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A 30-Year Study of 3 Generations at High Risk and Low Risk for Depression

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Abstract

IMPORTANCE—The increased risk of major depression in the offspring of depressed parents is well known. Whether the risk is transmitted beyond 2 generations is less well known. To our knowledge, no published study with direct interviews of family members and the generations in the age of risk for depression has evaluated beyond 2 generations. This information is important for detecting individuals at highest risk who may benefit from early intervention.

OBJECTIVE—To examine the familial aggregation of psychiatric disorder and functioning in grandchildren by their biological parents' and grandparents' depression status.

DESIGN, SETTING, AND PARTICIPANTS—Longitudinal retrospective cohort family study of 251 grandchildren (generation 3 [mean age, 18 years]) interviewed a mean of 2.0 times and their biological parents (generation 2) interviewed a mean of 4.6 times and grandparents (generation 1) interviewed up to 30 years. The study dates were January 1982 (wave 1) to June 2015 (wave 6).

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MAIN OUTCOMES AND MEASURES—Cumulative rates of psychiatric disorders and functioning collected for all generations by clinically trained interviewers and best-estimate diagnosis made blind to diagnoses in members of previous generations.

RESULTS—There were 91 families (G1) in the original sample, of whom 77 were eligible for inclusion (had a grandchild older than 5 years), and 80.5% (62 of 77) participated in the study. When first examining only 2 generations, the biological children (generation 3) of depressed compared with nondepressed parents (generation 2) had 2-fold increased risk for major depressive disorder (MDD) (hazard ratio [HR], 2.02; 95% CI, 1.08–3.79; $P = .03$), any disruptive disorder (HR, 1.70; 95% CI, 1.05–2.75; $P = .03$), substance dependence (HR, 2.96; 95% CI, 1.24–7.08; $P = .01$), any suicidal ideation or gesture (HR, 2.44; 95% CI, 1.28–4.66; $P = .007$), and poor functioning ($F = 38.25$, $P < .001$). When 3 generations were examined stratified by parental and grandparental depression status, association of a parent's MDD on the grandchild's MDD but not other disorders varied with the grandparent's depression status: grandchildren with both a depressed parent and grandparent (n = 38) were at highest risk for MDD. Among grandchildren without a depressed grandparent, those with (n = 14) vs without (n = 74) a depressed parent had overall poorer functioning ($F = 6.31$, $P = .01$) but not higher rates of any of the disorders. Potential confounding variables did not have a meaningful effect on the association between grandchild outcomes and parental or grandparental depression.

CONCLUSIONS AND RELEVANCE—In this study, biological offspring with 2 previous generations affected with major depression were at highest risk for major depression, suggesting the potential value of determining family history of depression in children and adolescents beyond 2 generations. Early intervention in offspring of 2 generations affected with moderate to severely impairing MDD seems warranted. The specificity of the transmission of depression across 3 generations may make this group a homogeneous sample for biological marker studies.

The increased risk of psychiatric disorders in the offspring of depressed parents is well known.[1–7] Whether this risk is transmitted beyond 2 generations is less well known. This information is important for detecting individuals who may benefit from early intervention and may be candidates for biological marker studies. There are no published studies of depression examining 3 generations with grandchildren in the age of risk for depression and with direct interviews of all family members.[4,5,8,9]

We have been following up a cohort of depressed and nondepressed probands and their biological offspring for approximately 30 years. There have been 6 waves of interviews by clinically trained interviewers who were unaware of the diagnosis of previous generations at 0, 2, 10, 20, 25, and 30 years.[10] The offspring themselves have had children. We began assessing the third generation—the grandchildren—at the 10-year follow-up when they were 6 years and older. At that time, there were 90 grandchildren, with a mean age of 11 years.[11,12] At the 20-year follow-up, there were 161 grandchildren, with a mean age of 12 years.[13,14] A large number were prepubertal and had not yet entered the age of risk for major depression. Despite their young age, we found high rates of psychiatric symptoms among the grandchildren with 2 previous generations affected.

The additional follow-up data presented herein at 30 years provide information on a larger and older sample of grandchildren. More grandchildren were born or became old enough to

be interviewed for the first time, and more of the grandchildren who had previously been assessed had entered the age of risk. There are now 251 grandchildren (interviewed a mean of 2.0 times), and their mean age is 18 years. Based on previous findings, we hypothesized that the highest rate of major depression would be in grandchildren with both a parent and grandparent with major depressive disorder (MDD).

Methods

In the original study, generation 1 (G1) probands with moderate to severely impairing MDD were outpatients receiving medication for depression. Nondepressed probands were selected from an epidemiologic sample in the same community and had no lifetime history of psychiatric illness, as determined by several interviews. The procedures and training remained similar across the waves to avoid variance in the methods.[12–16] For generation 3 (G3), high risk was defined as having 1 or more grandparents with MDD, and low risk was defined as having no grandparents with MDD. Generation 1 were all of European white race/ethnicity to reduce heterogeneity for future genetic studies, as was the custom when the study began. All interviews were approved by the Institutional Review Board of the New York State Psychiatric Institute. All adults provided written informed consent. For minors, the parent provided written informed consent, and the child provided verbal assent.

Assessments

The assessments described previously[12–16] are summarized herein. The diagnostic interview across all waves was the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L) for adults,[17] and the Kiddie-SADS child version modified for *DSM-IV* for individuals between 6 and 17 years old.[18,19] The Kiddie-SADS-e[18] was used in wave 3, and the Kiddie-SADS–PL version[19] was used subsequently in waves 4 through 6. Final diagnoses were obtained using a best-estimate procedure (see the eMethods in the Supplement for more details). Individuals were rated at each wave on the Global Assessment Scale (GAS)[20] or the child version of the scale (Children's Global Assessment Scale[21]) if they were younger than 18 years. The GAS, scored from 0 to 100 points, provides an overall estimate of current functioning, with higher scores denoting better functioning. To ensure similar severity thresholds for MDD in both generation 2 (G2) and G1, we applied an impairment criterion to G2 MDD diagnoses based on the individual's mean GAS score across waves, with 70 or below indicating moderate to severe MDD.[22] Parents and children completed the Parental Bonding Instrument,[23] which assesses care and protection or control in parenting behavior. Affectionless control on the Parental Bonding Instrument is defined as a combination of overprotection and low care, as determined by published cutoff scores. Cronbach α was .85 for the care sub-scale and .84 for the protection subscale.

Statistical Analysis

Differences in demographic characteristics of grandparents, parents, and grandchildren by grandparent's MDD status were examined by modeling each characteristic as the dependent variable in a regression model, with grandparental MDD as the independent variable. We specified the outcome as binary for sex and marital status, as ordinal for educational attainment and employment status, and as continuous for personal income, number of

children, number of interviews, and all age variables. These analyses were performed by applying a generalized estimating equation (GEE) approach[24] by means of a procedure (GENMOD in SAS, version 9.4, SAS Institute Inc[25]) to adjust for potential nonindependence of outcomes for offspring from the same family.

To account for unequal follow-up times among grandchildren, cumulative lifetime rates of grandchild diagnoses were estimated by means of the Kaplan-Meier method.[26] Effects of parental MDD on grandchild diagnoses were determined by examining the association between parental depression and grandchild diagnoses for families with and without grandpa-rental MDD by separately fitting modified Cox proportional hazards regression models[27] to adjust for intracluster correlation. We used the marginal Cox-type analysis approach by Lee et al[28] to estimate the regression parameters in this Cox model using a robust sandwich covariance matrix estimate to account for the intracluster dependence[29] to each of the 2 groups as follows: grandchild outcome was considered to be the dependent 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. To formally test if the association between parental depression and grandchild outcome varied with grandparental depression status, we included a term representing the interaction between grandparental and parental depression status, as well as a variable representing the main effect of grandparental depression status 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 G3 and G2 depression status did not vary with G1 depression status and fitted similar models with only main effects of parental and grandparental MDD status as independent variables. When the G3 outcome was a continuous variable (eg, the mean GAS score), we used linear regression analysis in a GEE framework to estimate the mean differences between groups, while adjusting for intracluster correlation and potential confounding variables.[27] The age and sex of offspring were considered a priori to be confounding variables and were retained in every model. These analyses were performed using the same GEE approach as described above to adjust for correlation within families.

Potential confounders of the association between parental MDD status and grandchild outcomes were handled as follows. Variables that have previously been shown in the literature to be risk factors for grandchild diagnoses and were found to be differently distributed across the 4 parent and grandparent groups using χ^2 tests were entered into the models to determine whether these potential confounders explained the association between parental MDD and grandchild outcomes. The potential confounder variables reflect other G2 disorders and G3 family environment when growing up.[30–32] If the inclusion of a potential confounder in a regression model changed the crude variable measuring association by 10% or more, we considered it a confounder, and we judged whether G2 MDD was still an important predictor of the G3 outcome by comparing its crude, adjusted hazard ratios (HRs), and 95% CIs.[33]

Results

Sample

There were 91 families (G1) in the original sample, of whom 77 were eligible for inclusion (had a grandchild older than 5 years), and 80.5% (62 of 77) participated in the study. Participation rates among families did not vary by G1 depression status. These 62 families had 371 biological grandchildren (G3). Sixteen G3 were too young to be interviewed, 3 died, and 1 was later found not to be biologically related to the parent (G2), resulting in 351 eligible G3, of whom 71.5% (251 of 351) participated. Their participation did not vary by G1 depression status.

Demographics

On entry to the study, G1 grandparents (n = 62) had a mean (SD) age of 48.1 (7.5) years, 59.7% (37 of 62) were female, 79.7% (47 of 59) were married, and the median educational attainment was a high school diploma (Table 1). None of these characteristics differed by depression status. Of the G2 parents (n = 127), 59.8% (76 of 127) were female, and the mean (SD) age at first interview was 20.2 (6.4) years. At the time of last interview, 73.3% (88 of 120) were married, the median educational attainment was beyond high school, and most (68.3% [82 of 120]) were employed full time. Parents were interviewed on average 4.6 times, and their mean (SD) age at last interview was 46.3 (8.3) years. The only G2 characteristic that differed by G1 risk group was the number of children: high-risk G2 had fewer children than low-risk G2 (mean [SD], 2.1 [0.9] vs 2.7 [1.1], $P = .007$).

The G3 grandchildren (n = 251) did not differ by G1 risk group on sex (52.2% [131 of 251] were female), educational attainment (one-third graduated from high school and one-third completed some college), number of interviews (mean [SD], 2.0 [1.0]), or age at first interview (mean [SD], 12.6 [5.1] years) or last interview (mean [SD], 18.2 [7.3] years) (Table 1). Three grandchildren (G3) in the high-risk group had died.

Diagnosis in Grandchildren (G3)

The original analysis of the parents (G2) by their proband parents (G1) at baseline and 2, 10, 20, and 30 years found increased rates of MDD (approximately 3-fold risk) and other disorders in the G2 offspring of high-risk vs low-risk G1 parents.[12,13] These analyses did not take into account any generations before G1 (eg, great-grandparents).

In our first analysis, we examined only 2 generations. We compared the grandchildren (G3) by their parents' (G2) depression status to determine if results in the next generation were similar to results in the previous generation (Table 2). We found an increased risk of MDD, any mood disorder, any disruptive disorder, any substance dependence, any disorder, and any suicidal ideation or gesture, with increased impairment in the offspring, in this case, G3 of depressed vs nondepressed parents (G2). We found no cases of bipolar disorder or schizophrenia in either group. These results showed that G3 with depressed parents had 2-fold increased risk of MDD, which is identical to what was seen previously in the G1 to G2 transmission.[12,13] When we controlled for G1 high-risk or low-risk status, the HRs changed little, indicating no main effect of G1 MDD on any of the G3 outcomes.

Taking into account all 3 generations, Table 3 summarizes the association between parental (G2) MDD and grandchildren's (G3) outcomes stratified by grandparents' MDD status. Before undertaking this analysis, we evaluated the distributions of age, sex, and educational attainment in the 4 groups and found no significant differences (eTable 1 in the Supplement).

Of note in the 4-group analysis was the inclusion of few depressed G2 parents (n = 6) in the low-risk group, reflecting the low rate of nonfamilial depression. Among the 88 grandchildren in the low-risk group, rates of disorders were generally similar regardless of parental MDD status. However, low-risk grandchildren with a depressed parent (n = 14) were functioning more poorly than those without a depressed parent (n = 74) ($P = .01$).

Grandchildren with both a depressed parent and depressed grandparent had the highest rate of psychiatric disorders, with 71.1% (27 of 38) having at least 1 disorder. Among the 163 grandchildren with a depressed grandparent, those with (vs without) a depressed parent had approximately 3 times the risk of MDD (HR, 2.70; 95% CI, 1.30–5.63; $P = .008$), any mood disorder (HR, 2.98; 95% CI, 1.61–5.51; $P < .001$), and substance dependence (HR, 3.14; 95% CI, 1.19–8.27; $P = .02$), as well as more than twice the risk of any suicidal ideation or gesture (HR, 2.60; 95% CI, 1.41–4.79; $P = .002$) and almost twice the risk of any anxiety disorder (HR, 1.61; 95% CI, 1.01–2.56; $P = .04$).

Whereas grandparental MDD status did not have a main effect on grandchild outcomes, there was a significant interaction effect (grandparental MDD status × parental MDD status) on grandchildren's risk for MDD ($P = .04$) and any mood disorder ($P = .001$) (Table 3). Therefore, the main effect seen in Table 2 of G2 MDD on G3 MDD and any mood disorder (HRs, approximately 2.00) depicts an "averaged" effect of G2 on G3.

Not taking into account G1 status, Table 2 summarizes, as before, that the offspring of moderate to severely depressed parents were at high risk for MDD and other disorders. In these analyses taking G1 status into account, we showed that embedded within the previous analysis was a group at highest risk, specifically for MDD (ie, the grandchildren with 2 previous generations affected). The rates of any mood disorder and MDD in the grandchildren were largely accounted for by the G3 from 2 generations affected with MDD.

We showed this result formally also. The role of G1 MDD is such that for high-risk grandchildren the HRs reflecting the significant effects of G2 MDD on G3 MDD and any mood disorder are 2.70 (95% CI, 1.30–5.63) and 2.98 (95% CI, 1.61–5.51), respectively, whereas there is no significant G2 effect for low-risk grandchildren, with HRs of 0.89 (95% CI, 0.50–1.59) and 0.75 (95% CI, 0.44–1.30), respectively.

We found no group differences in reported medical problems, but we found 3 deaths in the grandchildren, all from unnatural causes, including vehicular accident (at age 11 years), drug-related death (at age 22 years), and death in an infant from unknown reason. All of these deaths were in G3 with 2 previous generations affected with depression. There were no deaths from any other cause in the G3.

Potential Confounders

Factors that might explain the differential association between parental and grandparental depression and grandchild outcome were examined as potential confounders. The variables were identified based on results of our group's previous analyses of family risk factors and their effect on the rate of depression.[14,31,32] We included variables that were available for most grandchildren and that were positive for at least 1 member in each of the 4 grandchild groups defined by G1 and G2 MDD status. Table 4 summarizes the differential distribution of these risk factors across the 4 parent and grandparent groups. There was statistically significant variation in the distributions of the 2 risk factors of G2 substance abuse or dependence and G3 parental separation or divorce. These risk factors were not all concentrated in the highest-risk group (ie, G3 with a depressed parent and grandparent). For instance, G2 substance abuse or dependence and G2 parental separation or divorce were somewhat more prevalent among grandchildren (G3) of low-risk compared with high-risk depressed parents (G2). For most of the G3 outcomes, we tested for confounding in models collapsed across G1 MDD status because the effect of G2 MDD on these outcomes was found not to differ by G1 MDD. However, for the G3 MDD and any mood disorder outcomes, we stratified the models by G1 MDD status because of the significant interaction between G2 MDD and G1 MDD (Table 3).

Some of the significant associations between G2 MDD status and the G3 outcome summarized in Table 3 were at least partially confounded by G2 parental separation or divorce or G2 substance abuse or dependence. As summarized in eTable 2 in the Supplement, the association between G2 MDD status and any G3 disruptive disorder (crude HR, 1.70; 95% CI, 1.05–2.75) was confounded by G2 parental separation or divorce and substance abuse or dependence (adjusted HRs, 1.87 [95% CI, 1.08–3.23] and 1.56 [95% CI, 0.96–2.56], respectively), and the association between G2 MDD status and G3 substance dependence (crude HR, 2.96; 95% CI, 1.24–7.08) was confounded by G2 parental separation or divorce and substance abuse or dependence (adjusted HRs, 2.56 [95% CI, 0.81–8.08] and 2.58 [95% CI, 1.13–5.58], respectively). In addition, among high-risk G3 only, the association between G2 MDD status and G3 any mood disorder (crude HR, 2.98; 95% CI, 1.61–5.51) was confounded by G2 parental separation or divorce (adjusted HR, 2.01; 95% CI, 0.99–4.07). Overall, adjusting for parental separation or divorce and substance abuse or dependence in the models that warranted adjustment did not substantially diminish the effect of parental MDD on grandchild outcomes.

Discussion

The additional 10 years of follow-up with a larger and older sample of grandchildren again showed that the highest-risk grandchildren with 2 generations affected with MDD had high rates of a variety of psychiatric disorders. However, the specificity of transmission of MDD between generations becomes clearer. Only the association between parental and grandchild depression is moderated by grandparent major depression. When examining only 2 generations—the G3 offspring of their G2 parents—we replicated previous findings by us and others[2–7] of an increased risk of psychiatric disorders, mainly any mood disorder, substance abuse or dependence, any suicidal ideation or gesture, and poorer functioning in

the grandchildren (G3) of their depressed parents (G2). However, in our original analysis, we did not take into account the clinical status of the parents of G1, who would have been the grandparents of G2. We and others, to our knowledge, had not collected information beyond 2 generations when the study began.

With the use of data from all 3 generations, it became clear that embedded within the high-risk sample was a group of children at extremely high risk for MDD, namely, the grandchildren with 2 previous generations affected with MDD. This finding suggests the value of screening for MDD beyond 2 generations.

The 3 deaths from unnatural causes, along with the increase in any suicidal ideation or gesture in the highest-risk grandchildren, should be noted. In a full cohort of G2, which included individuals who did not have children, our group previously found an increase in deaths from unnatural causes in the high-risk offspring (G2) and a mean loss of 8 years of life.[16] Is this increase in any suicidal ideation or gesture in grandchildren with 2 generations affected a harbinger of future risk?

There are no published 3-generation studies of major depression for comparisons that include direct interviews of all 3 generations or samples of grandchildren in the age of risk.[8,9] The study by Hammen et al[4] of a large sample of 15-year-olds with grandmothers' information obtained from mothers is the most comparable. That study focused on interpersonal stress as a mediator and found that the main effect of G1 MDD on G3 MDD was mediated by G2 MDD and interpersonal stress. The authors concluded that maternal and grandmother MDD are risk factors for G3 MDD, noting that their effects operate through a mechanism of long-term maternal interpersonal stress, marital and family discord, and parenting that is perceived by the child to be negative. Our sample may not have been large enough to show this effect. However, we found adverse risks across all groups.

Our study has some limitations. The sample was still too small to test for sex effects or multiple risk factors, and the number of grandchildren with a depressed parent but no depressed grandparents was low. Ethnic diversity entered into the second generation but was too small to test the effect. The original probands were selected from an ambulatory depression clinic (Yale Depression Research Unit, New Haven, Connecticut) and may not be generalizable to community samples. Some grandchildren had not yet passed through the full period of age of risk for major depression and other disorders. We also do not know what the long-term effects will be for the group who have both a parent and grandparent with major depression. Grandparents were excluded from the original study if they had a history of bipolar disorder, schizophrenia, or primary substance abuse, which may account for the low rates of these disorders in G2 offspring. All of the original G1 pro-bands had onset of MDD before age 40 years and usually before age 30 years. We do not know if the effect on grandchildren of 2 generations affected with MDD would be the same if the onset of MDD was later. First onset of MDD after age 50 years is uncommon and may not have the same effect on transmission between the generations.

Conclusions

These findings show the potential value of extending family history of depression beyond 2 generations. There is now considerable data showing the positive effects on children of successful treatment of a depressed parent.[34–38] The specificity of the transmission of depression across 3 generations suggests that this group might be a homogeneous sample for future biological marker studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Is depression in an offspring of a depressed parent transmitted to the next generation?

Finding

In a longitudinal retrospective cohort study of 3 generations, the biological offspring with 2 previous generations affected with major depressive disorder (MDD) were the highest-risk group, with more than a 3-fold increased risk of MDD.

Meaning

Offspring with 2 previous generations affected with MDD may be targets for early intervention and biomarker studies.

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Table 1

Demographic Characteristics of Grandparents (Generation 1), Parents (Generation 2), and Grandchildren (Generation 3), by Grandparental (Generation 1) Depression Status[a]

Variable	Total	Neither Grandparent Had MDD	≥1 or More Grandparents Had MDD	Compaiison[b]	
				z Score	*P* Value
No. of Grandparents[c]					
Female sex, No. (%)	37/62 (59.7)	13/18 (72.2)	24/44 (54.5)	−1.27	.21
Age at baseline, mean (SD)	48.1 (7.5)	49.5 (5.1)	47.6 (8.2)	−1.10	.27
Educational attainment, No./total No. (%)					
<High school	11/59 (18.6)	1/17(5.9)	10/42 (23.8)		
High school	39/59 (66.1)	14/17 (82.4)	25/42 (59.5)	−0.90	.37
≥College	9/59 (15.3)	2/17 (11.8)	7/42 (16.7)		
Marital status, No./total No. (%)					
Married or remarried	47/59 (79.7)	14/17 (82.4)	33/42 (78.6)		
Separated or divorced	10/59 (16.9)	1/17 (5.9)	9/42 (21.4)	0.33[d]	.74
Widowed	2/59 (3.4)	2/17 (11.8)	0/42		
No. of Parents[e]					
Female sex, No. (%)	76/127 (59.8)	22/39 (56.4)	54/88 (61.4)	0.54	.59
Educational attainment, No. (%)					
<High school	2/127 (1.6)	0	2/88 (2.3)		
High school	56/127 (44.1)	22/39 (56.4)	34/88 (38.6)	1.21	.23
≥College	69/127 (54.3)	17/39 (43.6)	52/88 (59.1)		
Marital status, No./total No. (%)					
Single, never married	6/120 (5.0)	2/39 (5.1)	4/81 (4.9)		
Married or remarried	88/120 (73.3)	30/39 (76.9)	58/81 (71.6)		
Separated or divorced	24/120 (20.0)	5/39 (12.8)	19/81 (23.5)	−0.70[d]	.49
Widowed	2/120 (1.7)	2/39 (5.1)	0/81		
No. of children, mean (SD)	2.3 (0.1)	2.7 (1.1)	2.1 (0.9)	−2.68	.007
Personal income, mean (SD), $	51 513 (27 743)	51 764 (28 600)	51 400 (27 540)	−0.05	.96

Variable	Total	Neither Grandparent Had MDD	≥1 or More Grandparents Had MDD	Compaiison[b]	
				z Score	*P* Value
Employment status, No./total No. (%)					
Full time	82/120 (68.3)	24/39 (61.5)	58/81 (71.6)		
Part time	16/120 (13.3)	4/39 (10.3)	12/81 (14.8)	−1.64	.10
Occasional or not employed	22/120 (18.3)	11/39 (28.2)	11/81 (13.6)		
Age at first interview, mean (SD)	20.2 (6.4)	19.5 (5.4)	20.5 (6.8)	1.01	.31
Age at last interview mean (SD)	46.3 (8.3)	45.6 (7.2)	46.6 (8.7)	0.59	.56
No. of interviews, mean (SD)	4.6 (1.1)	4.6 (1.3)	4.6 (1.1)	0.24	.81
No. of Grandchildren[e]					
Female sex, No. (%)	131/251 (52.2)	50/88 (56.8)	81/163 (49.7)	−1.08	.28
Educational attainment, No./total No. (%)					
<High school	82/239 (34.3)	24/87 (27.6)	58/152 (38.2)		
High school	79/239 (33.1)	37/87 (42.5)	42/152 (27.6)	−0.43	.67
≥College	78/239 (32.6)	26/87 (29.9)	52/152 (34.2)		
Age at first interview, mean (SD)	12.6 (5.1)	11.7 (5.4)	13.1 (4.8)	1.32	.19
Age at last interview, mean (SD)	18.2 (7.3)	18.5 (6.5)	18.1 (7.8)	−0.30	.77
No. of interviews, mean (SD)	2.0 (1.0)	2.3 (1.1)	1.9 (1.0)	−1.86	.06

Abbreviation: MDD, major depressive disorder.

[a]The table summarizes characteristics of 62 grandparents, 127 parents, and 251 grandchildren. Numbers may vary because of missing data in some categories.

[b]The *z* score is an estimate of the difference between the 2 groups, derived from regressions that adjusted for intrafamily correlation using a generalized estimating equation approach. Each characteristic was modeled as an outcome specified as either binary (sex and marital status [married vs other]), ordinal (educational attainment and employment status), or continuous (personal income, number of children, number of interviews, and all age variables). Adjustments to *P* levels have not been made for multiple comparisons.

[c]All generation 1 characteristics reflect participants' status at wave 1 or at wave 2 if wave 1 status was not available.

[d]Married or remarried vs all other categories combined.

[e]All generation 2 and generation 3 characteristics except age at first interview reflect participants' status at their last interview.

Table 2

Cumulative Rates of Psychiatric Disorders in Grandchildren (Generation 3), by Parental (Generation 2) Depression Status

			Effect of Parental MDD[a]			
	Parental MDD, No. (%)		Not Adjusted for Generation 1 MDD Status		Adjusted for Generation 1 MDD Status	
Variable	No (n = 88)	Yes (n = 29)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
No. of grandchildren	**199**	**52**	**NA**	**NA**	**NA**	**NA**
Any mood disorder[b]	34 (17.1)	16 (30.8)	2.05 (1.11–3.79)	.02	2.04 (1.13–3.69)	.02
MDD	25 (12.6)	13 (25.0)	2.02 (1.08–3.79)	.03	2.00 (1.09–3.69)	.03
DDNOS	5 (2.5)	1 (1.9)	0.67 (0.08–5.66)	.71	0.71 (0.09–5.87)	.75
Dysthymic disorder	10 (5.0)	5 (9.6)	2.23 (0.70–7.11)	.18	2.06 (0.66–6.43)	.21
Any anxiety disorder	74 (37.2)	26 (50.0)	1.39 (0.89–2.18)	.14	1.39 (0.89–2.16)	.15
Any disruptive disorder	28 (14.1)	13 (25.0)	1.70 (1.05–2.75)	.03	1.69 (1.03–2.76)	.04
Substance abuse or dependence	28 (14.1)	16 (30.8)	2.67 (1.10–6.47)	.03	2.50 (1.02–6.15)	.046
Substance abuse	13 (6.5)	6 (11.5)	1.79 (0.67–4.74)	.24	1.75 (0.63–4.80)	.28
Substance dependence	23 (11.6)	14 (26.9)	2.96 (1.24–7.08)	.01	2.77 (1.15–6.67)	.02
Any disorder	96 (48.2)	36 (69.2)	1.56 (1.15–2.12)	.004	1.56 (1.15–2.13)	.005
Any suicidal ideation or gesture	40 (20.1)	19 (36.5)	2.44 (1.28–4.66)[c]	.007	2.37 (1.27–4.42)[c]	.007
Child global assessment scale score[d]	82.5 (7.4)	72.8 (10.8)	38.25	<.001	36.55	<.001

Abbreviations: DDNOS, depressive disorder not otherwise specified; MDD, major depressive disorder.

[a] All analyses are adjusted for age and sex of grandchild and correlation within family.

[b] Includes MDD, DDNOS, and dysthymic disorder.

[c] Estimate of relative risk (rather than HR) because age at onset was not available.

[d] Values reflect means (SDs) and *F* scores unless otherwise noted.

Table 3

Cumulative Rates of Psychiatric Disorders in Grandchildren (Generation 3), by Grandparental (Generation 1) and Parental (Generation 2) Depression Status

	Neither Grandparent Had MDD (n = 18)				≥1 or More Grandparents Had MDD (n = 44)				
Variable	**No Parental MDD (n = 33)**	**Parental MDD (n = 6)**	**HR (95% CI)[b]**	***P* Value**	**No Parental MDD (n = 65)**	**Parental MDD (n = 23)**	**HR (95% CI)[b]**	***P* Value**	***P* Value for Interaction[a]**
No. of grandchildren	**74**	**14**	**NA**	**NA**	**125**	**38**	**NA**	**NA**	**NA**
Generation 3 Diagnoses									
Any mood disorder[c]	20.3	14.3	0.75 (0.44–1.30)	.31	15.2	36.8	2.98 (1.61–5.51)	<.001	.001
MDD	14.9	14.3	0.89 (0.50–1.59)	.69	11.2	29.0	2.70 (1.30–5.63)	.008	.04
DDNOS	4.1	0.0	NC	NC	1.6	2.6	1.43 (0.17–12.23)	.74	NC
Dysthymic disorder	4.1	0.0	NC	NC	5.6	13.2	2.76 (0.85–8.99)	.09	NC
Any anxiety disorder	40.5	35.7	0.85 (0.38–1.91)	.70	35.2	55.3	1.61 (1.01–2.56)	.04	.21
Any disruptive disorder	12.2	28.6	2.21 (0.76–6.47)	.15	15.2	23.7	1.52 (0.89–2.61)	.13	.51
Substance abuse or dependence	12.2	14.3	1.43 (0.14–14.50)	.76	15.2	36.8	2.90 (1.05–8.02)	.04	.51
Substance abuse	6.9	7.1	1.54 (0.15–15.99)	.72	6.6	14.3	2.02 (0.62–6.57)	.24	.56
Substance dependence	9.6	14.3	1.93 (0.21–17.51)	.56	13.1	34.3	3.14 (1.19–8.27)	.02	.67
Any disorder	51.4	64.3	1.25 (0.85–1.83)	.26	46.4	71.1	1.71 (1.15–2.53)	.008	.28
Any suicidal ideation or gesture	17.6	28.6	1.77 (0.36–8.67)[d]	.48	21.6	42.1	2.60 (1.41–4.79)[d]	.002	.70
Child global assessment scale score[e]	82.4 (7.1)	76.9 (6.2)	6.31	.01	82.5 (7.6)	71.3 (11.8)	31.86	<.001	.10

Abbreviations: DDNOS, depressive disorder not otherwise specified; HR, hazard ratio; MDD, major depressive disorder; NA, not applicable; NC, not calculated.

[a]Column shows the *P* level of the interaction term representing grandparental MDD (yes or no) × parental MDD (yes or no).

[b] All analyses are adjusted for age and sex of grandchild and correlation within family.

[c] Includes MDD, DDNOS, and dysthymic disorder.

[d] Estimate of relative risk (rather than HR) because age at onset was not available.

[e] Values reflect means (SDs) and *F* scores unless otherwise noted.

Table 4

Parental (Generation 2) Psychiatric Disorders and Grandchildren's (Generation 3) Family Risk Factors When Growing Up, by Grandparental (Generation 1) and Parental (Generation 2) Depression Status

	Neither Grandparent Had MDD (n = 18)		≥1 Grandparents Had MDD (n = 44)		Group Comparisons		
Variable	**No Parental MDD (GroupA)**	**Parental MDD (Group B)**	**No Parental MDD (Group C)**	**Parental MDD (Group D)**	**Omnibu χ^2_3 Statistic**	***P* Value**	**Pairwise Differences[a]**
No. of parents	**33**	**6**	**65**	**23**	**NA**	**NA**	**NA**
Generation 2 Psychiatric Disorders, No. (%)							
Any anxiety disorder	16 (48.5)	4 (66.7)	41 (63.1)	18 (78.3)	5.24	.16[b]	NA
Substance abuse or dependence	9 (27.3)	6 (100.0)	23 (35.4)	18 (78.3)	24.29	<.001[b]	B, D > A, C
No. of grandchildren	**74**	**14**	**126**	**38**	**NA**	**NA**	**NA**
Generation 3 Family Risk Factors, No./Total No. (%)							
Parental separation or divorce	11/69 (15.9)	6/12 (50.0)	19/118 (16.1)	11/30 (36.7)	13.49	.004	B, D > A, C
Affectionless control							
Mother	25/48 (52.1)	4/8 (50.0)	28/64 (43.8)	13/22 (59.1)	1.78	.62	NA
Father	12/48 (25.0)	3/8 (37.5)	16/63 (25.4)	5/22 (22.7)	0.70	.87	NA

Abbreviations: MDD, major depressive disorder; NA, not applicable.

[a] Only pairs different at $P < .05$ are reported.

[b] The *P* values were calculated using Pearson χ^2 test except when there were any expected values that were low, in which case the *P* values were calculated using Fisher exact test.