Lifetime prevalence of mood and anxiety disorders in twin pairs discordant for schizophrenia

Michael J Lyons[1,2,3,4], Jonathan Huppert[1], Rosemary Toomey[2,3,4], Rebecca Harley[1], Jack Goldberg[5,6], Seth Eisen[7,8], William True[7,9], Stephen V Faraone[2,3] and Ming T Tsuang[2,3,4]

[1]Department of Psychology, Boston University
[2]Harvard Medical School Department of Psychiatry at Massachusetts Mental Health Center, Boston, MA
[3]Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA
[4]Department of Psychiatry, Brockton VA, Brockton, MA
[5]Department of Epidemiology, University of Illinois School of Public Health, Chicago, IL
[6]Hines VA Cooperative Studies Program Coordinating Center, Hines, IL
[7]Research and Medical Service, St Louis, MO
[8]Department of Medicine, Washington University, St Louis, MO
[9]School of Public Health, St Louis University, St Louis, MO, USA

There have been long questions about the relationship of schizophrenia to other mental disorders. Lifetime DSM-III-R diagnoses of mood and anxiety disorders in twins with clinically diagnosed schizophrenia ($n = 24$) and their non-affected co-twins ($n = 24$) were compared with twins from pairs without schizophrenia ($n = 3327$) using a sample from the Vietnam Era Twin Registry. Schizophrenic probands had significantly elevated rates of all included disorders (bipolar disorder, major depression, dysthymia, generalized anxiety disorder, panic disorder, and PTSD) compared with controls ($P < 0.01$). The odd ratios comparing co-twins of schizophrenic probands with controls was greater than three for every disorder, but did not attain statistical significance. A similar pattern was observed when analyses were restricted to only monozygotic twins ($n = 12$). Consistent with other studies, schizophrenics appeared to have higher rates of a range of mental disorders. Our results suggest that schizophrenia *per se* represents a risk factor for other psychiatric disorders, but the absence of significantly elevated risk among non-schizophrenic co-twins suggested that family environmental and/or genetic factors that contribute to risk of schizophrenia do not increase the risk of mood and anxiety disorders to the same extent that the risk of these other disorders is increased by the presence of schizophrenia. *Twin Research* (2000) **3**, 28–32.

Keywords: schizophrenia, twins, discordant, mood disorders, anxiety disorders

Introduction

The nature of the relationship, if any, between schizophrenia and other mental disorders has been an enduring issue in the field of psychopathology. Distinguishing between dementia praecox (schizophrenia) and manic-depressive illness is regarded as a central achievement of Kraepelin,[1] who is generally credited with originating modern psychiatric nosology. Others, such as Crow,[2] have argued that the distinction between schizophrenia and affective illness is incorrect. Although distinguishing between schizophrenia and affective illness has been the majority view,[3] Taylor[4] selectively reviewed

Correspondence: Michael J Lyons PhD, Psychology Department, Boston University, 64 Cummington Street, Boston, MA 02215, USA. Tel: (617)353 3820; Fax: (508)586 6791; E-mail: mlyons@bu.edu

previous research and identified a number of studies that do not support the distinction.

One approach to assessing the relationship between schizophrenia and other disorders is to examine whether they co-occur in the same individuals at rates that exceed what would be expected by chance. In an epidemiological study, Bland *et al*[5] demonstrated elevated odds ratios (above 10) for schizophrenia and manic episode, major depressive episode, obsessive compulsive disorder, phobia, panic, substance abuse/dependence, and any DSM-III diagnosis using lifetime prevalence. Robins and Regier[6] reported data from the Epidemiologic Catchment Area (ECA) study demonstrating elevated odds ratios (above 10) for schizophrenia and mania, depression, somatization, panic, obsessive compulsive disorder, and phobias using 12-month prevalences, and that 91% of all patients with schizophrenia or schizophreniform disorder had some other additional lifetime diagnosis. Kessler[7] reported data from the National Comorbidity Study (NCS)

demonstrating elevated odds ratios (above 10) for non-affective psychoses (schizophrenia, schizoaffective, schizophreniform, atypical psychosis, delusional disorders, and psychotic disorder NOS), and major depression, bipolar I, generalized anxiety disorders, and panic disorder according to DSM-III R criteria and using 12-month prevalences. He also reported that 93% of all people with nonaffective psychoses have some other disorder during their lifetime. In conclusion, there appear to be elevated prevalences of comorbid major depressive episodes, panic disorder, and bipolar disorders in people diagnosed with schizophrenia across epidemiological studies.

There are several alternative mechanisms that might be responsible for the observed comorbidity between schizophrenia and these other mental disorders.[8] One possibility is an overlap between the environmental and/or genetic factors that make an individual vulnerable to schizophrenia and vulnerable to these other disorders. The examination of non-schizophrenic relatives presents the opportunity to determine if individuals who share genetic and environmental characteristics with the schizophrenic proband also display an elevated risk for the other disorders, even in the absence of schizophrenia.

Kendler *et al*[9] reviewed studies evaluating risk for various mental disorders in relatives of schizophrenics. They reported five studies showing no increased risk of affective illnesses, two demonstrating an increased risk, and one showing a decreased risk for affective illnesses in the relatives of individuals with schizophrenia. They also reported four studies demonstrating no increased risk for anxiety disorders, and one study reporting decreased risk. Since Kendler *et al*'s review, we have identified four additional family studies using DSM-III-R or RDC criteria;[3,9,10,11] three studies reported no increases in risk for affective illness or anxiety disorders in relatives of schizophrenics, whilst the fourth (Maier) found an elevated risk for unipolar depression, but not bipolar disorder among first-degree relatives. Finally, a study of twins discordant for schizophrenia reported that none of 27 probands and their co-twins evidenced any any other Axis I disorder.[12]

If the same genetic and/or family environmental factors that impart risk for schizophrenia also impart risk for other mental disorders found to be co-morbid with schizophrenia, then the non-schizophrenic co-twins of schizophrenics might be particularly informative because they shared the same family environment with their schizophrenic twin and share either 50% of their genetic material with the schizophrenic twin in the case if dizygotic (DZ) twins or 100% of their genetic material in the case of monozygotic (MZ) twins. In this paper we report our findings based on pairs of twins discordant for schizophrenia from the Vietnam Era Twin Registry.

Materials and methods

Participants were 6744 men from the Vietnam Era Twin (VET) Registry, which has been described elsewhere.[13] Of 10 300 eligible individuals, 8169 (79.7%) were successfully interviewed by telephone following the granting of informed consent. This procedure for obtaining informed consent was approved by our university's institutional review board. The mean age of participants was 44.6 years.

Subjects were interviewed using the Diagnostic Interview Schedule Version III Revised (DIS-III-R), which yielded DSM-III-R diagnoses of mood and anxiety disorders. The psychosis section was not administered because we expected a low rate of schizophrenia in the overall sample and believed that the telephone format did not lend itself to the optimal identification of schizophrenia.

The presence of schizophrenia in probands was based on clinical diagnoses obtained from the Department of Veterans Affairs Patient Treatment Files (PTF). The PTF, a centralized computerized abstract of in-patient hospitalizations, is maintained by the Department of Veterans Affairs and includes International Classification of Disease (ICD) diagnostic codes. Diagnostic codes were assigned at the local hospital by trained personnel. The absence of schizophrenia in the non-schizophrenic co-twins was based on the absence of a PTF diagnosis and a negative response to a self-report questionnaire administered to Registry members by the National Heart, Lung and Blood Institute (NHLBI).

The PTF identified 12 monozygotic (MZ) and 12 dizygotic (DZ) twin pairs in which one twin had ICD-defined schizophrenia and the other twin had not. In 23 of these 24 pairs, the non-schizophrenic co-twin responded to the NHLBI questionnaire that he was not schizophrenic. In one pair, the non-schizophrenic co-twin did not respond to the NHLBI survey.

Results

For the purposes of the primary data analyses, subjects were divided into three groups: a) 24 schizophrenic probands; b) 24 non-schizophrenic co-twins of the schizophrenic probands; and 3) 3327 subjects from pairs without schizophrenia. One twin was randomly selected from every pair in which both twins responded and neither had schizophrenia. Odds ratios compared both schizophrenic

probands and their co-twins to controls. Statistical significance was determined by a 99% confidence interval that did not include 1. We selected the 99% confidence interval rather than the 95% confidence interval to avoid type I error due to the relatively high number (24) of individual comparisons carried out.

Table 1 includes lifetime prevalences in each group and odds ratios comparing both MZ and DZ schizophrenic probands and co-twins with controls. The odds ratios comparing participants with schizophrenia with controls was significant for every included disorder. Even the smallest odds ratio, 7.7 for major depression, was quite substantial. To evaluate the possibility that schizophrenia might increase the risk of experiencing trauma and thus be associated with elevated rates of PTSD, we examined prevalence of PTSD using only subjects who reported experiencing a qualifying trauma according to DSM-III-R. PTSD was more prevalent among traumatized individuals (controls = 18.4%; schizophrenic probands = 69.2%; non-schizophrenic co-twins = 27.3%), but the only significant comparison remained controls *vs* schizophrenic probands. Although all the odds ratios comparing co-twins of

schizophrenics with controls was over 2, none reached statistical significance. The small number of subjects and relative infrequency of psychopathology in co-twins resulted in very broad 99% confidence intervals.

The non-affected co-twins from discordant MZ pairs are of special interest because they share all their genes with the schizophrenic proband. Therefore, we examined the 12 MZ co-twins of schizophrenics separately (see Table 2). Similar to the results for the combined MZ and DZ analyses, the schizophrenic MZ probands were significantly more likely to have each one of the included mental disorder than were controls with the exception of bipolar disorder. None of the schizophrenic MZ probands received a diagnosis of bipolar disorder. Non-schizophrenic MZ co-twins did not differ significantly from controls for any disorder. However, every odds ratio was greater than 3.

Among the 24 schizophrenic probands, five had three or more additional disorders, three had two, nine had one, and seven had no additional disorders. Among the 24 non-schizophrenic co-twins, three had two or three disorders, three had one, and 18 had no psychiatric disorder.

Table 1 Prevalence of mood and anxiety disorders in controls, schizophrenic probands, and nonschizophrenic co-twins and odds ratios (with 99% confidence intervals) comparing both MZ and DZ twin schizophrenic probands and their co-twins with controls

Disorder	Prevalences			Odds ratios (99% confidence interval)	
	Controls (n = 3327)	MZ & DZ schizophrenic probands (n = 24)	MZ & DZ nonschizophrenic co-twins of probands (n = 24)	MZ & DZ schizophrenic probands (n = 24)	MZ & DZ nonschizophrenic co-twins of probands (n = 24)
Major depression	7.7%	43.5%	17.4%	7.7 (2.5–24.1)	2.1 (0.5–8.8)
Dysthymia	1.5%	12.5%	4.3%	8.2 (1.4–41.0)	2.6 (0.1–27.5)
Bipolar disorder	0.4%	8.4%	4.2%	20.1 (2.0–144.9)	9.6 (0.3–112.0)
Generalized anxiety disorder	1.0%	21.7%	4.3%	26.0 (5.9–106.7)	4.3 (0.1–46.1)
Panic disorder	1.2%	12.5%	4.2%	10.0 (1.6–50.6)	3.0 (0.1–32.2)
PTSD	8.3%	16.7%	5.3%	7.0 (2.1–22.3)	1.4 (0.2–6.9)

Table 2 Prevalence of mood and anxiety disorders in controls, schizophrenic probands, and nonschizophrenic co-twins and odds ratios (with 99% confidence intervals) comparing only MZ twin schizophrenic probands and their co-twins with controls

Disorder	Prevalences			Odds ratios (99% confidence interval)	
	Controls (n = 3327)	MZ schizophrenic probands (n = 12)	MZ nonschizophrenic co-twins of probands (n = 12)	MZ schizophrenic probands (n = 12)	MZ nonschizophrenic co-twins of probands (n = 12)
Major depression	7.7%	50.0%	25.0%	12.0 (2.5–57.1)	4.0 (0.6–22.3)
Dysthymia	1.5%	25.0%	8.3%	12.9 (3.2–127.8)	6.0 (0.2–68.3)
Bipolar disorder	0.4%	0.0%	8.3%	–	23.1 (0.7–305.4)
Generalized anxiety disorder	1.0%	25.0%	8.3%	33.3 (4.8–200.8)	9.1 (0.3–106.9)
Panic disorder	1.2%	16.7%	8.3%	16.4 (1.6–120.1)	7.5 (0.2–86.8)
PTSD	8.3%	50.0%	25.0%	11.1 (3.0–68.0)	3.7 (0.6–20.5)

Discussion

Subjects with schizophrenia were significantly more likely to be diagnosed with a range of mood and anxiety disorders than controls, whilst their co-twins were not. These results suggest that schizophrenia *per se* may be a risk factor for mood and anxiety disorders, ie schizophrenia may impart a risk for the development of other disorders. However, equally consistent with the observed pattern is the possibility that the occurrence of an anxiety or mood disorder could precipitate the onset of schizophrenia in vulnerable individuals. Cassano *et al*[14] have suggested that observed comorbidity might be more artifactual than substantive. Symptoms used to arrive at a diagnosis of a mood or anxiety disorder in an individual with schizophrenia could reflect non-specific by-products of psychosis rather than additional, distinct disorders. Apparent comorbidity might also reflect imprecise specification of symptoms for psychosis and the other disorders, as well as reflecting the effects of treatment and information bias.

The absence of significantly elevated risk among non-schizophrenic co-twins suggests that the genetic and family environmental factors that contribute to the risk of schizophrenia do not strongly influence the risk of mood and anxiety disorders in the absence of schizophrenia. These data are consistent with the view that mood and anxiety disorders are not in a genetic spectrum with schizophrenia. However, these results from the non-schizophrenic co-twins should be viewed with considerable caution because, whilst none of the odds ratios comparing non-schizophrenic co-twins of schizophrenic probands with controls was statistically significant, all were greater than 1 and five of the six were greater than 2.

When MZ twins alone were compared with controls, the odds ratios for co-twins were higher, but not significantly so, than in the combined MZ plus DZ analyses. Although it is tempting to speculate about these odds ratios, it is important to remember that four of the six odds ratios that were calculated reflect a single case of the disorder among the MZ co-twins and none of the odds ratios is based on more than three cases among the MZ co-twins.

There are several limitations of this study. Whilst diagnoses of mood and anxiety disorders were based on structured diagnostic interviews, the PTF diagnoses of schizophrenia (although based on the ICD) were not based on standardized data collection methods. An unknown number of VET twins may have schizophrenia, but could not be included in this study because they never received treatment at a VA facility. However, the chronic and debilitating nature of schizophrenia makes it more likely that

veterans with schizophrenia will receive treatment at a VA facility than will veterans with less serious mental disorders. Failure to be identified in the PTF as a schizophrenic is not strong evidence that the individual is not affected. However, co-twins were classified as non-schizophrenics according to the NHLBI study as well as PTF data; in 23 of 24 pairs the co-twin reported that he had never received a diagnosis of schizophrenia. Twin pairs that are discordant for schizophrenia may be different from twin pairs that are concordant for schizophrenia,[15] so this sample may not be representative of all cases of schizophrenia. The relatively small number of schizophrenia-discordant pairs and low prevalences of mood and anxiety disorders resulted in broad confidence intervals, which while not significant for comparisons involving non-schizophrenic co-twins, did include substantial associations within the confidence intervals. The lack of statistical significance in analyses involving co-twins, while not providing evidence for a familial relationship between these disorders and schizophrenia, should not be viewed as providing strong evidence against such an association. The strongest conclusions regarding these results involve the significantly elevated rates of mood and anxiety disorders among schizophrenics; conclusions regarding co-twins must be viewed as tentative. The fact that odds ratios for the other disorders were significant for the schizophrenic twins suggests that having schizophrenia is associated with an increased risk of these other disorders above and beyond any familial vulnerability that might be common to schizophrenia and anxiety or mood disorder.

Acknowledgements

References

1 Kraepelin E. *Clinical Psychiatry: A Textbook for Students and Physicians*. Macmillan Publishing Company Inc: New York, 1904.

2 Crow TJ. Nature of the genetic contribution to psychotic illness: a continuum viewpoint. *Acta Psychiatr Scand* 1990; **81**: 401–408.

3 Maier W, Lichterman D, Minges J, Hallmayer J, Heun R, Benkert O, Levinson DF. Continuity and discontinuity of affective disorders and schizophrenia. *Arch Gen Psychiatr* 1993; **50**: 871–883.

4 Taylor MA. Are schizophrenia and affective disorder related? A selective literature review. *Am J Psychiatr* 1992; **149**: 22–32.

5 Bland RC. Symptoms, diagnoses and comorbidity. *Acta Psychiatr Scand* 1994; **89**: 5–6 (Suppl 376).

6 Robins LN, Rieger DA. *Psychiatric Disorders in America*. Free Press: New York, 1991.

7 Kessler RC. The prevalence of psychiatric comorbidity. In: Wetzler S, Sanderson WC (eds). *Treatment Strategies for Patients with Psychiatric Comorbidity*. John Wiley and Sons: New York, 1997.

8 Lyons MJ, Tyrer P, Gunderson J, Tohen M. Heuristic models for the comorbidity of Axis I and Axis II disorders. *J Personal Disord* 1997; **11**: 260–269.

9 Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman W, Walsh D. The Roscommon Family Study IV: Affective illness, anxiety disorders, and alcoholism in relatives. *Arch Gen Psychiatr* 1993; **50**: 952–960.

10 Onstad S, Skre I, Edvardsen J, Torgersen S, Kringlen E. Mental disorders in first-degree relatives of schizophrenics. *Acta Psychiatr Scand* 1991; **83**: 463–467.

11 Parnas Y, Cannon TD, Jacobsen B, Schulsinger H, Schulsinger F, Mednick SA. Lifetime DSM-III-R diagnostic outcomes in the offspring of schizophrenic mothers. *Arch Gen Psychiatr* 1993; **50**: 707–714.

12 Torrey EF, Bowler AE, Taylor EH, Gottesman II. *Schizophrenia and Manic Depressive Disorder*. Basic Books: New York, 1994.

13 Eisen S, True W, Goldberg J, Henderson W, Robinette D. The Vietnam Era Twin (VET) Registry: Method of construction. *Acta Genet Med Gemellol (Roma)* 1987; **36**: 61–66.

14 Cassano GB, Pini S, Saettoni M, Rucci P, Dell'Osso L. Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. *J Clin Psychiatr* 1998; **59**: 60–68.

15 Lyons MJ, Kremen WS, Tsuang MT, Faraone SV. Investigating putative genetic and environmental forms of schizophrenia: Methods and findings. *Int Rev Psychiatr* 1989; **1**(4): 259–276.