Psychological Medicine, 2001, **31**, 1211–1222. © 2001 Cambridge University Press
DOI: 10.1017/S0033291701004585 Printed in the United Kingdom

Parents concordant for major depressive disorder and the effect of psychopathology in offspring

Y. NOMURA,[1] V. WARNER AND P. WICKRAMARATNE

From the Department of Psychiatry, College of Physicians and Surgeons of Columbia University; Division of Clinical and Genetic Epidemiology, New York State Psychiatric Institute; Divisions of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, USA

ABSTRACT

Background. Concordance for major depressive disorder (MDD) between parents could happen for different reasons. Regardless of the origin and the frequency of the concordance, the effect on offspring of having two parents affected with MDD may be serious. The sex of the affected parent and offspring may also be a important risk factor for MDD in offspring.

Methods. We examined the increased risk of psychopathology among offspring of the four parental mating groups: both parents affected with MDD ($N = 53$); only mother affected ($N = 31$); only father affected ($N = 65$); and, neither parents affected ($N = 33$). Parents and offspring were assessed by direct interview, conducted blind and independently of each other.

Results. Among the four parental mating groups, offspring of both parents affected had the highest risk of MDD, anxiety disorder and alcohol dependence, and the earliest age of onset for MDD. There were two exceptions: the highest risk of conduct disorder and of drug dependence was in the groups where only the father was affected and where only the mother was affected, respectively. Mother's MDD was a stronger predictor of MDD in male compared to female offspring. Father's MDD was a stronger predictor of MDD in female compared to male offspring.

Conclusion. Having two parents with MDD increases the risk of psychiatric disorders in offspring. A clear dose–response relationship between the number of affected parents and psychiatric disorders in offspring was observed. The sex of the affected parent and of the offspring is important in determining the risk to offspring. For an examination of the risk to psychopathology in offspring, diagnosis status of both parents should be considered.

INTRODUCTION

Spouse similarity on psychiatric illness between the couple in a mated pair has been studied since the late 1930s (Richardson, 1939; Roff, 1950; Kreitman, 1962; Dunner *et al*. 1976; Gershon *et al*. 1976). The most cited explanation for this concordance is assortative mating, the tendency for the mated pair to be similar in some attribute other than would be expected if they were chosen randomly (Merikangas, 1982). Concordance can also happen through marital interaction: over a period of time, a husband and wife living together tend to influence or even transfer their illness to the other (Merikangas, 1982; McLeod, 1993) due to their exposure to common sources of life stress (Coyne *et al*. 1987), or to social homogamy – the tendency for individuals from similar social backgrounds to marry (Vanyukov *et al*. 1996; Maes *et al*. 1998). In addition, concordance can happen by chance alone. However, regardless of the origin of the spouse similarity, the effects on their offspring of both parents suffering from psychiatric illness can be serious (Dierker *et al*. 1999; Merikangas *et al*. 1985, 1988*a*).

Vanyukov *et al*. (1996) noted that spouse similarity increases parent–offspring phenotypic correlations regardless of its origin, i.e. whether they are mostly genetic or environmental. It

[1] Address for correspondence: Dr Yoko Nomura, Department of Psychiatry, College of Physicians & Surgeons of Columbia University, 1051 Riverside Drive, Unit 24, New York, NY 10032, USA.

induces genetic correlations between unrelated spouses and also leads to environmental similarity between parents and their children since parents' phenotypic assortment induces correlations between spousal environment. Adverse environmental risk factors such as poor marital adjustment (Merikangas, 1984; Hammen *et al.* 1998), interpersonal conflict (Fendrich *et al.* 1990) and financial difficulties (Hammen *et al.* 1987) are more likely if both parents are ill. Moreover, couples who are concordant for affective disorder exhibit a higher divorce rate (Merikangas, 1984) and poorer social adjustment (Merikangas *et al.* 1983). The offspring of parents who are concordant for affective disorders compared with those who are not have been shown to have an elevated risk of affective disorder (Merikangas & Spiker, 1982; Hammen *et al.* 1987), alcoholism (Merikangas *et al.* 1988*b*), conduct disorder (Merikangas *et al.* 1985; Nigg & Hinshaw, 1998) and poorer social and school functioning (Hammen *et al.* 1987).

In a longitudinal study of offspring at high and low risk for major depressive disorder (MDD) by virtue of parental diagnosis, we examined the degree of concordance between probands with MDD and their spouses, and if the risk of a spouse being concordant for MDD varied by the sex of probands. Merikangas *et al.* showed the importance of including the diagnostic status of both parents using the same (baseline) data (Merikangas *et al.* 1988*a*). We examined the risk to offspring of having: both parents with MDD; only mother with MDD; only father with MDD; and neither parent with MDD, by exploiting the longer period of follow-up and the fact that these offspring have now passed through a greater period of risk. We hypothesized that the offspring of parents concordant for MDD would have the highest risk of MDD, anxiety disorder, alcohol dependence and drug dependence and the lowest age of onset for MDD, dysthymia, conduct disorder and substance use disorder.

METHOD

Sample

Offspring were initially selected for the presence or absence of a lifetime history of MDD in their parents based on Research Diagnostic Criteria (see Weissman *et al.* 1982, 1986, 1987, 1992, 1997 for description of design and sample assessment). The depressed probands had received treatment at the Yale University Depression Research Unit. The normal control subjects came from a 1975 community survey that was conducted in New Haven and had no history of psychiatric illness based on at least four direct interviews. All probands were white and group-matched for age and sex.

At the initial interview (Time 1), the sample consisted of 220 offspring between the ages of 6 and 23 years from 91 families. Of the 220 offspring, 182 (82·7%) were contacted 2 years (Time 2) and 10 years (Time 10) later for reassessment. The data in the current study are based on the 182 offspring from a total of 83 probands, with 52 (22 male and 30 female) depressed probands and 31 (13 male and 18 female) normal control subjects, and their spouses. The probands and their spouses will be referred to as the parents and their offspring as offspring.

Procedures

Probands, spouses of probands and offspring were independently interviewed with the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS) modified to include Research Diagnostic Criteria and DSM-III and DSM-III-R criteria (Mannuzza *et al.* 1986). All interviews of offspring were conducted blind to parents' status and the offspring's previous assessments. Each interview covered a period of assessment from the last interview until the present. Interviewers were experienced mental health professionals with a master's or a Ph.D. degree and received intensive training, monitoring, and inter-rater reliability testing (see Weissman *et al.* 1997).

Diagnosis of offspring were based on the Best Estimate (BE) procedure (Leckman *et al.* 1982). The diagnoses for the offspring were cumulative across Times 1, 2 and 10. The magnitude of concordance for MDD between the mated pair was based on the parental diagnosis at Time 1. A complete description of the BE procedure has been published elsewhere (Weissman *et al.* 1997).

Statistical analysis

From the demographic information collected during the interview with parents, three dichotomous variables (low *versus* middle and

high SES, intact *versus* non-intact families and presence *versus* absence of parental divorce) and two continuous variables (maternal and paternal age) were selected to see whether the four parent groups were different. The Hollingshead five-factor index was dichotomized with > 3 representing low SES and $\leqslant 3$ representing high and middle SES. Families where both biological parents were physically present in the home counted as an intact family and scored one; all others scored zero.

To determine to what extent the mating pair was concordant for MDD, univariate analyses were conducted using chi-square tests. The association was also evaluated by sex of the probands. In order to determine the magnitude of the concordance between pairs – female probands and their husbands and male probands and their wives – odds ratios were obtained. The Breslow–Day chi-square test for homogeneity was used to determine whether the magnitude of association was different by sex of the probands.

MDD status in the parents was stable over time. Only three subjects within the total of 166 probands and their spouses changed their status between the initial interview (Time 1) and follow-up (Time 10). Specifically, one female proband without MDD initially developed MDD and two spouses (one husband and one wife) of affected probands developed MDD by Time 10. Based on lifetime MDD at Time 10, parents were grouped into three categories – neither parent with MDD, one parent with MDD, and both parents with MDD – and tested for a linear trend for MDD anxiety disorder, alcohol dependence and drug dependence in the offspring using chi-square test linear by linear association.

The group of 'one parent with MDD' was then further divided into two – mothers with MDD in one, fathers with MDD in the other – in order to examine any qualitative difference between the two groups. Univariate analysis was conducted using chi-square tests to examine the difference in offspring diagnoses, namely MDD, anxiety disorder, alcohol dependence, and drug dependence, in the four parental groups. These univariate analyses were followed by multivariate analyses to adjust for the effect of potential confounders such as the age and sex of the offspring. Logistic regression analyses with diagnoses in offspring as the outcome variable and the parental group as a predictor variable were conducted. First, the age and the sex of the offspring were statistically controlled for in the model. In order to estimate the effect of sex difference on the association between the number of parents with MDD and psychopathology in the offspring, the same sets of logistic regression analyses adjusted only for the age of the offspring were conducted and were further stratified on the sex of the offspring. The neither parent with MDD group served as the reference group and a group comparison on the diagnoses in their offspring among the four parental groups was conducted. To evaluate the magnitude of the increased risk for the number of parents with MDD, an odds ratio with 95% confidence interval was obtained for each group in comparison to the reference group.

A number of arguments have been made for defining independence of two risk factors as adherence of the rates of disease (Rothman, 1976; Walter & Holford, 1978; Assmann *et al.* 1995). The choice between multiplicative or statistical interaction and additive or biological interaction, is controversial. In this paper, interaction – defined as the departure of disease rates from an additive model based on Rothman's 'index of synergism' – was evaluated (Rothman, 1976; Rothman *et al.* 1980; Saracci, 1980; Greenland & Rothman, 1998*a*), as it is more appropriate not to consider the effects of paternal and maternal depression as independent (Rothman *et al.* 1980). Interaction on an additive scale exists when the risk of both parents with MDD (as compared to the risk of neither parent with MDD) exceeds the sum of the risks of only the mother with MDD and of only the father with MDD (as compared to the risk of neither parent with MDD). The presence/absence of interaction on an additive scale can be examined by an index: RERI – the relative excess risk due to interaction. RERI allows us to evaluate how much excess risk interaction is responsible for (Rothman 1976; Flanders & Rothman, 1982; Greenland, 1983). AP – the attributable proportion of RERI due to the joint risk factors – is based on RERI and relative risk of joint exposure, maternal MDD and paternal MDD. It estimates the proportion of disease due to interaction among those with joint exposure (ranging 0 to 100%). No interaction corresponds to RERI = 0 and AP = 0. RERI and AP, as well as their 95% confidence intervals, were

estimated based on Hosmer & Lemeshow's confidence interval estimation of interaction (Hosmer & Lemeshow, 1992).

Analysis of covariance (ANCOVA) was conducted with the offspring of the parent group to see if there was a difference in the age of onset for depression, dysthymia, substance dependence, or conduct disorder. The sex of the offspring was considered *a priori* to be a potential confounder and included in the ANCOVA model as a covariate.

More than one offspring from the same family was included in this study, and consequently the assumption of independence of observations that underlies the computation of standard errors and confidence intervals in the usual manner may be violated. Standard errors for rates of psychopathology in offspring were computed using the Taylor series linearization method (Woodruff, 1971), and standard errors and confidence intervals for parameters estimated from the logistic analyses were computed using the method of weighted maximum likelihood, adapted for survey and clustered data (Binder, 1983) via implicit Taylor series. All analyses adjusting for possible non-independence of outcomes of family members were performed using the software package SUDDAN (Shah *et al.* 1996).

RESULTS

Characteristics of the sample

There were 83 eligible mated pairs with 182 offspring. Of the 182 offspring, 96 were girls and 86 were boys. Approximately 18% of the offspring were younger than 13; the mean age was 17·7. At Time 1, the mean age for fathers and mothers was 43·1 and 42·7 respectively; 51·9% of families were categorized as low SES; 18 (22·0%) were divorced by Time 1. Of the 18 divorcees, five mothers and three fathers remarried. One hundred and seventeen offspring (64·3%) lived with both biological parents, nine with a biological mother and stepfather, and six with a biological father and a stepmother. Thirty-four offspring lived with only a mother, six with only a father, and 10 with neither parent. One offspring lived with two stepsiblings, his mother and father. No offspring lived with two non-biological parents.

There was a significant difference in the proportion of low SES families among the four parental groups ($P = 0{\cdot}03$): families where only the mother was depressed were most likely (72·4%) to belong to the low SES; families where both parents were depressed were least likely (29·4%) to belong to the low SES. Maternal age, paternal age, proportion of intact families, or divorce rate were not significantly different among the four parental groups, neither was there any statistically significant difference in sex and age of the offspring among them.

Are mating pairs concordant for MDD?

The results revealed little evidence to show that mated pairs were concordant for MDD (OR = 1·5, $P = 0{\cdot}53$) (Table 1). The Breslow–Day chi-square test for homogeneity, however, showed a trend toward a difference in the odds ratios between the two strata ($\chi^2_{\mathrm{B-D}} = 2{\cdot}6$, df = 1, $P = 0{\cdot}10$). Having found a trend that the sex of the probands might be an effect modifier for the similarity in their MDD status, we conducted a stratified analysis based on the sex of the probands, even though it decreased the sample size further. When the same association, i.e. the disease status (MDD) of the spouse and the probands, was examined by the sex of the probands, we found that the association varied. Although final tests for any difference in odds ratio did not reach statistical significance, female probands with MDD were five times more likely (OR = 5·2, $P = 0{\cdot}09$) to mate with a man with MDD but male probands with MDD were slightly less likely to mate with a women with MDD (OR = 0·9, $P = 0{\cdot}57$).

Does a dose–response relationship exist between the number of parents with MDD and psychopathology in offspring?

To determine if there was a linear relationship between the number of parents having MDD and the rates of psychiatric illness in the offspring, the parents were categorized into the following three groups – neither parent with MDD, one parent with MDD, and both parents with MDD. Logistic regression analyses with statistical adjustment for the sex and age of the offspring showed that the three groups had significantly different risks for MDD, anxiety disorder, alcohol dependence and drug dependence in the offspring. Tests for a linear trend by chi-square test for linear by linear association

Table 1. *Frequencies and concordance on MDD at the baseline interview between probands and their spouses among all the probands and their spouses and stratified by the sex of the probands*

Spouses	Total *N*	Probands		OR	χ^2	*P*
		With MDD	Without MDD			
All	83	All	All			
With MDD		15	7	1·5	0·40	0·53
Without MDD		37	24			
Wives	35	Male	Male			
With MDD		8	6	0·9	0·33	0·57
Without MDD		14	7			
Husbands	48	Female	Female			
With MDD		7	1	5·2	2·9	0·087
Without MDD		23	17			

Breslow–Day test of homogeneity = 2·6, df = 1, $P = 0{\cdot}1$.

Table 2. *Rates per* 100 (*standard error*) *of MDD, anxiety disorder, alcohol dependency, and drug dependency in the offspring in the four parental mating groups based on parental MDD, overall group difference in the rate of the disorder and linear trend*

	Neither parent	Father only	Mother only	Both parents	χ^2	df	*P*	Linear trend $\chi^2(1)$	Linear trend *P*
Total ($N = 182$)	($N = 53$)	($N = 31$)	($N = 65$)	($N = 33$)					
MDD	26·4 (7·5)	41·9 (10·3)	50·8 (6·9)	69·7 (9·8)	10·8	3	0·02	16·0	0·00
Anxiety disorder	17·0 (4·8)	45·2 (9·0)	38·4 (8·9)	63·6 (8·1)	19·4	3	0·001	15·8	0·00
Alcohol dependence	3·8 (2·5)	9·7 (4·9)	18·5 (4·8)	18·2 (6·9)	8·6	3	0·04	6·1	0·01
Drug dependence	1·9 (1·8)	9·7 (5·1)	18·5 (4·2)	3·0 (2·9)	12·7	3	0·01	1·8	0·18
Boys ($N = 86$)	($N = 25$)	($N = 19$)	($N = 32$)	($N = 10$)					
MDD	16·0 (7·3)	21·1 (9·7)	50·0 (9·2)	50·0 (18·8)	9·2	3	0·03	8·3	0·004
Anxiety disorder	12·0 (6·9)	36·8 (11·4)	28·1 (8·3)	60·0 (18·2)	5·9	3	0·13	5·6	0·02
Alcohol dependence	8·0 (5·2)	15·8 (7·9)	21·9 (6·7)	20·0 (10·6)	2·9	3	0·41	1·7	0·19
Drug dependence	0	10·5 (7·0)	15·6 (6·5)	10·0 (8·9)	7·6	3	0·06	2·7	0·10
Girls ($N = 96$)	($N = 28$)	($N = 12$)	($N = 33$)	($N = 23$)					
MDD	35·7 (9·8)	75·0 (11·1)	51·5 (8·7)	78·3 (10·0)	9·7	3	0·03	6·5	0·01
Anxiety disorder	21·4 (7·3)	58·3 (12·3)	48·5 (11·1)	65·2 (8·9)	12·6	3	0·01	8·8	0·003
Alcohol dependence	0	0	15·2 (5·9)	17·4 (7·6)	10·6	3	0·02	6·2	0·01
Drug dependence	3·6 (3·3)	8·3 (8·3)	21·2 (6·9)	0	8·0	3	0·05	0·1	0·71

found that, except for drug dependence, there was a dose–response relationship between the number of affected parents and the risk of MDD ($\chi^2(1) = 16{\cdot}0$, $P < 0{\cdot}0001$), anxiety disorder ($\chi^2(1) = 15{\cdot}8$, $P < 0{\cdot}0001$), and alcohol dependence ($\chi^2(1) = 6{\cdot}1$, $P = 0{\cdot}01$) in the offspring.

The group of 'one parent with MDD' was then divided into two – mothers with MDD in one, fathers with MDD in the other – to determine whether there was any qualitative difference between mother and father being depressed. Table 2 shows the rate of MDD, anxiety disorder, alcohol dependence, and drug dependence in the offspring of the four parental mating groups. We found that the risk of MDD ($\chi^2(3) = 10{\cdot}8$, $P = 0{\cdot}02$), anxiety disorder ($\chi^2(3) = 19{\cdot}4$, $P = 0{\cdot}0001$), alcohol dependence ($\chi^2(3) = 8{\cdot}6$, $P = 0{\cdot}04$), and drug dependence ($\chi^2(3) = 12{\cdot}7$, $P = 0{\cdot}01$) in the offspring was significantly different. Stratified on the sex of the offspring, we found the same trend in both strata, although among male offspring the overall group differences for alcohol dependence and drug dependence did not reach a statistically significant level.

Table 3 shows the risk of one and more than one parent with MDD on psychopathology in offspring. The offspring of the group where both parents had MDD as compared to the offspring of the group where neither parent had MDD

Table 3. *Risk (and its 95% confidence interval) of selected psychiatric illnesses in the offspring when only the mother, only the father, or both parents had MDD with adjustment of the sex and age of the offspring*

	Father only with MDD *v.* neither parent with MDD	Mother only with MDD *v.* neither parent with MDD	Both parents with MDD *v.* neither patent with MDD
Total			
MDD	2·2 (0·7, 6·2)	3·4** (1·3, 8·3)	6·6** (1·9, 25·0)
Anxiety disorder	4·8** (1·7, 12·5)	3·2* (1·1, 9·1)	8·3**** (3·0, 20·0)
Alcohol dependence	2·3 (0·3, 16·7)	6·3* (1·3, 33·3)	7·1* (1·5, 33·3)
Drug dependence	5·0 (0·5, 50·0)	12·8* (1·5, 100·0)	1·5 (0·1, 25·0)
Boys			
MDD	1·4 (0·3, 6·7)	6·0** (1·6, 20·0)	7·4* (1·3, 50·0)
Anxiety disorder	4·2* (0·8, 20·0)	2·8* (0·6, 12·5)	10·3* (1·8, 100·0)
Girls			
MDD	4·4* (1·0, 20·6)	2·0 (0·7, 6·2)	6·3* (1·4, 33·3)
Anxiety disorder	5·6* (1·4, 20·0)	3·4* (1·0, 12·5)	7·0** (2·0, 25·0)

For analyses stratified on gender, only the age of the offspring was controlled for as a potential confounder.
* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$; **** $P < 0{\cdot}0001$.

Table 4. *Mean age of onset of MDD and dysthymia in the offspring of the four parental mating groups*

Parental group	Age of onset Mean	(S.E.)	Significant differences between groups
Onset for MDD			
1 Neither parent with MDD ($N = 14$)	17·6	(0·7)	$F(3,80) = 1{\cdot}79$
2 Father only with MDD ($N = 14$)	17·9	(2·2)	$1 < 4$†
3 Mother only with MDD ($N = 32$)	15·7	(0·9)	
4 Both parents with MDD ($N = 23$)	15·2	(1·1)	
Onset for dysthymia			
1 Neither parent with MDD ($N = 13$)	12·7	(1·5)	$F(3,48) = 1{\cdot}27$
2 Father only with MDD ($N = 8$)	13·3	(1·2)	
3 Mother only with MDD ($N = 19$)	10·6	(1·2)	
4 Both parents with MDD ($N = 11$)	9·5	(2·7)	
Onset for substance use disorder			
1 Neither parent with MDD ($N = 17$)	17·7	(0·7)	$F(3,54) = 1{\cdot}52$
2 Father only with MDD ($N = 7$)	17·3	(0·8)	
3 Mother only with MDD ($N = 22$)	15·8	(0·6)	
4 Both parents with MDD ($N = 11$)	17·0	(0·7)	
Onset for conduct disorder			
1 Neither parent with MDD ($N = 11$)	13·3	(0·9)	$F(3,52) = 7{\cdot}14$***
2 Father only with MDD ($N = 8$)	9·6	(0·8)	$2 < 1$***, 3***, 4***
3 Mother only with MDD ($N = 29$)	12·2	(0·5)	
4 Both parents with MDD ($N = 7$)	14·3	(0·7)	

† $P < 0{\cdot}10$; *** $P < 0{\cdot}001$.

had a significantly increase risk of MDD (OR = 6·6), anxiety disorder (OR = 8·3) and alcohol dependence (OR = 7·1). The offspring of the group where only the mother had MDD as compared to the offspring of the group where neither parent had MDD showed a significantly increased risk of MDD (OR = 3·4), anxiety disorder (OR = 3·2), alcohol dependence (OR = 6·3) and drug dependence (OR = 12·8). In the offspring of the group where only the father had MDD as compared to the offspring of the group where neither parent had MDD, there was a greater than two-fold increase in MDD and alcohol dependence and an almost five-fold

increase in anxiety disorder and drug dependence. However, only the elevated risk for anxiety disorder was statistically significant.

Table 3 also shows the risk of MDD and anxiety disorder in offspring by sex of the offspring in both strata. The risk of offspring having MDD was highest in the group where both parents had MDD. When only the mother had MDD, the risk of their male (OR = 6·0) not their female (OR = 2·0) offspring having MDD was close to the risk for MDD in offspring when both parents had MDD. Similarly, when only the father had MDD, the risk of their female (OR = 4·4) not their male (OR = 1·4) offspring having MDD was close to the risk of both parents with MDD. *Post-hoc* comparisons were done to examine the risk for MDD in the offspring between the two groups of parents – 'only the father had MDD' and 'only the mother had MDD' – stratified on the sex of the offspring. The results showed that female offspring had a close to four-fold increased risk of MDD (OR = 3·7, $P = 0·04$) when only their father as opposed to their mother was depressed, whereas the male offspring had a close to three-fold increased risk of MDD (OR = 2·8, $P = 0·17$) when only their mother as opposed to their father was depressed. The risk of the offspring having an anxiety disorder was higher when the father, not the mother, had MDD, although the difference was small. This was observed in both female and male offspring. As the prevalence of alcohol dependence was relatively low in female offspring and the prevalence of drug dependence was low in both male and female offspring, we were not able to conduct meaningful stratified analyses on the sex of the probands for these disorders.

Is there a qualitative difference between one and both parents having MDD on psychopathology in offspring?

We attempted to find if there was synergism in the number of the parents being depressed and, if so, whether the rates of disorder among offspring with both parents having MDD could be attributable to the interaction of mother having MDD and father having MDD (Greenland & Rothman, 1998*a*, *b*; Hosmer & Lemeshaw, 1992). We found that RERI, relative excess risk due to interaction, was 2·11 with 95% CI from −3·5 to 7·7. This indicates that exposure to both maternal and paternal MDD had an approximately two-fold excess risk of developing MDD in offspring as compared to the sum of the separate risk of maternal MDD and paternal MDD. AP, the proportion of MDD among those with both parents having MDD that is attributable to their interaction, was 0·32, indicating that 32% of the excess risk for MDD in offspring who had both parents having MDD was due to interaction. The 95% CI for AP was from −0·60 to 1·24. Although these 95% CI contained the null value, Assmann *et al.* (1995) have shown that when there is synergy, symmetric confidence intervals, such as those we have calculated, will tend to extend too far to the left and not far enough to the right. Thus, these results taken together suggest some evidence of synergism by maternal MDD and paternal MDD in increasing the risk of MDD in offspring. We found no indication of synergism for anxiety disorder, alcohol dependence or drug dependence.

Does parental MDD increase the risk for early onset of MDD, dysthymia, substance dependence and conduct disorder in the offspring?

Among the 182 offspring, 83 developed MDD, 51 developed dysthymia, 56 developed substance dependence and 55 developed conduct disorder between the initial interview and Time 10. Table 4 shows the mean age of onset for MDD and dysthymia in the offspring of the four parental mating groups. The age of onset for MDD ranged from 15·2 to 17·9 years. Onset of dysthymia occurred at a younger average age than that of MDD, ranging from 9·5 to 13·3 years. Except conduct disorder, the onset of the other disorders occurred at a later age in the groups where neither parent or only father had MDD than in the group where both parents had MDD. For MDD and dysthymia, the mean age of onset was earliest in the group where both parents had MDD. For substance use disorders, the group that had the youngest average age of onset was the group in which only the mother had MDD and for conduct disorder the group that had the youngest average age of onset was the one in which only the father had MDD.

Using ANCOVA with the sex of the offspring as a covariate, we found there was an overall statistically significant group difference in the age of onset for conduct disorder ($F(3,52) =$

7·14, $P < 0·001$), although no overall difference was found for MDD ($F(3,80) = 1·79$, $P = 0·15$), dysthymia ($F(3,48) = 1·27$, $P = 0·29$) and substance dependence ($F(4,52) = 1·52$, $P = 0·22$). In a group comparison, we found that the mean age of onset for conduct disorder was lower in the offspring of the group where only the father had MDD than any other group ($P < 0·05 \sim P < 0·001$). There was a marginally significant trend indicating that the mean age of onset for MDD was lower in the offspring of both parents with MDD compared to the offspring of neither parent with MDD (15·2 *v.* 17·6, $P = 0·06$). The mean age of onset for dysthymia in the offspring of the both parents with MDD group was the lowest among the three groups, although it did not reach a statistically significant level.

DISCUSSION

This paper examines the extent of parental concordance for MDD in a clinical sample and its effects on the psychopathology of the offspring. Using an earlier dataset of the same sample. Merikangas *et al.* (1985*a*) found that the lifetime prevalence of any psychiatric disorder including MDD, anxiety disorder and alcoholism, was significantly higher among the spouses of depressed probands compared to those of normal control. We restricted our analysis to examining whether there was concordance for MDD between spouses and found that the level of concordance between the spouses varied by gender of the probands. Although our results were consistent with those of Merikangas *et al.* (1988*a*) regarding the increased risk of offspring anxiety disorder by paternal MDD, the effect of maternal MDD on offspring was different. They reported that maternal MDD did not increase the risk of offspring psychopathology, whereas we found that maternal MDD was a strong risk factor for it, in analysing the effect of maternal and paternal MDD on offspring psychopathology. Although Merikangas *et al.* used multiplicative rather than our additive model, the discrepancy in results appear to be due to the longer period of follow-up time than difference in analytical approach. When we analysed the data using a multiplicative model, we found that maternal MDD remained a strong risk factor for psychopathology to the offspring over the 10-year period.

With regard to concordance for MDD in the couple, we found a marginally significant trend that it varied by the sex of the probands. Between male probands and their spouses there was no evidence for similarity on MDD, but there was a trend that depressed female probands had an increased risk of having a depressed spouse. Because of the small sample size in the stratified analysis this result has to be interpreted with caution. Nevertheless, the difference by gender of the probands deserves further attention. Some researchers have suggested that mate selection may be asymmetric with respect to sex (Kessler & Magee 1994; Maes *et al.* 1998), but only a few studies have examined cross-assortment (Merikangas & Spiker, 1982; Schuckit, 1982). The study by Merikangas and her colleagues (1985) found evidence for cross-assortment between depressed women and alcoholic men: since alcoholism in husbands was secondary to MDD, the study should be viewed as assortative mating on MDD when alcoholism coexisted in husbands. Nevertheless, the study was important for its finding that depressed women were more likely to marry depressed men who were later co-morbid with alcoholism. Contradictorily, Galbaud du Fort *et al.* (1994) tested the degree of symmetry between mating pairs for psychological distress and well-being in the population sample and found symmetry between the pairs. Except for the study by Maes *et al.* a clinical rather than general population was used and Galbaud du Fort *et al.* warned that the asymmetry between mated pairs by sex might be due to a higher prevalence for affective disorder and a greater propensity to seek professional help for emotional problems in females. Vanyukov *et al.* (1996) stated that the likelihood of having a mate with certain phenotypes depended on the gender of the probands. Thus, depending on the disorder and sex of the probands, we may observe different patterns of spouse similarities. Social norms operating in males and females, for example, may cause different patterns of assortment or cross-assortment, such as the one with depressed women and alcoholic men. It was reported that alcoholic women were more likely to be with alcoholic men but alcoholic men were not more likely to be with alcoholic women (Moskalenko *et al.*

1992). The sample size did not allow us to conduct analyses to see whether the strong concordance for MDD between female probands and their husbands was due, at least in part, to the husbands' co-morbidity with alcoholism. However, it is possible that the higher prevalence of alcoholism in men compared to women might explain the difference in the pattern of spouse similarity by the sex of the probands.

In our data, three subjects developed MDD between Time 2 and Time 10. Two of them were spouses of probands with MDD and one of them was a spouse of a proband without MDD. If concordance had been due to marital interaction, we would have seen more spouses of probands with MDD developing MDD. Three previous studies had examined this hypothesis and found no evidence to support it (Merikangas & Spiker, 1982; Heun & Maier, 1993; Maes *et al.* 1998). Neither sharing the source of mutual breakdown nor a reaction to the spouse's psychiatric illness is a good explanation for our finding, for the same reason as above. Because of our study design (high-risk study by virtue of parental depression), however, we were not able to determine whether association between parents was due to assortative mating.

We confirmed that diagnostic status of both parents should be considered in the design and analysis of studies of children. A clear dose–response relationship between the number of parents affected by MDD and the risk of MDD ($P < 0{\cdot}0001$), anxiety disorder ($P < 0{\cdot}0001$), and alcohol dependence ($P = 0{\cdot}01$) in their offspring was found. Increased prevalence rates for non-affective disorder in offspring of depressed parents might be explained in part by parents' co-morbid anxiety disorder. In our sample, 73·0% of mothers and 41·2% of fathers had anxiety disorder. In addition, 92·9% of depressed mothers compared to 50·0% of non-depressed mothers had anxiety disorder ($P < 0{\cdot}0001$, OR = 13·0). Similarly, 65·5% of depressed fathers compared to 28·0% of non-depressed fathers had anxiety disorder ($P < 0{\cdot}001$, OR = 4·9). Family environment caused by (or associated with) parental depression may also account for co-transmission of non-affective illness (Downy & Coyne, 1990). Depressed parents are more likely to exhibit a parenting style characterized as affectionless control (Fendrich *et al.* 1990). This has also been reported as a risk factor for anxiety disorder in offspring, as well as MDD (Silove *et al.* 1991; Bennet & Stirling, 1998). Affectionless control was more likely to be observed in depressed mothers *versus* non-depressed mothers (26·6% *v.* 12·2%, $P = 0{\cdot}03$, OR = 2·6). The same association between depression and affectionless control was found in fathers (39·5% *v.* 22·1%, $P = 0{\cdot}03$, OR = 2·3). Most of our findings, except for conduct disorder and drug dependence in offspring, supported the concept that offspring of parents concordant for MDD had the highest risk of psychopathology. The risk of drug dependence in offspring did not increase linearly depending on the number of parents with MDD. We should note that the highest rate of drug dependence was observed in offspring of the group where only the mother was depressed (18·5%), a 13-fold increased risk compared to the offspring of the group where neither parent was depressed, which was statistically significant. Similarly, the age of onset for substance abuse/dependence was also earliest in the offspring of the groups where only the mother had MDD. This could be explained by maternal co-morbidity of substance use disorder: in families where only the mother had MDD: the rate was higher (12·3%) than that for the group in which neither parent had MDD (7·5%), for the group in which only the father had MDD (3·2%) and for the group in which both parents had MDD (6·1%). The rate of substance use disorder in fathers was similar (approximately 50%), except for the group where neither parent had MDD (29·5%).

Our finding that offspring who had a depressed father and non-depressed mother were the highest risk group for conduct disorder deserves further attention. Merikangas *et al.* (1985) found that the offspring of one parent with co-morbid MDD and alcoholism, or two parents with MDD or alcoholism, had an increased risk of conduct disorder, and reported that conduct disorder is a reaction to environmental instability, a non-specific manifestation of psychopathology. Downey & Coyne (1990) explained that family environment, rather than parental depression, was a direct cause of externalizing problems in children. Families where the father is depressed and the mother is not depressed may have unique characteristics

that may be related to a more chaotic home environment. Possibly, the father sets limits and establishes routines; if the father is depressed, he has diminished ability to do so. It may also be possible that their wives without MDD can not offer appropriate support and nurturing to the offspring as they are under stress having to make up for their husbands' lack of effectiveness. As conduct disorder in adolescence was found to be a predictor for adult onset of MDD (Pine *et al.* 1998). Understanding the occurrence of conduct disorder among children/adolescents is important to prevent future onset of depression.

We found two qualitative differences in the familial transmission of MDD. First, depending on the sex of the offspring, a different pattern of MDD manifestation was found. Mother's MDD (rather than father's) had an almost three-fold stronger influence on the rate of MDD in male offspring compared to that in female offspring, and father's MDD (rather than mother's) had an almost four-fold stronger influence on the rate of MDD in female offspring compared to that in male offspring. Previous studies showed that maternal depression was associated with more negative outcomes in sons than daughters, such as poorer cognitive development (Murray *et al.* 1993), poorer social competence, more behavioural problems (Gross *et al.* 1995), and greater distractibility (Sinclair & Murray, 1998). Although when parents were depressed their children's own needs might be less likely to be attended to, there was a tendency that depressed mothers would respond better to their daughters than their sons (Sinclair & Murray, 1998; Murray *et al.* 1993). No studies have examined the influence of paternal depression on sons and daughters, but it is also possible that depressed fathers might respond better to their sons than their daughters. Future studies need to explore possible mechanisms of transmission of depression between fathers and daughters and between mothers and sons.

Secondly, there was a qualitative difference between both parents and one parent being depressed on offspring psychopathology. The estimated excess risk for MDD in offspring where both parents had MDD was higher (32%) than the sum of the risks for MDD when only the mother and only the father had MDD, suggesting an interaction in an additive scale. When both parents had MDD, the risk for MDD in offspring was accelerated. Having both parents with MDD may reflect a disorderly home environment and/or genetic vulnerability, or interplay of the two. It is possible that in families where only one parent had MDD, there is a pattern of the parent without MDD making up for, or preventing, potential damage to the home environment that may be introduced by their partner and this pattern alleviates the adverse effect on MDD in offspring, while families where both parents have MDD can not or are less able to do so. This knowledge could provide improved prospects for prevention of familial transmission of MDD to offspring.

There are some shortcomings to this study, however. We used a clinical sample. Selection bias caused by the use of clinical instead of population samples is one of the limitations. The probability of a mated pair being drawn from a clinical sample is dependent on whether one or both spouses are affected from the illness under examination. A couple with two affected partners has a greater chance of being selected as a sample (Galbaud du Fort *et al.* 1993; McLeod, 1993; Krueger *et al.* 1998). Moreover, treatment-seeking behaviour might be more similar within a family than between independent subjects. In other words, one spouse's help-seeking behaviour is not independent of the others. It is possible that we may have overestimated the magnitude of concordance for MDD between female probands and their spouse. Another limitation is the small sample size in examination of parental concordance for MDD. Although the detected marginal difference by sex of the probands in the pattern of concordance suggests the need to examine comorbid conditions and associated characteristics for the pattern of co-morbidity, our sample size does not allow a further examination of the possibility of asymmetric association in a mated pair. It is also possible that concordance on MDD might have occurred on factors other than the disorder itself, related to traits in the parents. An examination of covariates – conditions that are correlated both with MDD and mating patterns – might also help explain the sex difference in the pattern of concordance for MDD. If the strength of the association between the psychiatric status and a correlated condition differs according to sex, it could explain the different level of concordance

for MDD between pairs for female and male probands. Future studies should evaluate traits in parents that may be related to assortative and/or cross-assortative mating patterns in order to clarify the mechanism further.

This work was supported by the United States National Institute of Mental Health Grants MH-36197 and 5P50MH-43878-08 (Myrna M. Weissman, Principal Investigator). The authors would like to thank Myrna M. Weissman for her helpful comments, Sue E. Hodge for her consultation as ascertainment bias, and Steven Greenwald for his assistance with SUDDAN analyses during preparation of the manuscript.

REFERENCES

Assmann, S. F., Hosmer, D., Lemeshow, S. & Mundt, K. (1996). Confidence intervals for measures of interaction. *Epidemiology* **7**, 286–290.

Bennet, A. & Stirling, J. (1998). Vulnerability factors in the anxiety disorders. *British Journal of Medical Psychology* **71**, 311–321.

Binder, D. A. (1983). On the variances of asymptotically normal estimators from complex surveys. *International Statistical Review* **51**, 279–292.

Coyne, J. C., Kessler, R. C., Tal, M., Turnbull, J., Wortman, C. B. & Greden, J. F. (1987). Living with a depressed person. *Journal of Consulting and Clinical Psychology* **11**, 43–51.

Dierker, L. C., Merikangas, K. R. & Szatmari, P. (1999). Influence of parental concordance for psychiatric disorders on psychopathology in offspring. *Journal of American Academy of Child and Adolescent Psychiatry* **38**, 280–288.

Downey, G. & Coyne, J. C. (1990). Children of depressed parents: an integrative review. *Psychological Bulletin* **108**, 50–76.

Dunner, D. L., Fleiss, J. L., Addonizio, G. & Fieve, R. R. (1976). Assortative mating in primary affective disorder. *Biological Psychiatry* **11**, 43–51.

Fendrich, M., Warner, V. & Weissman, M. M. (1990). Family risk factors, parental depression, and psychopathology in offspring. *Developmental Psychology* **26**, 40–48.

Flanders, D. & Rothman, K. (1982). Interaction of alcohol and tobacco in laryngeal cancer. *American Journal of Epidemiology* **115**, 371–379.

Galbaud de Fort, Boivin J.-F. & Kovess, V. (1993). Selection bias in the study of spouse similarity for psychiatric morbidity in clinical samples. *Comprehensive Psychiatry* **34**, 424–431.

Galbaud de Fort, G., Kovess, V. & Boivin, J.-F. (1994). Spouse similarity for psychological distress and well-being: a population study. *Psychological Medicine* **24**, 431–447.

Gershon, E. S., Bunnery, Jr., W. E., Leckman, J. F., Van Eerdewegn, M. & DeBauche, B. A. (1976). The inheritance of affective disorders – a review of data and hypotheses. *Behavioral Genetics* **6**, 227–261.

Greenland, S. (1983). Tests for interaction in epidemiologic studies: a review and a study of power. *Statistics in Medicine* **2**, 243–251.

Greenland, S. & Rothman, K. (1998*a*). Concepts of interaction. In *Modern Epidemiology* (ed. K. Rothman and S. Greenland), pp. 329–342. Lippincott-Raven Publishers: Philadelphia.

Greenland, S. & Rothman, K. (1998*b*). Introduction to stratified analysis. In *Modern Epidemiology* (ed. K. Rothman and S. Greenland), pp. 329–342. Lippincott-Raven Publishers: Philadelphia.

Gross, D., Conrad, B., Fogg, L., Willis, L. & Garvey, C. (1995). A longitudinal study of maternal depression and preschool children's mental health. *Nursing Research* **44**, 96–101.

Hammen, C., Gordon, D., Burge, D., Adrian, C., Jaenicke, C. & Hiroto, D. (1987). Maternal affective disorders, illness, and stress: risk for children's psychopathology. *American Journal of Psychiatry* **144**, 736–741.

Hammen, C., Rudolph, K., Weisz, J., Rao, U. & Gurge, D. (1998). The context of depression in clinic-referred youth: neglected areas in treatment. *Journal of American Academy of Child and Adolescent Psychiatry* **38**, 64–71.

Heun, R. & Maier, W. (1993). Morbid risks for major disorders and frequencies of personality disorders among spouses of psychiatric inpatients and controls. *Comprehensive Psychiatry* **34**, 137–143.

Hosmer, D. & Lemeshow, S. (1992). Confidence interval estimation of interaction. *Epidemiology* **3**, 452–456.

Kessler, R. & Magee, W. J. (1994). Childhood family violence and adult recurrent depression. *Journal of Health and Social Behavior* **35**, 13–27.

Kreitman, N. (1962). Mental disorder in married couples (assortative mating). *Journal of Mental Science* **108**, 438–446.

Krueger, R. F., Moffitt, T. E., Caspi, A., Bleske, A. & Silva, P. A. (1998). Assortative mating for antisocial behavior: developmental and methodological implications. *Behavior Genetics* **28**, 173–186.

Leckman, J. F., Sholomskas, D., Thompson, D., Belanger, A. & Weissman, M. M. (1982). Best estimate of lifetime diagnosis: a methodological study. *Archives of General Psychiatry* **39**, 879–883.

McLeod, J. D. (1993). Spouse concordance for depressive disorders in a community sample. *Journal of Affective Disorders* **27**, 43–52.

Maes, H. H. M., Neale, M. C., Kendler, K. S., Hewitt, J. K., Silberg, J. L., Foley, D. L., Meyer, J. M., Rutter, M., Simonoff, E., Pickles, A. & Eaves, L. J. (1998). Assortative mating for major Psychiatric diagnoses in two population-based samples. *Psychological Medicine* **28**, 1389–1401.

Mannuzza, S., Fyer, A. J., Klein, D. F. & Endicott, J. (1986). Schedule for affective disorders and schizophrenia-lifetime version modified for the study of anxiety disorders (SADS-LA): rationale and conceptual development. *Journal of Psychiatric Research* **20**, 317–325.

Merikangas, K. R. (1984). Divorce and assortative mating among depressed patients. *American Journal of Psychiatry* **141**, 74–76.

Merikangas, K. R. & Spiker, D. G. (1982). Assortative mating among in-patients with primary affective disorder. *Psychological Medicine* **12**, 753–764.

Merikangas, K. R., Bromet, E. J. & Spiker, D. G. (1983). Assortative mating, social adjustment, and course of illness in primary affective disorder. *Archives of General Psychiatry* **40**, 795–800.

Merikangas, K. R., Weissman, M. M., Prusoff, B. A., Pauls, D. L. & Leckman, J. F. (1985). Depressives with secondary alcoholism: psychiatric disorders in offspring. *Journal of Studies on Alcoholism* **46**, 199–204.

Merikangas, K. R., Prusoff, B. A. & Weissman, M. M. (1988*a*). Parental concordance for affective disorders: psychopathology in offspring. *Journal of Affective Disorders* **15**, 279–290.

Merikangas, K. R., Weissman, M. M., Prusoff, B. A. & John, K. (1988*b*). Assortative mating and affective disorders: psychopathology in offspring. *Psychiatry* **51**, 48–57.

Moskalenko, V. D., Vanyukov, M. M., Solovyova, Z. V., Rakhamanova, T. V. & Vladimirsky, M. M. (1992). A genetic study of alcoholism in the Moscow population, preliminary findings. *Journal of Studies on Alcohol* **53**, 218–214.

Murray, L., Kempton, C., Woolgar, M. & Hooper, R. (1993). Depressed mothers' speech to their infants and its relation to infant gender and cognitive development. *Journal of Child Psychology and Psychiatry and Allied Disciplines* **34**, 1083–1101.

Nigg, J. T. & Hinshaw, S. P. (1998). Parent personality traits and psychopathology associated with antisocial behaviors in childhood attention-deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry* **39**, 145–159.

Pine, D., Cohen, P. & Gurley, D. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry* **55**, 56–64.

Richardson, H. M. (1939). Studies of mental resemblance between husbands and wives and between friends. *Psychological Bulletin* **36**, 104–120.

Roff, M. (1950). Intra-family resemblances in personality characteristics. *Journal of Psychology* **30**, 199–227.

Rothman, K. (1976). The estimation of synergy or antagonism. *American Journal of Epidemiology* **103**, 506–511.

Rothman, K., Greenland, S. & Walker, A. (1980). Concepts of interaction. *American Journal of Epidemiology* **112**, 467–470.

Saracci, R. (1980). Interaction and synergism. *American Journal of Epidemiology* **112**, 465–466.

Schuckit, M. A. (1982). The importance of family history of affective disorder in a group of young men. *Journal of Nervous and Mental Disease* **170**, 530–535.

Shah, B. V., Barnwell, B. G. & Bieler, G. S. (1996). *SUDAAN User's Manual*, *Version 6*, *2nd edn*. Research Triangle Institute: Research Triangle Park, NC.

Silove, D., Parker, G., Hadzi-Pavlovic, D., Manicavasagar, V. & Blaszczynski, A. (1991). Parental representations of patients with panic disorder and generalised anxiety disorder. *British Journal of Psychiatry* **159**, 835–841.

Sinclair, D. & Murray, L. (1998). Effects of postnatal depression on children's adjustment in school. *British Journal of Psychiatry* **172**, 58–63.

Vanyukov, M. M., Neale, M. C., Moss, H. B. & Tarter, R. E. (1996). Mating assortment and the liability to substance abuse. *Drug and Alcohol Dependence* **42**, 1–10.

Walter, S. D. & Holford, T. R. (1978). Additive, multiplicative, and other models for disease risks. *Journal of Epidemiology* **108**, 341–346.

Weissman, M. M., Kidd, K. K. & Prusoff, B. A. (1982). Variability in rates of affective disorders in relatives of depressed and normal probands. *Archives of General Psychiatry* **39**, 1397–1403.

Weissman, M. M., John, K., Merikangas, K. R., Wickramaratne, P., Prusoff, B. A. & Kidd, K. K. (1986). Depressed parents and their children: general health, social and psychiatric problems. *American Journal of Diseases in Children* **140**, 801–805.

Weisman, M. M., Gammon, G. D., John, K., Merikangas, K. R., Warner, V., Prusoff, B. A. & Sholomskas, D. (1987). Children of depressed parents: increased psychopathology and early onset of major depression. *Archives of General Psychiatry* **44**, 847–853.

Weissman, M. M., Fendrich, M., Warner, V. & Wickramaratne, P. (1992). Incidence of psychiatric disorder in offspring at high and low risk for depression. *Journal of American Academy of Child and Adolescent Psychiatry* **31**, 640–648.

Weissman, M. M., Warner, V., Wickramaratne, P., Moreau, D. & Olfson, M. (1997). Offspring of depressed parents: 10 years later. *Archives of General Psychiatry* **54**, 932–940.

Woodruff, R. S. (1971). A simple method for approximating the variance of a complicated estimate. *Journal of American Statistical Association* **66**, 411–414.