Coaggregation of Major Psychiatric Disorders in First-Degree Relatives of Individuals With Attention-Deficit/Hyperactivity Disorder:

A Nationwide Population-Based Study

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable mental illness that is easily passed from one generation to the next. Studies have shown that first-degree relatives (FDRs; ie, parents, offspring, and siblings) of individuals with ADHD had a higher risk of also having ADHD. However, the familial coaggregation of ADHD with other major psychiatric disorders, specifically schizophrenia (*ICD-9-CM* code 295), bipolar disorder (*ICD-9-CM* cods 296 except codes 296.2, 296.3, 296.9, and 296.82), major depressive disorder (*ICD-9-CM* codes 296.2 and 296.3), and autism spectrum disorder (ASD; *ICD-9-CM* code 299), remains unclear.

Methods: Among the entire Taiwanese population in 2010, there were 220,966 parents of children with ADHD (*ICD-9-CM* code 314), 174,460 siblings of children with ADHD, and 5,875 children of parents with ADHD. Matched control individuals who did not have FDRs with ADHD (1:4) were selected based on age, sex, and their relation to family members.

Results: FDRs (parents, offspring, siblings, and twins) of ADHD-diagnosed individuals had higher relative risks (95% CI) of major psychiatric disorders than the controls: 1.69 (1.60–1.79) for schizophrenia, 2.21 (2.10–2.32) for bipolar disorder, 2.08 (2.02–2.13) for major depressive disorder, 4.14 (3.90–4.39) for ASD, and 6.87 (6.73–7.01) for ADHD.

Discussion: These results show that ADHD coaggregated with other major psychiatric disorders, specifically schizophrenia, bipolar disorder, major depressive disorder, and ASD, within families. The results suggest that public health officials and psychiatrists should closely monitor and follow the mental health of FDRs of ADHD-diagnosed individuals, such as parents and siblings of children with ADHD.

J Clin Psychiatry 2019;80(3):18m12371

To cite: Chen M-H, Pan T-L, Huang K-L, et al. Coaggregation of major psychiatric disorders in first-degree relatives of individuals with attention-deficit/hyperactivity disorder: a nationwide population-based study. *J Clin Psychiatry.* 2019;80(3):18m12371.

To share: https://doi.org/10.4088/JCP.18m12371

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting approximately 5%–7% of children and adolescents worldwide; it manifests as an inability to marshal and sustain attention or to modulate activity levels and impulsive actions.[1–3] ADHD begins in childhood and usually persists into adulthood.[1–3] Its pathogenesis remains unclear and is assumed to be multifactorial, influenced by genetic and environmental factors.[1–3]

Increasing evidence suggests that ADHD is a hereditary mental disorder that commonly coaggregates within families.[4,5] Starck et al[5] evaluated ADHD symptoms using the Wender Utah Rating and ADHD Self-Report Scales in 75 mothers and 49 fathers of children with ADHD and found that 41.3% of the mothers and 51.0% of the fathers also had ADHD. Examining ADHD familial coaggregation in 132 children with ADHD and their parents, Smalley et al[4] reported that 55% of the families had at least one parent with ADHD. They further demonstrated that the frequency of having at least one parent with ADHD was higher in families with at least one affected girl (63%) compared with those that had only affected boys (45%).[4]

Studies have shown that ADHD and severe psychiatric disorders, including schizophrenia and bipolar disorder, were commonly clustered within families.[6–8] The Pittsburgh Bipolar Offspring Study[7] followed 121 offspring aged 2–5 years from 83 parents with bipolar disorder and 102 offspring from 65 demographically matched parents as controls and found that the offspring of parents with bipolar disorder, particularly those older than 4 years, showed a greater prevalence of ADHD (15.2%) compared with the control offspring (2.0%). Furthermore, a longitudinal study[6] investigated 391 children of parents with bipolar disorder and revealed that they had significantly higher rates of ADHD (30.7%) compared with community offspring (18.1%). A meta-analysis[8] of 33 studies that examined 3,863 children of

Clinical Points

- Attention-deficit/hyperactivity disorder (ADHD) coaggregated with schizophrenia, bipolar disorder, major depressive disorder, and autism spectrum disorder within families.
- Public health officials and psychiatrists should closely monitor and follow the mental health of individuals who have first-degree relatives with ADHD.

parents with severe mental disorders (schizophrenia, bipolar disorder, and major depressive disorder) and 3,158 control children determined that the relative rates of ADHD in children of parents with schizophrenia, bipolar disorder, and major depressive disorder were 1.76, 1.62, and 2.40, respectively, compared with the control children. Furthermore, Ghirardi et al[9] discovered that relatives of individuals with autism spectrum disorder (ASD) were at higher risk of having ADHD compared with relatives of individuals without ASD. The association of ASD and ADHD was stronger in monozygotic twins (odds ratio [OR] = 17.77) than in dizygotic twins (OR = 4.33) and full siblings (OR = 4.59).[9] However, in the aforementioned studies, samples were usually obtained from risk groups within a community but not from the entire population. In addition, the sample sizes used to investigate the risk of major psychiatric disorders with ADHD were somewhat limited.

In the present study, we sampled and obtained pedigree data from the entire Taiwanese population. Moreover, we investigated the familial risk of major psychiatric disorders (ie, schizophrenia, bipolar disorder, major depressive disorder, ADHD, and ASD) in individuals that had first-degree relatives (FDRs) with ADHD. We hypothesized that the FDRs (ie, parents, siblings, and offspring) of ADHD probands would have an increased risk of the 5 aforementioned major psychiatric disorders.

METHODS

Data Acquisition

Taiwan's National Health Insurance (NHI), a mandatory universal health insurance program, was implemented in 1995 and offers comprehensive medical care coverage to all Taiwanese residents. The National Health Research Institute (NHRI) manages the entire insurance claims database, the National Health Insurance Research Database (NHIRD), which comprises health care data from > 99% of Taiwan's population (https://nhird.nhri.org.tw/). The NHRI audits and releases the NHIRD for scientific studies. The insurance claim information of the subjects is anonymous to maintain privacy. Comprehensive information on insured subjects, such as demographic data, clinical visit dates, and disease diagnoses, is included in the database. Taiwanese researchers can apply the dataset for scientific purposes after Institutional Review Board approval of their studies. In this study, all of the information was linked using each resident's unique personal identification number. Subsequently, per the method of Kuo et al,[10] family kinships in the NHIRD were used for genealogy reconstruction. The diagnostic codes used were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). The NHIRD has been used extensively in many Taiwanese epidemiologic studies.[11–13] This study protocol was reviewed and accepted by the Institutional Review Board of Taipei Veterans General Hospital.

Identification of Family Relationships

We identified family relationships using the NHIRD genealogy reconstructions, according to previously reported methods.[10,14] Only blood relatives or spouses were qualified to be dependents of the insured patients. Using unique personal identifiers, we defined the following family relationship groups: parents, offspring, siblings, and twins. Sibling relationships were confirmed by subjects' having 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 could have had several different relationships within a family.

Inclusion Criteria

Our database population included all people (n = 23,258,175) registered in Taiwan in 2010. FDRs (parent, offspring, sibling, or twin) of individuals diagnosed with ADHD (*ICD-9-CM* code: 314) were assigned to the group of FDRs of ADHD-diagnosed individuals. Thus, 220,966 parents of children with ADHD, 174,460 siblings of children with ADHD, and 5,875 children of parents with ADHD were identified in our database. To reduce the confounding effects of age and sex, because ADHD is predominant in males and infrequently diagnosed in middle-aged to older Taiwanese adults, a 1:4 case-control matched analysis was conducted based on age, sex, and familial relationship. For example, a 28-year-old mother of a boy with ADHD would be matched with four 28-year-old mothers of boys without ADHD. If this woman had two distinct familial relationships, such as mother-son and sister-brother, she would be counted for each of these relationships and matched twice.

Disease Classification and Assessment of Covariates

Major psychiatric disorders included schizophrenia (*ICD-9-CM* code 295), bipolar disorder (*ICD-9-CM* code 296, except for codes 296.2, 296.3, 296.9, and 296.82), major depressive disorder (*ICD-9-CM* codes 296.2 and 296.3), ASD (*ICD-9-CM* code 299), and ADHD (*ICD-9-CM* code 314) in FDRs of ADHD-diagnosed individuals and age- and sex-matched controls. These disorders were diagnosed at least twice by board-certified psychiatrists on the basis of their clinical judgment and diagnostic interviews. 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 5 categories according to the level of urbanization.[15]

Statistical Methods

Chi-square statistics and independent *t* tests were used to compare categorical and continuous variables, respectively, between FDRs of ADHD-diagnosed individuals and controls. The prevalence between the two groups was assessed. The relative risks (RRs) and 95% CIs were calculated to determine the risks of the 5 major psychiatric disorders between the two groups. The RRs of major psychiatric disorders for each specific type of familial relationship were calculated as the prevalence of each major psychiatric disorder in FDRs of ADHD-diagnosed individuals divided by the prevalence of these disorders in controls. Additionally, as previously mentioned, each family cluster could contain more than one familial relationship. To manage the clustering effect, modified Poisson regression analysis with the robust variance estimation was an appropriate method for estimating the RRs in the clustered data.[16,17] The modified Poisson regression uses a log link and has the equation $\log[\pi_i] = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \ldots\ldots + \beta_k X_{ki}$, in which π_i is the probability of experiencing the outcome of interest for subject *i*, and X_{1i}, X_{2i}, … X_{ki} are predictor variables. However, the modified Poisson regression applies a Poisson distribution to the data, which produces consistent estimates of the parameters in the aforementioned equation but inconsistent variances, since the variance under a Poisson model is larger than the variance under a binomial model unless the outcome is rare. Robust variance estimation is therefore used to avoid overestimating standard errors of parameter estimates.[16,17] Additionally, subanalyses stratified by each relationship (parents, offspring, siblings, and twins) were conducted to investigate the risks of the disorders in the FDRs of ADHD-diagnosed individuals compared with controls. SPSS 21.0 for Windows (IBM, Armonk, New York) and SAS 9.2 (SAS Institute, Cary, North Carolina) were used for all statistical analyses, and PROC GENMOD in SAS was used to estimate the adjusted RRs. All tests were 2-tailed, and $P < .05$ was considered statistically significant.

RESULTS

Overall, 401,301 FDRs of ADHD-diagnosed individuals and 1,605,204 age- and sex-matched controls that did not have FDRs with ADHD were included in our study (Table 1). FDRs of ADHD-diagnosed individuals had a higher prevalence of major psychiatric disorders, including schizophrenia (0.46% vs 0.29%, $P < .001$), bipolar disorder (0.67% vs 0.31%, $P < .001$), major depressive disorder (2.11% vs 1.02%, $P < .001$), ADHD (6.15% vs 0.85%, $P < .001$), and ASD (0.59% vs 0.14%, $P < .001$) compared with controls (Table 2).

Table 2 shows that FDRs of ADHD-diagnosed individuals had higher risks (shown as RR [95% CI]) of major psychiatric disorders than the controls: 1.69 (1.60–1.79) for schizophrenia, 2.21 (2.10–2.32) for bipolar disorder, 2.08 (2.02–2.13) for major depressive disorder, 4.14 (3.90–4.39) for ASD, and 6.87 (6.73–7.01) for ADHD. We performed subanalyses of the risks of psychiatric disorders according to different familial relationships. Compared with controls, the RR (95% CI) of each psychiatric disorder was higher in FDRs of ADHD-diagnosed individuals, namely schizophrenia (parents: 3.10 [1.96–4.90]; offspring: 1.57 [1.48–1.68]; siblings: 1.98 [1.76–2.22]; twins: 7.29 [3.21–16.53]), bipolar disorder (parents: 5.09 [3.13–8.28]; offspring: 2.04 [1.93–2.16]; siblings: 2.78 [2.49–3.09]; twins: 8.28 [4.16–16.49]), major depressive disorder (parents: 2.89 [2.01–4.16]; offspring: 2.06 [2.00–2.12]; siblings: 2.16 [2.00–2.33]; twins: 2.89 [1.52–5.50]), ASD (parents: 6.83 [5.40–8.63]; offspring: 7.10 [3.60–13.99]; siblings: 3.88 [3.64–4.13]; twins: 6.97

Table 1. Characteristics of FDRs of ADHD-Diagnosed Individuals and Controls[a]

Variable	Male			Female			Total		
	FDRs of ADHD-Diagnosed Individuals (n = 201,025)	Controls (n = 804,100)	*P* Value	FDRs of ADHD-Diagnosed Individuals (n = 200,276)	Controls (n = 801,104)	*P* Value	FDRs of ADHD-Diagnosed Individuals (n = 401,301)	Controls (n = 1,605,204)	*P* Value
Age, mean (SD), y	30.7 (16.9)	30.7 (16.9)	…	28.7 (15.3)	28.7 (15.3)	…	29.7 (16.2)	29.7 (16.2)	…
Male	…	…	…	…	…	…	201,025 (50.1)	804,100 (50.1)	…
Monthly income, US $			<.001			<0.001			<.001
0–500	124,494 (61.9)	497,302 (61.8)		140,140 (70.0)	551,437 (68.8)		264,634 (65.9)	1,048,739 (65.3)	
501–800	38,796 (19.3)	177,219 (22.0)		37,539 (18.7)	168,528 (21.0)		76,335 (19.0)	345,747 (21.5)	
≥ 801	37,735 (18.8)	129,579 (16.1)		22,597 (11.3)	81,139 (10.1)		60,332 (15.0)	210,718 (13.1)	
Place of residence			<.001			<0.001			<.001
1 (Urban)	75,064 (37.3)	229,031 (28.5)		82,036 (41.0)	254,584 (31.8)		157,100 (39.1)	483,615 (30.1)	
2	61,470 (30.6)	236,189 (29.4)		63,171 (31.5)	242,489 (30.3)		124,641 (31.1)	478,678 (29.8)	
3	27,224 (13.5)	128,937 (16.0)		25,801 (12.9)	127,979 (16.0)		53,025 (13.2)	256,916 (16.0)	
4	16,569 (8.2)	99,769 (12.4)		16,043 (8.0)	97,128 (12.1)		32,612 (8.1)	196,897 (12.3)	
5 (Rural)	9,127 (4.5)	62,850 (7.8)		8,028 (4.0)	55,187 (6.9)		12,155 (3.0)	118,037 (7.4)	
Unknown	11,571 (5.8)	47,324 (5.9)		5,197 (2.6)	23,737 (3.0)		16,768 (4.2)	71,061 (4.4)	

[a]Values shown as n (%) unless otherwise noted.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, FDR = first-degree relative.

Table 2. Relative Risk of Different Psychiatric Disorders Between FDRs of ADHD-Diagnosed Individuals and Controls[a]

	Male			Female			Total		
Value	FDRs of ADHD-Diagnosed Individuals (n = 201,025)	Controls (n = 804,100)	Adjusted RR[b] (95% CI)	FDRs of ADHD-Diagnosed Individuals (n = 200,276)	Controls (n = 801,104)	Adjusted RR[b] (95% CI)	FDRs of ADHD-Diagnosed Individuals (n = 401,301)	Controls (n = 1,605,204)	Adjusted RR[b] (95% CI)
Schizophrenia	875 (0.44)	2,297 (0.29)	**1.63 (1.51–1.77)**	970 (0.48)	2,361 (0.29)	**1.75 (1.62–1.89)**	1,845 (0.46)	4,658 (0.29)	**1.69 (1.60–1.79)**
BD	1,027 (0.51)	1,991 (0.25)	**2.11 (1.96–2.29)**	1,662 (0.83)	2,973 (0.37)	**2.27 (2.13–2.42)**	2,689 (0.67)	4,964 (0.31)	**2.21 (2.10–2.32)**
MDD	2,461 (1.22)	5,613 (0.70)	**1.75 (1.67–1.84)**	6,023 (3.01)	10,761 (1.34)	**2.25 (2.18–2.32)**	8,484 (2.11)	16,374 (1.02)	**2.08 (2.02–2.13)**
ASD	1,927 (0.96)	1,816 (0.23)	**4.00 (3.75–4.27)**	453 (0.23)	355 (0.04)	**4.83 (4.18–5.58)**	2,380 (0.59)	2,171 (0.14)	**4.14 (3.90–4.39)**
ADHD	16,544 (8.23)	10,828 (1.35)	**5.87 (5.73–6.01)**	8,146 (4.07)	2,886 (0.36)	**10.65 (10.2–11.12)**	24,690 (6.15)	13,714 (0.85)	**6.87 (6.73–7.01)**

[a]Values shown as n (%) unless otherwise noted. Boldface type indicates statistical significance.
[b]Adjusted for age, sex, urbanization, and income level.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, BD = bipolar disorder, FDR = first-degree relative, RR = relative risk, MDD = major depressive disorder.

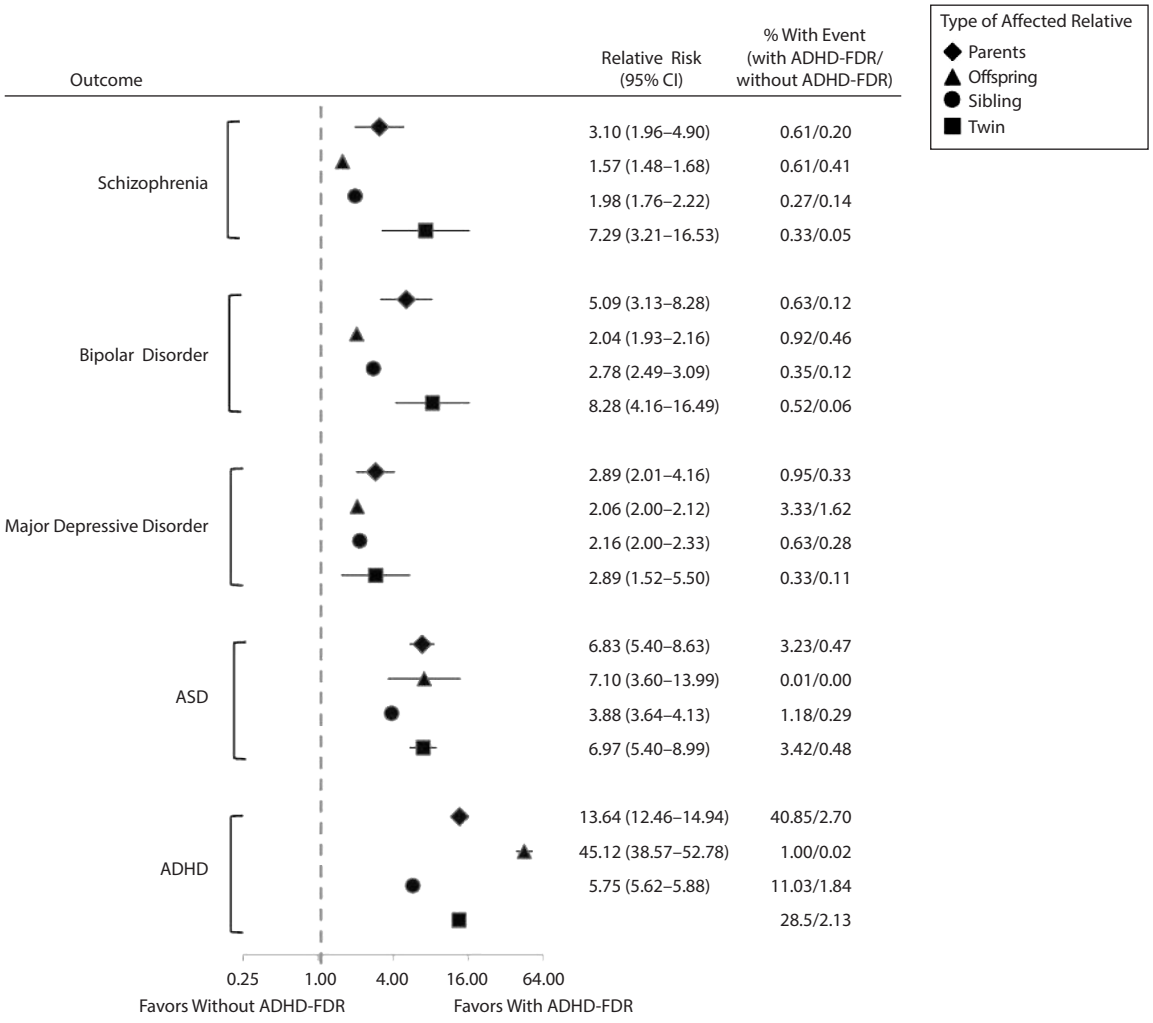
[5.40–8.99]), and ADHD (parents: 13.64 [12.46–14.94]; offspring: 45.12 [38.57–52.78]; siblings: 5.75 [5.62–5.88]; twins: 13.51 [12.09–15.08]) (Figure 1).

DISCUSSION

To our knowledge, this empirical study is the largest to determine a familial coaggregation of ADHD with other major psychiatric disorders, specifically schizophrenia, bipolar disorder, major depressive disorder, and ASD. Our results supported the study hypothesis that FDRs, including parents, offsprings, siblings, and twins, of ADHD-diagnosed individuals had increased risks of being diagnosed with other major psychiatric disorders compared with the controls. In particular, a twin of ADHD-diagnosed individuals showed the highest risks of schizophrenia and bipolar disorder. Parents of ADHD-diagnosed individuals had the highest risk of being diagnosed with ADHD. Our results of the coaggregation of ADHD with other major psychiatric disorders in families indicated that familial transmission of psychiatric disorders is heterotypic and suggest that ADHD exhibits interdiagnostic transmission within a family. However, our cross-sectional analyses cannot establish causality.

As we previously mentioned, studies have reported that parents of children with ADHD are more likely to be diagnosed with schizophrenia, bipolar disorder, and major depressive disorder compared with those of children without ADHD.[8] Our study found that the children of parents with ADHD were more likely to be diagnosed with schizophrenia, bipolar disorder, major depressive disorder, ADHD, and ASD compared with those of parents without ADHD. Moreover, the siblings, especially twins, of children with ADHD had an increased risk of developing one of these disorders compared with those of children without ADHD. Larsson et al[18] revealed that FDRs of ADHD probands were at an increased risk of having both bipolar disorder (ORs ranging from 1.84 to 2.54 for parents, offspring, and siblings) and schizophrenia (ORs ranging from 1.71 to 2.22 for parents, offspring, and siblings). Segenreich et al[19] analyzed the correlations of parental depression and the psychopathology of their offspring and showed that depressive and ADHD symptoms in both fathers and mothers were associated with ADHD symptoms in their children. Moreover, Yang et al[20] demonstrated that the siblings of ADHD children were more likely than control siblings to be diagnosed with depressive disorder and ADHD. Moreover, both Finnish[21] and Swedish[9] register-based cohort studies supported the familial coaggregation of ASD and ADHD. Furthermore, our study found that offspring and siblings of ADHD-diagnosed individuals seemed to be at lower risk of schizophrenia, bipolar disorder, and major depressive disorder than parents or twins, yet they had a comparable (or greater, for ADHD by offspring) risk versus parents and twins for ASD and ADHD. This epidemiologic phenomenon may imply different hereditary and familial coaggregation patterns in psychiatric disorders, which would require further investigation. By the evidence put forth in this study, we propose that within families, ADHD coaggregates with other major psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder, and ASD, which implies that these 5 major mental disorders share common genetic and environmental etiologies. While the RRs were not large, the prevalence estimates for offspring for depression and parents and twins for ASD were noticeably higher than those for the other FDRs on those disorders, which may remind clinicians that those FDRs should be monitored for those specific disorders.

Figure 1. Relative Risks for Major Psychiatric Disorder in FDRs of ADHD-Diagnosed Individuals Among Different Kinships



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, FDR = first-degree relative.

General psychopathology factors, such as executive dysfunction, reward dysregulation, and social dysfunction, may account for the familial coaggregation of ADHD with other major psychiatric disorders.[22] The Cross-Disorder Group of the Psychiatric Genomics Consortium[23,24] analyzed genome-wide single-nucleotide polymorphism (SNP) data for the 5 major psychiatric disorders in 33,332 case subjects and 27,888 controls of European ancestry and assessed whether these major psychiatric disorders share a common genetic etiology. They reported that SNPs explained 17%–29% of the variance in liability and suggested that the genetic correlation between ADHD and major depression, calculated using common SNPs, was moderate.[24] However, SNP-based coheritability was found to be less between ADHD and schizophrenia, bipolar disorder, or ASD.[24] This genome-wide association study could provide convincing evidence that specific genes shared by major psychiatric disorders are heritable within families, which results in highly variable psychiatric disorder endophenotypes; however, these results are not consistent with epidemiologic findings that indicate significant coheritability between ADHD and schizophrenia, bipolar disorder, or ASD.[7–9,23,24] Thus, clarifying the differences between genetics and clinical or psychopathologic assessment requires further investigation.

This study has several limitations. First, the prevalence of major psychiatric disorders may have been underestimated, because only those patients who sought medical consultation and treatment were included. However, the psychiatric disorders were diagnosed by board-certified psychiatrists twice, improving the diagnostic validity of this study. Second, although we used population-based data, the sample sizes of several subgroups were still small, probably because of the low prevalence of ASD and ADHD in the parents of children with ADHD. The low prevalence of adult ASD and ADHD has been discussed previously.[25] Therefore, further studies with larger sample sizes are necessary to validate our results. Third, given that our study with a cross-sectional study design supported a familial coaggregation of ADHD with other major psychiatric disorders, further studies with

a longitudinal study design would be necessary to validate our findings. Fourth, confounding factors, such as education level, environmental effects, or information detailing if siblings were full or half siblings, were studied; information about sibling relationships was not available in the NHIRD, which hampered our ability to assess these effects.

In conclusion, to our knowledge, this cohort study was the largest empirical study to confirm high familial coaggregation of ADHD with other major psychiatric disorders—schizophrenia, bipolar disorder, major depressive disorder, and ASD. Our results suggested that public health officials and psychiatrists should closely monitor and follow the mental health of FDRs of ADHD-diagnosed individuals, such as parents and siblings of children with ADHD. Identifying the risks of developing mental illness can help in early prevention of and intervention for major psychiatric disorders in children. Finally, further cross-diagnostic studies are required to understand the etiology of these disorders.

Submitted: May 22, 2018; accepted November 19, 2018.

Published online: April 30, 2019.

Author contributions: Drs M-H Chen, Hsu, and Bai and Prof. Pan designed the study and wrote the protocol; Drs M-H Chen and Prof Pan wrote the manuscript; Drs Tsai, Su, Hsu, Huang, Li, and Cheng assisted with the literature review and preparation and proofreading of the manuscript; and Drs Bai, T-J Chen, and M-H Chen performed and provided advice on the statistical analysis.

Potential conflicts of interest: No authors have financial relationships or conflicts of interest relevant to this article to disclose.

Funding/support: The study was supported by grants from Taipei Veterans General Hospital (V103E10-001, V104E10-002, V105E10-001-MY2-1, V105A-049, V106B-020, V107B-010, V107C-181) and Ministry of Science and Technology, Taiwan (107-2314-B-075-063-MY3).

Role of the sponsor: The funding sources had no role in any process of this study.

Acknowledgments: The authors thank Mr I-Fan Hu, MA (Courtauld Institute of Art, University of London; National Taiwan University) for his friendship and support. Mr Hu has no conflicts of interest relevant to the subject of this article.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.