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Sex Differences in Intergenerational Transfer Risk of Major Depressive Disorder

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The children of depressed parents are more likely to suffer from mental illness, particularly major depressive disorder (MDD). However, most data come from adolescent and young-adult populations, and published studies have reported inconsistent results regarding intergenerational transmission.





Material/Methods: We retrospectively investigated hospitalized depressed patients with positive family history (FHP) from 1 Jan 2008 to 31 Dec 2017 and analyzed the differences in sex distribution in the intergenerational transfer risk of major depressive disorder.

Results: We enrolled 528 patients with maternal or paternal positive FHP from a total of 4856 patients, and divided them into 4 groups: female patients with maternal FHP (FM: 220, 41.7%), female patients with paternal FHP (FP: 116, 22.0%), male patients with maternal FHP (MM: 96, 18.2%), and male patients with paternal FHP (MP: 96, 18.2%). In this study, 12.2% of hospitalized depressed patients had an FHP. The ratio of male: female patients with FHP was 2: 3. The ratio of male: female patients with maternal FHP was almost 1: 2. Analyses showed that the risk of depression in daughters was higher than in sons. Compared with children of depressed fathers, the children of depressed mothers were at higher risk of depression. Daughters and sons share an equal risk of depression with paternal FHP.

Conclusions: The results suggest a clear interaction of sex between patients and their depressed parents. Daughters of depressed mothers had the highest risk of suffering from depression compared with other offspring.

MeSH Keywords: **Depressive Disorder, Major • Family Characteristics • Gender Identity**

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Background

Mounting evidence has demonstrated that parents have large genetic and environmental influences on their offspring's cognition, behavior, and brain development [1]. Furthermore, intergenerational transmission is often observed in the development of psychiatric diseases. It is reported that genetic factors play an important role in the pathophysiology of major depressive disorder (MDD), which is one of the commonest, and sometimes fatal, psychiatric disorders [2–5]. Similarly, the children of depressed parents are at high risk of mental illness, including MDD. For example, Weissman and colleagues [6,7] found that the offspring of depressed parents are 2–3 times more likely to exhibit elevated depression levels than the offspring of nondepressed controls.

The prevalence of depression in males and females shows differing distribution between the sexes. The lifetime probability of depression is up to 30% in women and 15% in men. Offspring of depressed parents are more likely to suffer from depression than those of non-depressed controls, and also show differences in sex distribution [7]. Previous studies also observed depressed parents and their children, and explored the ratio of these differences in distribution of the sexes. However, the conclusions of these studies are not consistent. Some reported that it is maternal depression, not paternal depression, that affected the incidence of their offsprings' depression, including both sons and daughters [8]. Other research revealed that daughters' emotions were more likely to be affected by maternal depression, whereas sons' emotions were more likely to be affected by paternal depression. However, the reverse pattern has also been reported [9]. Moreover, a recent study found that the risk of depression in children (both sons and daughters) was related to depression in their mothers, but depression in fathers only increased the risk of depression in sons [10]. Furthermore, these data are mostly from adolescent and the young-adult populations suffering from depression.

In our study, we retrospectively investigated all depressed patients hospitalized at the Department of Psychiatry, Xijing Hospital, from 1 Jan 2008 to 31 Dec 2017. We recorded their positive family history, including that from mother, father, and secondary relatives, and then analyzed the difference in sex distribution in the intergenerational transfer risk of MDD.

Material and Methods

Design and samples

We reviewed patients with major depression hospitalized from 1 Jan 2008 to 31 Dec 2017 at the Department of Psychiatry, Xijing Hospital, and recorded their family history, including that

from their parents and secondary relatives, then analyzed the differences in sex distribution in the intergenerational transfer risk of MDD. The protocol of this study was approved by the Ethics Committee of Xijing Hospital, the Fourth Military Medical University, and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

In this study, 592 (12.2%) out of a total of 4856 patients had a positive family history (FHP) of MDD. Of these 592 individuals, 528 had maternal FHP or paternal FHP, and the remaining 64 had parental FHP. Females accounted for 59.8% and males accounted for 40.1% of patients with maternal or paternal FHP, respectively. The ratio of male: female patients with FHP was 2: 3.

Assessments protocol

The enrolled patients were aged from 15 to 65 years and diagnosed with MDD by at least 2 attending psychiatrists, according to DSM-4 without other Axis I or Axis II disorders. One patient who became manic at a later date was excluded from the study, according to our tracking system. Symptom status was assessed by the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). Data on patient sex, age of onset, and educational level were also obtained from medical records.

Ascertainment of family history

Family history was determined on the basis of past medical records. A positive family history of MDD can be directly confirmed by past psychiatric medical records diagnosing depression. If there were other medical records with diagnoses of neurosis or neurasthenia, but the symptoms were consistent with depression, confirmation was required from at least 2 family members or close relatives. Of 528 patients with maternal or paternal FHP, 423 were determined to have a family history of depression on the basis of past medical records diagnosing depression. The remaining 105 were determined by the confirmation of at least 2 family members or close relatives.

Statistical analysis

Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Measurement data were reported as mean±SEM. Statistical analyses of the data were performed using the *t* test, or one-way analysis of variance (ANOVA) with or without repeated measures, followed by the least significant difference post hoc test. Categorical variables were presented as the raw number and percentage (%), and analyzed by Pearson's χ^2 test or the Kruskal-Wallis test. Pearson's χ^2 test was used to examine bivariate associations. Statistical significance was set at $p < 0.05$.

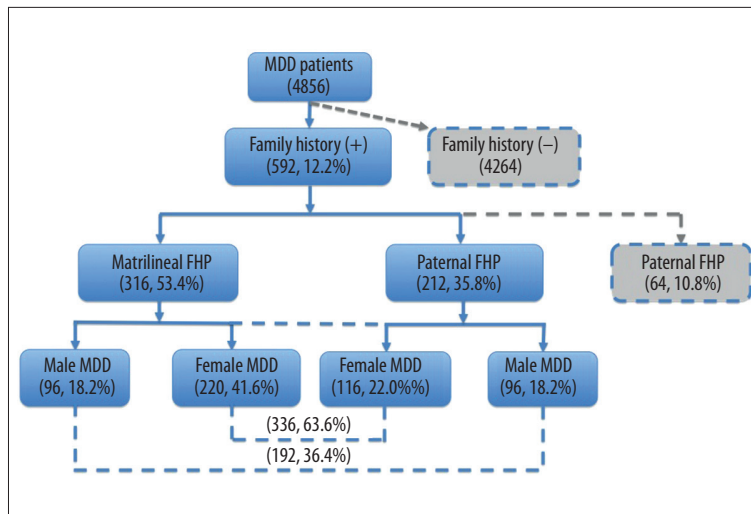


Figure 1. Sex differences in incidence of depression with FHP. FHP – positive family history; FM – Female MDD patients with maternal FHP; FP – Female MDD patients with paternal FHP; MM – Male MDD patients with maternal FHP; MP – Male MDD patients with paternal FHP. Family history was positive in 12.2% of patients.

Table 1. Baseline characteristics of patients with FHP.

Variables	FM	FP	MM	MP
Age (year)*	36.7±3.9	42.7±2.7	36.8±4.9	39.1±4.4
The onset age (year) *	33.8±4.2	38.2±3.5	33.3±3.6	36.9±4.6
Education**				
Low	33 (37.1%)	18 (38.3%)	15 (38.5%)	14 (35.9%)
Middle	34 (38.2%)	16 (34.0%)	14 (35.9%)	15 (38.5%)
High	22 (24.7%)	12 (25.5%)	10 (25.6%)	10 (25.6%)
Score of HAMD*	22.5±1.9	23.5±1.1	25.1±0.9	23.4±1.2
Score of HAMA*	11.7±1.1	10.5±1.4	12.5±1.2	10.9±1.6

Low – no education or less than 6 years; Middle – from 6 years to 12 years; High – more than 12 years. * Continuous data were expressed as mean±SEM and examined using one-way analysis of variance (ANOVA). No significant differences were observed among the groups. ** Categorical data were analyzed by using Kruskal-Wallis test. No statistically significant differences were observed among the groups.

Results

General characteristics of study population

The 528 study patients with maternal or paternal FHP were divided into 4 groups: female patients with maternal FHP (FM: 220, 41.6%), female patients with paternal FHP (FP: 116, 22.0%), male patients with maternal FHP (MM: 96, 18.2%) and male patients with paternal FHP (MP: 96, 18.2%). The male: female ratio of patients with maternal FHP was almost 1: 2 (Figure 1).

We analyzed basic information for these 4 groups, including age, educational level, and depression/anxiety score. Continuous data were expressed as mean±SEM and examined using ANOVA. No significant differences were observed among the groups in age, onset age of MDD, and HAMA/HAMD scores. Categorical data were analyzed using the Kruskal-Wallis test.

No significant difference in educational levels was observed among the groups (Table 1).

Prevalence of positive family history by sex combination

Prevalence of positive family history by sex combination between patient and their depressed parent is presented for each group of patients in Table 2. The ratio of male to female patients was about 2: 3 and almost 60% of patients had maternal FHP. The results suggested a clear interaction of sex between the patients and their depressed parents ($p < 0.05$). Further paired comparison showed that female MDD patients with maternal FHP had a higher prevalence ratio compared to the other 3 groups ($p < 0.05$). No difference was found between the male patients ($p > 0.05$). The interaction of sex between patients and their depressed parents was demonstrated by daughters having more risk of depression than sons. A similar phenomenon

Table 2. Prevalence of positive family history by sex of patients and sex of depressed parent (total n).

Variable (% , n)	Family history		Total (% , n)	χ^2	P
	M	P			
F	41.6 (220)*	22.0 (116)	63.6 (336)	11.540	0.001
M	18.2 (96)	18.2 (96)	36.4 (192)		
Total	59.8 (316)	40.2 (212)	100.0 (528)		

Data were expressed as raw number and percentage (%) and were analyzed by chi-square test. * P=0.001. Female MDD patients with maternal FHP had the highest prevalence ratio among the 4 groups. The ratio of female to male patients was about 3: 2 and almost 60% of patients were maternal FHP.

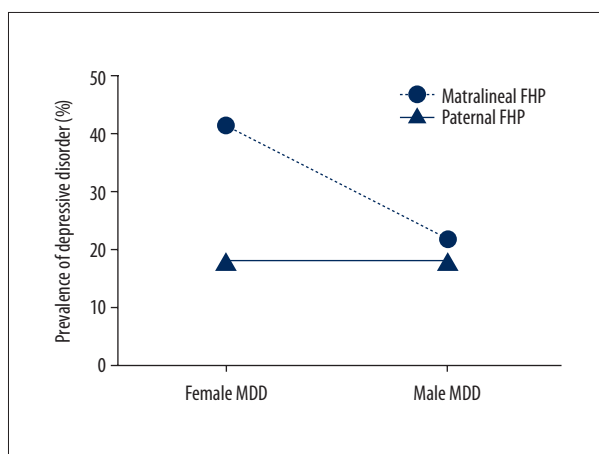


Figure 2. The sex interaction in the genetic risk of depression between patients and their depressive parents. Female MDD–Maternal FHP; Female MDD–Paternal FHP; Male MDD–Maternal FHP; Male MDD–Paternal FHP

was indicated in children of depressed mothers. Compared with other offspring-parent groups, sons and depressed fathers exhibited the lowest prevalence risk. The interaction of gender shows the strong heritability of MDD (Figure 2).

Discussion

In this study, we analyzed the difference in sex distribution in the intergenerational transfer risk of major depressive disorder by real-world study, and found a strong interaction of sex between patients and their depressed parents. Compared to depressed fathers, depressed mothers more strongly influenced the emotions of their offspring, and daughters were more vulnerable to suffering from depression than sons.

Previous genetic studies have mostly focused on the incidence of depressed offspring of depressed parents, in twin and adoption studies [11–13]. As opposed to previous research, we used a retrospective method to investigate genetic transmission patterns. It is reported that the prevalence of depression in China

is 3.02% [14], and 5% of men and 9% of women will experience a depressive disorder in their lifetime according to the World Health Organization [15]. The prevalence ratio of male: female is about 1: 2. In this study, we analyzed the FHP information of hospitalized MDD patients and then classified them ‘sex×sex’ into 4 groups. We obtained 592 samples with FHP from 4856 depressed patients. Of the hospitalized patients, 12.2% had positive FHP. The ratio of male: female patients with FHP was 2: 3. This result was lower than that of other studies [12]. Previous meta-analysis estimated the heritability for MDD to be 37% (95% confidence interval, 31–42%). Similarly, prevalence estimates for MDD are lower in China (3.6%) [16] than in the US (16.2%) [17].

In our study, we could not preclude the possibilities of inaccurate memory or lack of clear diagnosis based on information from parents or secondary relatives. Statistical analysis for patients with positive family history shows that depressed mothers have a greater effect on the emotions of their offspring, and daughters are more vulnerable to depression than are sons. The male: female ratio of patients with maternal FHP was almost 1: 2. Offspring had an equal risk of depression with paternal FHP. More strikingly, and consistent with previous studies, we found that the prevalence of MDD is higher in females [18–20].

As commonly believed, parents exert a strong genetic and environmental influence on their offspring, including the occurrence major depressive disorder [21–23]. In our study, we found no differences among daughter-father, son-father, and son-mother groups. This finding demonstrates 2 points. First, highest risk of depression was found in daughters of depressed parents. Second, the offspring of depressed mothers had a higher risk of depression. These findings are consistent with those of Goodman and colleagues [24,25], who reported clear intergenerational effects in depression between mothers and daughters. However, in contrast to a report of a relatively higher risk in daughter-depressed mother groups, we also found a relatively lower risk in sons of depressed parents (mother or father). Previous studies did not distinguish the

sons and daughters who were given more affection, because previous studies mostly focused on the sex of the parents, not the children [26]. In our study, we used the sex cross method to test differences in sex distribution in different group combinations, and found no difference in sons with maternal or paternal depression, but did find a difference for daughters with a depressed parent.

It is currently difficult to identify the precise underlying mechanism of the maternal transmission pattern. A growing number of animal and human neuroimaging studies have similarly found that corticolimbic circuitry is highly relevant in a wide range of processes, including mood regulation and depression [27,28]. Studies have revealed the participation of structural abnormalities in corticolimbic circuitry in healthy controls, with or without family history [29]. Other recent studies have demonstrated that daughters' corticolimbic morphology is more similar to their mothers' than that of other parent-offspring pairs. This specific similarity in the corticolimbic circuitry between daughter and mothers may be tightly linked to the greater vulnerability for daughters, but not sons, in developing depression when their mothers have depression [30].

Previous studies have mostly focused on family, twin, and adoption data. The samples in those studies are younger than in our patients because of different experimental designs. There is an inevitable possibility that a subject has not yet exhibited symptoms, such as the manic status of bipolar depression. In our study, we specifically focused on MDD patients, and retrospectively investigated family history information.

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Conclusions

Despite its limitations, this study shows a clear maternal transmission pattern between depressed parents and their offspring, especially between depressed mothers and their daughters.

Availability of data and materials

All data and materials related to the study can be obtained through contacting the first author at fanggx0881@163.com

Conflict of interest

Not applicable.

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