early- and late-remitting mothers decreased over time, but only the decrease in early-remitting mothers was statistically significant. Symptoms in children of nonremitting mothers increased over time, although this increase was not statistically significant (Table 2). A test of the interaction revealed marginally significant differences (p=0.057) among these groups on rate of change in Child Behavior Checklist total problem scores. Pairwise comparisons revealed that time trends in the children of early- and late-remitting mothers were significantly different from those of nonremitting mothers (early versus nonremitting: t=2.83, df=151, p=0.005; late versus nonremitting: t=3.14, df=113, p=0.002), but no significant differences were observed between the early- and late-remitting mothers. When Child Behavior Checklist internalizing scores were examined separately for each maternal remission group, we found statistically significant decreases for children of early- (p=0.03) and late-remitting (p=0.05) mothers, but not for children of nonremitting mothers. A formal test of the interaction was not statistically significant.

Child Behavior Checklist externalizing problem scores mirrored the patterns of change in total problem scores, with decreases in scores in children of early- and late-remitting mothers, although only decreases in children of early-remitting mothers reached statistical significance. There was a significant increase in scores of children of nonremitting mothers. A test of interaction showed that the variation in patterns of change in Child Behavior Checklist externalizing scores among the three maternal remission categories was statistically significant (p=0.03). Pairwise comparisons revealed that the time trend among children of nonremitting mothers was marginally different from those of early-remitting mothers (t=1.92, df=152, p=0.057) and significantly different from those of late-remitting mothers (t=3.01, df=114, p=0.003), but the difference between children of early- versus late-remitting mothers was nonsignificant.

Children's Global Assessment Scale scores showed a statistically significant improvement during the year after remission among children whose mothers were early remitters, but not among children of late remitters or nonremitters. However, rates of change across the three groups were not significantly different according to formal tests of interaction.

Because many (82%) of the children of late remitters dropped out of the study before the final assessment at the

TABLE 1. Baseline Demographic and Clinical Characteristics of Depressed Mothers and Their Children by Maternal Depression Remission Status (N=80)

Subject Group and Variable	Early Remitters (N=36)		Late Remitters (N=28)		Nonremitters (N=16)		Analysis		
	Mean	SD	Mean	SD	Mean	SD	ANOVA F	df	p
Mothers									
Age (years)	39.0	6.8	36.9	6.3	40.3	6.6	1.52	2, 77	0.22
Hamilton Depression Rating Scale score	21.8	4.2	23.8	5.3	26.9	4.5	6.79	2, 77	0.002
	N	%	N	%	N	%	χ^2	df	p
Race									0.77[a]
African American	10	27.8	11	39.3	6	37.5		6	
White	16	44.4	13	46.4	7	43.8			
Hispanic	7	19.4	4	14.3	3	18.8			
Other	3	8.3	0	0.0	0	0.0			
Education							3.51	2	0.17
Less than high school	4	11.1	3	10.7	3	18.8			
High school (<college)	19	52.8	20	71.4	11	68.8			
≥College	13	36.1	5	17.9	2	12.5			
Annual household income							7.69	2	0.02
Less than $15,000	4	11.4	7	25.9	5	33.3			
$15,000 to $39,999	11	31.4	11	40.7	7	46.7			
$40,000 or greater	20	57.1	9	33.3	3	20.0			
Marital status									0.047[a]
Currently married	23	63.9	10	35.7	4	25.0			
Separated or divorced	4	11.1	5	17.9	5	31.3			
Never married	9	25.0	13	46.4	7	43.8			
	N	%	N	%	N	%			p[a]
Offspring									
Boy	24	66.7	11	39.3	9	56.3			0.09
Girl	12	33.3	17	60.7	7	43.8			
	Mean	SD	Mean	SD	Mean	SD	ANOVA F	df	p
Age (years)	12.0	2.8	11.4	2.5	12.6	2.7	1.17	2, 77	0.32
K-SADS-PL[b]									
Symptoms (child report)	5.4	5.9	6.0	4.3	7.7	5.8	3.28[c]	2	0.19
Symptoms (mother report)	4.6	4.3	6.0	3.6	8.7	5.9	6.77[c]	2	0.03
Children's Global Assessment Scale	70.6	11.1	68.4	15.3	66.1	10.2	0.72	2, 76	0.49
Children's Behavior Checklist									
Total problems score	57.7	8.4	55.1	11.7	53.6	10.0	1.11	2, 77	0.33
Internalizing problems score	58.1	8.4	55.9	10.2	53.3	11.2	1.39	2, 75	0.25
Externalizing problems score	55.4	8.5	54.6	11.4	52.3	9.3	0.55	2, 77	0.58

[a] Fisher's exact test (calculated because >20% of the cells had expected counts <5).
[b] K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version.
[c] Kruskal-Wallis chi-square statistic.

end of the 12-month period following remission, we repeated the analyses over the 9-month period following remission (not shown). Beta coefficients representing rates of change in outcome measures over the 9-month period were very similar to those estimated over the 12-month period for all maternal remission categories. Further exploration of the 14 children of late remitters who dropped out of the study after the 9-month assessment showed on average greater improvement on all measures, compared with those who stayed in the study, although these differences did not reach statistical significance. In contrast, the four children of nonremitting mothers who dropped out after the 9-month assessment appeared to be doing less well on all measures compared with those who stayed in the study. These data suggest that our findings may in fact be conservative.

Children Receiving Treatment

If a child had a psychiatric diagnosis and was distressed, the interviewer offered feedback to the child and family, encouraged treatment, and provided appropriate referrals. There were no statistically significant differences in the proportion of children receiving treatment by maternal remission status, with six (17%), nine (32%), and six (38%) children of early-, late- and nonremitting mothers, respectively, receiving treatment. Of the 21 children receiving treatment, 20 received outpatient treatment and one received residential treatment. There were no sig-

TABLE 2. Current Symptoms and Functioning Over 1 Year for Children of Depressed Mothers, by Maternal Remission Status (N=80)[a]

Measure and Assessment Point	Early Remitters				Late Remitters				Nonremitters			
		Score		Time Trend		Score		Time Trend		Score		Time Trend
	N	Mean	SD	(Beta)	N	Mean	SD	(Beta)	N	Mean	SD	(Beta)
Child-reported symptoms[b]				−0.039**				−0.035*				−0.009
0	34	3.82	3.46		28	4.36	3.55		15	5.53	4.26	
3	30	3.23	4.55		25	4.72	3.63		14	5.93	5.84	
6	28	2.71	3.46		21	3.38	3.11		14	5.79	5.75	
9	27	2.63	3.59		19	3.05	2.70		11	6.27	4.67	
12	26	2.85	3.39		5	2.40	2.19		7	3.14	2.97	
Mother's report of children's symptoms[b]				−0.024*				−0.035*				−0.010
0	34	3.68	3.17		28	5.14	4.12		15	7.13	6.17	
3	30	3.37	3.87		25	4.32	3.89		14	7.21	6.60	
6	28	2.89	3.02		21	3.71	3.64		14	6.50	6.71	
9	27	3.04	3.33		19	3.21	3.38		11	7.64	6.30	
12	26	3.00	3.38		5	4.60	4.98		7	5.43	5.50	
Child Behavior Checklist												
Total problem score[c]				−0.315**				−0.271				0.187
0	34	45.65	10.27		28	49.14	11.64		15	54.40	13.90	
3	30	44.57	11.26		26	47.15	12.98		14	55.71	12.80	
6	28	44.54	8.32		21	46.48	13.16		13	54.92	11.64	
9	27	43.41	10.81		19	45.89	9.80		11	53.73	12.43	
12	26	42.04	10.78		5	50.20	14.75		7	52.00	11.36	
Internalizing problem score				−0.254*				−0.305[d]				0.120
0	33	46.79	8.76		27	50.85	10.54		15	54.53	11.83	
3	30	47.23	9.35		26	48.58	11.62		14	56.50	11.35	
6	28	47.46	7.69		21	49.24	11.47		13	54.23	8.70	
9	27	46.74	9.76		18	47.67	9.73		11	52.55	11.72	
12	26	43.58	9.45		5	50.20	10.71		7	54.00	11.46	
Externalizing problem score[e]				−0.224*				−0.107				0.338*
0	34	46.94	8.78		28	48.43	9.69		15	52.80	12.98	
3	30	46.60	11.22		26	47.58	9.46		14	52.14	14.33	
6	28	46.04	8.92		21	46.52	10.22		13	53.38	11.83	
9	27	45.04	9.99		19	46.26	7.95		11	53.00	10.83	
12	26	45.35	9.61		5	50.60	13.28		7	50.43	9.31	
Children's Global Assessment Scale score				0.345**				0.154				0.169
0	32	75.56	9.85		27	72.78	11.38		13	70.85	13.30	
3	30	77.87	11.32		24	72.88	10.93		14	70.07	12.97	
6	27	76.78	10.56		20	73.90	11.54		14	70.93	12.02	
9	27	79.33	9.75		19	74.68	12.65		10	68.40	10.66	
12	25	79.24	10.09		5	74.60	13.35		7	74.00	8.16	

[a] In all regressions, we controlled for household income; mother's marital status (except for the outcome of mother's report of children's symptoms, which was not significantly associated with marital status); mother's baseline Hamilton Depression Rating Scale score, generalized anxiety disorder at baseline (1=yes, 0=no), and substance-related disorder at baseline (1=yes, 0=no); and child's age, gender, baseline score on the particular measure being analyzed, and whether he or she received mental health treatment at any time during the study (1=yes, 0=no).

[b] Symptoms from the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version.

[c] There was a marginally significant difference in time trend of Child Behavior Checklist total scores among the three groups (F=2.90, df=2, 221, p=0.057). Post hoc tests revealed that the time trend for children of nonremitters was different from the time trends for children of early (t=2.83, df=151, p=0.005) and late (t=3.14, df=113, p=0.002) remitters. The time trends for children of early and late remitters were not significantly different from each other.

[d] p=0.051.

[e] There was a significant difference in time trend of Child Behavior Checklist externalizing scores among the three groups (F=3.59, df=2, 220, p=0.03). Post hoc tests revealed that the time trend for children of nonremitters was different from the time trends for children of early (t=1.92, df=152, p=0.057) and late (t=3.01, df=114, p=0.003) remitters. The time trends for children of early and late remitters were not significantly different from each other.

* p<0.05; **p<0.01.

nificant differences in type of treatment children received (medication, psychotherapy, or both) by maternal remission status.

Discussion

During the year following remission of maternal depression, children of early- and late-remitting mothers continued to show a significant decrease in psychiatric symptoms, as evidenced by child and maternal reports of total symptom count on the K-SADS-PL. When Child Behavior Checklist symptoms were considered, there was a significant decrease in symptoms among children of early-remitting mothers, which parallels the finding based on K-SADS-PL symptoms. Although Child Behavior Checklist outcomes for late-remitting mothers did not show statistically significant decreases for total and externalizing scores when considered alone, pairwise comparisons of decreases in symptoms of children of early- and late-remitting mothers did not show statistically significant differences. These results suggest that there is a significant decrease in children's symptoms and problem behaviors in the 1-year period following maternal remission, which does not vary with length of time to maternal remission. Among children of nonremitting mothers, there were no significant changes in either symptoms or behavior scores, with the exception of Child Behavior Checklist externalizing problem scores, which increased significantly over the study period.

Child functioning as assessed with the Children's Global Assessment Scale showed significant improvement only among children of early-remitting mothers during the time they were in the study. Their mothers were less depressed at baseline and remained depressed for a shorter time, suggesting that early remission, lower illness severity, and shorter duration of maternal depressive episodes may be important in relation to their children's adaptation.

The less consistent statistically significant decreases in symptoms and functioning among children of late-remitting mothers (compared with the decreases in children of early-remitting mothers) are probably due to the heterogeneous nature of this group, which includes mothers who remitted between 3 and 12 months after initiation of treatment. In contrast, children of mothers who did not remit over the 24-month follow-up showed no significant improvement on any outcomes during the 12–24 months after initiation of mothers' treatment. In fact, there was a significant increase in children's externalizing problems among offspring of nonremitters. This group was small, and these findings should be viewed cautiously. The sample size of nonremitters by the end of the study was small to a large extent because of the STAR*D design, which was to provide treatment until the patient went into remission.

Even with a relatively small sample size, particularly of nonremitters, we observed some differences in patterns of change in child outcomes by mother's remission status. It is likely, however, that this small sample size reduced the ability to detect statistically significant differences, especially for analyses of interactions. In addition, since our findings in this phase of the study are based on symptoms and not diagnoses, the clinical significance of the findings may be limited. Other limitations should be noted. These analyses could not take into account the type of maternal treatment (psychotherapy versus medication). Because only one-third of the patients in STAR*D were open to receiving psychotherapy (39), there were too few mothers who had been treated with psychotherapy in our study to conduct meaningful comparisons. Our study included only depressed mothers. The effect of treating depressed fathers is being studied. Children were followed for varying lengths of time from study initiation based on their mother's remission status, and it is possible that children followed for longer periods were more likely to have an increase (or decrease) in symptoms or behavioral problems merely as a function of follow-up time and not of mother's remission status. Our focus was the 1-year period following mother's remission, and therefore the varying length of follow-up time is reflected only in the length of time between study initiation and mother's remission. Our results suggest that for most outcomes there is little difference between the postremission rates of improvement in children of late- versus early-remitting mothers, which implies that it is unlikely that the length of time spent in the study is the primary factor related to our findings.

It is possible that mothers who maintained remission over the 1-year postremission period did so because their children continued to improve. In mothers who did not remit, their children's continued behavior problems may have contributed to maternal depressive symptoms. There were too few mothers who relapsed in this sample to conduct a meaningful analysis of this hypothesis. However, in the year following initiation of treatment for maternal depression, we found little evidence that mothers became less depressed in reaction to positive changes experienced by their children (25). This could be because most of the mothers in this study were moderately to severely depressed and were being aggressively treated for depression.

No causal conclusions can be drawn from these observational data. Although these results are consistent with the hypothesis that treating depressed parents to remission benefits their children, we cannot attribute the mothers' remission to the treatment itself or attribute children's better outcomes to their mothers' remission. It is possible that some unmeasured third variables (e.g., genes, stress) explain both mothers' remission and children's symptom decline.

The first published study to document the relation between remission of a mother's depression and her child's clinical state appeared relatively recently (40), and around the same time a report from a randomized clinical trial (23) provided data consistent with our results. The trial compared the outcome of school-age children whose depressed mothers were randomly assigned to receive interpersonal

psychotherapy (N=26) or treatment as usual (N=21) for eight sessions. The mothers and children were assessed at baseline and at 3 and 9 months. Mothers assigned to interpersonal psychotherapy had lower levels of depressive symptoms and higher functioning at both follow-up assessments. Moreover, differences were found in their children's depressive symptoms at the 9-month follow-up. Maternal improvement preceded improvement in offspring. Although the sample was small, treatment was randomized from the beginning, unlike the design of STAR*D.

Another recent study (22) was a randomized clinical trial to determine the effect of CBT in preventing the onset of depression in adolescents at risk for depression. It was found that while CBT was generally superior to usual care, adolescents with a currently depressed parent had poorer outcomes with CBT. On a similar note, a study by Brent et al. (41) showed that the presence of maternal depression at baseline predicted poorer outcomes in depressed adolescents who received CBT.

Our findings, taken together with the studies described above, indicate that remission of depression in mothers is associated with positive outcomes in their children. Continuing the mother's treatment until remission is achieved may be warranted, as even later remission of maternal depression was associated with decreases in children's symptoms. Finally, there may be benefit to the child in having the mother remain in treatment even if she does not achieve full remission immediately. The barriers to implementing programs that provide continuous treatment of depressed parents to remission are primarily related to treatment access and retention as well as to financial obstacles in our health care system (42).

Received Jan. 8, 2010; revision received Nov. 18, 2010; accepted Dec. 13, 2010 (doi: 10.1176.appi.ajp.2010.10010032). From Columbia University and the New York State Psychiatric Institute; the University of Texas Southwestern Medical Center; Duke University-National University of Singapore; Vanderbilt University; the University of North Carolina; the University of Michigan; the University of California at San Diego; Virginia Commonwealth University; Harvard University; and the University of Pittsburgh. Address correspondence and reprint requests to Dr. Weissman, Columbia University and New York State Psychiatric Institute, Unit 24, 1051 Riverside Dr., New York, NY 10032; mmw3@columbia.edu (e-mail).

Dr. Pilowsky reports financial support from NIMH, NIDA, and CDC. Dr. Alpert receives research support from Aspect Medical Systems, Eli Lilly, PamLab, and Pfizer, and he receives honoraria from Reed Medical Education and Belvoir Publishing. Dr. Trivedi has received research support from the Agency for Healthcare Research and Quality (AHRQ), Corcept Therapeutics, Cyberonics, Merck, National Alliance for Research in Schizophrenia and Depression, NIMH, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix EPIX Pharmaceuticals, Solvay Pharmaceuticals, and Targacept. He has received consulting and speaker fees from Abbott Laboratories, Abdi Ibrahim, Akzo (Organon Pharmaceuticals), AstraZeneca, Bristol-Myers Squibb, Cephalon, Evotec, Fabre Kramer Pharmaceuticals, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, Johnson & Johnson PRD, Eli Lilly, Meade Johnson, Medtronic, Neuronetics, Otsuka Pharmaceuticals, Parke-Davis Pharmaceuticals, Pfizer, Sepracor, SHIRE Development, VantagePoint, and Wyeth-Ayerst Laboratories. Dr. Fava has received research support, advisory or consulting fees, and speaking or publishing fees from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Novartis AG, Organon Pharmaceuticals, and Pfizer. He has received research support and advisory or consulting fees from Abbott Laboratories, Alkermes, Aspect Medical Systems, BrainCells, CeNeRx BioPharma, Clinical Trials Solutions, Euthymics Bioscience, i3 Innovus/Ingenix, Johnson & Johnson PRD, Lorex Pharmaceuticals, PamLab, Pharmavite, Roche, RCT Logic, Sanofi-Aventis US, Solvay Pharmaceuticals, and Synthelabo. Dr. Fava has also received research support from BioResearch, Clintara, Covidien, EnVivo Pharmaceuticals, Ganeden Biotech, Icon Clinical Research, Lichtwer Pharma GmbH, NARSAD, NCCAM, NIDA, NIMH, Photothera, Shire, and Wyeth-Ayerst Laboratories. He has also received advisory or consulting fees from Affectis Pharmaceuticals AG, Amarin Pharma, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management, BioMarin Pharmaceuticals, Biovail Corporation, CNS Response, Compellis Pharmaceuticals, Cypress Pharmaceutical, DiagnoSearch Life Sciences, Dinippon Sumitomo Pharma, Dov Pharmaceuticals, Edgemont Pharmaceuticals, Eisai Inc., ePharmaSolutions, EPIX Pharmaceuticals, Fabre-Kramer Pharmaceuticals, GenOmind, Grunenthal GmbH, Janssen Pharmaceutica, Jazz Pharmaceuticals, Knoll Pharmaceuticals, Labopharm, Lundbeck, MedAvante, Merck, MSI Methylation Sciences, Naurex, Neuronetics, NextWave Pharmaceuticals, Nutrition 21, Orexigen Therapeutics, Otsuka Pharmaceuticals, PharmaStar, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa Pharmaceuticals, Puretech Ventures, PsychoGenics, Psylin Neurosciences, Rexahn Pharmaceuticals, Ridge Diagnostics, Sepracor, Servier Laboratories, Schering-Plough Corporation, Somaxon Pharmaceuticals, Somerset Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Pharmaceutical Company Limited, Tal Medical, Tetragenex Pharmaceuticals, TransForm Pharmaceuticals, Transcept Pharmaceuticals, and Vanda Pharmaceuticals. Dr. Fava has also received speaking or publishing fees from Adamed, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, Belvoir Media Group, Boehringer Ingelheim GmbH, CME Institute/Physicians Postgraduate Press, Imedex, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, PharmaStar, United BioSource, and Wyeth-Ayerst Laboratories. Dr. Fava has equity holdings in Compellis and receives royalty, patent, or other income from a patent for SPCD and patent application for a combination of azapirones and bupropion in major depressive disorder, copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER. He has a patent for research and licensing of SPCD with RCT Logic; Lippincott, Williams & Wilkins. Dr. Rush has received consultant fees from Advanced Neuromodulation Systems, AstraZeneca, Best Practice Project Management, Brain Resource, Bristol-Myers Squibb/Otsuka, Cyberonics, Forest Pharmaceuticals, Gerson Lehrman Group, GlaxoSmithKline, Jazz Pharmaceuticals, Magellan Health Services, Merck & Company, Neuronetics, Novartis Pharmaceuticals, Ono Pharmaceuticals, Organon, Otsuka Pharmaceuticals, Pamlab, Pfizer, The University of Michigan, Transcept Pharmaceuticals, Urban Institute and Wyeth Ayerst; speaking fees from Cyberonics, Forest Laboratories, GlaxoSmithKline, and Otsuka; royalties from Guilford Publications, Healthcare Technology Systems, and The University of Texas Southwestern Medical Center; and research support from NIMH and the Stanley Medical Research Institute. He has owned shares of stock in Pfizer. Dr. Wisniewski has received consultant fees from Cyberonics, ImaRx Therapeutics, Bristol-Myers Squibb Company, Organon, Case-Western University, Singapore Clinical Research Institute, Dey Pharmaceuticals, Venebio, and Dey. The remaining authors report no financial relationships with commercial interests.

Supported by NIMH grant R01MH063852 (Dr. Weissman, principal investigator) and by an NIMH contract (N01 MH90003) (Dr. Rush, principal investigator). Dr. Garber was supported in part by an Independent Scientist Award K02 MH66249 from NIMH.

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

References

1. Weissman MM, Gammon GD, John K, Merikangas KR, Warner V, Prusoff BA, Sholomskas D: Children of depressed parents:

increased psychopathology and early onset of major depression. Arch Gen Psychiatry 1987; 44:847–853
2. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H: Offspring of depressed parents: 20 years later. Am J Psychiatry 2006; 163:1001–1008
3. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Verdeli H, Pilowsky DJ, Grillon C, Bruder G: Families at high and low risk for depression: a 3-generation study. Arch Gen Psychiatry 2005; 62:29–36
4. Klein DN, Lewinsohn PM, Seeley JR, Rohde P: A family study of major depressive disorder in a community sample of adolescents. Arch Gen Psychiatry 2001; 58:13–20
5. Sullivan PF, Neale MC, Kendler KS: Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000; 157:1552–1562
6. Downey G, Coyne JC: Children of depressed parents: an integrative review. Psychol Bull 1990; 108:50–76
7. 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
8. Lieb R, Isensee B, Hofler M, Pfister H, Wittchen HU: Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. Arch Gen Psychiatry 2002; 59:365–374
9. Hammen C, Burge D, Burney E, Adrian C: Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. Arch Gen Psychiatry 1990; 47:1112–1117
10. Williamson DE, Birmaher B, Axelson DA, Ryan ND, Dahl RE: First episode of depression in children at low and high familial risk for depression. J Am Acad Child Adolesc Psychiatry 2004; 43:291–297
11. Brennan PA, Hammen C, Katz AR, Le Brocque RM: Maternal depression, paternal psychopathology, and adolescent diagnostic outcomes. J Consult Clin Psychol 2002; 70:1075–1085
12. Orvaschel H, Walsh-Allis G, Ye WJ: Psychopathology in children of parents with recurrent depression. J Abnorm Child Psychol 1988; 16:17–28
13. Kendler KS, Gardner CO, Prescott CA: Toward a comprehensive developmental model for major depression in women. Am J Psychiatry 2002; 159:1133–1145
14. Holmans P, Weissman MM, Zubenko GS, Scheftner WA, Crowe RR, Depaulo JR Jr, Knowles JA, Zubenko WN, Murphy-Eberenz K, Marta DH, Boutelle S, McInnis MG, Adams P, Gladis M, Steele J, Miller EB, Potash JB, Mackinnon DF, Levinson DF: Genetics of recurrent early-onset major depression (GenRED): final genome scan report. Am J Psychiatry 2007; 164:248–258
15. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R: Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003; 301:386–389
16. Cicchetti D, Rogosch FA, Toth SL: Maternal depressive disorder and contextual risk: contributions to the development of attachment insecurity and behavior problems in toddlerhood. Dev Psychopathol 1998; 10:283–300
17. Weissman MM, Pilowsky DJ, Wickramaratne PJ, Talati A, Wisniewski SR, Fava M, Hughes CW, Garber J, Malloy E, King CA, Cerda G, Sood AB, Alpert JE, Trivedi MH, Rush AJ; STAR*D-Child Team: Remissions in maternal depression and child psychopathology: a STAR*D-Child report. JAMA 2006; 295:1389–1398
18. Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, Quitkin FM, Wisniewski SR, Lavori PW, Rosenbaum JF, Kupfer DJ: Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Psychiatr Clin North Am 2003; 26:457–494
19. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G; STAR*D Investigators Group: Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials 2004; 25:119–142
20. Beardslee WR, Gladstone TR, Wright EJ, Cooper AB: A family-based approach to the prevention of depressive symptoms in children at risk: evidence of parental and child change. Pediatrics 2003; 112:e119–e131
21. Verdeli H, Ferro T, Wickramaratne P, Greenwald S, Blanco C, Weissman MM: Treatment of depressed mothers of depressed children: pilot study of feasibility. Depress Anxiety 2004; 19:51–58
22. Garber J, Clarke GN, Weersing VR, Beardslee WR, Brent DA, Gladstone TR, DeBar LL, Lynch FL, D'Angelo E, Hollon SD, Shamseddeen W, Iyengar S: Prevention of depression in at-risk adolescents: a randomized controlled trial. JAMA 2009; 301:2215–2224
23. Swartz HA, Frank E, Zuckoff A, Cyranowski JM, Houck PR, Cheng Y, Fleming MA, Grote NK, Brent DA, Shear MK: Brief interpersonal psychotherapy for depressed mothers whose children are receiving psychiatric treatment. Am J Psychiatry 2008; 165:1155–1162
24. Pilowsky DJ, Wickramaratne PJ, Rush AJ, Hughes CW, Garber J, Malloy E, King CA, Cerda G, Sood AB, Alpert JE, Wisniewski SR, Trivedi MH, Talati A, Carlson MM, Liu HH, Fava M, Weissman MM: Children of currently depressed mothers: a STAR*D ancillary study. J Clin Psychiatry 2006; 67:126–136
25. Pilowsky DJ, Wickramaratne P, Talati A, Tang M, Hughes CW, Garber J, Malloy E, King C, Cerda G, Sood AB, Alpert JE, Trivedi MH, Fava M, Rush AJ, Wisniewski S, Weissman MM: Children of depressed mothers 1 year after the initiation of maternal treatment: findings from the STAR*D-Child study. Am J Psychiatry 2008; 165:1136–1147
26. Rush AJ, Trivedi M, Fava M: Depression, IV: STAR*D treatment trial for depression. Am J Psychiatry 2003; 160:237
27. Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, Nierenberg AA: STAR*D: revising conventional wisdom. CNS Drugs 2009; 23:627–647
28. Endicott J, Cohen J, Nee J, Fleiss J, Sarantakos S: Hamilton Depression Rating Scale: extracted from Regular and Change Versions of the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 1981; 38:98–103
29. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
30. Rush AJ, Trivedi MH, Carmody TJ, Ibrahim HM, Markowitz JC, Keitner GI, Kornstein SG, Arnow B, Klein DN, Manber R, Dunner DL, Gelenberg AJ, Kocsis JH, Nemeroff CB, Fawcett J, Thase ME, Russell JM, Jody DN, Borian FE, Keller MB: Self-reported depressive symptom measures: sensitivity to detecting change in a randomized, controlled trial of chronically depressed, nonpsychotic outpatients. Neuropsychopharmacology 2005; 30:405–416
31. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB: The 16-item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003; 54:573–583
32. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M; STAR*D Study Team: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
33. Kaufman J, Martin A, King RA, Charney D: Are child-, adolescent-, and adult-onset depression one and the same disorder? Biol Psychiatry 2001; 49:980–1001
34. Weissman MM, Warner V, Wickramaratne P, Moreau D, Olfson M: Offspring of depressed parents: 10 years later. Arch Gen Psychiatry 1997; 54:932–940

35. Achenbach TM, Howell CT, Quay HC, Conners CK: National survey of problems and competencies among four- to sixteen-year-olds: parents' reports for normative and clinical samples. Monogr Soc Res Child Dev 1991; 56:1–131
36. Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S: A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry 1983; 40:1228–1231
37. Liang KY, Zeger SL: Longitudinal data analysis using generalized linear models. Biometrika 1986; 73:13–22
38. Galecki AT: General class of covariance structures for two or more repeated factors in longitudinal data analysis. Communications in Statistics 1994; 23:3105–3120
39. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905–1917
40. Gunlicks ML, Weissman MM: Change in child psychopathology with improvement in parental depression: a systematic review. J Am Acad Child Adolesc Psychiatry 2008; 47:379–389
41. Brent DA, Kolko DJ, Birmaher B, Baugher M, Bridge J, Roth C, Holder D: Predictors of treatment efficacy in a clinical trial of three psychosocial treatments for adolescent depression. J Am Acad Child Adolesc Psychiatry 1998; 37:906–914
42. Weissman MM, Olfson M: Translating intergenerational research on depression into clinical practice. JAMA 2009; 302:2695–2696

Clinical Guidance: Effect of Treatment of Maternal Depression on Children's Behavior

Children whose mothers are depressed have increased prevalence of psychiatric symptoms and behavioral dysfunction. However, children ages 7–17 years whose mothers' depression remitted in the course of the STAR*D studies showed substantial decrease in externalizing symptoms and improved psychosocial function, as reported by Wickramaratne et al. Birmaher in an editorial (p. 563) points out that clinicians treating women need to be alert to the possibility of illness in their children and that standard treatments of the children, such as cognitive-behavioral therapy for depression, may not be successful until the mother's depression has remitted.