Schizophrenia Research 209 (2019) 58–63

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Risk of schizophrenia among people with obsessive-compulsive disorder: A nationwide population-based cohort study

Yu-Fang Cheng [a,b], Vincent Chin-Hung Chen [a,c,d,1], Yao-Hsu Yang [c,e,f], Ko-Jung Chen [c], Yi-Chen Lee [a,c], Mong-Liang Lu [g,h,*]

[a] Department of Psychiatry, Chang Gung Memorial Hospital, Chiayi Branch, Chiayi, Taiwan
[b] Department of Applied Science (Occupational Therapy), University of Western Sydney, Australia
[c] Health Information and Epidemiology Laboratory, Chang Gung Memorial Hospital, Chiayi Branch, Chiayi, Taiwan
[d] School of Medicine, Chang Gung University, Taoyuan, Taiwan
[e] Department of Traditional Chinese Medicine, Chang Gung Memorial Hospital, Chiayi Branch, Chiayi, Taiwan
[f] Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan
[g] Department of Psychiatry & Psychiatric Research Center, Wan-Fang Hospital, Taipei Medical University, Taipei, Taiwan
[h] Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 12 October 2018
Received in revised form 11 May 2019
Accepted 11 May 2019
Available online 24 May 2019

Keywords:
Obsessive-compulsive disorder
Schizophrenia
Gender
Age of onset
Autistic disorder

ABSTRACT

High comorbidity of obsessive-compulsive disorder (OCD) has been reported in patients with schizophrenia. The sequence of OCD and schizophrenia onset might clarify the underlying pathophysiological relationships between these two disorders, but available evidence is limited. In this study, we used a population-based cohort to investigate the risk of schizophrenia in people with newly diagnosed OCD. Patients who were first diagnosed with OCD from 2000 to 2013 were selected from the Longitudinal Health Insurance Research Database. The non-OCD group was randomly sampled, and matched with the OCD group by gender, age, urbanization level, and income. Cox regression analyses and competing risk model were used to estimate the risk of schizophrenia, adjusting for potential confounding factors. In total, 2009 patients with OCD and 8036 controls were identified. The crude incidences of schizophrenia in the OCD and non-OCD groups were 876.2 per 100,000 person-years and 28.7 per 100,000 person-years, respectively. After adjustment, a substantially higher risk of schizophrenia was observed in the OCD group (hazard ratio = 30.29, 95% confidence interval = 17.91–51.21). Male gender, age of OCD onset before 20 years, and antipsychotic prescription were associated with schizophrenia. Patients with comorbidity of autistic disorder have higher risk of schizophrenia (hazard ratio = 4.63, 95% confidence interval = 1.58–13.56). In conclusion, OCD diagnosis, male gender, age of OCD onset before 20 years, comorbidity of autistic disorder, and antipsychotic use were associated with higher risk of schizophrenia. It is essential for psychiatrists to note that OCD may be the initial presentation of schizophrenia.

1. Introduction

Schizophrenia and obsessive-compulsive disorder (OCD) are two chronic and debilitating mental disorders. The lifetime prevalence of schizophrenia is approximately 0.55% (McGrath et al., 2008), and that of OCD is 2%–3% (Rasmussen and Eisen, 1992; Ruscio et al., 2010). Meta-analyses revealed that OCD comorbidity rates in subjects with schizophrenia were approximately 12%–23% (Achim et al., 2011; Buckley et al., 2009; Swets et al., 2014). The prevalence of cormorbid OCD in patients with schizophrenia is significantly higher than those expected to occur independently. The greater-than-chance rate of comorbid OCD in patients with schizophrenia suggests a possible pathophysiological link between these two diseases (Berrios, 1989; Buckley et al., 2009; Hall, 2017; Poyurovsky et al., 2004).

Earlier studies have reported that the appearance of obsessive-compulsive symptoms (OCS) or OCD in patients with schizophrenia can prevent psychosis progression (Rosen, 1957). However, later studies generally have not supported this observation. Clinically, comorbid OCD in patients with schizophrenia is associated with earlier onset of psychosis, higher prevalence of comorbid depression, more severe

Abbreviations: HR, hazard ratio; ICD-9, International Classification of Disease, Ninth revision; LHID, Longitudinal Health Insurance Database; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; OCD, obsessive-compulsive disorder; UHR, ultra-high risk.

* Corresponding author at: Department of Psychiatry, Wan-Fang Hospital, No. 111, Sec. 3, Hsin-Long Road, Taipei 116, Taiwan.
E-mail address: mongliang@hotmail.com (M.-L. Lu).

[1] Dr. Vincent Chin-Hung Chen contributed equally to the first author.

https://doi.org/10.1016/j.schres.2019.05.024
0920-9964/

psychopathology, poorer social function, and higher rates of hospitalization (Cunill et al., 2009; Cunill et al., 2013; Faragian et al., 2012; Grover et al., 2017).

OCD onset can occur at any time throughout the entire course of schizophrenia (Poyurovsky et al., 2012; Schirmbeck and Zink, 2013; Zink, 2014). The temporal relationships between OCD and schizophrenia might present in five different modes. Firstly, OCD occurs before schizophrenia as an independent diagnosis. Secondly, OCD occurs before psychosis as a part of the at-risk mental state. Third, OCD occurs simultaneously with schizophrenia onset. Fourth, OCD occurs after the first psychotic episode of schizophrenia. Fifth, OCD occurrence in patients with schizophrenia is the result of antipsychotic medication (Grillault Laroche and Gaillard, 2016).

The transition from OCD to schizophrenia has been described in the literature (Berrios, 1989; Cederlof et al., 2015; Devulapalli et al., 2008). A meta-analysis of four studies revealed that no difference exists in the mean age of onset between OCD and schizophrenia in patients comorbid with both disorders (Devulapalli et al., 2008). However, this meta-analysis is limited due to its small number and heterogeneity of studies (Devulapalli et al., 2008). Several sequential studies have revealed that there is a tendency of earlier onset of OCD than schizophrenia among patients comorbid with OCD schizophrenia (Faragian et al., 2012; Seedat et al., 2007; Sterk et al., 2011).

Recently two national cohort studies investigated the longitudinal risk of schizophrenia in patients first diagnosed with OCD. Analyzing the data from Swedish National Patient Register, Cederlof et al. (2015) concluded that patients with OCD diagnosis have a 2.7-folds higher risk of a subsequent diagnosis of schizophrenia compared with those without OCD. Using the data from longitudinal nationwide Danish registers, Meier et al. (2014) reported that patients with pre-existing OCD diagnosis have a higher risk of schizophrenia (incidence ratio = 6.90) and schizophrenia spectrum disorders (incidence ratio = 5.77).

The temporal relationship of OCD and schizophrenia is worth further studies. We used the nationwide population-based cohort study design to explore the sequential risk of schizophrenia in patients with an initial diagnosis of OCD.

2. Method

2.1. Database

In this population-based retrospective cohort study, we used data from the Longitudinal Health Insurance Database (LHID) consisting of 1,000,000 people randomly sampled from the Taiwan's National Health Insurance Research Database (NHIRD). The Taiwanese government established the National Health Insurance (NHI) program on March 1, 1995. The NHI covers approximately 99.9% of the 23 million Taiwanese population and provides a comprehensive health care system for the enrollees. For research purposes, the National Health Insurance Administration commissioned the National Health Research Institutes (NHRI) to establish the Longitudinal Health Insurance Database (LHID). The LHID is open to scientists for research and contained all claims of reimbursement data from 1997 to 2013. Those in the LHID and the full registry are not statistically different in age, gender, or healthcare utilization costs.

2.2. Participants

The objective of this study was to compare the incidence of schizophrenia between patients with and without OCD from 1997 to 2013. Patients with OCD were identified based on recorded International Classification of Disease, Ninth revision (ICD-9) code of 300.3, and schizophrenia cases were identified using ICD-9 code of 295. The diagnosis is made and documented by board-certificated psychiatrists. The NHI database is claims-based and diagnosis codes are linked to reimbursements. The NHI Administration randomly chose the records of 1 in 100 ambulatory care visits, and 1 in 20 inpatient claims to verify the accuracy of the diagnoses, and several studies have demonstrated the high accuracy and validity of the diagnoses in the NHIRD (Lin et al., 2018; Wu et al., 2014). To increase the diagnosis validity of OCD and schizophrenia in this study, we only enrolled patients with one diagnosis during inpatient hospitalization or two diagnoses during outpatient clinic visit. Patients with unclear gender status were excluded. To ensure OCD patients were new cases and the correct direction of causality, we excluded subjects who died before 2000, who were diagnosed with OCD between 1997 and 2000, and who were diagnosed with schizophrenia prior to OCD diagnosis. In total, 2009 patients with OCD were selected for further analysis. The age of early onset of OCD was defined as 20 years (Anholt et al., 2014). The non-OCD group was randomly sampled from the LHID and 4:1 matched with the OCD group by gender, age, urbanization level, and monthly income (Fig. 1). Using the codes from the Anatomical Therapeutic Chemical Classification System, we identified all dispensed prescriptions of antipsychotics (typical antipsychotics and atypical antipsychotics) and antidepressants selective serotonin reuptake inhibitors [SSRI], serotonin and norepinephrine reuptake inhibitors [SNRI], and other antidepressants). The exposures of antipsychotics and antidepressants were retrieved and quantified using the World Health Organization's Defined Daily Dose [DDD]. Cumulative doses were graded into 0–27 DDD and no less than 28 DDD (≧28 DDD). The LHID is composed of anonymized data for research purposes. The institutional review board at Chang Gung Memorial Hospital approved the study protocol.

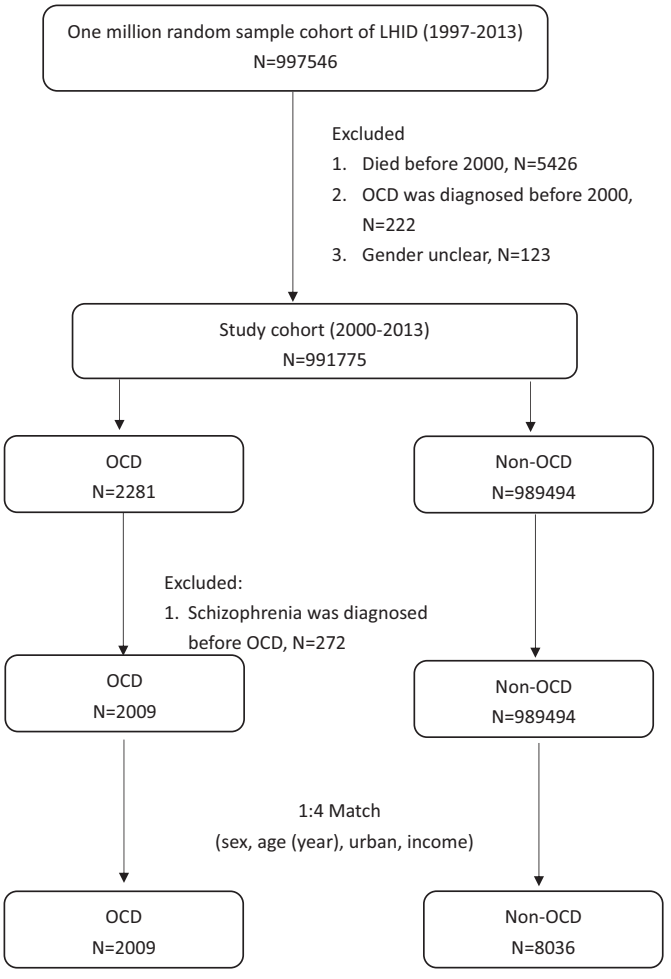

Fig. 1. Flow chart of data collection in this study. LHID = Longitudinal Health Insurance Database, OCD = obsessive-compulsive disorder.

2.3. Statistical analysis

Demographic characteristics and frequency of comorbid disorders between patients with and without OCD were compared using chi-squared test. The index date was defined as the OCD diagnosis date, and the same index date was selected for matched patients without OCD. We used the Kaplan-Meier log-rank test to compare the cumulative incidence of schizophrenia between patients with and without OCD, and the Cox regression model to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariable regression adjusted for gender, age, urbanized level of residence classified into four levels (1 being the most urbanized and 4 the least urbanized), monthly income (New Taiwan [NT] $1–15,840, NT$15,841–25,000, and ≥NT $25,000; average exchange rate in 2013, US$1.00 = NT$29.95), and medical comorbidities including autistic disorder (ICD-9 code 299.0), attention deficit hyperactivity disorder (ADHD) (ICD-9 code 314), bulimia nervosa (ICD-9 code 307.51), and anorexia nervosa (ICD-9 code 307.1). Death or dropping out from the insurance plan was considered as censored data and competing risk regression as described by Fine and Gray (1999) was applied. Two-tailed p-value<0.05 was considered statistically significant. All statistical analysis was performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. The characteristics of participants

The study participants were comprised of 2009 individuals with OCD and 8036 sex-, age-, urbanization-, and income-matched individuals ascertained from NHIRD. Table 1 shows the characteristics of study subjects. Compared to the non-OCD group, the OCD group had more comorbidities of autistic disorder, ADHD, bulimia nervosa, and anorexia nervosa.

Table 1
Sociodemographic and clinical variables of the OCD and non-OCD groups.

Variables	OCD (N = 2009)		Non-OCD (N = 8036)		p value
	n	%	n	%	
Gender					1.0000
Male	982	48.88	3928	48.88	
Female	1027	51.12	4108	51.12	
Age (year)					1.0000
<20	376	18.72	1504	18.72	
20–39	833	41.46	3332	41.46	
≥40	800	39.82	3200	39.82	
Urbanization level					1.0000
1(City)	680	33.85	2720	33.85	
2	946	47.09	3784	47.09	
3	265	13.19	1060	13.19	
4(Villages)	118	5.87	472	5.87	
Income					1.0000
0	1019	50.72	4076	50.72	
1–15,840	282	14.04	1128	14.04	
15,841–25,000	468	23.30	1872	23.30	
>25,000	240	11.95	960	11.95	
Comorbidities					
Autistic disorder					<0.0001
Yes	23	1.14	5	0.06	
No	1986	98.86	8031	99.94	
ADHD					<0.0001
Yes	83	4.13	50	0.62	
No	1926	95.87	7986	99.38	
Bulimia nervosa					<0.0001
Yes	26	1.29	3	0.04	
No	1983	98.71	8033	99.96	
Anorexia nervosa					<0.0001
Yes	9	0.45	2	0.02	
No	2000	99.55	8034	99.98	

OCD: obsessive-compulsive disorder, ADHD: attention deficit hyperactivity disorder.

Among the 10,045 subjects followed up from 2000 to 2013, 131 patients developed schizophrenia during 68,916 person-years (Table 2). The mean follow-up interval for the OCD group and non-OCD group was 6.5 years and 6.9 years, respectively. The crude incidences of schizophrenia in the OCD group and non-OCD group were 876.2 per 100,000 person-years and 28.7 per 100,000 person-years, respectively.

Kaplan–Meier analysis revealed that the OCD group exhibited a significantly higher cumulative incidence of schizophrenia than the control group (Fig. 2). The effect of an OCD diagnosis on the risk of developing schizophrenia gradually decreased over time (Table 3).

3.2. Unadjusted analyses

As shown in Table 4, patients with a history of OCD had significantly increased HRs of schizophrenia (HR = 30.17, 95% CI: 17.88–50.90). The crude HR of schizophrenia in men was higher than that in women (HR = 1.58, 95% CI: 1.11–2.24). Compared with the patients with age of OCD onset below 20 years, patients with age of OCD onset over 40 years were at a significantly lower risk of schizophrenia (HR = 0.45, 95% CI: 0.28–0.72). Furthermore, patients with comorbidity of autistic disorder (HR = 15.31, 95% CI: 5.65–41.48) and bulimia nervosa (HR = 6.88, 95% CI: 1.70–27.81) had higher risks of schizophrenia. No change in the sequential risk of schizophrenia was observed in OCD patients receiving antidepressant treatment (including SSRI, SNRI, or other antidepressants). OCD patients receiving antipsychotic medication (including typical antipsychotics and atypical antipsychotics) >28 DDD had substantially increased the sequential risk of receiving a later diagnosis of schizophrenia.

3.3. Adjusted analyses

After adjustment for covariates (sex, age, urbanization, income, and comorbidities), the strength of association between OCD and the risk of schizophrenia (HR = 30.29, 95% CI: 17.91–51.21) was similar to the unadjusted value. The adjusted HR of schizophrenia in men was higher than the ratio in women (HR = 1.63, 95% CI: 1.13–2.34). Compared with the patients with age of OCD onset below 20 years, patients with age of OCD onset over 40 years had the lowest risk (HR = 0.38, 95% CI: 0.20–0.72), followed by the patients with age of OCD onset between 20 and 40 years (HR = 0.60, 95% CI: 0.37–0.98). Patients with comorbidity of autistic disorder (HR = 4.63, 95% CI: 1.58–13.56) also have higher risk of schizophrenia. OCD patients receiving antipsychotic medication (including typical antipsychotics and atypical antipsychotics) >28 DDD had substantially increased the risk of developing schizophrenia.

4. Discussion

This nationwide population-based cohort study showed that schizophrenia was more prevalent in patients with pre-existing OCD diagnosis. In longitudinal analyses, the initial OCD diagnosis tended to increase the risk of the subsequent schizophrenia diagnosis.

Compared with individuals without OCD, those with initial diagnosis of OCD had an approximately 30-fold increased risk of developing schizophrenia later. This result is in line with previous large cohort studies (Cederlof et al., 2015; Meier et al., 2014), the effect of an OCD diagnosis on the longitudinal risk of developing schizophrenia gradually decreased over time, but the magnitude of the risk in this study was higher than them. Studies involving individuals at the first episode of psychosis and ultra-high risk (UHR) for psychosis have shown that OCS and OCD can lead to the first psychotic manifestation (Marine et al., 2015; Sterk et al., 2011). Studies about prevalence in UHR samples have reported wide ranges of differences from 2.7% to 77% for OCS and from 1.5% to 30% for OCD, respectively (DeVylder et al., 2012; Hui et al., 2013; Niendam et al., 2009; Sterk et al., 2011; Zink et al., 2014). The variations of OCS/OCD prevalence in UHR samples mainly differ

Table 2
Incidence rate of schizophrenia in the OCD and non-OCD groups.

	Schizophrenia	Total follow-up (person-year)	Incidence rate[a]	95% CI		Mean follow-up(year)
OCD (n = 2009)	115	13,123.1	876.3	729.9	1052.1	6.5
Non-OCD(n = 8036)	16	55,793.0	28.7	17.6	46.8	6.9

[a] Per 100,000 person-years.

due to diversities in diagnostic tools and assessment methods. The OCS/OCD in the UHR group was associated with male sex (Iida et al., 1995), long duration of attenuated psychosis syndrome (Soyata et al., 2018), high levels of psychotic and depressive symptoms (DeVylder et al., 2012; Hur et al., 2012), and impaired psychosocial functioning (Zink et al., 2014). The high prevalence of OCS/OCD in the UHR patients leads to develop the hypothesis that OCS is a part of the fundamental symptom clusters in early schizophrenia (Ebel et al., 1989). Although the underlying mechanism remains unclear, OCD in considered as a potential marker of patients at high risk for psychosis (Cederlof et al., 2015). Therefore, it is crucial for psychiatrists to note that OCS may sometimes be the initial presentation of schizophrenia.

Our study revealed that men had a higher risk of schizophrenia than women. Tukel et al. (2004) reported that comorbidity rates of schizophrenia among patients with OCD are higher in men. Eisen and Rasmussen (1993) also reported that patients with OCD and psychotic features are more likely to be male. In addition, men with comorbidity of schizophrenia and OCD have an earlier age-of-onset of schizophrenic and obsessive-compulsive symptoms compared to women (Faragian et al., 2012). The gender-related differences in comorbidity of schizophrenia and OCD need further investigations.

Our study showed that an early age of OCD onset (below 20 years old) significantly increased the risk of schizophrenia. Both schizophrenia and OCD occur during adolescence and are neurodevelopmental disorders (Poyurovsky et al., 2004). The precedence of OCD in schizophrenia may exert a major impact on the pathophysiology of schizophrenia. However, the underlying mechanisms of age effect warrant further studies.

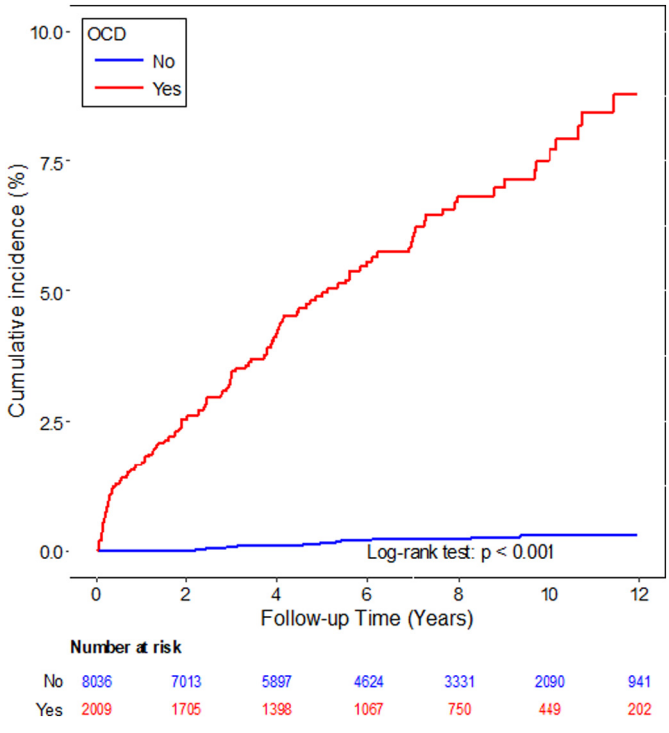

Fig. 2. Cumulative incidence of schizophrenia in the OCD and non-OCD groups. OCD = obsessive-compulsive disorder.

We found that prior diagnosis of autistic disorder increased the risk of schizophrenia. The associations between schizophrenia and autistic disorder have been identified for a long time. The disorganized behaviors and negative symptoms of schizophrenia share several common features with the clinical manifestations of autistic disorder. Given the shared clinical presentations of schizophrenia and autistic disorder, these two disorders tend to co-occur frequently. Nearly 12.8% of the population with autism spectrum disorder has a comorbidity of schizophrenia spectrum disorder (Chisholm et al., 2015). Epidemiologic studies have suggested an association between previous diagnosis of autism spectrum disorder and later appearance of psychotic episodes (Cederlof et al., 2016; Sullivan et al., 2013).

We found that antidepressant medication did not change the risk of developing schizophrenia. However, the patients with OCD receiving antipsychotic medication had increased the risk of schizophrenia. A possible explanation is that those receiving antipsychotics had treatment resistant OCD and therefore were prescribed antipsychotics as augmentation (Hirschtritt et al., 2017). Another possible explanation is that individuals not yet diagnosed as having schizophrenia may have nonspecific psychiatric symptoms and possible initial misclassification (Niendam et al., 2009), which could be the reason for prescribing antipsychotics. Accordingly, some patients might have been diagnosed solely as having OCD even though they already had coexisting psychosis. Further studies with prospective samples are required to identify the effects of psychotropic medication on the longitudinal course of OCD.

The nationally representative sample population and longitudinal dataset are the main strengths of our study. However, this study has some limitations. First, the diagnoses of OCD and schizophrenia were based on *ICD* code from the dataset and not further verified with structured clinical interview. Differences among psychiatrists in the diagnosis of schizophrenia and OCD were not controlled. The misdiagnoses might also happen especially in individuals with atypical presentation of psychiatric symptoms. Second, we could not control the possible influence of other potential confounding variables not assessed, such as parental mental health and substance use history. Third, the period of follow-up was not long enough to verify all possible cases. Some patients may present their first psychotic episode after the end of the

Table 3
The incidence rate ratios of schizophrenia in patients with a prior diagnosis of OCD.

Time since OCD, year	Case number	Crude incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)[a]
<1	34	116.04 (15.87–848.39)	103.31 (14.08–758.22)
1	17	57.00 (7.56–429.79)	47.93 (6.26–366.93)
2	18	12.50 (4.12–37.98)	10.61 (3.41–33.00)
3	15	23.78 (5.37–105.36)	23.50 (5.26–105.01)
4	12	18.66 (4.09–85.18)	18.08 (3.86–84.66)
5	10	9.21 (2.38–35.63)	7.71 (1.85–32.11)
6	5	16.39 (1.83–146.60)	16.70 (1.85–150.76)
7	8	NA	NA
8	3	8.11 (0.74–89.49)	7.43 (0.65–84.95)
9	3	8.38 (0.76–92.41)	9.00 (0.81–99.54)
10	4	NA	NA
11	1	NA	NA
12	1	NA	NA
≥13	0	NA	NA
Non-OCD	16	1 (reference)	1 (reference)

[a] Adjustment for covariates (sex, age, urbanization, income, and comorbidities).

Table 4
Adjusted Cox regression analysis of incident schizophrenia in the OCD and non-OCD groups.

Variables	Crude			Adjusted[a]		
	HR	95% CI	p value	HR	95% CI	p value
OCD						
Yes	30.17	[17.88, 50.90]	<0.0001	30.29	[17.91, 51.21]	<0.0001
No	1.00	Reference		1.00	Reference	
Gender						
Male	1.58	[1.11, 2.24]	0.0106	1.63	[1.13, 2.34]	0.0085
Female	1.00	Reference		1.00	Reference	
Age (year)						
<20	1.00	Reference		1.00	Reference	
20–39	0.74	[0.49, 1.12]	0.1485	0.60	[0.37, 0.98]	0.0400
≥40	0.45	[0.28, 0.72]	0.0008	0.38	[0.20, 0.72]	0.0028
Urbanization level						
1 (City)	0.71	[0.34, 1.47]	0.3546	0.67	[0.32, 1.41]	0.2903
2	1.03	[0.51, 2.06]	0.9433	1.01	[0.50, 2.04]	0.9694
3	1.01	[0.46, 2.23]	0.9826	0.92	[0.42, 2.04]	0.8361
4 (Villages)	1.00	Reference		1.00	Reference	
Income						
0	1.00	Reference		1.00	Reference	
1–15,840	1.15	[0.73, 1.81]	0.5593	1.70	[1.00, 2.90]	0.0502
15,841–25,000	0.85	[0.55, 1.29]	0.4384	1.48	[0.86, 2.54]	0.1544
>25,000	0.34	[0.15, 0.78]	0.0110	0.55	[0.22, 1.39]	0.2051
Comorbidity (Yes/No)						
Autistic disorder	15.31	[5.65, 41.48]	<0.0001	4.63	[1.58, 13.56]	0.0052
ADHD	2.62	[0.97, 7.09]	0.0580	0.37	[0.12, 1.09]	0.0710
Bulimia nervosa	6.88	[1.70, 27.81]	0.0068	1.93	[0.46, 8.12]	0.3682
Anorexia nervosa	7.05	[0.99, 50.41]	0.0516	2.44	[0.32, 18.41]	0.3870
SSRIs antidepressants						
<28 cDDD	1.00	Reference		1.00	Reference	
≥28 cDDD	1.13	[0.71, 1.80]	0.6025	0.82	[0.51, 1.32]	0.4145
SNRIs antidepressants						
<28 cDDD	1.00	Reference		1.00	Reference	
≥28 cDDD	1.50	[0.97, 2.34]	0.0716	0.90	[0.54, 1.51]	0.6873
Others antidepressants						
<28 cDDD	1.00	Reference		1.00	Reference	
≥28 cDDD	1.26	[0.85, 1.86]	0.2519	0.80	[0.50, 1.28]	0.3466
Typical antipsychotics						
<28 cDDD	1.00	Reference		1.00	Reference	
≥28 cDDD	4.00	[2.74, 5.83]	<0.0001	3.03	[1.96, 4.68]	<0.0001
Atypical antipsychotics						
<28 cDDD	1.00	Reference		1.00	Reference	
≥28 cDDD	4.18	[2.89, 6.05]	<0.0001	3.09	[2.01, 4.74]	<0.0001

[a] Adjustment for covariates (sex, age, urbanization, income, and comorbidities).

study period. Fourth, the information about psychometric testing and disease severity is lacking in this study.

Our findings indicated that a prior OCD diagnosis was associated with higher rates of subsequent schizophrenia. Male gender, age of OCD onset below 20 years, comorbidity of autistic disorder, and antipsychotic use were associated with a high risk of schizophrenia. Clinicians should be aware that after diagnosis of OCD the risk for manifestation of psychotic symptoms is increased.

Contributors

Drs. Cheng, Chan, and Lu designed the study, wrote the protocol and wrote manuscript. Dr. Chen, Miss Chen, and Dr. Lee undertook statistical analysis and wrote manuscript. All authors contributed to and have approved the final manuscript.

Role of funding source

No funding body agreements. See list of funders under acknowledgments.

Declaration of Competing Interest

All authors have no conflict of interest to report.

Acknowledgements

The study was supported by grants from Ministry of Science and Technology (MOST 105-2314-B-038-043-MY3), Taipei, Taiwan. This work was supported by the Health Information and Epidemiology Laboratory, Chang Gung Memorial Hospital, Chiayi Branch (CLRPG6G0041, CLRPG6G0042). This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

References

Achim, A.M., Maziade, M., Raymond, E., Olivier, D., Merette, C., Roy, M.A., 2011. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. Schizophr. Bull. 37 (4), 811–821.

Anholt, G.E., Aderka, I.M., van Balkom, A.J., Smit, J.H., Schruers, K., van der Wee, N.J., Eikelenboom, M., De Luca, V., van Oppen, P., 2014. Age of onset in obsessive-compulsive disorder: admixture analysis with a large sample. Psychol. Med. 44 (1), 185–194.

Berrios, G.E., 1989. Obsessive-compulsive disorder: its conceptual history in France during the 19th century. Compr. Psychiatry 30 (4), 283–295.

Buckley, P.F., Miller, B.J., Lehrer, D.S., Castle, D.J., 2009. Psychiatric comorbidities and schizophrenia. Schizophr. Bull. 35 (2), 383–402.

Cederlof, M., Lichtenstein, P., Larsson, H., Boman, M., Ruck, C., Landen, M., Mataix-Cols, D., 2015. Obsessive-compulsive disorder, psychosis, and bipolarity: a longitudinal cohort and multigenerational family study. Schizophr. Bull. 41 (5), 1076–1083.

Cederlof, M., Pettersson, E., Sariaslan, A., Larsson, H., Ostberg, P., Kelleher, I., Langstrom, N., Gumpert, C.H., Lundstrom, S., Lichtenstein, P., 2016. The association between childhood autistic traits and adolescent psychotic experiences is explained by general neuropsychiatric problems. Am. J. Med. Genet. B Neuropsychiatr. Genet. 171B (2), 153–159.

Chisholm, K., Lin, A., Abu-Akel, A., Wood, S.J., 2015. The association between autism and schizophrenia spectrum disorders: a review of eight alternate models of co-occurrence. Neurosci. Biobehav. Rev. 55, 173–183.

Cunill, R., Castells, X., Simeon, D., 2009. Relationships between obsessive-compulsive symptomatology and severity of psychosis in schizophrenia: a systematic review and meta-analysis. J. Clin. Psychiatry 70 (1), 70–82.

Cunill, R., Huerta-Ramos, E., Castells, X., 2013. The effect of obsessive-compulsive symptomatology on executive functions in schizophrenia: a systematic review and meta-analysis. Psychiatry Res. 210 (1), 21–28.

Devulapalli, K.K., Welge, J.A., Nasrallah, H.A., 2008. Temporal sequence of clinical manifestation in schizophrenia with co-morbid OCD: review and meta-analysis. Psychiatry Res. 161 (1), 105–108.

DeVylder, J.E., Oh, A.J., Ben-David, S., Azimov, N., Harkavy-Friedman, J.M., Corcoran, C.M., 2012. Obsessive compulsive symptoms in individuals at clinical risk for psychosis: association with depressive symptoms and suicidal ideation. Schizophr. Res. 140 (1–3), 110–113.

Ebel, H., Gross, G., Klosterkotter, J., Huber, G., 1989. Basic symptoms in schizophrenic and affective psychoses. Psychopathology 22 (4), 224–232.

Eisen, J.L., Rasmussen, S.A., 1993. Obsessive compulsive disorder with psychotic features. J. Clin. Psychiatry 54 (10), 373–379.

Faragian, S., Fuchs, C., Pashinian, A., Weizman, R., Weizman, A., Poyurovsky, M., 2012. Age-of-onset of schizophrenic and obsessive-compulsive symptoms in patients with schizo-obsessive disorder. Psychiatry Res. 197 (1–2), 19–22.

Fine, J.P., Gray, R.J., 1999. A proportional hazards model for the subdistribution of a competing risk. J. Am. Stat. Assoc. 94 (446), 496–509.

Grillault Laroche, D., Gaillard, A., 2016. Induced Obsessive Compulsive Symptoms (OCS) in schizophrenia patients under Atypical 2 Antipsychotics (AAPs): review and hypotheses. Psychiatry Res. 246, 119–128.

Grover, S., Dua, D., Chakrabarti, S., Avasthi, A., 2017. Obsessive compulsive symptoms/disorder in patients with schizophrenia: prevalence, relationship with other symptom dimensions and impact on functioning. Psychiatry Res. 250, 277–284.

Hall, J., 2017. Schizophrenia - an anxiety disorder? Br. J. Psychiatry 211 (5), 262–263.

Hirschtritt, M.E., Bloch, M.H., Mathews, C.A., 2017. Obsessive-compulsive Disorder: Advances in Diagnosis and Treatment. JAMA 317 (13), 1358–1367.

Hui, C., Morcillo, C., Russo, D.A., Stochl, J., Shelley, G.F., Painter, M., Jones, P.B., Perez, J., 2013. Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. Schizophr. Res. 148 (1–3), 175–180.

Hur, J.W., Shin, N.Y., Jang, J.H., Shim, G., Park, H.Y., Hwang, J.Y., Kim, S.N., Yoo, J.H., Hong, K.S., Kwon, J.S., 2012. Clinical and neurocognitive profiles of subjects at high risk for psychosis with and without obsessive-compulsive symptoms. Aust. N. Z. J. Psychiatry 46 (2), 161–169.

Iida, J., Iwasaka, H., Hirao, F., Hashino, K., Matsumura, K., Tahara, K., Aoyama, F., Sakiyama, S., Tsujimoto, H., Kawabata, Y., Ikawa, G., 1995. Clinical features of childhood-onset schizophrenia with obsessive-compulsive symptoms during the prodromal phase. Psychiatry Clin. Neurosci. 49 (4), 201–207.

Lin, L.Y., Warren-Gash, C., Smeeth, L., Chen, P.C., 2018. Data resource profile: the National Health Insurance Research Database (NHIRD). Epidemiol Health 40(0), e2018062–2018060.

Marine, R., Creus, M., Sole, M., Cabezas, A., Algora, M.J., Moreno, I., Izquierdo, E., Stojanovic-Perez, A., Labad, J., 2015. Clinical correlates of obsessive-compulsive symptom dimensions in at-risk mental states and psychotic disorders at early stages. Psychiatry Res. 228 (3), 363–367.
McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol. Rev. 30, 67–76.
Meier, S.M., Petersen, L., Pedersen, M.G., Arendt, M.C., Nielsen, P.R., Mattheisen, M., Mors, O., Mortensen, P.B., 2014. Obsessive-compulsive disorder as a risk factor for schizophrenia: a nationwide study. JAMA Psychiat. 71 (11), 1215–1221.
Niendam, T.A., Berzak, J., Cannon, T.D., Bearden, C.E., 2009. Obsessive compulsive symptoms in the psychosis prodrome: correlates of clinical and functional outcome. Schizophr. Res. 108 (1–3), 170–175.
Poyurovsky, M., Weizman, A., Weizman, R., 2004. Obsessive-compulsive disorder in schizophrenia: clinical characteristics and treatment. CNS Drugs 18 (14), 989–1010.
Poyurovsky, M., Zohar, J., Glick, I., Koran, L.M., Weizman, R., Tandon, R., Weizman, A., 2012. Obsessive-compulsive symptoms in schizophrenia: implications for future psychiatric classifications. Compr. Psychiatry 53 (5), 480–483.
Rasmussen, S.A., Eisen, J.L., 1992. The epidemiology and differential diagnosis of obsessive compulsive disorder. J. Clin. Psychiatry 53, 4–10 Suppl.
Rosen, I., 1957. The clinical significance of obsessions in schizophrenia. J. Ment. Sci. 103 (433), 773–785.
Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol. Psychiatry 15 (1), 53–63.
Schirmbeck, F., Zink, M., 2013. Comorbid obsessive-compulsive symptoms in schizophrenia: contributions of pharmacological and genetic factors. Front. Pharmacol. 4, 99.
Seedat, F., Roos, J.L., Pretorius, H.W., Karayiorgou, M., Nel, B., 2007. Prevalence and clinical characteristics of obsessive-compulsive disorder and obsessive compulsive symptoms in Afrikaner schizophrenia and schizoaffective disorder patients. Afr. J. Psychiatry (Johannesburg) 10 (4), 219–224.
Soyata, A.Z., Akisik, S., Inhanli, D., Noyan, H., Ucok, A., 2018. Relationship of obsessive-compulsive symptoms to clinical variables and cognitive functions in individuals at ultra high risk for psychosis. Psychiatry Res. 261, 332–337.
Sterk, B., Lankreijer, K., Linszen, D.H., de Haan, L., 2011. Obsessive-compulsive symptoms in first episode psychosis and in subjects at ultra high risk for developing psychosis; onset and relationship to psychotic symptoms. Aust. N. Z. J. Psychiatry 45 (5), 400–406.
Sullivan, S., Rai, D., Golding, J., Zammit, S., Steer, C., 2013. The association between autism spectrum disorder and psychotic experiences in the Avon longitudinal study of parents and children (ALSPAC) birth cohort. J. Am. Acad. Child Adolesc. Psychiatry 52 (8), 806–814 (e802).
Swets, M., Dekker, J., van Emmerik-van Oortmerssen, K., Smid, G.E., Smit, F., de Haan, L., Schoevers, R.A., 2014. The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates. Schizophr. Res. 152 (2–3), 458–468.
Tukel, R., Polat, A., Genc, A., Bozkurt, O., Atli, H., 2004. Gender-related differences among Turkish patients with obsessive-compulsive disorder. Compr. Psychiatry 45 (5), 362–366.
Wu, C.S., Lai, M.S., Gau, S.S., Wang, S.C., Tsai, H.J., 2014. Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. PLoS One 9 (12), e112257.
Zink, M., 2014. Comorbid obsessive-compulsive symptoms in schizophrenia: insight into Pathomechanisms facilitates treatment. Adv. Med. Sci. 2014, 317980.
Zink, M., Schirmbeck, F., Rausch, F., Eifler, S., Elkin, H., Solojenkina, X., Englisch, S., Wagner, M., Maier, W., Lautenschlager, M., Heinz, A., Gudlowski, Y., Janssen, B., Gaebel, W., Michel, T.M., Schneider, F., Lambert, M., Naber, D., Juckel, G., Krueger-Oezguerdal, S., Wobrock, T., Hasan, A., Riedel, M., Muller, H., Klosterkotter, J., Bechdolf, A., 2014. Obsessive-compulsive symptoms in at-risk mental states for psychosis: associations with clinical impairment and cognitive function. Acta Psychiatr. Scand. 130 (3), 214–226.