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Lifetime comorbidities between phobic disorders and major depression in Japan: Results from the World Mental Health Japan 2002-2004 Survey

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Abstract

Background—Although often considered of minor significance in themselves, evidence exists that early-onset phobic disorders might be predictors of later more serious disorders, such as major depressive disorder (MDD). The purpose of this study was to investigate the association of phobic disorders with the onset of MDD in the community in Japan.

Methods—Data from the World Mental Health Japan 2002-2004 Survey were analyzed. A total of 2,436 community residents aged 20 and older were interviewed using the WHO Composite

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International Diagnostic Interview 3.0 (response rate, 58.4%). A Cox proportional hazards model was used to predict the onset of MDD as a function of prior history of DSM-IV specific phobia, agoraphobia, or social phobia, adjusting for gender, birth cohort, other anxiety disorders, education, and marital status at survey.

Results—Social phobia was strongly associated with the subsequent onset of MDD (hazard ratio [HR] = 4.1 [95%CI: 2.0-8.7]) after adjusting for sex, birth cohort, and the number of other anxiety disorders. The association between agoraphobia or specific phobia and MDD was not statistically significant after adjusting for these variables.

Conclusions—Social phobia is a powerful predictor of the subsequent first onset of MDD in Japan. While this finding argues against a simple neurobiological model and in favor of a model in which the cultural meanings of phobia play a part in promoting MDD, an elucidation of causal pathways will require more fine-grained comparative research.

Keywords

phobia; major depressive disorder; comorbidity; proportional hazard model; cultural difference; World Mental Health

INTRODUCTION

Phobic disorders and major depressive disorder (MDD) are both highly prevalent mental disorders in communities [Kawakami et al., 2005; Kessler et al., 2005b; Shen et al., 2006], and these disorders often co-occur over the life course [Choy et al., 2007; Kendler et al., 1993; Magee et al., 1996]. While the mechanism still remains unclear [Wittchen et al., 2003], possible explanations for the association between phobias and MDD are common biological and psychopathological factors [Foote, 1999; Kaufman and Charney, 2000; LeDoux, 2000; Lopez et al., 1999]. There might also be socio-cultural factors that contribute to comorbidity between these two disorders.

Most previous studies of the association between phobic disorders and MDD have been carried out in Western countries [Beesdo et al., 2007; Bittner et al., 2004; Brown et al., 2001; Goodwin, 2002; Kessler et al., 1996; Kessler et al., 1999; Magee et al., 1996; Regier et al., 1998; Stein et al., 2001; Wittchen et al., 2000]. In cross-sectional analyses, the relative-odds of lifetime phobic disorders with lifetime MDD in these studies have been in the range of 1.3-3.7 for social phobia, 0.9-4.6 for specific phobia, and 1.1-4.9 for agoraphobia [Brown et al., 2001; Choy et al., 2007; Magee et al., 1996]. In both prospective and retrospective cohort studies, the relative-odds of lifetime phobias predicting the subsequent first onset of MDD have been in the range 2.0-5.4 for social phobia, 1.7-2.7 for specific phobia, and 2.3-3.7 for agoraphobia [Beesdo et al., 2007; Bittner et al., 2004; Goodwin, 2002; Hettema et al., 2003; Kessler et al., 1996; Kessler et al., 1999; Stein et al., 2001; Wittchen et al., 2000]. Recent cross-sectional studies in the Middle-East, including Iran [Mohammadi et al., 2006] and Saudi Arabia [Bassiony, 2005], have reported higher cross-sectional associations between lifetime social phobia and MDD (odds-ratios of 5.8 and 4.0, respectively) than those found in Western studies, raising the possibility that the processing linking phobias to later MDD might be different than in Western countries.

To the best of our knowledge, no community-based epidemiological study on this topic has previously been conducted in Asia. Japan is known to have a collectivism-oriented culture [Nakane, 1970], which might result in the interactional impairments known to be associated with phobias, especially social phobia and agoraphobia [Degonda and Angst, 1993; McCarthy and Shean, 1996], to be associated with greater risk of subsequent MDD than in Western countries. On the other hand, if the association between phobias and MDD is solely

explained by common neurobiological factors, the strength of this association would be expected to be similar across countries.

The current report presents preliminary data on the above issue by examining the associations between temporally primary phobic disorders and the subsequent onset of MDD in a large community-based sample of adults in Japan. The issue considered, as a first step investigation is whether the magnitude of this association is comparable to or larger than found in previous studies carried out in Western countries. While documentation that the association is significantly larger than in Western studies would provide no information about mechanisms, which would require more in-depth comparative studies to sort out, documentation that the association is comparable to those found in Western studies despite the stronger collectivistic orientation in Japan would argue strongly in favor of the neurobiological rather than environmental pathways accounting for the association.

METHODS

Subjects

The data used to examine the association between temporally primary phobic disorders and subsequent MDD come from the World Mental Health Japan (WMH-J) 2002-2004 Survey [Kawakami et al., 2005]. The WMH-J is an epidemiologic survey of household residents aged 20 and older of seven areas in Japan, including two urban cities and five rural municipalities, that was carried out as part of the World Health Organization's World Mental Health (WMH) Survey Initiative [Kessler and Ustun, 2004]. The seven WMH-J sites were selected based on their geographic variation, availability of site investigators, and cooperation of the local governments. Mainly due to the last two factors, all survey sites were located in the western part of Japan. Interviews were carried out face-to-face with a total of 2,437 respondents across the sites. One respondent was eliminated from further analysis because of coding errors. The total response rate was 58.4%.

The data reported here were weighted to adjust for differential probabilities of selection and non-response. Details of the WMHJ design, field procedure and sample weights have been reported previously [Kawakami et al., 2005]. The Human Subjects Committees of Okayama University, Japan National Center of Neurology and Psychiatry and Nagasaki University approved the recruitment, consent, and field procedures.

Diagnosis of phobic disorders and major depression

WMH-J diagnoses are based on Version 3.0 of the WHO Composite International Diagnostic Interview (CIDI) [Kessler and Ustun, 2004], a structured diagnostic interview designed to be administered by trained interviewers who are not clinicians to generate diagnoses of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [American Psychiatric Association., 1994]. The disorders of primary interest were social phobia, specific phobia, agoraphobia without panic disorder, and major depressive disorder. In addition, lifetime diagnoses of panic disorder and generalized anxiety disorder were also used for an adjustment purpose. Organic exclusion rules and hierarchy rules were used to make all diagnoses.

Age of onset

Retrospective age-of-onset (AOO) reports were obtained in the CIDI using a series of questions designed to avoid the implausible response patterns obtained in previous structured diagnostic interviews [Simon and VonKorff, 1995]. A detailed description of this approach is presented elsewhere [Kessler et al., 2005a; Lee et al., 2007]. Methodological

research has documented that this questioning approach does, in fact, yield plausible AOO reports [Knäuper et al., 1999].

Demographic variables

The demographic characteristics used in the analysis were gender, age at survey (birth cohort), and marital status and education at survey, collected between 2002 and 2004. Age at survey was classified into four categories: 20-34 years old; 35-49 years old; 50-64 years old; and 65 years old. Marital status at survey was classified into three categories: married/cohabitating; separated/widowed/divorced; never married. Education at survey was classified into four categories: middle school or less (0-11 years); high school (12 years); some college (13-15 years); college or higher (16 years or more).

Statistical Analysis

All analyses were performed using survey procedures in SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA) or SAS-callable SUDAAN version 9.0 (Research Triangle Institute, Research Triangle Park, NC, USA) to account for the survey design of the WMH-J (see Kawakami *et al.*, 2005 for details). The associations between phobic disorders and MDD were examined according to the following procedures. First, in order to replicate previous findings using a similar type of analysis, we examined cross-sectional association of lifetime comorbidities between phobic disorders and MDD using logistic regression analysis adjusted for sex, age-cohort (age at survey), where age-cohort was adjusted to avoid a possible pseudo-correlation [Kraemer et al., 2006]. A similar analysis was conducted additionally adjusting for the number of lifetime diagnoses of anxiety disorders at survey other than a phobic disorder concerned (0-4), as well as marital status and education. Second, temporal priorities between phobic disorders and MDD were calculated using retrospective AOO. Third, to clarify any temporal effects of prior phobic disorders on the succeeding onset of major depression, we used Cox proportional hazards models to calculate hazard ratios (HRs) for the onset of major depression, with the comorbid phobic disorders as time-dependent covariates adjusted for sex, age-cohort, [Kraemer et al., 2006], the number of lifetime diagnoses of other anxiety disorders at survey, marital status and education. In this proportional hazard analysis, in order to yield a conservative estimate it was assumed that a phobic disorder appeared after major depression if the two disorders had the same age-of-onset. Statistical significance was evaluated using 2-sided, design-based $P < 0.05$ -level tests.

RESULTS

Comorbidities between phobic disorders and MDD

Among phobic disorders, specific phobia was most prevalent (Table 1). The lifetime prevalence of each phobic disorder among respondents who had a lifetime history of major depression was high compared with those who had reported never having major depression. Controlling for socio-demographic variables, lifetime experience of each phobic disorder was significantly and positively associated with lifetime history of major depression ($p < 0.05$). After controlling for the number of other anxiety disorders, marital status, and education, the association between phobias and major depression still remained significant. Logistic regression analysis revealed that social phobia was associated with a four-times greater risk of having major depression; agoraphobia without panic disorder and specific phobia were associated with six-times and twice greater risks of major depression, respectively.

Temporal relationship between phobic disorders and MDD

Among respondents with a lifetime history of both social phobia and MDD, more than 80% had social phobia first, while among respondents with a history of both specific phobia and MDD, 70% had specific phobia first (Table 2). Among respondents with a history of both agoraphobia and MDD, about half had the same age of onset for agoraphobia and MDD, while for roughly half of the remaining half agoraphobia occurred before MDD.

Effects of phobic disorders on the subsequent first onset of MDD

All phobic disorders were significantly and positively associated with the succeeding onset of MDD after adjusting for sex and birth cohort ($p < 0.05$, Table 3). Respondents who experienced social phobia had a significantly higher risk of subsequent onset of MDD (HR, 4.1, 95% CI, 2.0-8.7), after additionally adjusting for the number of anxiety disorders. The HR substantially decreased after adjustment of education and marital status at survey, but remained significant. Hazard ratios for agoraphobia without panic disorder and specific phobia on subsequent risk of depression were no longer statistically significant after the adjustment for the number of anxiety disorders.

DISCUSSION

Consistent with many previous studies in Western countries, we confirmed that social phobia was significantly associated with an elevated risk of subsequent MDD in a sample of community residents in Japan. Social phobia was associated with a seven-time greater risk of MDD after controlling for sex and birth-cohort, and with a four-times greater risk even after adjusting for the number of other anxiety disorders, while the association substantially decreased after adjusting for education and marital status at survey. Agoraphobia without panic disorder was initially significantly and strongly associated with MDD when age and birth-cohort were adjusted, but the association was not significant after adjusting for the number of other anxiety disorders.

The present study provides additional evidence that the association between social phobia and MDD, which were well-observed in Western countries [Bittner et al., 2004; Brown et al., 2001; Choy et al., 2007; Goodwin, 2002; Hettema et al., 2003; Kessler et al., 1996; Magee et al., 1996; Wittchen et al., 2000] and in some Middle-East countries [Bassiony, 2005; Mohammadi et al., 2006] is also seen in Japan, i.e., an Asian country. The magnitude of the sex and birth cohort-adjusted association between social phobia and MDD was greater in the present study than that observed in Western countries (sex and age-adjusted odds ratio [OR] = 2.4-3.5 [or relative risk = 1.5-1.9] in previous cohort studies [Beesdo et al., 2007; Bittner et al., 2004; Stein et al., 2001; Wittchen et al., 2000], and OR = 2.3-2.5 in two previous cohort [and retrospective cohort] studies adjusting for comorbid mental disorders [Bittner et al., 2004; Goodwin, 2002; Kessler et al., 1999]). Social phobia may be associated with a greater risk of MDD in Japan than in the Western countries. However, while the HR substantially decreased to the magnitude of one comparable to these previous studies after adjusting for education and marital status, this may be a too conservative estimate because social phobia may affect the onset of MDD through these social variables as a possible mediator [Breslau et al., 2008; Kessler et al., 1995]. There was no previous study which examined the association between the two disorders adjusting for education and marital status with which the present finding could be compared, which warrants a further cross-country research. One also should be careful because the 95% confident intervals were quite wide because of the small number of cases in the sample.

It is beyond the scope of this initial report to carry out a systematic cross-national comparative analysis of the association between social phobia and MDD, but the value of

doing so is certainly suggested by the current results. A plausible interpretation of the possible greater associations observed in the present study is that social phobia might lead to more impairment of social interaction in Japan than in Western countries because of the collectivistic orientation of Japanese society. Because interpersonal relationships are well-known risk factors of depression [Garber, 2006; Rudolph et al., 2000], this presumed greater social impairment could then lead to higher risk of secondary MDD in Japan. In a collectivism-oriented society which value social harmony, people are not required to show their contribution (e.g., expressing their ideas and opinions or doing good things) to groups [Heinrichs et al., 2006], such as the neighborhoods and workplaces to which they belong; rather, people are strongly expected to join in group activities to show their commitment and maintain group collectivism [Chang, 1997; Nakane, 1970]. Social phobia may interfere with people going to a group activity, which could result in low social support from group members and less of a feeling of belonging in the society, or even difficulty in finding a spouse/partner, which may lead to a greater risk of major depression in the long run. This seems to particularly be the case in Japan, a collective society. This is consistent with our observation that the hazard ratio of MDD associated with phobic disorder substantially decreased after adjustment of education and marital status in our sample, which is partly attributable that people with social phobia tend to have a difficulty in getting married or completing school. The above proposed interpretation is only tentative because no direct measures of social role impairment were examined and no comparisons were made between the Japanese data and data from parallel surveys carried out in Western countries. A future study should investigate the effects of social phobia on a wide variety of indicators of social impairment and lack of social support as mediators in the prediction of MDD in a cross-national comparative framework.

Another possibility includes that some of the cases diagnosed as having social phobia may suffer Taijin Kyofusho (TKS), a Japanese form of social anxiety centered around concern for offending others with inappropriate behavior or offensive appearance [Yamashita, 2002], which may result in more social impairment particularly in the collectivism-oriented countries. The current WHO-CIDI 3.0 does not specifically assess the TSK, but diagnoses and symptoms of TKS and social anxiety disorder often overlaps [Kinoshita et al., 2008; Kleinknecht et al., 1997]. This possibility should also be addressed in future research.

Agoraphobia and specific phobia were associated with a non-significant, but slightly greater risk of subsequent MDD in this sample in Japan. However, the magnitude of the association was similar to that previously reported in studies of Western countries for agoraphobia [Bittner et al., 2004; Goodwin, 2002; Kessler et al., 1996; Wittchen et al., 2000] and specific phobia [Bittner et al., 2004; Goodwin, 2002; Wittchen et al., 2000]. Comorbid agoraphobia is not usually primary to major depression [Magee et al., 1996]. The proportions of comorbidity in our study were substantially lower than those of previous studies [Kendler et al., 1993; Kessler et al., 1996; Kessler et al., 1999], with the exception of a previous finding of specific phobia among females having a similar percentage to that found in our study [Kendler et al., 1993]. Impairment in role functioning due to agoraphobia or specific phobia is not necessarily related to one's social situation. Because the disorders are expected to have less impact on social interaction, collectivism-individualism cultural differences may not have a modifying effect on the association between the disorders and MDD. The effect of agoraphobia and specific phobia on later onset of MDD may be attributable to common biological and environmental factors that underlie the two disorders [Kendler et al., 1993], other types of role impairment due to these disorders, or even other comorbid anxiety disorders. However, it should be noted that specific phobia might have clinical relevance despite its modest effect on subsequent major depression because of its early onset and high prevalence.

Limitations

In addition to those already mentioned earlier, the present findings must be considered within the following limitations. First, diagnoses and ages of onset for major depression and the comorbid phobic disorders were assessed by retrospective reporting, which is subject to recall bias. Second, the diagnoses of phobic disorders solely depended on the WHO-CIDI, which operationally defines a diagnostic threshold for each phobic disorder according to the DSM-IV criteria. This may artificially affect the severity of each phobic disorder and thus result in differential associations of phobic disorders with MDD. Finally, the present findings might be further explained if, for example, an ethnicity-specific (or non-Western) gene is found to underlie the strong association of social phobia with MDD in the Japanese population. This possibility should also be pursued in future research.

Even within the context of these limitations, we found a substantive impact of prior onset of social phobia on subsequent onset of MDD in Japan. To our knowledge, this is the first community-based epidemiological study to examine the association between phobic disorders and MDD, and in particular focusing on the temporal relationships among East Asian countries. The present study demonstrated a possible cross-national difference in the magnitude of the association between prior social phobia and MDD.

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Table 1

Lifetime prevalence of DSM-IV phobic disorders among respondents with lifetime diagnosis of major depression in community residents in Japan: The World Mental Health Japan Survey 2002-2004

Lifetime prevalence of phobic disorder and major depression			Association between phobic disorder and major depression								
Mental disorders	Number of cases (weighted n)	%	Number of cases with comorbidities (weighted n)	Lifetime prevalence of major depression among those with lifetime phobic disorder (%) [†]	Lifetime prevalence of phobic disorder among those with lifetime major depression (%) [‡]	Sex and birth cohort-adjusted		Sex, birth cohort, and no. of other anxiety disorders-adjusted		Sex, birth cohort, no. of other anxiety disorders, marital status and education-adjusted	
						OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
	Social phobia	29.0	1.2	11.3	38.9	6.9	9.6	(4.3-21.6)	4.9	(1.7-13.7)	3.9
Agoraphobia without PD	8.4	0.4	5.8	68.7	3.5	24.1	(5.6-104.5)	6.2	(1.4-27.9)	6.4	(1.4-30.0)
Specific phobia	89.5	3.7	19.5	21.8	12.0	3.7	(2.1-6.5)	2.1	(1.1-4.0)	2.3	(1.2-4.5)
Major depression	162.7	6.7	—	—	—	—	—	—	—	—	—

PD: Panic disorder; OR: Odds ratio; 95% CI: 95% confidence interval.

[†]Percentage column reports the lifetime prevalences of major depressive disorder among respondents with a lifetime diagnosis of a given phobic disorders.

[‡]Percentage column reports the lifetime prevalences of phobic disorder among respondents with a lifetime diagnosis of major depression.

Table 2

Temporal ordering of age of onset of DSM-IV phobic disorders and major depression on (MDD) among community residents with a history of both disorders in Japan: The World Mental Health Japan Survey 2002-2004

Phobic disorders	Precedes MDD onset (%)	Follows MDD onset (%)	Same year as MDD onset (%)
Social phobia	83.2	16.8	-
Agoraphobia without PD	25.1	22.3	52.6
Specific phobia	70.1	18.1	11.9

PD: Panic disorder

-: No cases.

Table 3

Effects (hazard ratio and the 95% confidence intervals [CIs]) of temporally primary phobia in predicting first onset of major depression among community residents in Japan: The World Mental Health Japan Survey 2002-2004

	<u>Sex and birth cohort-adjusted</u>		<u>Sex, birth cohort, no. of other anxiety disorders-adjusted</u>		<u>Sex, birth cohort, no. of other anxiety disorders, education, and marital status-adjusted</u>	
	HR [†]	(95% CI)	HR [†]	(95% CI)	HR [†]	(95% CI)
Social phobia	7.2	(3.8-13.7)	4.1	(2.0-8.7)	2.6	(1.2-6.0)
Agoraphobia without PD	7.5	(1.3-42.0)	2.3	(0.5-11.5)	2.5	(0.5-14.4)
Specific phobia	2.4	(1.4-4.3)	1.3	(0.7-2.4)	1.5	(0.8-2.8)

PD: Panic disorder; HR: Hazard ratio; 95%CI: 95% confidence interval.

[†]HR and 95% CI of major depression were estimated using Cox's proportional hazard model, adjusted for each set of covariates indicated above.