Psychological Medicine, 2006, **36**, 1275–1281. © 2006 Cambridge University Press
doi:10.1017/S0033291706007732 First published online 15 May 2006 Printed in the United Kingdom

A population-based family study of DSM-III generalized anxiety disorder

STEPHEN C. NEWMAN* AND ROGER C. BLAND

Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

ABSTRACT

Background. A recent meta-analysis provides evidence that generalized anxiety disorder (GAD) is familial. However, two of the key studies relied on subjects who were self-selected or recruited from the clinic setting, thereby limiting generalizability.

Method. We conducted a family study of GAD in which probands and controls came from a community sample originally enrolled in a prevalence study in Edmonton, Canada. One hundred and sixty probands, 764 controls and 2386 first-degree relatives (FDRs) were interviewed using the Diagnostic Interview Schedule (DIS); lifetime diagnoses were made according to DSM-III criteria without exclusions. Logistic regression analysis was performed with GAD (in a proband) as the 'exposure', and GAD in an FDR as the 'outcome'. Several analytic strategies were used to control for potential confounding by major depressive disorder (MDD) and several anxiety disorders (panic disorder, phobic disorders, obsessive–compulsive disorder, and post-traumatic stress disorder).

Results. The odds ratios for the association between GAD in a proband and GAD in an FDR were in the range 1·4–1·8 when the entire FDR sample was analysed, and in the range 2·1–2·8 when we restricted to FDRs who were children of probands and controls.

Conclusion. In the community setting, GAD exhibits mild to moderate familial aggregation.

INTRODUCTION

According to DSM-III (APA, 1980) criteria, the diagnosis of generalized anxiety disorder (GAD) requires persistent anxiety for 1 month or more, with at least one symptom from three of the following areas: apprehensive expectation, motor tension, autonomic hyperactivity, and vigilance and scanning. Importantly, GAD is excluded by the presence of panic disorder, phobic disorder or obsessive–compulsive disorder, making GAD a residual category. Spitzer and Williams (1984) expressed concern that the 1-month criterion 'makes it difficult to distinguish this category from relatively transient stress reactions' and that 'only' one symptom from three of four areas is required. These issues were addressed in DSM-III-R (APA, 1987), where the diagnosis of GAD requires 'unrealistic and excessive anxiety and worry (apprehensive expectation) about two or more life circumstances' for at least 6 months, with six or more of 18 symptoms. Another significant change in the DSM-III-R criteria is that GAD is no longer regarded as a residual category, but can be diagnosed in the presence of other anxiety disorders. The 6-month requirement in the DSM-III-R criteria, and to a lesser extent the increase in the number of symptoms required, markedly lowers current and period prevalence rates of GAD compared with those based on DSM-III criteria, while at the same time increases co-morbidity with major depressive disorder (MDD) (Breslau & Davis, 1985). In the DSM-IV (APA, 1994), the criteria for GAD changed again; three of six symptoms must be met and the symptoms have to cause 'clinically significant distress or impairment'.

* Address for correspondence: Stephen C. Newman, M.D., Department of Psychiatry, Mackenzie Centre, University of Alberta, Edmonton, Alberta T6G 2B7, Canada.
(Email: stephen.newman@ualberta.ca)

The change in diagnostic criteria for GAD in successive editions of the DSM reflects concern over the validity of GAD as a distinct diagnostic entity (Breier *et al.* 1985; Barlow *et al.* 1986*a*, *b*; Barlow & DiNardo, 1991; Noyes *et al.* 1992; Brown *et al.* 1994; Wolk *et al.* 1996). However, it is not clear that adopting more stringent criteria has had the intended effect of increasing validity (Breslau & Davis, 1985; Kendler, 1993).

When present, familial aggregation is a strong indicator of the validity of a psychiatric syndrome (Robins & Guze, 1970). Hettema *et al.* (2001) conducted a meta-analysis of the genetic epidemiology of anxiety disorders, including GAD. Studies meeting the following requirements were included: (1) use of operationalized diagnostic criteria, (2) systematic ascertainment of probands and relatives, (3) direct interviews of a majority of subjects, (4) diagnostic assessment of relatives performed with investigators blind to proband diagnosis, and (5) for family studies, inclusion of a comparison group. The only family study of GAD meeting all five criteria was that by Mendlewicz *et al.* (1993). A family study by Noyes *et al.* (1987), although not satisfying the condition of blind assessment, was also included in the meta-analysis.

Mendlewicz *et al.* (1993) interviewed 25 probands with 'pure' GAD recruited from either a hospital-based sleep laboratory or an outpatient clinic, 25 controls described as 'normal persons with no personal or family history of psychiatric illness', and 232 'available' first-degree relatives (FDRs). Probands and controls were matched on age (within 5 years) and sex. GAD in probands was diagnosed using the Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978) and Research Diagnostic Criteria (RDC) (Spitzer *et al.* 1978). Probands were also interviewed using the Structured Clinical Interview for DSM-III – Upjohn version (Williams, 1983), as were controls. FDRs received diagnoses using the methods of Andreason *et al.* (1977) and Endicott *et al.* (1978). The age-adjusted morbidity risk ratio for GAD in proband FDRs compared with GAD in control FDRs was 4·7.

Noyes *et al.* (1987) interviewed 20 probands with GAD recruited through newspaper advertisements, 20 surgical patients and hospital employees who formed the control group, and 236 'available' FDRs. Probands and controls were administered a 'structured interview' and diagnoses were made by psychiatrists using DSM-III criteria. A similar approach was taken with those FDRs who could be interviewed in person. For FDRs where direct interview was not possible, family history information was obtained from probands, controls and family members using a 'brief interview schedule', and diagnoses were made using Family History Research Diagnostic Criteria (Andreason *et al.* 1977), except for GAD, panic disorder and agoraphobia, which were diagnosed using DSM-III criteria. The odds ratio for GAD in proband FDRs compared with GAD in control FDRs, without correction for age or sex, was 6·7.

These studies provide evidence that GAD is a familial disorder, but they have the drawback of relying on probands and controls recruited from the clinic setting or through self-selection, thus limiting the generalizability of findings. In this paper, we report the results of a large community-based family study of DSM-III GAD meeting the five criteria of Hettema *et al.* (2001).

METHOD

In the remainder of this paper, all diagnoses are on a lifetime basis, and the terms proband and control refer to subjects with and without GAD respectively.

Prevalence sample

The probands and controls for the present study came from the follow-up of a community sample originally recruited for a prevalence study conducted in Edmonton, Canada. The methods of the prevalence study are identical to those used in an earlier prevalence study reported by our research group (Orn *et al.* 1988). In brief, during 1984–1989, residents of Edmonton were sampled using a two-stage procedure. First, addresses were chosen from a residential list using systematic sampling, then one occupant per household aged 18 years or older was chosen with the aid of a selection grid. No proxy interviews or substitutions were permitted. For the prevalence study, as well as for the reinterview and family studies described below, data were collected by trained non-clinician interviewers using version III of the Diagnostic Interview Schedule (DIS; Robins *et al.* 1981).

Table 1. *Reinterview status of prevalence sample and overall prevalence rates of 16 disorders in Bland et al. (1988) (unweighted)*

Reinterview status	Total (%) ($n=3956$)	Prevalence rate (%)
Eligible and contact attempted	2482 (62·7)	37·0
Reinterviewed	1964 (49·6)	35·6
Refused	324 (8·2)	34·3
Unable to locate	74 (1·9)	35·1
Other	120 (3·0)	68·3
Eligible but not approached	1156 (29·2)	24·3
Ineligible	318 (8·0)	51·3
Died	54 (1·4)	35·2
Moved out of province	264 (6·7)	54·5

The prevalence sample consisted of 3956 subjects (response rate 72%).

After the prevalence study was under way, DIS modules on GAD and post-traumatic stress disorder (PTSD) became available. Therefore, GAD and PTSD data were not collected on 886 and 892 subjects respectively. The GAD module begins with the question 'Have you ever had a period of a month or more when most of the time you felt worried or anxious, perhaps afraid that something bad was going to happen either to you yourself or to someone you cared about?' For subjects giving an affirmative response, a symptom checklist follows that covers symptoms of motor tension (eight items), autonomic hyperactivity (11 items), and vigilance and scanning (three items).

DSM-III diagnoses were made using DIS diagnostic software, without hierarchies; in particular, GAD was not excluded by another anxiety disorder.

Reinterview and proband-control sample

The methods of the reinterview study are described in greater detail elsewhere (Newman & Bland, 1998). In brief, we asked subjects enrolled in the prevalence study for permission to reinterview them at some later time. For reasons of cost, those who moved out of the province after the initial interview were ineligible. Subjects were selected using systematic sampling, except for the last year of the study when we oversampled subjects with MDD. Table 1 gives the reinterview status of the 3956 subjects in the prevalence sample: 2482 (63%) were eligible to be reinterviewed and contact was attempted, 1156 (29%) were eligible but were not approached, and 318 (8%) were ineligible. Also shown are the overall prevalence rates of the 16 DIS/DSM-III disorders reported in Bland *et al.* (1988); GAD and PTSD are not included. Those who had moved out of the province exhibited a larger prevalence rate than most of the others. Reinterviews were conducted during 1987–1991, with interviewers blind to diagnoses in the prevalence study. The reinterview sample consisted of 1964 subjects (response rate 79%).

For the present study, we consider only the 924 reinterview subjects having an FDR who completed an interview: 160 of these individuals had a history of GAD and became the proband sample; the remaining 764 were the controls.

FDR sample

As part of the reinterview process, all 8960 FDRs were enumerated, 7262 (81%) of whom were living. We asked 1677 (85%) of the 1964 reinterview subjects for permission to contact their FDRs for the family study; 1375 (82%) gave consent for us to contact some or all of their FDRs. Of the 7262 living FDRs, 4829 (67%) resided in the province and were therefore eligible to be interviewed. Of these, 3345 (69%) were approached for the family study: 2386 (71%) completed an interview, 647 (19%) refused, and 312 (9%) were excluded for a variety of reasons (response rate 79%). The FDR interviews were conducted during 1987–1991, with interviewers blind to the diagnostic status of probands and controls.

Data analysis

Family studies have features of both case–control and cohort designs (Susser & Susser, 1989; Khoury *et al.* 1993). Here we view the FDR sample as a cohort that is followed from birth until the time of interview, with onset of GAD as the 'outcome', and with GAD (in a proband) as the 'exposure'. We analysed the data using logistic regression. All models included terms for age (group) and sex of FDRs, the former to account for length of time spent at risk of GAD, the latter because GAD is more prevalent in females (Table 2). A term for the family relationship of the FDR to the proband or control (parent, sibling, child) was not statistically significant in any the logistic regression models once a term for age of FDR had been

https://doi.org/10.1017/S0033291706007732 Published online by Cambridge University Press

Table 2. *Characteristics of prevalence, reinterview, proband-control and FDR samples*

Characteristic	Prevalence ($n=3956$)	Reinterview ($n=1964$)	Proband-control ($n=924$)	FDR ($n=2386$)
Age, yr (unweighted, %)				
18–24	18·3	5·8	6·6	12·5
25–34	30·9	26·9	26·8	26·6
35–44	17·7	23·1	20·0	19·4
45–54	11·0	13·2	14·0	14·0
55–64	10·4	12·8	14·6	14·9
65+	11·8	18·1	18·4	12·6
Sex (unweighted, %)				
Male	37·6	35·7	34·6	43·1
Female	62·4	64·3	65·4	56·9
Prevalence rate (weighted, %)				
GAD	14·3[a]	16·7	16·3	18·3
Panic disorder	1·8	3·1	3·1	2·4
Phobic disorders[b]	4·2	9·8	11·8	7·3
Obsessive–compulsive disorder	1·7	2·0	2·4	1·4
Post-traumatic stress disorder	2·6[c]	2·8	3·5	2·5
Major depressive disorder	11·9	18·4	20·1	11·5

FDR, first-degree relative; GAD, generalized anxiety disorder.
[a] 886 missing; [b] agoraphobia, social phobia, simple phobia; [c] 892 missing.

included. To account for correlation among family members, we used generalized estimating equations (Liang & Zeger, 1986) as implemented in the SAS procedure PROC GENMOD (SAS Institute Inc., 1999). The results reported below, based on an 'exchangeable' correlation structure, are nearly identical to those assuming an 'independent' correlation structure, as well as to those obtained using standard logistic regression. An alternative statistical method that explicitly accounts for age at risk is Cox (proportional hazards) regression (Cox, 1972). We chose not to adopt this technique because of concerns about the validity of age of onset information as collected by the DIS (Newman & Bland, 1998).

Co-morbidity is an important consideration in the analysis of family data. For example, in the proband-control and FDR samples, the crude odds ratios for the association between GAD and MDD are 4·6 and 5·9 respectively. Using the above logistic regression methods, but with MDD in place of GAD, the odds ratio for MDD in proband FDRs compared with MDD in control FDRs is 1·8 (95% confidence interval 1·3–2·4, $p<0·0001$), which supports the well-known observation that MDD is familial; see, for example, Weissman *et al.* (1984), where the odds ratios are in the range 2·1–2·7. To the extent that GAD is a 'cause' of MDD in probands and controls, and MDD is a 'cause' of GAD in FDRs, MDD being familial means that GAD might appear to be familial only because of co-morbidity with MDD.

Unfortunately, it is not possible to decide questions of causation from community data such as those considered here. As an alternative we address the issue of confounding by using a number of analytical strategies based on restriction and regression adjustment. Of the potential confounders among the DIS disorders, we confine ourselves to MDD and the non-GAD anxiety disorders (panic disorder, phobic disorders, obsessive–compulsive disorder, PTSD), the latter considered as a group; the phobic disorders included here are agoraphobia, social phobia and simple phobia. In strategy 1, the proband-control and FDR samples are not restricted and there is no adjustment for MDD or the non-GAD anxiety disorders. In strategy 2(*a*) we adjust for MDD in the FDR sample, and in strategy 2(*b*) we adjust for both MDD and the non-GAD anxiety disorders. In strategy 3(*a*) we restrict the proband and control samples by dropping subjects with a history of MDD; in strategy 3(*b*) we restrict on the basis of both MDD and the non-GAD anxiety disorders. Strategies 3(*a*) and 3(*b*) are an attempt to exclude probands and controls where MDD and non-GAD anxiety disorders might be a 'cause' of GAD, and conversely. This is similar to the use of 'pure' GAD probands

Table 3. *Prevalence rates of GAD in FDRs of probands and controls, and crude odds ratios (unweighted)*

	FDRs of probands			FDRs of controls			
Strategy	*n*	Cases of GAD	Prevalence rate (%)	*n*	Cases of GAD	Prevalence rate (%)	Odds ratio
1, 2(*a*), 2(*b*)	430	116	27·0	1956	331	16·9	1·81
3(*a*)	218	49	22·5	1605	260	16·2	1·50
3(*b*)	150	31	20·7	1451	231	15·9	1·38

GAD, generalized anxiety disorder; FDR, first-degree relative; *n*, number of subjects.

and 'normal' controls in Mendlewicz *et al.* (1993). There is debate surrounding the use of probands and controls having less pathology than the general population (Tsuang *et al.* 1988; Kendler, 1990, 1995; Klein, 1993). In the absence of information on causation, strategies 2(*a*)–3(*b*) may overadjust for potential confounding, with the consequence that the odds ratio could be biased towards the null.

RESULTS

Table 2 compares the prevalence, reinterview, proband-control and FDR samples on selected characteristics. The age distribution of the prevalence sample is close to that of the 1986 Edmonton (census) population (not shown). By comparison, the reinterview and proband-control samples under- and over-represent the youngest and oldest age groups respectively. Males are under-represented in all samples, but less so in the FDR sample. Overall, the FDR sample has the age–sex distribution closest to that of the Edmonton population.

Table 2 also gives weighted lifetime prevalence rates of MDD and the anxiety disorders under consideration. The weights account for household size (except for the FDR sample, where this information was not collected) and post-stratify to the age and sex distribution of the 1986 Edmonton population. There is no adjustment for oversampling of cases of MDD in the reinterview sample. The prevalence rates in the reinterview sample are somewhat larger than those in the prevalence sample. This probably reflects the accumulation of lifetime diagnoses during the interval between the two interviews (mean duration 2·8 years, range 1·5–6·0), and, more importantly, oversampling of subjects with MDD for reinterview, along with the co-morbidity associated with MDD. The prevalence rates of GAD and phobic disorders in the FDR sample are larger than those in the prevalence sample, which is an indication that the FDR sample may not be altogether representative of the general population.

Table 4. *Logistic regression odds ratios comparing GAD in proband FDRs with GAD in control FDRs (unweighted), for the cohort consisting of all FDRs and the cohort consisting of FDRs who are children of probands and controls*

	All FDRs ($n=2386$)			FDRs who are children ($n=746$)		
Strategy	OR	95% CI	*p* value	OR	95% CI	*p* value
1[a]	1·81	1·40–2·35	<0·0001	2·84	1·81–4·45	<0·0001
2(*a*)[b]	1·70	1·32–2·20	<0·0001	2·78	1·78–4·34	<0·0001
2(*b*)[c]	1·61	1·23–2·10	0·0005	2·66	1·65–4·27	<0·0001
3(*a*)[a]	1·50	1·07–2·10	0·02	2·37	1·24–4·54	0·009
3(*b*)[a]	1·38	0·93–2·05	0·11	2·11	1·04–4·29	0·04

GAD, generalized anxiety disorder; FDR, first-degree relative; OR, odds ratio; CI, confidence interval.
[a] Adjusted for age and sex in FDRs.
[b] Adjusted for age, sex and MDD in FDRs.
[c] Adjusted for age, sex, MDD and non-GAD anxiety disorders in FDRs.

Table 3 gives the crude odds ratios for each of the analytic strategies outlined above. The odds ratios fall in the range 1·4–1·8. Table 4 gives the results of the corresponding logistic regression analyses, and again the odds ratios are in the range 1·4–1·8. In fact, for strategies 1, 3(*a*) and 3(*b*), the odds ratios in Table 4 for all FDRs are almost identical to their counterparts in Table 3, and except for strategy 3(*b*), all the odds ratios are statistically significant.

A conceptual problem that results from retaining the entire FDR sample in the cohort is that GAD (in a proband) is treated as an exposure for GAD in sibs and parents, which

https://doi.org/10.1017/S0033291706007732 Published online by Cambridge University Press

means that in some families, outcome precedes exposure. A way of addressing this difficulty is to restrict the cohort to the 746 FDRs who are the children of probands and controls. The results of this analysis are also shown in Table 4. The odds ratios are in the range 2·1–2·8, and they are all statistically significant. Despite our misgivings about the validity of DIS age of onset information, for completeness we conducted a Cox regression analysis using strategy 1, taking the entire FDR sample as the cohort. The hazard ratio was 1·7 (95% confidence interval 1·4–2·1, $p<0·0001$), which is close to the odds ratio result for all FDRs in Table 4.

DISCUSSION

We conducted a family study of GAD meeting the five criteria of Hettema *et al.* (2001) and found odds ratios in the range 1·4–1·8 when the entire FDR sample was analysed, and 2·1–2·8 when we restricted to FDRs who were children of probands and controls. Although greater than unity and (with one exception) statistically significant, these odds ratios are considerably smaller than the morbidity risk ratio (4·7) of Mendlewicz *et al.* (1993) and the odds ratio (6·7) of Noyes *et al.* (1987). The explanation for the disparate findings may lie in the different methods used; in particular, the recruitment of probands. In the Mendlewicz *et al.* study, probands were drawn from the clinic setting, and in the Noyes *et al.* study they were self-selected from the community. By contrast, probands for the present study came from a reinterview study that originated as a community-based prevalence study. Although we believe that our samples of probands, controls and FDRs are reasonably representative, the possibility remains that due to financial and other considerations this may not be the case.

The prevalence rate of GAD in each of the prevalence, reinterview, proband-control and FDR samples is above 14%, which seems quite high, while the prevalence rate of panic disorder is comparatively low (Table 2). This raises the possibility that there has been a systematic overdiagnosis of GAD and a corresponding underdiagnosis of panic disorder. We did not conduct a reliability study of the DIS, and to our knowledge the only reliability studies that have been reported on version III of the DIS did not include GAD (Anthony *et al.* 1985; Helzer *et al.* 1985).

Somers *et al.* (2006) have recently reviewed the literature on prevalence studies of anxiety disorders. There are six community surveys reporting lifetime prevalence rates of GAD based on DSM-III criteria (Lee *et al.* 1987; Faravelli *et al.* 1989; Hwu *et al.* 1989; Oakley-Brown *et al.* 1989; Blazer *et al.* 1991; Chen *et al.* 1993), two of which are particularly relevant to the present study.

Oakley-Brown *et al.* (1989) interviewed 1498 community residents of Christchurch, New Zealand using version III of the DIS and found a remarkably high lifetime prevalence rate of GAD of 31·1%. Blazer *et al.* (1991) reported on reinterviews conducted in three sites of the Epidemiologic Catchment Area (ECA) study using version III of the DIS and found lifetime prevalence rates of GAD in the range 4·1–6·6%. The diagnosis of GAD was excluded if 'its first appearance was preceded by panic attacks or a depressive episode'. It is not clear if, by this, the authors mean a DIS/DSM-III disorder or merely what is referred to in the DIS as an 'episode', the latter representing a syndrome that might not reach the diagnostic threshold. We recalculated the prevalence rate of GAD from our data, first with the two DIS/DSM-III disorders as exclusions and then with the corresponding DIS episodes as exclusions. This produced rates of 10·6% and 7·7% respectively. It appears that our prevalence rates are not inconsistent with those reported from the Christchurch and ECA studies.

DECLARATION OF INTEREST

None.

REFERENCES

Andreason, N. C., Endicott, J., Spitzer, R. L. & Winokur, G. (1977). The family history method using diagnostic criteria: reliability and validity. *Archives of General Psychiatry* **34**, 1229–1235.

Anthony, J. C., Folstein, M., Romanoski, A. J., Von Korff, M. R., Nestadt, G. R., Chahal, R., Merchant, A., Brown, C. H., Shapiro, S., Kramer, M. & Gruenberg, E. M. (1985). Comparison of the lay Diagnostic Interview Schedule and a standardized psychiatric diagnosis. *Archives of General Psychiatry* **42**, 667–675.

APA (1980). *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn) (DSM-III). American Psychiatric Association: Washington, DC.

APA (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III-R). American Psychiatric Association: Washington, DC.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM-IV). American Psychiatric Association: Washington, DC.

Barlow, D. H., Blanchard, E. B., Vermilyea, J. A., Vermilyea, B. B. & DiNardo, P. A. (1986*a*). Generalized anxiety and generalized anxiety disorder: description and reconceptualization. *American Journal of Psychiatry* **143**, 40–44.

Barlow, D. H. & DiNardo, P. A. (1991). The diagnosis of generalized anxiety disorder: development, current status, and future directions. In *Chronic Anxiety: Generalized Anxiety Disorder and Mixed Anxiety-Depression* (ed. R. M. Rapee and D. H. Barlow), pp. 95–118. Guilford Press: New York.

Barlow, D. H., DiNardo, P. A., Vermilyea, B. B., Vermilyea, J. & Blanchard, E. B. (1986*b*). Comorbidity and depression among the anxiety disorders: issues in diagnosis and classification. *Journal of Nervous and Mental Disease* **174**, 63–72.

Bland, R. C., Newman, S. C. & Orn, H. (1988). Lifetime prevalence of psychiatric disorders in Edmonton. *Acta Psychiatrica Scandinavica* **77** (Suppl. 338), 24–32.

Blazer, D. G., Hughes, D., George, L. K., Swartz, M. & Boyer, R. (1991). Generalized anxiety disorder. In *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study* (ed. L. N. Robins and D. A. Regier), pp. 180–203. The Free Press: New York.

Breier, A., Charney, D. S. & Heninger, G. R. (1985). The diagnostic validity of anxiety disorders and their relationship to depressive illness. *American Journal of Psychiatry* **142**, 787–797.

Breslau, N. & Davis, G. C. (1985). DSM-III generalized anxiety disorder: an empirical investigation of more stringent criteria. *Psychiatry Research* **14**, 231–238.

Brown, T. A., Barlow, D. H. & Liebowitz, M. R. (1994). The empirical basis of generalized anxiety disorder. *American Journal of Psychiatry* **151**, 1272–1280.

Chen, C.-N., Wong, J., Lee, N., Chan-Lo, M.-W., Lau, J. T.-F. & Fung, M. (1993). The Shatin community mental health survey in Hong Kong: II. Major findings. *Archives of General Psychiatry* **50**, 125–133.

Cox, D. R. (1972). Regression models and life tables (with discussion). *Journal of the Royal Statistical Society, Series B* **74**, 187–220.

Endicott, J., Andreason, N. & Spitzer, R. L. (1978). *Family History. Research Diagnostic Criteria* (3rd edn). Biometrics Research Division, New York State Psychiatric Institute: New York.

Endicott, J. & Spitzer, R. L. (1978). A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Archives of General Psychiatry* **35**, 837–844.

Faravelli, C., Degl'Innocenti, B. G. & Giardinelli, L. (1989). Epidemiology of anxiety disorders in Florence. *Acta Psychiatrica Scandinavica* **79**, 308–312.

Helzer, J. E., Robins, L. N., McEvoy, L. T., Spitznagel, E. L., Stoltzman, R. K., Farmer, A. & Brockington, I. F. (1985) A comparison of clinical and Diagnostic Interview Schedule diagnoses: physician reexamination of lay-interviewed cases in the general population. *Archives of General Psychiatry* **42**, 657–666.

Hettema, J. M., Neale, M. C. & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry* **158**, 1568–1578.

Hwu, H. G., Yeh, E. K. & Chang, L. Y. (1989). Prevalence of psychiatric disorders in Taiwan defined by the Chinese Diagnostic Interview Schedule. *Acta Psychiatrica Scandinavica* **79**, 136–147.

Kendler, K. S. (1990). The super-normal control group in psychiatric genetics: possible artifactual evidence for coaggregation. *Psychiatric Genetics* **1**, 45–53.

Kendler, K. S. (1993). In reply to 'Diagnostic validity in genetics research on generalized anxiety disorder'. *Archives of General Psychiatry* **50**, 916–917.

Kendler, K. S. (1995). Methods of proband ascertainment in psychiatric genetics: an historical and epidemiologic perspective. *International Journal of Methods in Psychiatric Research* **5**, 111–121.

Khoury, M. J., Beatty, T. H. & Cohen, B. H. (1993). *Fundamentals of Genetic Epidemiology*, pp. 164–199. Oxford University Press: New York.

Klein, D. F. (1993). The utility of the super-normal control group in psychiatric genetics. *Psychiatric Genetics* **3**, 17–19.

Lee, C. K., Kwak, Y. S., Rhee, H., Kim, Y. S., Han, J. H., Choi, J. O. & Lee, Y. H. (1987). The nationwide epidemiological study of mental disorders in Korea. *Journal of Korean Medical Science* **2**, 19–34.

Liang, K. Y. & Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika* **73**, 13–22.

Mendlewicz, J., Papadimitriou, G. & Wilmotte, J. (1993). Family study of panic disorder: comparison with generalized anxiety disorder, major depression and normal subjects. *Psychiatric Genetics* **3**, 73–78.

Newman, S. C. & Bland, R. C. (1998). Incidence of mental disorders in Edmonton: estimates of rates and methodological issues. *Journal of Psychiatric Research* **32**, 273–282.

Noyes Jr., R., Clarkson, C., Crowe, R. R., Yates, W. R. & McChesney, C. M. (1987). A family study of generalized anxiety disorder. *American Journal of Psychiatry* **144**, 1019–1024.

Noyes Jr., R., Woodman, C., Garvey, M. J., Cook, B. L., Suelzer, M., Clancy, J. & Anderson, D. J. (1992). Generalized anxiety disorder vs. panic disorder: distinguishing characteristics and patterns of comorbidity. *Journal of Nervous and Mental Disease* **180**, 369–379.

Oakley-Brown, M. A., Joyce, P. R., Wells, J. E., Bushnell, J. A. & Hornblow, A. R. (1989). Christchurch Psychiatric Epidemiology Study, Part II: Six month and other period prevalences of specific psychiatric disorders. *Australian and New Zealand Journal of Psychiatry* **23**, 327–340.

Orn, H., Newman, S. C. & Bland, R. C. (1988). Design and field methods of the Edmonton survey of psychiatric disorders. *Acta Psychiatrica Scandinavica* **77** (Suppl. 338), 17–23.

Robins, E. & Guze, S. B. (1970). Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *American Journal of Psychiatry* **126**, 983–987.

Robins, L. N., Helzer, J. E., Croughan, J. & Ratcliff, K. S. (1981). National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Archives General Psychiatry* **38**, 381–389.

SAS Institute Inc. (1999). *SAS/STAT User's Guide. Version 8. Volume 2*. SAS Institute Inc.: Cary, NC.

Somers, J. M., Goldner, E. M., Waraich, P. & Hsu, L. (2006). Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. *Canadian Journal of Psychiatry* **51**, 100–113.

Spitzer, R. L., Endicott, J. & Robins, E. (1978). Research Diagnostic Criteria: rationale and reliability. *Archives of General Psychiatry* **35**, 773–782.

Spitzer, R. L. & Williams, J. B. W. (1984). Diagnostic issues in the DSM-III classification of the anxiety disorders. In *Psychiatry Update*, vol. III. (ed. L. Grinspoon), pp. 392–402. American Psychiatric Press: Washington, DC.

Susser, E. & Susser, M. (1989). Familial aggregation studies: a note on their epidemiologic properties. *American Journal of Epidemiology* **129**, 23–30.

Tsuang, M. T., Fleming, J. A., Kendler, K. S. & Gruenberg, A. S. (1988). Selection of controls for family studies. *Archives of General Psychiatry* **45**, 1006–1008.

Weissman, M. M., Gershon, E. S., Kidd, K. K., Prusoff, B. A., Leckman, J. F., Dibble, E., Hamovit, J., Thompson, W. D., Pauls, D. L. & Guroff, J. J. (1984). Psychiatric disorders in the relatives of probands with affective disorders: the Yale University–National Institute of Mental Health Collaborative Study. *Archives of General Psychiatry* **41**, 13–21.

Williams, J. B. W. (1983). *Structured Clinical Interview for DSM-III–Upjohn Version*. Biometric Research Division, New York State Psychiatric Institute: New York.

Wolk, S. I., Horwath, E., Goldstein, R. B., Wickramaratne, P. & Weissman, M. M. (1996). Comparison of RDC, DSM-III, DSM-III-R diagnostic criteria for generalized anxiety disorder. *Anxiety* **2**, 71–79.