

Research Article

GENETIC AND ENVIRONMENTAL INFLUENCES ON THE CO-MORBIDITY BETWEEN DEPRESSION, PANIC DISORDER, AGORAPHOBIA, AND SOCIAL PHOBIA: A TWIN STUDY

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Background: Major depression (MD) and anxiety disorders such as panic disorder (PD), agoraphobia (AG), and social phobia (SP) are heritable and highly co-morbid. However, the relative importance of genetic and environmental etiology of the covariation between these disorders, particularly the relationship between PD and AG, is less clear. **Methods:** This study measured MD, PD, and AG in a population sample of 5,440 twin pairs and 1,245 single twins, about 45% of whom were also scored for SP. Prevalences, within individual co-morbidity and twin odds ratios for co-morbidity, are reported. A behavioral genetic analysis of the four disorders using the classical twin design was conducted. **Results:** Odds ratios for MD, PD, AG, and SP in twins of individuals diagnosed with one of the four disorders were increased. Heritability estimates under a threshold-liability model for MD, PD, AG, and SP respectively were .33 (CI: 0.30–0.42), .38 (CI: 0.24–0.55), .48 (CI: 0.37–0.65), and .39 (CI: 0.16–0.65), with no evidence for any variance explained by the common environment shared by twins. We find that a common genetic factor explains a moderate proportion of variance in these four disorders. The genetic correlation between PD and AG was .83. **Conclusion:** MD, PD, AG, and SP strongly co-aggregate within families and common genetic factors explain a moderate proportion of variance in these four disorders. The high genetic correlation between PD and AG and the increased odds ratio for PD and AG in siblings of those with AG without PD suggests a common genetic etiology for PD and AG. *Depression and Anxiety* 26:1004–1011, 2009. Published 2009 Wiley-Liss, Inc.[†]

Key words: anxiety; depression; comorbidity; panic; agoraphobia; twin design

INTRODUCTION

Major depression (MD) and anxiety disorders such as panic disorder (PD), agoraphobia (AG), and social phobia (SP) carry a substantial burden of impairment because of their disabling and chronic course. A recent survey of the burden of disease in Australia in terms of

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loss of life-years^[1] ranked anxiety and depression as the first and third burdens of disease in women and men respectively, implying substantial financial and economical costs to society. Lifetime prevalence rates are reported to be between 3 and 25% for MD,^[2-4] 7 and 13% for SP,^[5,6] 1 and 3.5% for PD,^[7,8] and around 5.3% for AG.^[8]

Even though prevalence rates vary between studies, it has been consistently reported that women are approximately twice as likely as men to experience MD.^[1,4,9] Similar sex differences have also been reported for most anxiety disorders in community-based and epidemiological studies.^[1,7,8,10] PD without AG, for example, occurs twice as often in females as in males, while PD with AG is diagnosed up to three times as often in females as in males. Finally, AG without PD is diagnosed more often in females than males and the female-to-male ratio in SP has been shown to be approximately 3:2.^[5,11]

It is well-established that the symptoms of anxiety and depression commonly co-occur and that anxiety disorders exhibit high levels of lifetime co-morbidity.^[12,13] For example, more than half of all individuals with MD also develop an anxiety disorder during their lifetime.^[14,15] About 50% of community members with a diagnosis of SP report a concomitant anxiety disorder such as PD, AG, or generalized anxiety disorder and 20% meet lifetime criteria for MD.^[11,16,17] Similarly, of the individuals diagnosed with PD, 10–65% have co-morbid MD and approximately one-third to one-half show agoraphobic avoidance behavior.^[7,8] Patients with a diagnosis of PD with AG were found to be at increased risk of developing MD as compared to patients diagnosed with PD only.^[7,18]

Co-morbidity between diseases may reflect overlapping diagnostic criteria, conditions that are different phases of the same disorder, or one disorder being a risk factor for the other disorder.^[19] Family studies can provide insight into the shared etiology of disorders and the availability of different types of family relationships allows dissection into relative contributions of shared genetic and environmental causes. Clinical and non-clinical family studies reveal evidence for familial aggregation in the etiology of depression,^[20,21] SP,^[20,22,23] PD,^[22,24-27] and AG.^[23,24,26-28] Twin studies also suggest that genetic influences play a significant role in the familial aggregation of depression and anxiety disorders.^[29-35] For example, twin studies found heritability estimates of 30–60% for MD,^[36-38] 28–50% for SP,^[36,39,40] 30–40% for PD,^[31,34,35,41,42] and 30–40% for AG.^[31] However, the genetic and environmental components of the co-morbidity of anxiety disorders with one another and with MD is less clear as studies have yielded inconsistent results.^[37] While some studies found common genetic factors to be responsible for the relationship between these disorders,^[31,39,43-46] other controlled family studies reported unique genetic influences on the relation between anxiety disorders and MD.^[26,47-49] Nevertheless, taking into account only the

twin studies, it seems that shared genetic risk factors largely account for this co-morbidity, with genetic correlations ranging between .35 and .80.^[30-32,38,39] Most of the few existing twin studies of these phenotypes and their co-morbidity used relatively small sample sizes ranging from 81 to 6,744 twin individuals and report partly inconsistent findings. As such, the specific role of the genetic factors remains unclear.^[37]

The relationship between PD and AG is particularly controversial and the ongoing debate has been summarized by Hayward and Wilson.^[50] Briefly, in the clinical setting AG is viewed as a complication of panic symptoms, formally recognized through the DSM-IV diagnostic classifications of PD without AG and PD with AG. The DSM-IV classification of AG without PD is not frequently observed in the clinical setting, despite high prevalence estimates (5.3%^[8]) in population-based studies. This inconsistency between clinical and population-based prevalence likely reflects self-management by those not experiencing panic attacks despite their agoraphobic fear. In contrast, the distress caused by panic attacks is more likely to lead to treatment seeking.^[10] It has been argued that AG without a history of PD is part of a PD syndrome^[10] and has been shown to be predictive of onset of PD in a longitudinal study.^[51] However, Wittchen et al.^[24] have argued that AG exists as a clinically significant phobic condition independent of PD.^[8] Evidence for a common genetic etiology of AG without PD and PD would provide support for AG being part of a PD syndrome, but few family studies have been published and their interpretation is limited by small sample size, clinical setting, and historical nosology.^[24] In a community setting (young adults ($N = 3,021$) and their parents), there was no evidence for increased prevalence of panic attacks, PD or AG in children of parents with AG without PD. By comparison, the odds (maximum 5.1) of all three conditions was increased in children of parents with PD (with and without AG) compared to children of unaffected parents^[24] supporting the view that AG without PD is an etiologically independent disorder.

The aim of this study is to examine familial aggregation and co-morbidity of MD, PD, AG, and SP using a large community-based sample of approximately 6,000 twin pairs. By reporting prevalence rates and odds-ratios for co-morbidity as well as heritability estimates of MD, PD, AG, and SP this study aims to contribute to the knowledge about familial aggregation and heritability of these disorders. Further, we investigate the genetic and environmental etiology of PD and AG and their co-morbidity to clarify the diagnostic (in)dependence of AG.

METHODS

PARTICIPANTS

The population-based sample was derived from the Australian Twin Registry, a volunteer register initiated in 1978. Data from two telephone-based surveys conducted between 1992–1993 and

1996–2000 were used for this study. Both studies utilized the “Semi-Structured Assessment for the Genetics of Alcoholism” (SSAGA),^[52–54] adapted for use in Australia. The SSAGA is a highly reliable, semistructured interview developed to assess physical, psychological, and social manifestations of alcoholism, medication, and drug-use, and co-morbid psychopathology such as depression and related disorders in adults and is based on previously validated research interviews (e.g., DIS, CIDI, HELPER, SAM, SADS, and SCID). Among other measures, it includes DSM-III-R diagnostic items (subsequently adapted to DSM-IV) for MD, PD, AG, and SP. The first survey (1992–1993) assessed 2,729 complete twin pairs and 557 single twins ranging from 27 to 90 years of age (mean: 44.0 ± 12.4), while the second survey (1996–2000) assessed 2,765 complete twin pairs and 688 single twins ranging from 23 to 39 years of age (mean: 29.9 ± 2.5). Both studies were approved by the Queensland Institute of Medical Research Human Research Ethics Committee. Interviewers received extensive training in administering the interview by phone and were blind to the results of a co-twin’s assessment. Further details are described elsewhere.^[55]

Nineteen participants were assessed in both surveys. Multiple entries for these individuals were removed from the merged dataset, and inconsistent diagnoses were treated as missing. The resulting dataset contained one record for each of 12,214 individuals (5,440 twin pairs), of which 83 individuals had missing values for any of the MD/PD/AG phenotypes. Of these, 5,995 twin individuals (2,721 twin pairs) were assessed for SP, as this phenotype was included in the first survey only. The zygosity of 32 individuals (11 complete pairs) was unknown. These individuals were only included in the calculation of the within-individual prevalences and co-morbidities.

MEASURES

DSM-IV diagnoses of the anxiety disorders (PD (with or without AG), AG (with or without PD), and SP) and MD were derived using computer algorithms applied to individual questionnaire item responses. All participants were assessed for AG irrespective of their answers to the panic related questions. Furthermore, the respondents’ fear did not have to be specifically related to fear of panic attacks. In addition, the following four diagnostic categories were considered: PD with AG, PD without AG, AG without PD, and PD or AG.

STATISTICAL ANALYSIS

Prior to analysis we tested for participation bias and for differences in the distribution of scores by zygosity for each variable. Disorder prevalences and probability of co-morbidity within individuals were calculated for each sex. Probandwise odds-ratios were calculated for monozygotic and dizygotic twins from logistic regression including sex and age as covariates, both within and between disorders.

For genetic modelling analyses, the liability to develop a disorder is assumed to be a continuous normal distribution with a threshold above which individuals develop the disorder.^[56] This liability distribution receives contributions from both independent normally distributed genetic and environmental effects. The classical twin design allows partitioning of variance in and covariance between traits into that due to additive genetic (A) and environmental (shared within twin pairs, C, and nonshared, E) influences. This is possible as A, C, and E influences each predict different patterns of identical (monozygotic; MZ) and nonidentical (dizygotic; DZ) twin pair correlations. The classical twin design assumes that the only difference between MZ and DZ twins is that MZ twins share all their genes and DZ twins share on average half their genes and that trait-relevant environments are similar for MZ and DZ twin pairs.^[57] Normally, twin correlations can be explained by a combination of these three parameters (A, C, and E) and structural equation

modelling can be used to determine the combination that best explains the observed data. Despite the large sample size, the number of twin pairs who both reported a disorder was low, owing to the low prevalences of some of the disorders; therefore, it was not possible to explore differences in variance components between sexes in the genetic modelling analysis.

Data were analyzed using Maximum-Likelihood (ML) methods in Mx,^[58] utilizing threshold modelling for ordinal data.^[59] In this procedure, each twin group (MZ and DZ twins) has two thresholds (one for each twin) for each of the variables reflecting prevalence. Initially, a saturated model is fitted estimating all parameters, and then subsequently more restricted models are compared to the preceding model. Specific hypotheses regarding the significance of particular parameters can be tested statistically by comparing the goodness-of-fit of various models using the minus two times log-likelihood ($-2LL$) statistics (distributed as χ^2).

Prior to genetic modeling, we tested for age and sex effects on the thresholds. A multivariate model was fitted to assess genetic and environmental factors that mediate the phenotypic covariation between depression and the three anxiety disorders. After estimating the relative magnitude of all parameters, submodels were fit to test the significance of specific parameters and to determine the simplest model explaining the phenotypic variance of the four variables. Model reduction started with dropping the paths with the smallest parameter estimates. To confirm the accuracy of the multivariate modelling results we also conducted univariate modelling.

RESULTS

PRELIMINARY ANALYSIS

No significant ($P < .05$) differences were found in the prevalence rates/thresholds within twin pairs or across zygosity groups for all variables. MD, PD, and AG showed significant age effects on thresholds, with the probability to report a past episode of PA and AG increasing with age while the probability of reporting MD decreased. MD also showed a sex effect, with females being more likely to report a depressive episode, so age and sex were retained as covariates in subsequent modeling. To control for participation bias, we checked whether the likelihood of being diagnosed with one of the disorders was different in singletons (co-twin not participating) compared to complete twin pairs.^[60,61] There was no significant difference in diagnosis rates between full twin pairs and singletons, so participation rates appear to be independent of the psychological measures.

WITHIN-TWIN PREVALENCE AND CO-MORBIDITY

Lifetime prevalence and co-morbidity of psychopathology within the twin individuals are presented in Table 1. The prevalences of the anxiety disorders ranged between ~1 and 3%. As expected, MD was the most common disorder in the sample with 19% of the male participants being affected during their lifetime and females were approximately 1.5 times as likely as males to be diagnosed with MD. Lifetime prevalence of MD for half of the present cohort have been reported previously by Bierut et al.^[62] Similar sex differences in

TABLE 1. Prevalence for each disorder (in bold) on diagonal and the comorbidity within an individual of column diagnosis given a row diagnosis for males/females separately

	PD ^a	AG ^a	PD or AG ^a	PD and AG ^a	PD no AG ^a	AG no PD ^a	MD ^a	SP ^b
PD	0.02/0.03	0.33/0.38	NA	0.31/0.38	NA	NA	0.51/0.65	0.20/0.14
AG	0.39/0.40	0.01/0.03	NA	0.36/0.39	NA	NA	0.52/0.68	0.38/0.18
PD or AG	NA	NA	0.02/0.05	NA	NA	NA	0.52/0.63	0.26/0.14
PD and AG	NA	NA	NA	0.01/0.01	NA	NA	0.52/0.83	0.41/0.26
PD no AG	NA	NA	NA	NA	0.01/0.02	NA	0.51/0.54	0.08/0.09
AG no PD	NA	NA	NA	NA	NA	0.01/0.02	0.54/0.58	0.39/0.12
MD	0.04/0.08	0.04/0.09	0.07/0.13	0.01/0.04	0.03/0.04	0.02/0.04	0.19/0.27	0.06/0.06
SP	0.23/0.28	0.41/0.37	0.46/0.49	0.18/0.15	0.05/0.12	0.23/0.19	0.42/0.59	0.02/0.02

Note. PD, panic disorder; AG, agoraphobia; PD and AG, panic with agoraphobia; PD no AG, panic without agoraphobia; AG no PD, agoraphobia without panic; MD, depression; SP, social phobia. Standard error ranged between .0007 and .006.

^aN = 5,862 male twin individuals (1,514 complete twin pairs and 1,254 opposite-sex male twin individuals and 580 incomplete twin pairs) and 7,352 female twin individuals (2,683 complete twin pairs and 1,254 opposite-sex female twin individuals and 732 incomplete twin pairs).

^bN = 2,087 male twin individuals (637 complete twin pairs and 655 opposite-sex male twin individuals and 158 incomplete twin pairs) and 3,908 female twin individuals (1,480 complete twin pairs and 729 opposite-sex female twin individuals and 219 incomplete twin pairs).

TABLE 2. Probandwise odds ratios for monozygotic and dizygotic twins of column diagnosis if twin has row diagnosis adjusted for sex and age

	PD ^a	AG ^a	PD or AG ^a	PD and AG ^a	PD no AG ^a	AG no PD ^a	MD ^a	SP ^b
Monozygotic twins								
PD	5.8 (3.5; 9.6)							
AG	5.1 (2.9; 8.9)	10.3 (6.3; 16.8)						
PD or AG	5.9 (3.8; 9.1)	8.1 (5.2; 12.4)	7.7 (5.4; 11.0)					
PD and AG	5.3 (2.3; 12.0)	7.2 (3.3; 15.9)	6.0 (3.0; 12.0)	8.4 (2.9; 24.5)				
PD no AG	5.5 (3.0; 10.2)	3.6 (1.7; 7.6)	5.3 (3.1; 9.1)	3.2 (1.0; 10.4)	6.5 (3.2; 13.0)			
AG no PD	5.0 (2.4; 10.4)	11.1 (6.0; 20.4)	9.1 (5.2; 15.7)	6.0 (2.1; 17.3)	4.0 (1.6; 10.3)	12.8 (6.2; 26.6)		
MD	2.8 (2.0; 4.0)	2.6 (1.8; 3.8)	2.7 (2.0; 3.5)	3.7 (2.1; 6.5)	2.4 (1.6; 3.7)	2.2 (1.4; 3.7)	2.9 (2.5; 3.3)	
SP	3.6 (1.5; 8.8)	6.5 (3.1; 13.9)	5.6 (2.9; 10.8)	4.0 (0.9; 17.5)	3.3 (1.1; 9.4)	6.6 (2.7; 16.2)	2.6 (1.5; 4.5)	11.9 (3.7; 38.8)
Dizygotic twins								
PD	3.6 (1.7; 6.6)							
AG	1.1 (0.4; 2.9)	4.6 (2.5; 7.5)						
PD or AG	2.7 (1.4; 4.4)	3.3 (1.9; 5.2)	3.5 (2.2; 5.0)					
PD and AG	0.9 (0.1; 6.3)	1.6 (0.4; 6.5)	1.6 (0.5; 5.1)	0.0 (0.0; Inf)				
PD no AG	5.2 (2.4; 9.9)	0.9 (0.2; 3.3)	3.2 (1.5; 5.8)	1.4 (0.2; 9.7)	7.5 (3.2; 14.7)			
AG no PD	1.4 (0.4; 4.0)	6.7 (3.5; 11.3)	4.6 (2.4; 7.5)	2.6 (0.6; 10.5)	0.7 (0.1; 4.5)	9.4 (4.5; 16.5)		
MD	1.7 (1.2; 2.5)	1.4 (1.0; 2.0)	1.6 (1.3; 2.2)	1.3 (0.7; 2.4)	1.9 (1.3; 3.2)	1.5 (1.0; 2.4)	1.5 (1.3; 1.7)	
SP	2.9 (1.1; 7.4)	1.8 (0.6; 5.0)	2.1 (0.9; 4.7)	3.6 (0.8; 15.4)	2.5 (0.7; 8.1)	1.2 (0.3; 5.1)	1.5 (0.8; 2.6)	1.5 (0.2; 11.0)

Note. PD, panic disorder; AG, agoraphobia; PD or AG, panic or agoraphobia; PD and AG, panic with agoraphobia; PD no AG, panic without agoraphobia; AG no PD, agoraphobia without panic; MD, depression; SP, social phobia.

^aN = 2,495 monozygotic and 2,945 dizygotic twin pairs.

^bN = 1,337 monozygotic and 1,384 dizygotic twin pairs.

prevalence rates were found for the anxiety disorders, with women being 1.5–2.0 times as likely as men to be diagnosed, with the exception of SP where the prevalence rates did not differ between sexes.

The co-morbidity probability for the various anxiety disorders with each other ranged between .20 and .41 for males and .14 and .40 for females. The probability of having an anxiety disorder when diagnosed with MD was very low (.04–.06 for males and .06–.09 for females) as opposed to the chance of having MD when diagnosed with an anxiety disorder (.42–.52 for males and .59–.69 for females).

BETWEEN-TWIN CO-MORBIDITY

Table 2 presents the probandwise odds-ratios for diagnosis with a disorder if the co-twin has been diagnosed with the same, or a different disorder for MZ and DZ twins respectively. The odds-ratios ranged between 2.2 and 12.8 for MZ twins and this was slightly higher than the odds-ratios for DZ twins, which ranged between 0 and 9.4. Despite the large sample size, the confidence intervals were relatively wide and often overlapping, indicating that the MZ and DZ odds ratios were mostly not significantly different.

GENETIC MODELLING

A general multivariate ACE model was fitted to MD, PD, AG, and SP, in which proportions of A, C, and E were constrained to be equal in males and females. Estimates for individual traits were consistent between the univariate and multivariate analyses. As expected from the MZ and DZ odds ratios, the shared-environmental (C) effects were very small: .00, .11, .04, and .02 for MD, PD, AG, and SP, respectively. All C influences could be dropped without a significant loss of model-fit ($\Delta\chi^2_{10} = 1.9, P > .05$), indicating that the most parsimonious explanation for the observed pattern of twin correlations was a general AE model. We could also remove the shared A factors between AG and SP and PD and SP in the Cholesky decomposition ($\Delta\chi^2_1 = 1.4 - 2.7, P > .05$) but no other A or E factors ($\Delta\chi^2_1 = 4.2 - 12.5, P < .05$). The full and the most parsimonious multivariate models are shown in Figure 1.

Heritabilities, genetic, and environmental correlations on the liability scale calculated under the best fitting model, together with phenotypic correlations between pairs of disorders are listed in Table 3. The genetic correlation between PD and AG is particularly high at .83. The lower environmental correlations between MD and the anxiety disorders partially result from the differences in prevalence rates. Sixty-three

percent (i.e. $.49^2 / .38 \times 100$) of the genetic variance in PD, 48% of the genetic variance in AG, and 59% of the genetic variance in SP was explained by genetic factors shared with MD. A further 21% of the genetic variance in AG was explained by genetic factors in common with PD. Three to 39% of the variance due to nonshared environmental influences of PD, AG, and SP were explained by factors common with MD.

DISCUSSION

This study aimed to investigate familial aggregation of MD, PD, AG, and SP as well as the genetic and environmental etiology of the four disorders and their co-morbidity. The sample prevalences were comparable to those found in general population studies for MD and PD, and were slightly lower than expected for AG and SP.^[7,8,63] As expected, women were 1.5–2 times as likely to be diagnosed with MD or an anxiety disorder as men. For SP the absence of a sex difference for prevalence may reflect the smaller sample size compared to the other variables.

The co-morbidity between the anxiety disorders was moderate, ranging between .14 and .41. Although only 4–6% of males and 6–9% of the female participants with a diagnosis of MD also suffered from an anxiety disorder, 42–52% of males and 59–69% of females with

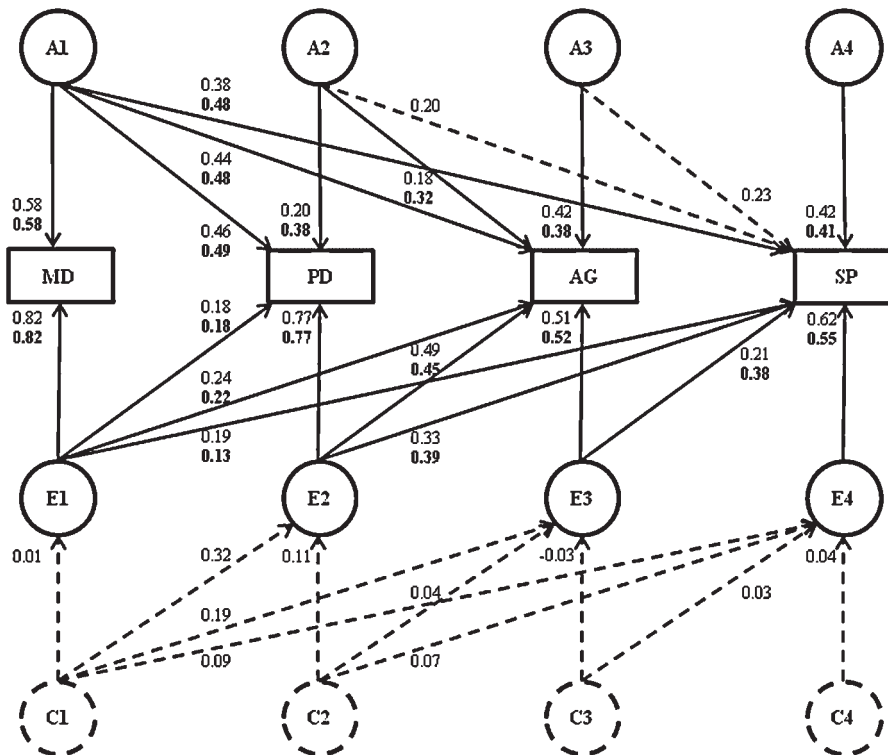


Figure 1. Full multivariate model in which a Cholesky decomposition is applied to the genetic and environmental variance–covariance matrices with standardized path coefficients showing the relationship between MD, PD, AG, and SP. Path coefficients can be squared to get the percentage of variance accounted for. The Cholesky factors have been decomposed into additive genetic (A), shared (C), and nonshared environmental (E) influences. The most parsimonious model is shown with solid lines and path estimates in bold.

TABLE 3. Heritabilities, genetic, environmental, and phenotypic correlations on the liability scale under the most parsimonious model

	MD	PD	AG	SP
Heritabilities	.33	.38	.48	.39
95% CI ^a	0.30–0.42	0.24–0.55	0.37–0.65	0.16–0.65
<i>Genetic correlations</i>				
MD		.79	.70	.76
PD			.83	.60
AG				.53
<i>Environmental correlations</i>				
MD		.22	.30	.17
PD			.67	.52
AG				.71
<i>Phenotypic correlations</i>				
MD		.42	.45	.37
PD			.73	.54
AG				.63

Note. PD, panic disorder; AG, aAgoraphobia; MD, depression; SP, social phobia.

^a95% confidence interval calculated in the univariate analyses.

an anxiety disorder were also diagnosed with MD, this asymmetry reflects the large differential in prevalence between MD and the anxiety disorders. These findings show that the anxiety disorders are highly co-morbid with each other and with MD and are consistent with past studies in community and clinical samples.^[4,37]

The between-twin odds-ratios (Table 2) strongly point toward familial aggregation of MD, PD, AG, and SP and their co-morbidity and indicate that genetic factors play a role in the variation and covariation of these disorders, which is in line with findings of past studies.^[21,22,24] However, despite the large sample size confidence intervals in this study were very wide due to the low prevalences of some disorders and therefore the differences in odds ratios between MZ and DZ twins, which were substantial, were not significant. Nonetheless, genetic modelling revealed that the most parsimonious model to explain the observed familial aggregation on the liability scale is one with moderate genetic influences on the variance of the MD, PD, AG, and SP, with heritabilities of .33 (CI: 0.30–0.42), .38 (CI: 0.24–0.55), .48 (CI: 0.37–0.65), and .39 (CI: 0.16–0.65) respectively, leaving the largest proportion of the variance in liability to be explained by nonshared environmental factors. Previous meta-analyses have consistently attributed 30–40% of the variance in liability to anxiety disorders and MD to additive genetic influences with little evidence for shared environmental contribution to any of these disorders and this is in agreement with the findings of this study.

Genetic variance in PD, AG, and SP shared with MD was 63, 48, and 59% respectively, corresponding to genetic correlations of .79, .70, and .76 (Table 3). This indicates that overlapping etiological factors explain most of the co-morbidity between MD and all three anxiety disorders and is consistent with previous studies

suggesting genetic mediation of the phenotypic associations between MD and anxiety disorders.^[31,43–45,64–66] Genetic correlations were lower between PD and SP (.60) and between AG and SP (.53) than for the other pairs of disorders. It has been shown previously that SP seems to share less genetic liability with AG than other phobic disorders share among each other.^[46,67] The genetic correlation between PD and AG was very high at .83.

In an attempt to replicate the finding of Nocon et al.^[24] who reported no familial component to the disorder of AG without PD, we considered the mutually exclusive diagnostic classes of PD without AG, PD with AG, and AG without PD. Despite the large confidence intervals, the MZ and DZ odds ratios for AG without PD of 12.8 (CI: 6.2–26.6) and 9.4 (CI: 4.5–16.5) respectively suggest that there is a heritable component to this disorder. Moreover, the MZ and DZ odds ratios for AG without PD in twin siblings of those with PD with AG of 6.0 (CI: 2.1–17.3) and 2.6 (CI: 0.6–10.5) are suggestive that AG without PD is part of the PD spectrum (as suggested, amongst others, by Andrews and Slade),^[10] rather than an etiologically distinct disorder as advocated in the related studies of Wittchen et al.^[8] and Nocon et al.^[24] Unfortunately, the low prevalence rates did not allow for genetic bivariate modelling of PD and AG without PD, which would have given further information on the (in)dependence of AG and PD.

Our results must be interpreted recognizing the limitations of our study. Our structured telephone interviews were administered by trained lay interviewers who were closely supervised by a clinical psychologist. Some population-based studies have been shown to misclassify those with specific phobias as AG resulting in an overestimation of AG, for example, prevalence of AG without PD was estimated to be 8.5% in a community sample, but this was later revised to 3.5% after clinical review.^[68] However, in this study prevalence of AG without PD was less than 2% suggesting that we did not over-diagnose. Despite our large study sample of 12,125 individuals (including 5,440 complete twin pairs) the low prevalence rates of each disorder necessarily mean large confidence interval for estimated parameters. In particular, the sample size for SP was much smaller than the sample for the other three measures as SP was only assessed in one of the two surveys included in this study. The low prevalence rates also complicated the multivariate genetic modelling. Furthermore, it has been shown that a boundary problem may arise for multivariate genetic analysis, but it is not clear to date how much this affects the analysis with ordinal variables nor has a good solution to prevent this problem been suggested.^[69] However, consistent estimates of heritability between the univariate and multivariate models provides some confidence in the validity of the estimates of genetic and environmental covariance. The overlapping confidence intervals for MZ and DZ odds ratios

indicate that partitioning the variance into genetic and environmental components would be compromised. Nonetheless, the best point estimates of the C components were very small relative to the A components justifying dropping C first.

In conclusion, a community sample of 5,440 twin pairs showed that MD, PD, AG, and SP strongly co-aggregate within families and that common genetic factors explain a moderate-to-high proportion of variance in these four disorders with no evidence for influences of common environment. The high genetic correlation (.83) between PD and AG and the increased odds ratio for PD and AG in siblings of those with AG without PD supports the theory of a common genetic etiology for PD and AG.

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