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Life events and depression in a community sample of siblings

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ABSTRACT

Background. The overall aim of the GENESiS project is to identify quantitative trait loci (QTLs) for anxiety/depression, and to examine the interaction between these loci and psychosocial adversity. Here we present life-events data with the aim of clarifying: (*i*) the aetiology of life events as inferred from sibling correlations; (*ii*) the relationship between life events and measures of anxiety and depression, as well as neuroticism; and (*iii*) the interaction between life events and neuroticism on anxiety/depression indices.

Methods. We assessed the occurrence of one network and three personal life-event categories and multiple indices of anxiety/depression including General Health Questionnaire, Anhedonic Depression, Anxious Arousal and Neuroticism in a large community-based sample of 2150 sib pairs, 410 trios and 81 quads. Liability threshold models and raw ordinal maximum likelihood were used to estimate within-individual and between-sibling correlations of life events. The relationship between life events and indices of emotional states and personality were assessed by multiple linear regression and canonical correlations.

Results. Life events showed sibling correlations of 0·37 for network events and between 0·10 and 0·19 for personal events. Adverse life events were related to anxiety and depression and, to a less extent, neuroticism. Trait-vulnerability (as indexed by co-sib's neuroticism, anxiety and depression) accounted for 11% and life events for 3% of the variance in emotional states. There were no interaction effects.

Conclusions. Life events show moderate familiality and are significantly related to symptoms of anxiety and depression in the community. Appropriate modelling of life events in linkage and association analyses should help to identify QTLs for depression and anxiety.

INTRODUCTION

The relationship between life events and psychopathology has been the subject of extensive psychiatric research. There is a large body of evidence supporting an association between exposure to adverse life events and the onset of depression (Brown & Harris, 1989; Brown *et al*. 1996; Brown, 1998). However, the extent to which life events constitute a 'cause' of depression, rather than the effect of a shared vulnerability, is controversial (Kessler, 1997). Behavioural genetic findings support a substantial shared genetic component for depression and anxiety, and are consistent with a model where clinical illness is produced by a combination of genetic vulnerability and environmental risk factors (Kendler *et al*. 1993*a*, *b*, 1995, 1999; Kendler & Karkowski-Shuman, 1997; Kendler, 1998). However, attempts to measure putative environmental risk factors such as adverse life events have led to the interesting finding that some of these variables themselves are familial and indeed genetic.

In the Camberwell Depression Study, patients as well as their relatives were found to have high levels of recent stressful life events (Bebbington

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et al. 1988; McGuffin *et al*. 1988). Similarly, Breslau *et al*. (1991) found that exposure to life events was significantly predicted by a family history of psychiatric illness. While family studies are limited only to show familial resemblance that could be due to genetic or shared environmental factors, twin studies can potentially untangle these familial factors. Using a twin design, Kendler & Karkowski-Shuman (1997) reported that a high genetic risk for depression was associated with an increased risk of experiencing life events. Several twin studies have attempted to measure the heritability of life events. Plomin *et al*. (1990) reported a heritability of 40% for total lifetime difficulties, but found no shared environmental effects. Kendler *et al*. (1993*a*) found that total life events reported over the last year in a large sample of twins was influenced by both genetic and common environmental factors, each accounting for around 20% for the variance. Self-report life events in childhood and adolescence have also been shown to be influenced by genetic factors (Billing *et al*. 1996; Thapar & McGuffin, 1996).

The impact of genetic factors on a distal phenotype such as reported life events has been suggested to work via genetically influenced personality traits, for example, those that affect the probability of risk-taking behaviour or those that increase the impact and therefore the reporting of events. The effects of life events on emotional distress could be mediated by neuroticism. Neuroticism has been shown in prospective studies: (*i*) to predict onset, duration, and outcome of emotional disorders (Hirschfeld *et al*. 1989; Kendler *et al*. 1993*b*; Duggan *et al*. 1995); (*ii*) to influence exposure to stressful situations (Fergusson & Horwood, 1987; Ormel & Wohlfarth, 1991; Poulton & Andrews, 1992); and (*iii*) to amplify the negative effects of life stress on risk of onset (Ormel *et al*. 1989; Bolger & Schilling, 1991). Behavioural genetic studies show that neuroticism is heritable (Heath *et al*. 1988; Pedersen *et al*. 1988; Loehlin, 1992) and that the strong relationship between neuroticism and depression is genetically mediated (Jardine *et al*. 1984; Kendler *et al*. 1993*b*, *c*; Carey & DiLalla, 1994).

The genetic association between depression and life events may therefore be mediated by neuroticism, which predisposes to both depression and life events (Kendler & Karkowski-Shuman, 1997). Genes for neuroticism might express themselves by increasing an individual's proneness to experience stressful life events. Studies that have directly examined the genetic relationship between life events and personality are scarce. In older females, genetic influences on life events appeared to be entirely mediated by the personality dimensions of Neuroticism, Extraversion and Openness to Experience (Saudino *et al*. 1997). In adolescent males, the correlation between dependent (controllable) individual events and personality was, in part, genetically mediated (Billig *et al*. 1996).

Life-events questionnaires consist of items concerning diverse categories of events. Different categories may vary in the importance of the different sources of variance. Kendler *et al*. (1993*a*) found that resemblance in network events (with primary impact on significant others in the social environment) was solely due to common environment. Resemblance in personal events (with primary impact on the respondent) appeared to tap shared genetic factors, with heritabilities ranging from 14% (marital problems) to 40% (financial problems). For interpersonal difficulties both common (familial) environment and genes appeared to play a role. Plomin *et al*. (1990) earlier reported higher heritabilities for controllable events (which are personal events) as compared to uncontrollable events (which largely include network events). Billig *et al*. (1996) found no genetic influences for family and individual uncontrollable events, whereas the heritability for individual controllable events was estimated to be 49%. Saudino *et al*. (1997) also reported significant genetic variance for controllable events, whether desirable or undesirable, for females. There was no significant genetic variance for either sex for uncontrollable events.

The GENESiS (Genetic–Environmental Nature of Emotional States in Siblings) project is a community-based study, set up to investigate genetic and environmental risk factors for anxiety/depression in a sample of siblings. The overall aim of the project is to identify quantitative trait loci (QTLs) for anxiety and depression, and to examine the interaction between these loci and psychosocial adversity. In this article, we present an analysis of the life-events data in the sample, with the aim of clarifying: (*i*) the aetiology of life events as inferred from the

correlation between siblings; (*ii*) the relationship between life events and measures of anxiety and depression, as well as neuroticism; and (*iii*) the interaction between life events and neuroticism on anxiety/depression indices.

GENESiS is limited to one familial relationship (i.e. siblings), so that it is not possible to test more sophisticated behavioural genetic models (e.g. partitioning of familial resemblance into genetic and common environmental influences). The strengths of the study are its large sample size, the need to compare the results of twin studies to non-twin familial relationships, and the availability of multiple indices of anxiety/depression and personality. Moreover, sibling correlations can be used to estimate the upper limit of the heritability. The current analysis aims to improve our understanding of the familiality of life events and their relationship with personality traits and emotional states. This will facilitate the appropriate modelling of life event data in future linkage and association analyses in order to identify QTLs for depression and anxiety, and to explore their interactions with life events.

METHOD

Sample and method of selection

The GENESiS sample was recruited from the UK Medical Research Council's General Practice Research Framework, which was set up more than 20 years ago to enable high quality data to be collected on large-scale community samples. The recruited GPs in this study reflect the full range of rural and urban practices in the UK. A questionnaire with an introductory letter from the doctor of the practice was sent to all patients between the ages of 20 to 55 years in the practice's register. Those subjects who responded from this mailing, whom we refer to as 'index siblings', were then asked to provide contact information for their 'non-index siblings'. At the time of the current analyses, a mailing list of 51 806 people had been generated. The GPs were asked to exclude adults with severe learning disabilities, those with psychotic illness, and those who are particularly vulnerable (e.g. with terminal illnesses). A total 421 people were taken out of the mailing list on this basis. A further 1799 questionnaires were returned due to incorrect addresses. This left a maximum total of 49 586 people who received a letter from GENESiS. The total number of fully completed returned questionnaires from index siblings is 22 087.

From the returned index sibling questionnaires, name and contact information was provided for 11 656 non-index siblings. By March 1999, 3682 non-index siblings had returned questionnaires. The index and non-index siblings constituted 16 274 sibships; the numbers of sibships of size 1, 2, 3, 4 and 5 were 13 548, 2212, 425, 82 and 7 respectively. A small proportion of questionnaires contained missing data, and these were excluded in some of the analyses. The smallest sample (i.e. those without missing data) on which analyses were based consisted of 6503 males (mean age = 41·84, S.D. 10·10) and 9972 females (mean age = 40·74, S.D. 10·14).

Measures

Questionnaire data on psychiatric symptoms and personality included the General Health Questionnaire (12-item version; GHQ-12, Goldberg *et al.* 1997); the Mood and Anxiety Symptoms Questionnaire (short forms of the Anxious Arousal and High Positive Affect scales: MASQ-AA and MASQ-HPA, Watson *et al.* 1995); the 12-item version of the neuroticism scale from the Eysenck Personality Questionnaire (EPQ-N, Eysenck *et al.* 1985). These measures were sex- and age-adjusted and standardized to have mean 0 and variance 1. Their distributions were approximately normal. Because of missing data on sex and age there are fewer observations for the sex and age regressed anxiety and depression measures compared to life-event data.

Life events in the last 6 months were assessed by the List of Threatening Events (LTE; Brugha & Cragg, 1990). Following Kendler *et al.* (1993*a*), the 12 items were reduced to four life events categories by factor analysis. The four categories contained three clusters of personal events (primary impact on the respondent) and one cluster of network events (primary impact on significant others in the social environment). The first personal event category consisted of items concerning intimate relationships assessed by LTE items 5 and 6 ('marital difficulties', 'break-up of steady relationship'); the second category concerned financial problems assessed

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by LTE items 8, 9 and 10 ('became unemployed or seeking work for more than one month', 'sacked from job', 'major financial crisis'); the third category involved a less clear cluster of illness, injury and other personal events: assessed by LTE items 1, 7, 11 and 12 ('you yourself suffered serious illness, injury or assault', 'problems with close friend, neighbour or relative', problems with the police and court appearance', 'something you valued was lost or stolen'). The network category was assessed by LTE items 2, 3 and 4 ('serious illness, injury or assault in close relative', 'death of parent, child or spouse', 'death of close family friend or another relative'). All four categories of life events were classified as being absent or present in each subject.

Statistical analyses

Correlations between categories of life events

Since life-events category scores were dichotomous ('no' = 0, 'yes' = 1), tetrachoric correlations between life events were calculated using Mx (Neale, 1999). These correlations were estimated from two-way contingency tables of frequencies in reported life events for all six pairwise combinations of the four life-events categories. The observed frequencies were fitted to a liability-threshold model that assumes that each life-event category has an underlying bivariate normal distribution of liability with a discrete threshold. These thresholds were z scores corresponding to the prevalence of the four categories of life events (proportion of subject reporting a particular category of life event in the last 6 months).

Sibling correlations in liability to life events

Sibling correlations in the liability to the four life events were estimated in Mx by means of raw ordinal maximum likelihood. The dichotomous variables (a life event present or absent) are assumed to underlie a normal distribution. The boundary between the two categories is translated into a threshold with an associated z score, allowing each category to be represented as an area under a normal curve. This modification for ordinal data provides better tetrachoric correlation estimates. An additional advantage of this approach is that sibships of size 1 can also be included in the analyses for a more precise estimation of the thresholds. Sibships of size 2, 3 and 4 provided information for the sibling correlation estimation. Sibships of size 5 ($N = 12$) were excluded.

Relationship between life events and anxiety, depression, and neuroticism

The relationship between life events (i.e. the 12 individual life-event items and the four life-event categories) and the four measures of anxiety and depression (i.e. EPQ-N, GHQ-12, MASQ-HPA, MASQ-AA) was examined by simple linear regression analyses. In addition, a canonical correlation analysis was performed to find the linear combination of the four life-events categories and the linear combination of the anxiety/depression measures that are most highly correlated with each other.

Interaction between vulnerability and life events

Regarding neuroticism as a vulnerability index, we examined the effects of neuroticism and life events on GHQ-12, MASQ-HPA and MASQ-AA. The latter three variables were treated as the dependent variables in a series of multiple linear regression analyses in which neuroticism and life events were the independent variables.

We then proceeded to exploit the sib-pair structure of our data to derive an index of 'familial vulnerability'. In a DF (DeFries–Fulker) regression analysis, the genetic vulnerability of a twin is indexed by the product of the trait value of the co-twin and zygosity. The current sample consists only of sib-pairs, so we obtained an index of familial vulnerability of an individual from their sibling's trait values. This familial vulnerability will include both common genetic and common environmental effects. The situation here is complicated by the fact that the trait, i.e. anxiety and depression, is multivariate (EPQ-N, GHQ-12, MASQ-HPA, MASQ-AA). It is also complicated by our need to model the effects of the four categories of life events. We have, therefore, adopted a two-stage analytical procedure. We first reduced each class of variables (i.e. vulnerability, life event, and anxiety/depression) to a single composite variable and then proceeded to a simple linear regression analysis. The index of familial vulnerability was constructed by conducting a canonical correlation analysis on doubly entered EPQ-N, GHQ, MASQ-HPA and MASQ-AA

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scores of sib 1 and sib 2. In other words, we are using the linear combination of the four variables, which is most highly correlated between sib 1 and sib 2 as an index of familial vulnerability. Individual scores of this vulnerability index were defined by applying the canonical weights in Table 7 on the co-sib scores.

A composite index of life events and of state anxiety/depression were obtained by a canonical correlation analysis of the four life-events categories and the four anxiety/depression measures. Individual scores of the life-event and emotional state indices were defined by the canonical weights presented in Table 5. We then regressed the emotional state index of an individual on the familial vulnerability index and the life-event index. The linear interaction between vulnerability and life events was examined by entering into the regression model the product of these two composite indices.

RESULTS

Table 1 shows the sociodemographic characteristics of the whole GENESiS sample compared to the sibships of the final sample used in the analyses. In general, the final sample is reasonably representative in terms of education level, ethnicity, sex and age.

The summary statistics for the anxiety/depression measures are reported in Table 2. For life events the smallest number of observations was 19280. The frequencies of reported life events and individual LTE items for the total sample, or stratified by sex and age, are listed in Table 3. Sex and age-band differences in the LTE items and life event categories were examined by means of chi-squared tests. Females showed significantly higher prevalence for life events concerning relationships, personal events and for the network event ($\chi^2(1) = 9{\cdot}12$, 49·79 and 63·33, $P < 0{\cdot}001$, respectively). There were no sex differences in reported financial life events.

Age effects in reported life events were examined by partitioning the sample in three agebands: individuals between 16 and 35 years of age, between 36 and 50 and 51 years and older. For personal life events no age differences were observed, whereas all other three categories showed significant age effects. Network events were slightly more common in older age groups: 28%, 31% and 32% ($\chi^2(2) = 24{\cdot}7$, $P < 0{\cdot}001$), whereas relationship and financial events were

Table 1. *Sociodemographic characteristics* (*percentages*) *of the GENESiS sample*

Sociodemographic characteristics	Whole sample %	Sibships %	Sociodemographic characteristics	Whole sample %	Sibships %
Age, years			Employment		
20–29	16	12	Manager	15	16
30–39	29	31	Professional	17	23
40–49	31	35	Associate professional / technical	7	6
⩾ 50	24	22	Clerical / secretarial	13	13
			Craft / manual	8	5
Gender	42	36	Service	7	5
Male			Sales	6	5
Ethnicity	98	99	Plant / machine operative	2	2
White			Looking after home	12	10
Accommodation			Unemployed	3	2
Own home	76	82	FT student	2	2
Rent	10	8	Self-employed	6	7
LHA / council	5	4	Never-worked	0·3	0·1
Living with parents	8	5	Other	2	4
Other	1	1			
			Highest educational level		
Religion	75	81	No qualifications	16	10
Not religious			CSE	9	8
			O-level / GCSE	31	30
			A / AS / S level	14	15
			HNC	5	4
			HND	4	4
			Degree	16	22
			Postgraduate	5	7

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Table 2. *Summary statistics of the depression/anxiety measures*

	EPQ-N Mean (S.D.)		GHQ-12 Mean (S.D.)		MASQ-HPA Mean (S.D.)		MASQ-AA Mean (S.D.)	
	Male	Female	Male	Female	Male	Female	Male	Female
Age	4·88	6·30	11·50	12·84	29·73	27·48	14·39	14·44
< 36	(3·42)	(3·13)	(5·53)	(5·83)	(8·13)	(8·42)	(5·47)	(5·33)
	4·31	5·71	11·68	12·60	28·62	27·27	13·23	13·91
36–50	(3·30)	(3·31)	(5·53)	(5·70)	(7·96)	(8·29)	(4·89)	(5·18)
	3·74	5·18	11·08	12·13	28·89	27·67	12·70	14·13
51–80	(3·27)	(3·32)	(5·23)	(5·62)	(8·04)	(8·25)	(4·25)	(5·05)
Total sample	4·33	5·79	11·48	12·58	29·01	27·43	13·43	14·14
	(3·35)	(3·28)	(5·40)	(5·73)	(8·04)	(8·33)	(4·96)	(5·21)
Mean age	41·84	40·74	41·86	40·86	41·90	40·79	41·90	40·76
(S.D.)	(10·10)	(10·14)	(10·09)	(10·13)	(10·11)	(10·13)	(10·11)	(10·13)
N	6503	9972	6690	10385	6728	10473	6720	10415

Table 3. *Frequencies of reported individual LTE items and life-event categories (%)*

	Total sample	Gender		Age bands		
		Male	Female	< 36	36–50	51–80
Individual LTE items						
1 'serious illness, injury or assault to self'	6·9	7·2	6·5	7·1	7·0	7·1
2 'serious illness, injury or assault close relative'	18·3	16·0	19·8*	16·7	19·0	19·4*
3 'parent, child or spouse died'	4·0	0·3	4·3*	2·8	3·8	5·3*
4 'close friend or other relative died'	16·4	15·1	17·2*	15·9	16·1	17·8*
5 'separation due to marital problems'	3·1	2·7	3·3*	3·4	3·5	1·8*
6 'broke off steady relationship'	5·3	4·6	5·6*	10·0	3·6	1·7*
7 'serious problems close friend, neighbour or relative'	18·6	14·4	21·6*	18·7	19·2	18·2
8 'became unemployed or seeking work for more than 1 month'	6·6	7·7	5·8*	8·4	5·8	5·8*
9 'sacked from job'	2·2	2·0	1·2*	1·7	1·4	1·3
10 'major financial crisis'	11·9	11·5	12·1	15·3	11·4	7·6*
11 'problems with police + court appearance'	2·0	2·7	1·6*	2·6	2·0	1·1*
12 'something you valued was lost or stolen'	5·6	5·6	5·7	6·4	5·8	4·3*
Life-events categories						
Relationships (5, 6)	7·1	6·4	7·5*	11·6	5·9	2·9*
Network (2, 3, 4)	30·1	26·9	31·9*	27·8	30·5	32·4*
Finances (8, 9, 10)	16·7	16·4	15·9	20·2	15·4	11·8*
Personal (1, 7, 11, 12)	27·4	24·2	29·6*	27·8	27·7	26·7

* Significant differences: for gender $\chi^2(1) > 3{\cdot}84$; for age bands $\chi^2(2) > 5{\cdot}99$.

Table 4. *Correlations between life events within individuals (off-diagonal) and sibling correlations for the same life events (diagonal, bold type) with 95% CI*

	Network	Relationships	Finances	Personal
Network	**0·37 (0·32–0·42)**			
Relationships	0·06 (0·03–0·10)	**0·21 (0·09–0·32)**		
Finances	0·10 (0·08–0·13)	0·35 (0·32–0·39)	**0·10 (0·04–0·17)**	
Personal	0·23 (0·21–0·25)	0·31 (0·28–0·34)	0·31 (0·29–0·34)	**0·10 (0·04–0·16)**

Within-individual correlations estimates were based on a sample of 19237 individuals. Sibling correlations were estimated on 2150 sib pairs, 410 sib trios and 81 sib quads.

more common among younger subjects (for relationships, 12%, 6% and 3% ($\chi^2(2) = 302{\cdot}2$, $P < 0{\cdot}001$); for financial events, 20%, 15% and 12% ($\chi^2(2) = 130{\cdot}2$, $P < 0{\cdot}001$).

Total sample sizes for life event categories ranged between 19280 and 19532. Sex differences tests are based on smaller samples, ranging from 17698 to 17940. Age differences

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Table 5. *First canonical correlation between vulnerability indices (EPQ-N, GHQ, MASQ-HPA and MASQ-AA) and life-event categories*

	Weights	S.E.	*T*	$P > \|t\|$	95% CI	
EPQ-N	0·181	0·0289	6·289	0·000	0·125	0·238
GHQ-12	0·676	0·0315	21·442	0·000	0·614	0·738
MASQ-HPA	−0·058	0·0292	1·985	0·047	0·001	0·115
MASQ-AA	0·388	0·0266	14·565	0·000	0·336	0·441
Network	0·245	0·0501	4·904	0·000	0·147	0·343
Relationships	1·219	0·0917	13·291	0·000	1·039	1·399
Finances	1·594	0·0637	25·033	0·000	1·469	1·719
Personal	1·260	0·0525	23·968	0·000	1·157	1·363

First canonical correlation = 0·3364. Other canonical correlations (i.e. for 2nd, 3rd, 4th sets of linear combinations) were much smaller (0·0716, 0·0443 0·0116) and therefore not interpreted. Number of observations = 15215.

tests are based on smaller samples ranging from 17371 to 17640.

Correlations between life events

Tetrachoric correlations between the four categories of life events are shown on the off-diagonal cells of Table 4. The estimated thresholds for life event correspond to the proportion of cases reporting that event: 30% for network events, 7% for relationships, 17% for finances and 27% for personal events. All the correlations were positive. The personal events showed the highest correlations with both the network event and the other categories of personal events. The three personal categories correlate between 0·31 and 0·35. The lowest correlations were observed between the network life-event category and the three personal life-event categories.

Sib-pair correlations in liability to life events

Estimated sibling correlations in liability to the four categories of life-events between sib-pairs are shown in the diagonal elements of Table 4. The sib correlation for the three personal categories was 0·14 on average. The sib correlation for the network category was 0·37. The high sib correlation for the network event is probably due to the nature of the LTE items for this scale, which includes events necessarily shared within families (i.e. death of a parent).

Association between life events, depression/anxiety indices and neuroticism

Regression of the four measures of anxiety/depression (Neuroticism, GHQ, MASQ-HPA and MASQ-AA) on the life-event categories and LTE items show that the individual contributions to the variances are generally low. Overall, life events are more closely associated with GHQ and MASQ-AA than with MASQ-HPA and neuroticism. The life-event categories 'Finances' and 'personal' had the highest contributions to all four anxiety/depression variables: both 5% to GHQ; 3 and 4% to AA; both 3% to neuroticism; 3 and 1% to HPA ($P < 0·001$). The 'Network' life event showed the lowest impact, ranging from 0·03% on HPA to 1% on AA ($P < 0·001$).

This pattern is confirmed by the results from the canonical correlation analysis presented in Table 5. The first canonical correlation was 0·34; the correlations for the other linear combinations were small (0·07, 0·04 and 0·01) and therefore not considered. The coefficients of the first linear combination suggest that individuals who had experienced higher levels of emotional distress over the last weeks (higher GHQ scores and higher anxious arousal levels) also had a higher frequency of reported life events (especially personal events) in the last 6 months. The more stable trait (personality) variables (i.e. neuroticism) seem to be more robust against influences of recent adverse events.

Interactions between personality and life events in predicting depression and anxiety

In Table 6 the main effects of neuroticism and life events and their interactions, on GHQ, MASQ-HPA and MASQ-AA are reported. The main effects of neuroticism and life events were highest for GHQ. The interaction effect was quite small, and only explained 0·3% of the variance of GHQ.

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Table 6. *Regression of depression and anxiety measures of life-event categories and neuroticism*

	R^2		
	GHQ-12	MASQ-AA	MASQ-HPA
Main effects N	0·302	0·181	0·253
Main effect LE	0·099	0·068	0·038
Main effects N and LE	0·338	0·208	0·259
Main + interaction effects N and LE	0·341	0·215	0·260
Interaction effects LE and N	0·003	0·007	0·001

N, Neuroticism; LE, life events.
Significance of all regressions: $P < 0{\cdot}001$. N = EPQ-N.

Table 7. *First canonical correlation between anxiety/depression measures* (*EPQ-N*, *GHQ*, *MASQ-HPA and MASQ-AA*) *of siblings*

	Weights	S.E.	T	$P > \|t\|$	95% CI	
EPQ-N	0·7063	0·1135	6·222	0·000	0·4837	0·9289
GHQ-12	0·0103	0·1268	0·881	0·935	−0·2383	0·2590
MASQ-HPA	−0·1915	0·1166	−1·641	0·101	−0·4203	0·0373
MASQ-AA	0·3836	0·1137	3·373	0·001	0·1606	0·6066

First canonical correlation = 0·209. Other canonical correlations (i.e. for 2nd, 3rd, 4th sets of linear combinations) were smaller (0·106, 0·053 0·011) and therefore not interpreted. Number of observations = 2746 pairs.

For exploring the interaction between familial vulnerability and life events we used the sibling structure of the data. The index of familial vulnerability was constructed by conducting a canonical correlation analysis on doubly entered EPQ-N, GHQ, MASQ-HPA and MASQ-AA scores of sib 1 and sib 2. The first linear combination (representing the combination of variables which is most highly correlated between sib 1 and sib 2) had the highest canonical weight on EPQ-N (0·71) and the second largest weight on MASQ-AA (0·38), and a canonical correlation of 0·21 (Table 7).

For the indices of emotional state and life events, we took the linear combinations described in Table 5. We then regressed an individuals emotional state index on the familial vulnerability index, the life-event index, and their interaction. The familial vulnerability index explained 3% of the total variance of emotional state; the life-event index accounted for 11%, and there was no significant interaction.

DISCUSSION

With respect to the first aim of this study, our results confirm previous findings of small to modest familial correlations in life events. The sibling correlations for life events in this study are in close agreement with previously reported DZ twin correlations for similar events (Foley *et al*. 1996) and with sib-pair correlations (Farmer *et al*. 2000). The sibling correlation was 0·13 (on average) for the three categories of personal events, and 0·37 for the network event. Different categories have been shown to vary in the importance of the different sources of variance. Our sibling correlation in personal events, while small, are consistent with reported DZ correlations by Foley *et al*. (1996) who estimated heritabilities to be around 30%. Familiality in personal events has been reported to be mediated by genetic influences, whereas the more substantial resemblance in network events is explained by both genetic and common environmental influences (Kendler *et al*. 1993*a*; Foley *et al*. 1996).

With regard to the relationship between the four categories of life events and the four measures of anxiety and depression, our findings are that personal life events are more closely associated with the anxiety/depression measures than network events do, and that the association is higher for GHQ and MASQ-AA than for EPQ-N. These findings suggest that neuroticism may be a relatively stable trait measure that is fairly robust to environmental influences, whereas GHQ and anxious arousal could be regarded as emotional states that are more responsive to stress. This provides some support for regarding neuroticism as a personality trait.

On the third question of a possible interaction between vulnerability and life events, our analyses seem to suggest that while both vulnerability and life events are potent determinants of anxious and depressive symptoms, there are little or no interactive effects. This conclusion was reached whether we assumed neuroticism to be a measure of vulnerability, or considered a more empirical approach based on canonical correlations. Of the three variables, GHQ, MASQ-HPA and MASQ-AA, the one that was most strongly related to neuroticism and life events was GHQ. We estimated that approxi-

mately 30% and 10% of the variance of GHQ was explained by neuroticism and life events, respectively. The limitation of this approach is that neuroticism will fluctuate to some extent with life events and other sources of stress, and is therefore unlikely to be a pure index of vulnerability.

With the more sophisticated approach of using a sibling's anxiety/depression measures to provide an index of familial (genetic and environmental) vulnerability, we showed that neuroticism, more than the other three anxiety/depression measures in sib 1, predicted anxiety and depression in sib 2. The sibling-based vulnerability index explained 3% of the total variance of emotional state index; while life-event index accounted for a further 11% of the variance, with no evidence of interaction. The low predictive power of the sibling-based vulnerability index on the emotional state index is due to the fact that it is a very indirect measure of a person's vulnerability. A more direct genetic vulnerability index would probably explain a greater part of the trait variance.

The picture that emerges from this study is that life events and vulnerability are familial, and that they contribute substantially in an additive fashion to the variation in the levels of anxious and depressive symptoms in the community. This conclusion must be qualified by the nature of the measures we used. Our vulnerability measure, based primarily on neuroticism, is likely to reflect an individual's long-term average level of anxious and depressive symptoms. It is possible that if vulnerability is measured at a more fundamental level, either cognitively, neurochemically, or genetically, then there will be a greater degree of interaction with life events. Our measure of life events is based on questionnaire items rather than personal interview. One might expect that a more accurate measure of life events from personal interview would be even more predictive of anxiety and depression, and possibly demonstrate an interaction with vulnerability.

Another limitation of the current study is that our sibling design does not allow the detailed exploration of the complex causal relationships between personality, life events and anxiety/depression. Nevertheless, the finding of a rather modest association between neuroticism and life events and a much stronger relationship between anxiety/depression and life events, indicates that the association between life events and anxiety/depression is unlikely to be entirely accounted for by neuroticism. In a co-twin control design Kendler *et al.* (1999) were able to examine the direction of causation; stressful life events were reported to have a substantial causal relationship with the onset of depression. However, one-third of the association was non-causal, being due to a correlation between the vulnerability to depression and exposure to life events.

If life events are largely environmental and do have a substantial causal relationship to anxiety and depression, then adjusting for them in QTL mapping should result in increased statistical power. However, for QTLs whose effects on anxiety and depression are mediated through life events, adjusting for life events will actually reduce power of detection. The current findings, when taken in the context of previous studies, suggest that the true situation is somewhere in between these two scenarios. There is likely to be a modest overlap between the genetic vulnerability to anxiety and depression and the genetic vulnerability to life events, and in addition, life events have a direct causal relationship on anxiety and depression. Further work is necessary both to clarify the precise causes and effects of life events, and how they should be incorporated in QTL mapping.

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