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ORIGINAL ARTICLE

Co-aggregation of major psychiatric disorders in individuals with first-degree relatives with schizophrenia: a nationwide population-based study

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A previous genetic study has suggested that schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) share common disease-associated genes. However, whether individuals with first-degree relatives (FDRs) with schizophrenia have a higher risk of these major psychiatric disorders requires further investigation. This study used Taiwan's National Health Insurance Research Database and identified 151 650 patients with schizophrenia and 227 967 individuals with FDRs with schizophrenia. The relative risks (RRs) of schizophrenia and other major psychiatric disorders were assessed in individuals with FDRs with schizophrenia. The individuals with FDRs with schizophrenia exhibited higher RRs (95% confidence interval) of major psychiatric disorders, namely schizophrenia (4.76, 4.65–4.88), bipolar disorder (3.23, 3.12–3.35), major depressive disorder (2.05, 2.00–2.10), ASD (2.55, 2.35–2.77) and ADHD (1.31, 1.25–1.37) than were found in the total population. Several sensitivity analyses were conducted to confirm these results. A dose-dependent relationship was observed between the risks of major psychiatric disorders and the numbers of FDRs with schizophrenia. The increased risks of major psychiatric disorders were consistent in different family relationships, namely among parents, offspring, siblings and twins. Our study supports the familial dose-dependent co-aggregation of schizophrenia, bipolar disorder, major depressive disorder, ASD and ADHD, and our results may prompt governmental public health departments and psychiatrists to focus on the mental health of individuals with FDRs with schizophrenia.

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INTRODUCTION

Schizophrenia is a highly heritable psychiatric disorder with a heritability rate of up to 70%, and it has been considered the strongest indicator of schizophrenia risk in a family.[1] Several previous studies have not found other psychiatric disorders beyond schizophrenia spectrum disorders, such as affective disorders, in the first-degree relatives (FDRs) of patients with schizophrenia and the offspring of parents with schizophrenia.[2,3] Moreover, a longitudinal study of 61 families has not found an association between parental schizophrenia and offspring lifetime affective disorders.[4] However, the limited statistical power due to small-sample sizes and the low prevalence of psychiatric disorders in previous studies have been considered reasons for the failure to detect the familial aggregation of major psychiatric disorders with schizophrenia. Previous studies have additionally noted that a sample size of at least 7800 FDRs would be required to investigate the potential familial aggregation between affective disorders and schizophrenia.[5]

In recent decades, clinical, epidemiological and genetic studies have increasingly reported the co-occurrence of schizophrenia with other major psychiatric disorders in individuals and their family members.[3–20] A meta-analysis of 38 family studies has found a familial co-aggregation of schizophrenia and bipolar disorder.[5] Buckley *et al.*[8] have reported a high prevalence of anxiety and depressive disorders in patients with schizophrenia, and the Bipolar and Schizophrenia Young Offspring Study has found that the offspring of parents with schizophrenia had a higher risk of attention deficit hyperactivity disorder (ADHD) than did the community controls (OR, odds ratio = 4.39).[13] A population-based study has reported 2.2- to 2.5-fold higher rates of parents with schizophrenia in offspring with autism spectrum disorder (ASD).[17] Furthermore, the Helsinki High-Risk Study, following 179 offspring of mothers with schizophrenia, has observed that 6.7% of the offspring developed schizophrenia, and 10.6% developed nonpsychotic disorders.[19] In a Danish population-based cohort study, the proportion of any psychiatric disorder in the 270 offspring of 196 schizophrenic couples was found to be 67.5%.[16] Mortensen *et al.*[11] have further confirmed that schizophrenic patients have an increased risk of having FDRs with a broader range of mental disorders. A recent population-based study has also shown that the relative risk (RR) of major affective disorder is 3.49 in individuals with FDRs with schizophrenia.[14] However, in the above studies, the categories of psychiatric disorders except schizophrenia have been broad and vague, and the sample sizes used to investigate risk of nonpsychotic disorders with schizophrenia have been somewhat

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Table 1. Characteristics of the Individuals with FDRs with schizophrenia and total population

	Male			*Female*			*Total*		
No. (%)	*Individuals with FDRs with schizophrenia*	*Total population*	P-*value*	*Individuals with FDRs with schizophrenia*	*Total Population*	P-*value*	*Individuals with FDRs with schizophrenia*	*Total Population*	P-value
No.	114 554	11 456 759		113 413	11 801 416		227 967	23 258 175	
Age, mean (s.d.)	38.4 (19.7)	37.5 (20.8)	< 0.001*	37.6 (18.9)	38.1 (20.6)	< 0.001*	38.0 (19.4)	37.8 (20.7)	< 0.001*
Male	–	–		–	–		114 554 (50.3)	11 456 759 (49.3)	< 0.001*
Monthly income			*< 0.001**			*< 0.001**			*< 0.001**
0–500 USD	77 799 (67.9)	7 041 037 (61.4)	< 0.001*	81 831 (72.2)	7 708 661 (65.3)	< 0.001*	159 630 (70.0)	14 749 698 (63.5)	< 0.001*
501–800 USD	22 222 (19.4)	2 666 560 (23.3)	< 0.001*	21 890 (19.3)	2 971 185 (25.2)	< 0.001*	44 112 (19.4)	5 637 745 (24.2)	< 0.001*
⩾801 USD	14 533 (12.7)	1 749 162 (15.3)	< 0.001*	9 692 (8.5)	1 121 570 (9.5)	< 0.001*	24 225 (10.6)	2 870 732 (12.3)	< 0.001*
Place of Residence			*< 0.001**			*< 0.001**			*< 0.001**
1 (Urban)	36 036 (31.5)	3 734 313 (32.6)	< 0.001*	39 155 (34.5)	4 123 979 (34.9)	0.0031*	75 191 (33.0)	7 858 292 (33.8)	< 0.001*
2	36 644 (31.9)	3 532 823 (30.8)	< 0.001*	35 712 (31.5)	3 608 434 (30.6)	< 0.001*	72 356 (31.7)	7 141 257 (30.7)	< 0.001*
3	18 345 (16.0)	1 864 605 (16.3)	0.0173	16 932 (14.9)	1 746 289 (14.8)	0.2120	35 277 (15.5)	3 610 894 (15.5)	0.5063
4	14 508 (12.7)	1 410 872 (12.3)	0.0003*	13 528 (11.9)	1 411 297 (12.0)	0.7518	28 036 (12.3)	2 822 169 (12.1)	0.0169
5 (Rural)	8603 (7.5)	871 168 (7.6)	0.2325	7650 (6.8)	865 971 (7.3)	< 0.001*	16 253 (7.1)	1 737 139 (7.5)	< 0.001*
Unknown	418 (0.4)	42 978 (0.4)	0.5727	436 (0.4)	45 446 (0.4)	0.9718	854 (0.4)	88 424 (0.4)	0.6672

Abbreviation: FDR, first-degree relative. *$P < 0.05$.

limited; hence, additional studies are needed to clarify the relationship between schizophrenia and other major psychiatric disorders in FDRs by using a population-based large-sample study design.[10]

Notably, several large genome-wide association studies have indicated the possibility of common underlying genetic vulnerability among major psychiatric disorders, namely schizophrenia, bipolar disorder, major depressive disorder, ADHD and ASD.[15,18] However, whether the reported comprehensive genome-wide association studies results can be duplicated in a single epidemiological study with good statistical power warrants further investigation.

Using a nationwide population-based sample and pedigree data from the entire population in Taiwan, we determined the familial risk of major psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, ADHD and ASD, in individuals with FDRs with schizophrenia. We hypothesized that these individuals would have an increased risk of the aforementioned disorders and that a higher number of FDRs with schizophrenia would be related to a higher risk of these disorders.

MATERIALS AND METHODS

Source of data

The Taiwan National Health Insurance (NHI) program, established in 1995, is a universal single-payer system that provides compulsory health insurance to approximately all residents of Taiwan (~23 million); its coverage rate was ~99.6% at the end of 2010. The NHI Research Database (NHIRD), released and audited by the Department of Health and Bureau of the NHI program, provides comprehensive information about the insured subjects. Registration files contain details of demographics (date of birth, sex, residential location, income status, family relationships) and claims data (outpatient and inpatient care, medical diagnoses, prescriptions, operations). To protect individual privacy, every insured subject is assigned a 32-digit unique and anonymous identifier by the National Health Research Institutes before data are released to researchers; thus, every subject can be followed continuously by using this unique identifier. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for diagnosing diseases during the study period.[21–23] A specialized data set of mental disorders including all psychiatric medical records of insured patients between 1 January 2001 and 31 December 2010 was used to identify the major psychiatric disorders in our study. This study protocol was reviewed by the Institutional Review Board of Taipei Veterans General Hospital.

Disease classification

Major psychiatric disorders, including schizophrenia (ICD-9-CM: 295), bipolar disorder (ICD-9-CM: 296 except 296.2, 296.3, 296.9 and 296.82), major depressive disorder (ICD-9-CM: 296.2 and 296.3), ASD (ICD-9-CM: 299) and ADHD (ICD-9-CM: 314) in individuals with FDRs with schizophrenia and the total population ($n = 23\,258\,175$), were identified from a specialized data set of mental disorders in the NHIRD. These disorders were diagnosed at least twice by board-certified psychiatrists on the basis of their clinical judgment and diagnostic interviews, as in previously published NHIRD studies.[22–24]

Identification of family relationships

We identified family relationships using the NHIRD for genealogy reconstruction, according to previously reported methods.[25,26] Only blood relatives or spouses were qualified to be dependents of the insured patients. With unique personal identifiers, we identified the following family relationship groups: parents, offspring, siblings and twins. The sibling relationship was confirmed if subjects had the same father or mother. Siblings were identified as twins if they shared a birth date; however, twin zygosity could not be determined from the NHIRD. Each subject may have had several types of relationships in a family. Among all individuals in the registry of beneficiaries ($n = 23\,258\,175$), 14.4% ($n = 3\,340\,999$) could not be determined to have any relatives.

Assessment of covariates

Demographic data, including age, sex, place of residence and income status in 2010, are displayed in Table 1 and were adjusted in our study. The place of residence was classified into five categories according to the level of urbanization.[27]

Inclusion and exclusion criteria

Our study population included all persons registered in Taiwan in 2010. We excluded subjects born before 1 January 1890 or after 31 December 2010 and those without valid insurance status or with unknown sex status ($n = 2$, $< 0.01\%$). Any individual who had at least one FDR (parent, offspring, sibling or twin) with schizophrenia was assigned to the group with FDRs with schizophrenia. We identified 23 258 175 individuals in the registry of beneficiaries in Taiwan in 2010. A total of 151 650 schizophrenia patients were identified, and 227 967 individuals with FDRs with schizophrenia were identified through linkage.

Sensitivity analyses

To further assess the robustness of our results, we performed four sensitivity analyses to minimize the influence of potential bias in our study. First, to further improve the diagnostic validity and stability, the thresholds for the inclusion criteria of diagnoses were increased at least three times by board-certified psychiatrists in model 1. Second, to minimize confounding effects of other major psychiatric disorders and to independently clarify the influence of schizophrenia on the risk of major psychiatric disorders in individuals, we conducted a multivariable analysis with adjustment of demographic data and other major psychiatric disorders in both the group of individuals with FDRs with schizophrenia and the total population group in model 2. Third, to eliminate the comorbid effect of schizophrenia with other major psychiatric disorders, such as ASD and ADHD, in a single individual, individuals with schizophrenia were excluded from model 3 so that we could assess the risks of other psychiatric disorders independently between individuals with FDRs with schizophrenia and the total population. Finally, we conducted a 1:4 case–control matched analysis to decrease the influence of age, sex and types of familial relations. For example, a 30-year-old man with a schizophrenic mother would be matched with four 30-year-old men without schizophrenic mothers. If this man had two types of familial relationships, such as mother–son and sister–brother relationships, he would be counted for each of these relationships and matched twice. The sensitivity analyses were also performed in the case–control matched design (results not shown here; please see Supplementary Tables 8-11).

Statistical methods

Chi-squared and independent *t*-tests were used to compare categorical and continuous variables, respectively, between individuals with FDRs with schizophrenia and the total population. The prevalence between the two groups was assessed. The RRs and 95% confidence intervals (CIs) were calculated to determine the risks of the five major psychiatric disorders between the two groups. Risk was defined by the ratio of cases of schizophrenia (numerator) and the number of the total population or individuals with FDRs with schizophrenia (denominator). We performed the same analyses for comparison between individuals with FDRs with schizophrenia and individuals without FDRs with schizophrenia. The RRs of major psychiatric disorders for each specific type of familial relationship (parents, offspring, siblings and twins) were calculated as the prevalence of each major psychiatric disorder among individuals with FDRs with schizophrenia divided by the prevalence among individuals without FDRs with schizophrenia.

In addition, each family cluster could contain more than one relative relationship (that is, siblings and parents–children). To manage the effects of clusters, we used Poisson regression models with a robust error variance to estimate the RRs for clustered data after adjustment for demographic data (age, sex, residence and income).[28] We also assessed the dose-dependent relationship between the risks of major psychiatric disorders and numbers (1 or $\geqslant 2$) of FDRs with schizophrenia. In addition, sub-analyses stratified by each relationship (parents, offspring, siblings and twins) were conducted to investigate the risks of the disorders in the individuals with FDRs with schizophrenia compared with those without FDRs with schizophrenia. All statistical analyses were performed using SPSS version 21.0 for Windows (IBM, Armonk, NY, USA) and SAS version 9.2 (SAS Institute, Cary, NC, USA). PROC GENMOD in SAS was used to estimate the adjusted RRs in our study. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

We identified 23 258 175 individuals in the total population (49% male) and 227 967 individuals with FDRs with schizophrenia who had 231 558 identifiers of relationships, including parents ($n = 74\,801$), offspring ($n = 77\,547$), siblings ($n = 78\,603$) and twins ($n = 607$). In the total population and among individuals with FDRs with schizophrenia, 151 650 (0.65%) and 7398 (3.25%) were diagnosed with schizophrenia, respectively. Table 1 presents the demographic data in 2010 and shows that, compared with the total population, individuals with FDRs with schizophrenia were younger, had lower incomes and were predominantly men.

Table 2 shows that the individuals with FDRs with schizophrenia had higher risks (RRs, 95% CI) of major psychiatric disorders than the total population: 4.76 (4.65–4.88) for schizophrenia, 3.23 (3.12–3.35) for bipolar disorder, 2.05 (2.00–2.10) for major depressive disorder, 2.55 (2.35–2.77) for ASD and 1.31 (1.25–1.37) for ADHD. Similar and consistent results were also obtained in the comparison between individuals with and individuals without FDRs with schizophrenia (Supplementary Tables 1) and in a case–control matched design (Supplementary Tables 8–9). A dose-dependent relationship was observed between the numbers of FDRs with schizophrenia and the risks of all five major psychiatric disorders, namely schizophrenia (1 FDR: 4.75, 4.63–4.86; $\geqslant 2$ FDRs: 20.75, 18.9–22.8), bipolar disorder (3.23, 3.11–3.35; 9.28, 7.77–11.10), major depressive disorder (2.05, 2.00–2.10; 4.01, 3.42–4.70), ASD (2.52, 2.32–2.74; 6.95, 4.69–10.28) and ADHD (1.61, 1.54–1.69; 2.45, 1.82–3.29). That is, an individual's risk of major psychiatric disorders increased with the number of the individual's FDRs with schizophrenia (Table 3).

The sensitivity analyses in models 1–3 consistently showed that individuals with FDRs with schizophrenia, compared with the total population, had elevated risks of five psychiatric disorders. Specifically, model 1 presented these consistent findings when we used the stricter inclusion criteria to define the diagnoses of psychiatric disorders (RRs in model 1; schizophrenia: 4.87, 4.75–4.99; bipolar disorder: 3.22, 3.11–3.34; major depressive disorder: 2.05, 2.00–2.10; ASD: 2.48, 2.27–2.70; ADHD: 1.59, 1.51–1.67). In model 2, we conducted a multivariable analysis to decrease the confounding effects of other psychiatric disorders. There were still higher risks of each major psychiatric disorder after adjusting for other psychiatric disorders for those individuals with FDRs with schizophrenia. In model 3, we excluded individuals diagnosed with schizophrenia to eliminate the potential comorbid effect of schizophrenia. The results confirmed that there were still elevated risks of other psychiatric disorders, thus indicating an independent effect of individual's FDRs with schizophrenia on the risk of other psychiatric disorders in the individuals (RRs in model 3; bipolar disorder: 2.71, 2.59–2.83; major depressive disorder: 1.88, 1.83–1.93; ASD: 2.13, 1.94–2.34; ADHD: 1.59, 1.51–1.66) (Table 4). In addition, these findings remained robust and were confirmed in the case–control matched design (Supplementary Table 10).

We performed sub-analyses of the risks of psychiatric disorders according to different relationships. Compared with individuals who had no FDRs with schizophrenia, the RR (95% CI) of each psychiatric disorder was higher in individuals with FDRs with schizophrenia, namely schizophrenia (parents: 6.00, 5.74–6.26; offspring: 5.51, 5.26–5.78; siblings: 7.75, 7.49–8.02; twins: 46.88, 39.50–55.65), bipolar disorder (parents: 3.35, 3.13–3.59; offspring: 3.10, 2.92–3.30; siblings: 3.74, 3.54–3.96; twins: 15.13, 11.17–20.48), major depressive disorder (parents: 2.19, 2.08–2.30; offspring: 1.98, 1.91–2.06; siblings: 2.16, 2.07–2.26; twins: 5.60, 4.14–7.58), ASD (parents: 2.29, 2.05–2.55; offspring: 8.58, 4.47–16.50; siblings: 3.25, 2.86–3.69; twins: 12.27, 7.03–21.43) and ADHD (parents: 1.78, 1.69–

Table 2. Relative risk of different psychiatric disorders between individuals with FDRs with schizophrenia and total population

Number. (%)	*Male*			*Female*			*All*		
	Individuals with FDRs with schizophrenia	*Total Population*	*RR[a] (95% CI)*	*Individuals with FDRs with schizophrenia*	*Total Population*	*RR[a] (95% CI)*	*Individuals with FDRs with schizophrenia*	*Total Population*	*RR[a] (95% CI)*
No.	114 554	11 456 759		113 413	11 801 416		227 967	23 258 175	
SCZ	3763 (3.28)	78 903 (0.69)	4.52 (4.38–4.67)	3635 (3.21)	72 747 (0.62)	5.06 (4.89–5.23)	7398 (3.25)	151 650 (0.65)	4.76 (4.65–4.88)
BD	1422 (1.24)	41 938 (0.37)	3.29 (2.12–3.47)	1736 (1.53)	56 221 (0.48)	3.19 (3.04–3.35)	3158 (1.39)	98 159 (0.42)	3.23 (3.12–3.35)
MDD	2509 (2.19)	114 625 (1.00)	2.13 (2.05–2.21)	3996 (3.52)	211 354 (1.79)	2.00 (1.94–2.06)	6505 (2.85)	325 979 (1.40)	2.05 (2.00–2.10)
ASD	427 (0.37)	22 133 (0.19)	2.34 (2.13–2.58)	154 (0.14)	4854 (0.04)	3.47 (2.95–4.07)	581 (0.25)	26 987 (0.12)	2.55 (2.35–2.77)
ADHD	1449 (1.26)	118 010 (1.03)	1.23 (1.17–1.29)	482 (0.42)	32678 (0.28)	1.54 (1.40–1.68)	1931 (0.85)	150 688 (0.65)	1.31 (1.25–1.37)

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CI, confidence interval; FDR, first-degree relative; MDD, major depressive disorder; RR, relative risk; SCZ, Schizophrenia. [a]Adjusted for age, sex, urbanization, income level.

Table 3. Relative risk of different psychiatric disorders and the number of the individual's FDRs with schizophrenia

Number of the individual's FDRs with schizophrenia	*Schizophrenia*		*Bipolar disorder*		*Major depressive disorder*		*ASD*		*ADHD*	
	No. (%)	*RR[a] (95% CI)*	*No. (%)*	*RR[a] (95% CI)*	*No. (%)*	*RR[a] (95% CI)*	*No. (%)*	*RR[a] (95% CI)*	*No. (%)*	*RR[a] (95% CI)*
0 ($n = 23\,030\,208$)	144 252 (0.63)	1.00 (ref. group)	95 001 (0.41)	1.00 (ref. group)	319 474 (1.39)	1.00 (ref. group)	26 406 (0.11)	1.00 (ref. group)	148 757 (0.65)	1.00 (ref. group)
1 ($n = 224\,422$)	6977 (3.11)	4.75 (4.63–4.86)	3037 (1.35)	3.23 (3.11–3.35)	6352 (2.83)	2.05 (2.00–2.10)	556 (0.25)	2.52 (2.32–2.74)	1887 (0.84)	1.61 (1.54–1.69)
$\geqslant 2$ ($n = 3545$)	421 (11.88)	20.75 (18.9–22.8)	121 (3.41)	9.28 (7.77–11.10)	153 (4.32)	4.01 (3.42–4.70)	25 (0.71)	6.95 (4.69–10.3)	44 (1.24)	2.45 (1.82–3.29)
P for trend		< 0.001		< 0.001		< 0.001		< 0.001		< 0.001

Abbreviations: ASD, autism spectrum disorder; ADHD, attention deficit/hyperactivity disorder; FDR, first-degree relative; RR, relative risk. [a]Adjusted for age, sex, urbanization, income level.

Table 4. Relative risk of different psychiatric disorders between individuals with FDRs with schizophrenia and total population

Adjusted RR (95% CI)	*Model 1*			*Model 2*			*Model 3*		
	Male	*Female*	*All*	*Male*	*Female*	*All*	*Male*	*Female*	*All*
No.									
Individuals with FDRs with schizophrenia	105 886	104 877	210 763	114 554	113 413	227 967	110 791	109 778	220 569
Total populations	11 456 759	11 801 416	23 258 175	11 456 759	11 801 416	23 258 175	11 377 856	11 728 669	23 106 525
SCZ	4.63 (4.48–4.79)	5.16 (4.98–5.34)	4.87 (4.75–4.99)	3.53 (3.41–3.64)	3.80 (3.67–3.93)	3.66 (3.57–3.74)	–	–	–
BD	3.28 (3.11–3.47)	3.17 (3.02–3.33)	3.22 (3.11–3.34)	1.72 (1.63–1.82)	1.64 (1.57–1.73)	1.68 (1.62–1.74)	2.67 (2.49–2.85)	2.74 (2.59–2.9)	2.71 (2.59–2.83)
MDD	2.14 (2.06–2.23)	2.00 (1.94–2.07)	2.05 (2.00–2.10)	1.54 (1.48–1.61)	1.53 (1.48–1.58)	1.54 (1.50–1.58)	1.92 (1.84–2.01)	1.85 (1.79–1.91)	1.88 (1.83–1.93)
ASD	2.23 (2.01–2.47)	3.54 (3.00–4.18)	2.48 (2.27–2.70)	1.54 (1.40–1.70)	1.92 (1.63–2.26)	1.62 (1.49–1.76)	2.01 (1.80–2.24)	2.70 (2.21–3.28)	2.13 (1.94–2.34)
ADHD	1.54 (1.46–1.62)	1.76 (1.60–1.94)	1.59 (1.51–1.67)	1.41 (1.33–1.48)	1.53 (1.40–1.68)	1.44 (1.38–1.51)	1.54 (1.46–1.62)	1.76 (1.6–1.93)	1.59 (1.51–1.66)

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; FDR, first-degree relative; MDD, major depressive disorder; SCZ, schizophrenia. Model 1: Psychiatric diagnosis given by board-certified psychiatrists at least three times. Model 2: Adjusted for age, sex, urbanization, income level and other major psychiatric disorders. Model 3: Excluding individuals with schizophrenia and adjusted for age, sex, urbanization, income level.

1.87; offspring: 2.40, 1.71–3.35; siblings: 1.17, 1.06–1.28; twins: 2.10, 1.19–3.71; Supplementary Table 3–7 and Figure 1).

DISCUSSION

Our population-based cohort study comprised more than 23 million cases, and we identified a total of 151 650 schizophrenia patients and 227 967 individuals with FDRs with schizophrenia from the NHIRD. We identified increased risks of schizophrenia and other major psychiatric disorders, namely bipolar disorder, major depressive disorder, ASD and ADHD, in a dose-dependent manner in individuals with FDRs with schizophrenia. In particular, individuals with a twin with schizophrenia showed the highest risks of schizophrenia, bipolar disorder, major depressive disorder and ASD. In a large sample with high coverage, our results of the familial co-aggregation of schizophrenia with other major psychiatric disorders indicated that the familial transmission of psychiatric disorders is heterotypic and suggested that schizophrenia is transmitted interdiagnostically within a family. The risks of other major psychiatric disorders were also significantly elevated even when we adjusted for or excluded certain psychiatric disorders in the sensitivity analysis. Our findings firmly supported the previous findings of genome-wide association studies that the risks of schizophrenia, bipolar disorder, major depressive disorder, ASD and ADHD may be hereditary.[15,29]

Many previous studies have supported a higher risk of concordant schizophrenia or schizophrenia spectrum disorder in offspring with two affected parents than in those with only one affected parent;[5,14,16] however, studies demonstrating similar dose-dependent effects on disorders beyond the psychotic spectrum disorders are relatively rare. These studies typically have used broadly defined categories of disorders (nonaffective or affective psychosis, psychiatric disorders or any psychiatric contact) in parents or subjects with limited relationships, such as parents and offspring, to assess the dose-dependent effects.[10,17] Owing to limitations in previous studies, such as low statistical power, selection bias and presentation bias,[6,20] it has been difficult to demonstrate dose-dependent effects and effects beyond those on schizophrenia spectrum disorder in traditional family studies. In this study, compared with other population-based studies, we used a larger sample size and more comprehensive analysis focusing on the five major psychiatric disorders.

Increasing evidence suggests co-aggregation of schizophrenia with other major psychiatric disorders, such as bipolar disorder, major depressive disorder, ASD and ADHD. Although the contributions of genetic versus environmental factors are still debated in terms of the crossing boundaries of major psychiatric disorders, cumulative findings, including those from large-scale association studies and genetic studies, have supported the former hypothesis. One study reviewing 3863 offspring of parents with severe mental illness (schizophrenia, bipolar disorder or major depressive disorder) has reported an elevated risk of affective disorders in these individuals (RR = 1.62).[12] Another meta-analysis has examined the familial co-aggregation of schizophrenia and bipolar disorder and has found that individuals with FDRs with schizophrenia show a twofold elevated risk of bipolar disorder.[5] Two large population-based studies have demonstrated evidence of a shared genetic risk for schizophrenia and bipolar disorder.[6,16] To date, increasing genetic evidence also supports the existence of an overlap in genetic susceptibility across schizophrenia, bipolar disorder and major depressive disorder.[7,30–34]

The association between schizophrenia and ADHD has received much less attention than that between schizophrenia and affective disorders in previous studies.[12,13,35–37] A small-sample-size study has demonstrated that the offspring of parents with schizophrenia have a higher rate of ADHD (OR = 4.39) than do community controls.[13] Rasic *et al.*[12] have reported that there are

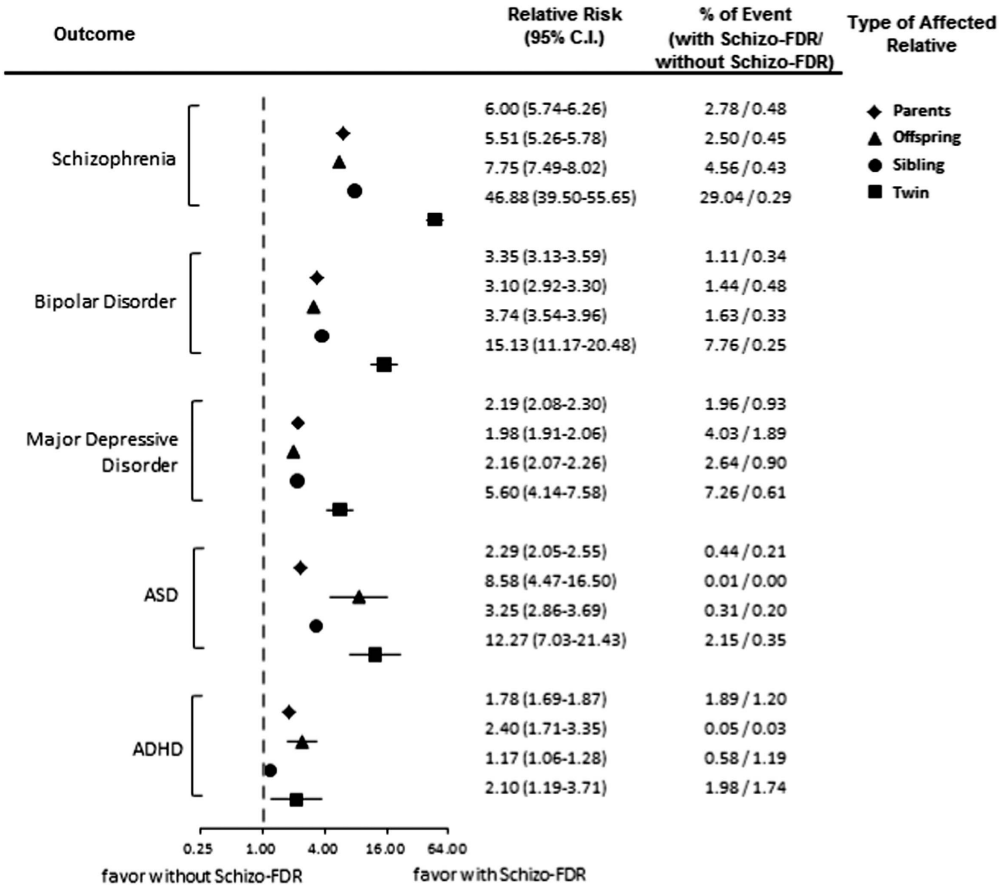

Figure 1. Relative risks for major psychiatric disorder in individuals with FDRs with schizophrenia among different kinships. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; FDR, first-degree relatives.

few or no data from family studies on childhood ADHD, because most previous studies of the offspring of parents with schizophrenia have assessed the offspring only in adulthood. Recently, a Swedish population-based study has confirmed shared genetic factors between ADHD and schizophrenia and has found that individuals of FDRs with ADHD are at increased risk of schizophrenia (OR = 1.71–2.22), findings similar to our results.[35] These findings are also consistent with findings of copy number variants and the neurocognitive deficit overlap between ADHD and schizophrenia.[38,39]

In addition, the limitation of low statistical power has affected previous family linkage studies of the ASD-schizophrenia association;[9] however, several recent population-based studies have overcome this limitation and successfully demonstrated a higher ASD risk for individuals with FDRs with schizophrenia (OR = 2.0–2.5, similar to our results).[17,40,41] The shared genetic etiology between ASD and schizophrenia has also been discussed.[9,42–45]

The Cross-Disorder Group of the Psychiatric Genomics Consortium has analyzed genome-wide SNP (single-nucleotide polymorphism) data for these disorders and has identified several specific genetic associations across the disorders, including a set of four risk loci on chromosomes 3 and 10 as well as an SNP of two genes involved in neuronal calcium channel signaling.[15] This group has further demonstrated that SNPs explain 17–29% of the variance in liability and has reported a high genetic correlation between schizophrenia and bipolar disorder, a moderate correlation between schizophrenia and major depressive disorder and a low correlation between schizophrenia and ASD.[29] In pleiotrophy, multiple clinical phenotypic traits can be caused by one gene, which may be hereditary within a family.[46,47] Although the aforementioned disorders may share genes, these genes may develop a diverse psychopathology under different circumstances.[46,47] On the basis of the above evidence, particularly large molecular genetic studies and population-based studies in Sweden, Finland and Denmark, our findings further support the possibility of familial co-aggregation among five major psychiatric disorders in the Chinese population. As a result, we believe that there are common genetic etiologies among these five psychiatric disorders.

In our study, there was an ~1% excess of males among individuals with FDRs with schizophrenia compared with the total population, possibly as a result of selection bias. In Taiwan, individuals who do not or cannot work, such as children or patients with major psychiatric disorders, are typically dependents of their insured male FDRs. Hence, we may have identified more male data than female data, thus resulting in this 1% excess. However, to minimize the potential sex-related bias, we further examined an age- and sex-matched study and found consistent findings that both men and women with FDRs with schizophrenia were likely to have major psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, ASD and ADHD. Furthermore, regarding sex in the risks of major psychiatric disorders, we found that the risks for major psychiatric disorders, except ASD, were similar between men and women. Women with FDRs with schizophrenia showed a slightly higher risk of ASD than men. The lower prevalence of ASD, a male-predominant disorder,[48] in the female total population may be

related to the higher risk of ASD in females than in males. This result was also found in our case–control model: the difference in risk of ASD in women was slightly higher than that in men, thus suggesting that having FDRs with schizophrenia is an important factor for ASD in females. Moreover, diagnostic bias may occur when psychiatrists judge a diagnosis without comprehensive information on a family's psychiatric history. Diagnostic validity challenges commonly exist in population-based registry studies and family studies.[6,10,11,16] To minimize the potential diagnostic bias, we recruited only patients with a consistent diagnosis given by psychiatrists at least twice, or possibly three times. Moreover, to assess the independent effects of schizophrenia on the risks of major psychiatric disorders, we used two sensitivity analyses (models 2 and 3) to confirm our results. Although several different population-based studies have applied different inclusion criteria, our findings were still compatible with previous results, thereby indicating the familial co-aggregation of these major psychiatric disorders. In addition, in contrast to previous studies relying on hospital inpatient data only, in this study, our database included outpatient and inpatient visits so that we could more precisely determine the real clinical association when investigating disorders with low inpatient contact, such as ASD or ADHD

This study has several limitations. First, the prevalence of major psychiatric disorders may have been underestimated, because only patients who sought medical consultation and treatment between 2001 and 2010 were included in our study. Thus, lifetime prevalence could not be measured in our study. In addition, the possibility of misclassification of diagnoses cannot be completely excluded. However, the psychiatric disorders were diagnosed by board-certified psychiatrists twice or even three times, thus yielding improved diagnostic validity and stability. Further studies are necessary to investigate the diagnostic validity of psychiatric disorders in the NHIRD. Second, although population-based data were used in our study, the sample sizes of several subgroups were still small, probably because of the low prevalence of disorders such as ASD and ADHD in the parents of offspring with schizophrenia. The low prevalence of adult ASD and ADHD has been discussed previously.[49] Further large-sample studies are necessary to validate our results. Third, some factors, such as education level, environment or information about full or half siblings, were unavailable in the NHIRD. Without these data, we could not assess their effects. Fourth, we presented the results as closely as possible to real-world clinical conditions, to ensure that we investigated the risk of major psychiatric disorders in individuals with FDRs with schizophrenia. The diagnoses of major psychiatric disorders in the study group before and after the diagnoses of FDRs with schizophrenia would have been included in our study.

In conclusion, to our knowledge, this empirical cohort study is the largest used in a study to confirm the high co-aggregation of schizophrenia with other major psychiatric disorders, namely bipolar disorder, major depressive disorder, ASD and ADHD, within families in a dose-dependent manner. Our results suggest that public health officials and psychiatrists should closely monitor and follow the mental health of individuals with FDRs with schizophrenia. In addition, our comprehensive findings may be useful for genetic counseling in clinical practice and may further represent a step toward in development of nosographic systems for psychiatric disorders. Cross-diagnostic studies are necessary to understand the etiology of these disorders and to develop suitable preventive interventions in the early period.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Dr Mu-Hong Chen, Dr Chih-Ming Cheng, Miss Wen-Han Chang and Dr Ya-Mei Bai designed the study and wrote the protocol. Dr Mu-Hong Chen and Dr Chih-Ming Cheng wrote the manuscript. Dr Tung-Ping Su, Dr Ju-Wei Hsu, Dr Kai-Lin Huang, Dr Chia-Fen Tsai, Dr Shih-Jen Tsai, Dr Cheng-Ta Li and Dr Wei-Chen Lin assisted with the literature review and preparation and proof-reading of the manuscript. Dr Ya-Mei Bai, Dr Tzeng-Ji Chen, Miss Wen-Han Chang and Dr Mu-Hong Chen performed and provided advice on the statistical analysis.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)