Families at High and Low Risk for Depression

A 3-Generation Study

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Background: The familial nature of early-onset major depressive disorder (MDD) has been documented in numerous family studies of adults and is supported by studies of offspring of parents with MDD, for whom the risk is more than 3-fold. None of the published high-risk studies have gone beyond 2 generations, and few have a longitudinal design. We report results of an approximately 20-year follow-up of families at high and low risk for depression. The first 2 generations were interviewed 4 times during this period. The offspring from the second generation are now adults and have children of their own, the third generation of the original cohort.

Objective: To examine the familial aggregation of psychiatric disorders and functioning in grandchildren by their parents' and grandparents' depression status.

Design: Longitudinal, retrospective cohort, family study.

Participants: One hundred sixty-one grandchildren and their parents and grandparents.

Main Outcome Measures: Lifetime rate of psychiatric disorder and functioning in grandchildren, stratified by parental and by grandparental depression status, collected by clinicians blind to diagnoses of previous generations and to previous interviews.

Results: There were high rates of psychiatric disorders, particularly anxiety disorders, in the grandchildren with 2 generations of major depression, with 59.2% of these grandchildren (mean age, 12 years) already having a psychiatric disorder. The effect of parental depression on grandchildren's outcomes differed significantly with grandparental depression status. Among families with a depressed grandparent, increased risk of anxiety (relative risk, 5.17; 95% confidence interval, 1.4-18.7; $P=.01$) and increased risk of any disorder (relative risk, 5.52; 95% confidence interval, 2.0-15.4; $P=.002$) were observed in grandchildren with a depressed parent as compared with those with nondepressed parents. The severity of parental depression, as measured by impairment, significantly increased the rate of a mood disorder in these grandchildren (relative risk, 2.44; 95% confidence interval, 1.1-5.5; $P=.03$). In contrast, among grandchildren with nonfamilial depression, ie, depressed parents with no depressed grandparents, there was no significant effect of parental MDD on grandchildren diagnoses. However, parental MDD, regardless of whether families had a depressed grandparent, had a significant impact on the grandchildren's overall functioning. Potential confounding variables did not affect the strength of the association with parental and grandparental depression.

Conclusions: The association between parental MDD and child diagnosis is moderated by grandparental MDD status. The rates of psychopathology are highest in grandchildren of parents and grandparents with a moderately to severely impairing depression. Anxiety disorders are the early sign of psychopathology in the young grandchildren. Early interventions in the offspring of 2 generations affected with moderately to severely impairing MDD seem warranted. This familial group may be the target for neuroimaging, genetic, and other biological studies.

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THE FAMILIAL NATURE OF MAjor depressive disorder (MDD) has been documented in numerous family studies,[1-4] with a 2-fold increased risk of MDD in the first-degree relatives of depressed patients as compared with controls.[5] Retrospective data on the onset and course of MDD from family studies show that an early age at onset and recurrence are associated with increased familial clustering of MDD.[6,7] These findings are supported by studies of offspring of parents with MDD, where there is more than a 3-fold increased risk among child and adolescent offspring.[8-14] None of the published high-risk studies have gone beyond 2 generations. Few[12,14-16] have a longitudinal design. We have been observing the offspring of depressed and nondepressed parents (generation 1) for about 20 years. The offspring (genera-

tion 2) are now adults and also have children of their own (generation 3), the grandchildren of the original cohort. Previously, we published results from a 10-year follow-up of the first 2 generations[17] and preliminary results on a sample of grandchildren.[13] We showed that grandchildren in families with multiple generations of MDD were at a high risk for psychopathology. At that time, the second generation had not fully passed through the age of risk for MDD,[17] and there were only 90 grandchildren.[13] In this article, we report the results from the first 2 generations and 161 grandchildren.

We hypothesized that multigenerational MDD (ie, presence of MDD in both a grandparent and a parent) would be associated with a significantly greater risk of mood and anxiety disorders among grandchildren. A number of the grandchildren were prepubertal, and our previous analysis of the first 2 generations,[18] as well as results of other studies,[19-25] have shown that anxiety disorders usually preceded depression in the sequence of onset. Therefore, we expected that the young grandchildren in the high-risk groups, like their parents and grandparents, would have a high risk of anxiety disorders. Generation 1 was selected to have moderate to severe MDD. Generation 2 was their offspring. We had shown at the 10-year follow up of this sample that the MDD in generation 2 varied in severity[6] by generation 1 depression status in terms of course, impairment, and risk factors.[26,27] If depressed, the offspring of nondepressed parents had a less severe or impairing MDD. We hypothesized that the impact of generation 2 MDD for generation 3 would vary by the severity of generation 2 MDD, as measured by impairment. As others have shown,[28] we expected that the rates would be higher in grandchildren with a parent who had an impairing MDD. This article presents the clinical findings on the third generation. Data on biological markers, ie, electroencephalographic and startle reaction findings, are presented separately.[29,30]

METHODS

In the original study, probands (generation 1) with major depression were selected from outpatient clinical specialty settings for the treatment of mood disorders and had moderate to severe MDD that resulted in impairment. Nondepressed probands were selected, at the same time, from a sample of adults from the same community. They were required to have no lifetime history of psychiatric illness, based on several interviews. Full details of the methods for wave 1 (baseline), wave 2 (year 2), and wave 3 (10-year follow-up) have been previously described.[1,17,31] The study was initiated in 1982, and wave 4, reported in this article, ended in 2002. The procedures were kept similar across the waves, with few exceptions, to avoid introducing method variation bias. The proband, spouse, offspring, and grandchildren of each generation were interviewed independently, and the interviewers were blind to the clinical status of the previous generations. After the second wave, 2 spouses of the normal control group, ie, generation 1, subsequently developed a first major depression, as determined by an independent best-estimate diagnosis, which was made by a clinician blind to the initial proband and offspring data. The 2 spouses and their 4 offspring were reassigned to the depressed proband generation 1 group. We did not remove any generation 2 or generation 3 participants if they developed any disorders because their diagnoses were the study outcome. This wave was approved by the institutional review board at New York State Psychiatric Institute/Columbia University, and informed consent was obtained.

SAMPLE

There were 188 grandchildren eligible for inclusion, ie, older than 5 at wave 4. Of the eligible grandchildren, information was obtained on 156 (83%) at wave 4. An additional 15 grandchildren (8%) who were interviewed at wave 3 were unavailable at wave 4, and their wave 3 interview data were added to wave 4. Thus, 171 of the 188 grandchildren provided information at wave 3 or 4. While completing the family collections, we found that 10 of the 171 grandchildren (4 from the depressed generation 1 group and 6 from the nondepressed generation 1 group) were not biologically related to generation 1 or generation 2 but were adopted or were offspring of married-in subjects. They were removed from the analysis, yielding a final sample of 161 (85.6%) of the 188 grandchildren. Information was available from direct interviews of 133 (83%) of 161 grandchildren. Twenty-eight (17%) of the 161 grandchildren had information provided by the parent only. There were no significant differences in grandchildren with interview vs informant-only information by generation 1 diagnostic status. Ninety-three percent (80/86) of the second generation with eligible children were re-interviewed at wave 4. The first generation, the grandparents (n=47) who had grandchildren, were not re-interviewed at wave 4 because they were on average 63 years of age by that time and had passed the age of risk of first onsets of MDD. Best-estimate diagnoses of the grandparents combining waves 1, 2, and 3 assessments were used for these analyses.

ASSESSMENTS

The diagnostic interviews across all waves were conducted using a semistructured diagnostic assessment (the Schedule for Affective Disorders and Schizophrenia–Lifetime Version for adults[32] and the child version modified for the *DSM-IV*[33] for subjects between ages 6 and 17 years).[34] At wave 4, the Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version for Children was used.[35] The Global Assessment Scale (GAS)[36] was completed by persons making the best-estimate diagnosis at all waves. The instrument is rated on a 100% scale and provides an overall estimate of the person's current functional adjustment based on all available information. A child version of the GAS (C-GAS)[37] was used for children between the ages of 6 and 17 years. Lower scores on the GAS indicate greater overall impairment in functioning. The parents completed the Peabody Picture Vocabulary Test.[38] Higher scores indicate higher IQ, with 100 as an average norm.

Parents completed the Parental Bonding Instrument,[39] a 25-item self report that includes assessments of care, overprotection, and affectionless control in parenting behavior. Family discord included marital discord[40]; parent-child discord recording the degree of arguing or tension between either parent and at least 1 child in the family; low family cohesion, derived from the Cohesion subscale of the Family Adaptability and Cohesion Evaluation Scale[41]; and divorce in the first and second generations.

INTERVIEWERS AND BEST-ESTIMATE PROCEDURES

The diagnostic assessments were administered by trained doctoral- and masters-level mental health professionals, who were blind to the clinical status of the parents and grandparents and to previous history information. (The training, which remained the same across waves, has been previously described.[17]) Mul-

tiple sources of information were obtained. Final diagnosis of all generations was based on the best-estimate procedure.[42] Two experienced clinicians, a child psychiatrist (D.P.) and a psychologist (H.V.) who were not involved in the interviewing, independently and blind to the diagnostic status of the previous generation or prior assessments reviewed all the material and assigned a *DSM-IV* diagnosis and a GAS score. One hundred seventy-eight cases randomly selected from all generations were co-rated by the 2 diagnosticians. Interrater reliability κ scores were good to excellent (MDD, 0.82; dysthymia, 0.89; anxiety disorder, 0.65; alcohol abuse/dependency, 0.94; and drug abuse/dependency, 1.00). The diagnoses were cumulative across all waves. *DSM-IV* diagnoses at the probable/definite level of certainty were used for the grandchildren because of their young age and at the definite level for parents and grandparents.

STATISTICAL ANALYSIS

Initially, univariate analyses to test for the association between grandparental MDD with grandchild diagnoses and C-GAS scores were performed as follows: group differences by grandparental MDD status for grandchild outcome variables were tested using χ^2 tests for categorical variables and *t* tests for continuous variables. The univariate models were followed by multivariate models to adjust for the effect of potential confounders. Cox proportional hazard regression models,[43] which adjust for differences in follow-up time among grandchildren, were used and were modified to adjust for clustered data (W. L. Williams, G. S. Bieler, unpublished data, 1995).[44] Grandchild diagnoses as the outcomes and grandparental MDD status as the predictors were fitted using SUDAAN software (Research Triangle Institute, Research Triangle Park, NC).[45] The adjustment for clustered data was necessary to account for potential nonindependence of outcomes among grandchildren from the same family. Because the disorder status of grandchildren (generation 3) from the same family may not be independent, the assumption of independence of the outcome variable implicit in the use of the standard proportional hazard model may be violated. To overcome this problem, we used the methods of Binder,[44] who extended the methods of Lin and Wei,[46] who proposed a method for estimating the covariance matrix of the estimated parameters when the model is misspecified in those situations in which there is correlation among sample units. We used SUDAAN to obtain the appropriate adjusted variance for the relevant parameters.[45] Analysis of covariance models were fit with the C-GAS score as the outcome and grandparental MDD as the predictor.[47] Age at the interview and sex of the grandchild were considered a priori to be potential confounders.

For analyses using the Cox proportional hazards model, only sex was included in the model as a covariate because these analyses implicitly adjust for differences in follow-up time (ie, age at the last interview). For analysis of covariance models, both age at the last interview and sex were included as covariates in the model.

To determine the effects of parental MDD on grandchild outcomes, we performed the following series of analyses. First, we examined the association of parental depression with grandchild outcomes for families with and without grandparental MDD by separately fitting the modified Cox proportional hazards regression models and analysis of covariance models described previously (depending on whether the outcome is categorical or continuous) to each of these 2 groups as follows: grandchild outcome was considered to be the dependent variable, parental depression status was regarded as the predictor variable, and the age and sex of the grandchild were included as potential confounders. The analysis was stratified by grandparental MDD status to reflect the original design of the study. Next, to formally test if the association between parental depression and grandchild outcome varied with grandparental depression status, we performed the following analysis: a term representing the interaction between grandparental and parental depression status as well as a variable representing the main effect of grandparental depression status were included in the models, in addition to the variables described previously. If the interaction term was not found to be statistically significant, we concluded that the association between generation 3 outcome and generation 2 depression status did not vary with generation 1 depression status. Potential confounders of the association between parental MDD status and grandchild outcomes were handled as follows: variables that have previously been shown to be related to both parental MDD and grandchild diagnoses and functioning were entered into the models to determine whether the potential confounder explained the association between parental MDD and child outcomes in either of the 2 groups. The confounder variables include generation 2 demographics, generation 2 family risk factors, generation 2 disorders and functioning, and family environment while growing up.[27] Effects of parental characteristics other than parental MDD and their interaction with grandparental MDD status were explored in a similar manner.

RESULTS

DEMOGRAPHICS

Grandparents (n=47) (generation 1) in the depressed (high-risk) and nondepressed (low-risk) groups at the last interview did not vary by sex (58% female), age (mean age, 56 years at wave 3 because the first generation was not interviewed at wave 4), marital status (81.2% married), employment status (60% employed full-time), mean household income ($42 570), and mean number of children (3.7).

Offspring (n=86) (generation 2) did not vary by their parents' depression status, sex (64.8% female), age (mean age, 38 years), marital status (70.5% married), employment status (66.7% employed full-time), mean years of education (13.8 years), mean household income ($62 559), or mean number of children (2.1).

Grandchildren (n=161) (generation 3) did not differ by the grandparents' depression status or by sex (54% female) but did differ by age. Grandchildren from the low-risk group had a mean age of 10.7 years, and those from the high-risk group had a mean age of 13.8 years. All analyses were adjusted for age.

DIAGNOSES

After controlling for the age and sex of generation 3, grandchildren of depressed as compared with nondepressed grandparents had more than a 2-fold statistically significant increased risk of any anxiety disorder ($P<.03$). While the relative risks were elevated for many disorders in the grandchildren of depressed vs nondepressed grandparents, these results did not reach formal levels of significance (data available on request).

These results reflect the original design of the study but do not take into account the combined effect of the depression status of both grandparents (generation 1) and parents (generation 2) on the grandchildren (generation 3). Grandchildren with both depressed parents and depressed grandparents had the highest rates of psychopathology, with 59.2% having at least 1 psychiatric dis-

Table 1. Cumulative Rates of Disorders and Impairment in Grandchildren (Generation 3) by Parental (Generation 2) and Grandparental (Generation 1) Diagnoses*

	Neither Grandparent Had MDD				1 or More Grandparents Had MDD				
	Parental MDD				Parental MDD				
	No	Yes	Relative Risk (95% CI)	*P* Value	No	Yes	Relative Risk (95% CI)	*P* Value	Interaction† *P* Value
No. of grandchildren	35	25			30	71			
Grandchild diagnoses, No. (%)									
Any mood disorder	4 (11.4)	1 (4.0)	0.2 (0.01-3.8)	.27	3 (10.0)	22 (30.1)	2.80 (0.74-10.55)	.12	.10
MDD	3 (8.6)	0	0	1.00	2 (6.7)	13 (18.3)	2.33 (0.49-11.08)	.28	NE
Dysthymia	1 (2.9)	0	0	1.00	1 (3.3)	11 (15.5)	4.02 (0.44-36.97)	.21	NE
Any anxiety	5 (14.3)	3 (12.0)	0.8 (0.20-3.2)	.75	3 (10.0)	32 (45.1)	4.98 (1.38-17.95)	.01	.05
Phobias	4 (11.4)	2 (8.0)	0.7 (0.16-3.3)	.67	3 (10.0)	22 (31.0)	3.23 (0.85-12.32)	.08	.09
Any disruptive disorder	5 (14.3)	3 (12.0)	0.9 (0.19-4.3)	1.00	1 (3.3)	19 (26.8)	7.89 (0.94-66.35)	.05	.09
Any substance abuse	1 (2.9)	0	0	1.00	1 (3.3)	10 (14.1)	3.55 (0.50-25.34)	.20	<.001
Any disorder	10 (28.6)	5 (20.0)	0.6 (0.16-1.9)	.33	4 (13.3)	42 (59.2)	5.40 (1.93-15.12)	.002	.003

	Mean (SE)	Mean (SE)	F	*df*	*P* Value	Mean (SE)	Mean (SE)	F	*df*	*P* Value	Interaction *P* Value
C-GAS score‡	81.8 (1.6)	77.6 (2.0)	3.60	1	.06	84.3 (1.3)	76.8 (1.4)	16.57	1	<.001	.41

Abbreviations: C-GAS, Children's Global Assessment Scale; CI, confidence interval; MDD, major depressive disorder; NE, not estimable.

*The analysis is based on 161 generation 3 participants. Diagnoses are at the probable or definite level of certainty. Possible nonindependence of outcomes of family members was adjusted using the software package SUDAAN. The relative risk was adjusted for the sex of the grandchild using Cox proportional hazards regression models. The C-GAS score was adjusted for the age and sex of the grandchild using analysis of covariance models.

†Interaction between grandparental MDD and parental MDD.

‡Higher C-GAS scores denote better functioning.

order (**Table 1**). These grandchildren, the group hypothesized to be at the highest risk, as compared with grandchildren with a depressed grandparent but without a depressed parent, had more than a 5-fold increased risk of an anxiety disorder ($P=.01$), more than a 7-fold increased risk of disruptive disorder ($P=.056$), and more than a 5-fold increased risk of any psychiatric disorder ($P=.002$). The risk of a mood disorder is also elevated in this group (more than 2-fold) but did not reach a formal level of significance.

In the low-risk group (defined as having a nondepressed grandparent), grandchildren with a depressed parent were at no greater risk for any of the diagnoses, as compared with grandchildren whose parents were not depressed. This suggests that nonfamilial parental depression was not a risk factor for psychopathology in grandchildren in this group (Table 1). The effect of parental depression on grandchild outcomes was moderated by the depression status of their grandparents. A formal test of this hypothesis is given by the significance of the interaction term indicated by the *P* value shown in the right-most column of Table 1. This hypothesis is supported for anxiety disorders and any disorder and shows a trend for the other disorders.

These highest-risk grandchildren also were the most impaired, as indicated by lower C-GAS scores. However, there was no significant interaction; instead, there was a main effect for the depression status of the parents (generation 2) on grandchild functioning. Grandchildren with a depressed parent, regardless of their grandparents' depression status, had poor functioning (lower C-GAS scores), which was highly significant ($P<.001$)in the grandchildren from the high-risk group and marginally significant ($P=.07$) in the low-risk group. Overall, these findings suggest that a depressed parent has an impact on his or her child's functioning, even if the parent's depression is not familial. While nonfamilial parental depression (ie, depression in generation 2 but not in generation 1) resulted in poorer functioning in the grandchildren, it did not transmit a specific diagnosis to the grandchildren.

DEPRESSION AND IMPAIRMENT IN PARENTS

The original probands, the grandparents, were selected to have moderate to severe depression. They had sought pharmacologic treatment for depression in a tertiary care center. While many of the second-generation participants had moderate or severe depression, some of these parents were only mildly ill. To determine the impact of the severity of the depression in the second generation on their offspring, the grandchildren, we divided the parents (generation 2) by the impairment status of their MDD based on their mean GAS score from each of the 4 waves, with 70 and below considered lower functioning. Previous research has suggested that impairment at a GAS score of 70 or lower is an indication of impairment.[48,49] The grandchildren of the second-generation parents, who had an MDD with impairment, were compared with those who did not have an MDD with impairment, ie, they either had no MDD or had MDD with no impairment as reflected in a GAS score of 70 or higher.

Table 2 shows that adding impairment criteria to the MDD diagnosis in the second generation achieved better separation of the grandchildren's diagnosis by the previous generation. Now 67.6% of the grandchildren with 2 generations affected with depression had a psychiatric disorder. Relative risks ranged from nearly a 2-fold to more than a 6-fold increased risk for disorders in the grandchildren in the highest-risk group, as compared with those with a depressed grandparent but a nondepressed par-

Table 2. Cumulative Rates of Disorders and Impairment in Grandchildren (Generation 3) by Grandparental (Generation 1) Diagnosis and Parental (Generation 2) Depression Status With Impairment*†

	Neither Grandparent Had MDD					1 or More Grandparents Had MDD				
	Parents					Parents				
	No MDD With Impairment	MDD With Impairment	Relative Risk		*P* Value	No MDD With Impairment	MDD With Impairment	Relative Risk		*P* Value
No. of grandchildren	47	13				64	37			
Grandchild diagnosis, No. (%)										
Any mood disorder	4 (8.5)	1 (7.9)	.68		.72	10 (15.6)	15 (40.5)	2.42		.04
MDD	3 (6.4)	0	0		1.00	6 (9.4)	9 (24.3)	2.08		.13
Dysthymia	1 (2.1)	0	0		1.00	3 (4.7)	9 (24.3)	3.93		.05
Any anxiety	5 (10.6)	3 (23.1)	2.04		.98	15 (23.4)	20 (54.1)	1.00		.90
Phobia	4 (8.5)	2 (15.4)	1.71		.82	8 (12.5)	17 (45.9)	3.82		.006
Any disruptive disorder	5 (10.6)	3 (23.1)	2.62		.38	5 (7.8)	15 (40.5)	6.05		.001
Any substance abuse	1 (2.1)	0	0		1.00	3 (4.7)	8 (21.6)	2.81		.12
Any disorder	10 (21.3)	5 (38.5)	1.64		.54	20 (31.3)	25 (67.6)	2.90		.003
	Mean (SE)	Mean (SE)	F	*df*	*P* Value	Mean (SE)	Mean (SE)	F	*df*	*P* Value
C-GAS score	81.8 (1.3)	75.2 (2.9)	5.69	1	.02	83.1 (1.2)	72.4 (2.0)	20.75	1	<.001

Abbreviations: C-GAS, Children's Global Assessment Scale; MDD, major depressive disorder.

*Diagnoses are at the probable or definite level of certainty. Relative risk was adjusted for the sex of the grandchild using Cox proportional hazards regression models. The C-GAS score was adjusted for the age and sex of the grandchild using analysis of covariance models. The SUDAAN software package was used to take account of a clustering effect within a family.

†The impairment status in generation 2 is based on GAS scores: those with GAS scores of 70 or lower were considered generation 2 with impairment. Those who had GAS scores higher than 70 and MDD were not considered depressed and were combined with generation 2 participants who were not depressed.

ent. Now mood disorders were significant. There was more than a 2-fold increased risk of a mood disorder in the grandchildren in the highest risk group ($P=.03$). The rates of dysthymia ($P=.03$), anxiety ($P=.004$), phobias ($P=.002$), and any disruptive disorders ($P=.001$) were now all significant in the grandchildren from the highest-risk group. The sample in the low-risk groups was too small to draw any conclusion. However, there was a significant effect on functioning (C-GAS scores) in the grandchildren from the low-risk group. If their parents had an impairing depression, the grandchildren were also more impaired. The same results were seen in the grandchildren from the high-risk groups.

POTENTIAL CONFOUNDERS

We examined factors that could explain the differential association between parental and grandparental depression and grandchild outcome. We selected the factors based on our analysis of the previous generation.[26,27] We first screened for potential confounders by determining whether factors hypothesized to be related to childhood diagnosis differed between the 4 groups, characterized by grandparental/parental depression status. The potential confounding factors examined were the characteristics of the second generation listed in **Table 3**, including the second-generation demographics, family risk factors, comorbid diagnosis, overall functioning, and IQ. We also included the family environment of the second generation while they were growing up. We found that there was significant variation in the distribution of the following factors across the 4 groups: family income, anxiety disorders, and impairment in the second generation and the family environment of the second generation while growing up.

Based on these results, we performed a multivariate analysis with generation 3 diagnoses as the outcome and both generation 2 depression status and each of the significant potential confounding variables as independent variables. Because of the extremely low prevalence of diagnoses in the grandchildren from the low-risk groups and the fact that no significant association was found between generation 2 MDD and generation 3 outcomes in these groups (except for generation 3 functioning), the analysis was restricted to the high-risk groups, the grandchildren with depressed grandparents. Functioning in the grandchildren of both depressed and nondepressed grandparents was also analyzed.

The question asked was whether these potential confounders explained, in whole or in part, the association between grandchild outcome and parental MDD. Results of this analysis showed that the inclusion of the potential confounding variables did not have a significant impact on the strength of the association (as measured by the relative risk) between MDD diagnosis in the second generation and grandchild outcomes in the high-risk groups. The results are not shown here but are available on request. The only exception was phobias in the grandchildren, where the inclusion of generation 2 family income and generation 2 functioning decreased the significant association between generation 3 phobia and generation 2 depression (relative risk, 3.2) to a nonsignificant one (relative risk, 2.1 and 2.0, respectively). The significant association between generation 2 MDD and generation 3 functioning in the lower-risk groups, as measured by the β coefficient in the regression model, became nonsignificant with the inclusion of generation 2 family income and generation 1 parent-child discord, respectively.

Table 3. Demographic Characteristics, Family Risk Factors, Psychiatric Disorders, Functioning, and Family Environment While Growing Up in Parents (Generation 2) by Parental (Generation 2) and Grandparental (Generation 1) Depression Status*

	Neither Grandparent Had MDD		1 or More Grandparents Had MDD		
	Parental MDD		Parental MDD		
	No	Yes	No	Yes	Statistics
No. of parents	17	11	17	41	
Generation 2 demographics	Group 1	Group 2	Group 3	Group 4	
Age at interview, y, mean (SD)	37.0 (4.4)	38.7 (5.0)	38.1 (10.0)	40.2 (5.4)	$F = 1.19$, $P = .32$
Sex, No. (%) female	10 (58.8)	7 (63.6)	9 (52.9)	27 (65.9)	$\chi^2_3 = .93$, $P = .82$
Family income, US $, mean (SD)	73125 (25811)	54000 (30983)	70312 (31170)	54714 (27995)	$F = 3.25$, $P = .03$
Work, No. (%)					
Full time	12 (70.6)	9 (81.8)	11 (68.8)	25 (61.0)	$\chi^2 = 2.26$, $P = .90$
Part time	2 (11.8)	1 (9.1)	3 (18.8)	8 (19.5)	
Irregular/no work	3 (17.6)	1 (9.1)	2 (12.5)	8 (19.5)	
Marital status, No. (%)					
Single	3 (17.6)	1 (9.1)	0	5 (12.2)	$\chi^2_9 = 9.47$, $P = .40$
Married	12 (70.6)	7 (63.6)	14 (87.5)	26 (63.4)	
Separated/divorced	2 (11.8)	2 (18.2)	2 (12.5)	10 (24.4)	
Widowed	0	1 (9.1)	0	0	
Generation 2 family risk factors, No. (%)					
Divorce	1 (5.9)	2 (18.2)	2 (11.8)	10 (25.0)	$\chi^2_3 = 3.5$, $P = .32$
Affectionless control (mother)	6 (50.0)	4 (57.1)	3 (30.0)	9 (37.5)	$\chi^2_3 = 1.77$, $P = .62$
Affectionless control (father)	12 (100)	6 (85.7)	9 (81.8)	19 (79.2)	$\chi^2_3 = 2.89$, $P = .41$
Poor marital adjustment	6 (37.5)	7 (70.0)	9 (56.3)	24 (61.5)	$\chi^2_3 = 3.50$, $P = .32$
Low family cohesion	6 (31.3)	3 (30.0)	9 (56.3)	17 (43.6)	$\chi^2_3 = 2.73$, $P = .44$
No. of children	2.2 (1.0)	2.3 (1.3)	1.6 (0.79)	1.7 (0.74)	$F = 2.1$, $P = .10$
Generation 2 disorders and functioning					
Anxiety disorder, No. (%)	3 (17.6)	7 (63.6)	7 (41.2)	25 (62.5)	$\chi^2_3 = 11.0$, $P = .01$
Alcohol abuse, No. (%)	1 (5.9)	4 (40.0)	3 (35.3)	15 (37.5)	$\chi^2_3 = 2.9$, $P = .13$
Drug use, No. (%)	3 (17.6)	1 (10.0)	3 (23.1)	13 (33.3)	$\chi^2_3 = 1.3$, $P = .74$
Substance use, No. (%)	3 (17.6)	5 (45.5)	6 (23.1)	10 (25.0)	$\chi^2_3 = 2.9$, $P = .41$
Average GAS score, mean (SD)	83.2 (5.5)	73.2 (7.7)	75.5 (13.0)	70.5 (8.8)	$F = 7.81$, $P<.001$
IQ (PPVT), mean (SD)	97.9 (14.1)	96.9 (9.3)	86.4 (12.6)	96.9 (13.1)	$F = 1.6$, $P = .20$
Generation 2's family environment while growing up, No. (%)					
Generation 1 divorce	0	1 (9.1)	3 (17.6)	16 (42.1)	$\chi^2_3 = 11.9$, $P<.001$
Generation 1 and generation 2 discord	2 (11.8)	0	3 (17.6)	16 (42.1)	$\chi^2_3 = .11.6$, $P = .009$
Generation 1 poor marital adjustment	0	3 (37.5)	12 (80.0)	16 (57.1)	$\chi^2_3 = 21.3$, $P<.001$
Generation 1 low family cohesion	6 (35.3)	6 (54.5)	9 (60.0)	20 (69.0)	$\chi^2_3 = 5.4$, $P = .17$

Abbreviations: GAS, Global Assessment Scale; MDD, major depressive disorder; PPVT, Peabody Picture Vocabulary Test.

*The analysis is based on 161 generation 3 participants using analysis of variance for continuous outcomes (F statistics) and χ^2 analysis for dichotomous outcomes (χ^2 statistics). Numbers may vary because of missing data in some categories. Four groups are based on generation 1 and generation 2 MDD status: group 1 = neither generation 1 nor generation 2 depressed, group 2 = generation 1 not depressed but generation 2 depressed, group 3 = generation 1 depressed but generation 2 not depressed, and group 4 = both generation 1 and generation 2 depressed.

COMMENT

The major findings of this 3-generation study are the moderating effects of grandparental depression on the association between parental depression and grandchild diagnoses, the importance of impairment in depression criteria, and the stability of the finding that anxiety disorders are an early sign of psychopathology in children from depressed families. Nearly 60% of the grandchildren (mean age, 12 years) with 2 generations of depression already had some psychiatric disorders. The increase in anxiety disorder in the grandchildren from high-risk grandparents was consistent with the findings from their parents when they were the same age as the grandchildren.[13,50] Anxiety disorders in children as the precursor of later depression in adolescents and young adulthood have been shown in our data on the previous generations,[50] in community studies of children[19,24,51] and of adults,[20,22,25] and in other high-risk studies.[21] Taken together, these findings suggest that anxiety can be viewed as an age-dependent expression of the same underlying disorder. A large number of the grandchildren in our study were prepubertal. If anxiety is a precursor of depression, we expect that the risk for depression will begin to increase in adolescence in the high-risk grandchildren who are showing prepubertal anxiety.

Nonfamilial MDD (ie, depression in the second generation with nondepressed grandparents) was of low prevalence and transmitted impairment but not specific psychiatric disorder to the grandchildren. We found, previously, that offspring from low-risk families who became depressed had an older age at onset, and their MDD was associated with family risk factors.[26,27] Inclusion of parents

only with moderate to severe depression, as measured by impairment, significantly increased the number of grandchildren with mood disorder in the high-risk group. Impairment added to MDD criteria has been shown to increase familial aggregation in twin[52] and family[28] studies. Our findings confirm that impairment should be considered an additional criteria for MDD when looking at familial transmission. Impairment in a depressed parent may decrease the age at onset of MDD in the next generation, and the offspring of parents with less impairing MDD may have an older age at onset of MDD.

This study has limitations. We only focused on participants from the original sample with 3 generations available. Therefore, the sample is too small to test the effect of sex and age between the generations or the effects of multiple risk factors. The original probands were selected from an ambulatory depression clinic, so results may not be generalizable to community samples. We did not have a nonaffective psychiatric control group in the original study. We had multiple comparisons and post hoc comparisons. The results, however, have been consistent across generations, and the post hoc analyses using impairment criteria were guided by previous findings in separate family studies.[28] The grandchildren are still young and have not fully passed through the age of risk.

When we planned the study, there were no studies of children of depressed patients. There were few clinical measures for assessing children, and there were no epidemiologic studies of youths using clinical diagnostic criteria. There was still a question about whether children had sufficient ego development to become depressed. It took years to collect data on 3 generations at risk for depression. We would recommend a different epidemiologic approach to a 3-generation study. We would select probands from a community sample and would include varying severities of depression. We would include 2 control groups: another psychiatric control condition and a normal control. We would begin with probands from the second generation who were old enough to have children but young enough to have living parents. With generation 2 as the probands, we would assess their parents (generation 1) and their children (generation 3). Longitudinal assessment of the youngest generation, the grandchildren, would still be important to see the sequence and early signs of disorder unfolding. It would be unnecessary to observe the older generations extensively because most would have passed through the age at first onset of MDD. This design would provide 3 generations without a wait and would allow testing of hypotheses about effect on transmission of severity and specificity of major depression. No study design is without limitations. This proposed design may miss episodes of depression in generation 1 and generation 2 because of the use of lifetime recall and could thus increase false negatives. A similar study is under way (Peter Lewinsohn, PhD, written communication, April 2004) and even in the context of these limitations may provide an opportunity to see if our findings replicate.

Our findings have clinical and research implications. Obtaining family history of depression and its severity and impairment in previous generations should help to identify persons at high risk for psychopathology at a young age. There are relatively simple family history screens available to obtain this information.[53] Children with 2 generations of MDD should be identified and considered for treatment if they develop anxiety disorders. A study has yet to be done to test whether treating anxiety disorders or possibly disruptive disorders in prepubertal youths from high-risk families will delay or even prevent the onset of MDD later. Delaying the onset of MDD in adolescence when choices about education, work, and life partners are being formed could have an impact on reducing the disability of MDD. The high rate and early onset of illness in the grandchildren from 2 generations of depression suggest that this group, as contrasted with the low-risk groups, could provide promising contrasts for neuroimaging, genetic, and other biologic studies. In collaboration with Bradley Peterson, MD, we are now conducting functional and anatomical magnetic resonance imaging studies of the 3 generations to develop hypotheses about brain endophenotypes. Our findings, if replicated, also point out the heterogeneity of major depression and the potential confounding in biological studies of including depressed patients without obtaining a detailed family history. Our findings also suggest that nonimpairing MDD may be a phenocopy and that impairment criteria should continue to be used in genetic studies of depression.

Caspi et al[54] have shown that a functional polymorphism in the promoter region of the serotonin transporter gene moderated the effect of life events on developing depression. They showed that the effects of the genes are conditional on exposure to environmental risks. Our findings suggest another point of heterogeneity in depression. The development of depression in a young person may be conditional on both a parent and a grandparent having a moderate to severe depression. These effects may be independent of environmental confounders. Whether these generations also carry the functional polymorphism is an interesting, unanswered question. Because parents may provide both high-risk genes and a high-risk rearing environment, disentangling psychosocial and biological factors mediating the transmission of risk across generations is a challenge.

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