

# Personality traits in unaffected twins discordant for affective disorder

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**Objective:** To examine whether a high genetic liability to develop affective disorder is associated with specific personality traits.

**Method:** A cross-sectional, high-risk, case-control study. Through nation-wide registers, healthy monozygotic (MZ) and dizygotic (DZ) twins with (high-risk twins) and without (the control group/low-risk twins) a co-twin history of affective disorder were identified.

Personality traits were compared for a total of 211 high-risk and low-risk twins.

**Results:** In univariate analyses, the high-risk twins had a higher level of neuroticism than the control twins ( $P = 0.03$ ). In multivariate analyses, a high genetic liability to affective disorder was not significantly associated with neuroticism but correlated to sex, minor psychopathology and recent life events.

**Conclusion:** A high genetic liability to affective disorder showed an association with neuroticism, but the association interacts with other predictors of affective disorder such as female gender, minor psychopathology and recent adversity.

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Key words: mood disorders; personality; comorbidity; life change event

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## Significant outcomes

- A high genetic liability to affective disorder may be associated with neuroticism, but not unambiguously.
- A higher level of neuroticism was associated with female sex.
- The association between genetic liability to affective disorder and neuroticism seems to be mediated through an increased prevalence of general minor psychopathology and recent life events.

## Limitations

- The sample is restricted to twins born in Denmark who had accepted to be contacted through the Danish Twin Registry. It is unsure whether these results can be extrapolated to other ethnic or geographical populations.
- Assessment of neuroticism and life events was based on self-report questionnaires.
- The study was cross-sectional.

## Introduction

Personality traits may be associated with the risk of developing affective disorder (1). Thus, neuroticism has been found to be both cross-sectionally and prospectively associated with the risk of developing unipolar depression while findings on extroversion are inconsistent (2–5). A few studies have concentrated on personality traits as a risk

factor of bipolar disorder and the association between personality traits and bipolar disorder is unclear (2, 6, 7). Genetic risk factors for neuroticism and depression are related and may interact with other risk factors of affective disorder (8, 9). Rarely investigated, stressful life events and neuroticism seem to have an additive effect by increasing the overall risk of affective disorder (10).

### Aims of the study

The aim of the present study was to test the hypothesis that genetic liability to affective disorder is associated with neuroticism and to test whether such an association is mediated through other risk factors (sex, subthreshold disorders, subclinical anxiety and subclinical depressive symptoms and recent adverse life events) of affective disorder.

### Material and methods

#### The registers

The Danish Civil Registration System assigns a unique personal identification number for all Danish residents. This number is linked to information on name, address, and date of birth. All other Danish registers use the same unique identifier and thus Danish residents can be tracked in all the public registers through record linkage. The Danish Psychiatric Central Research Register is nationwide, with registration of all psychiatric admissions and out-patient hospital contacts in Denmark for the country's 5.3 million inhabitants (11). From April 1969 to December 1993, diseases were classified according to the International Classification of Diseases, '8th' (ICD-8) (12) and from January 1994 according to the International Classification of Diseases, '10th' (ICD-10) (13). The Danish Twin Registry was initiated in 1953 and contains information on 75 000 twin pairs born from 1870 to 2003. The completeness varies with the date of birth and is approximately 70% for the period before and close to 100% for the period after the Civil Registration System was established (14, 15). The Twin Registry contains information about the zygosity of twins of same-sexed twins based on mailed questionnaires. The questionnaire method used in the Danish Twin Register has been found to result in error rates of < 5% when compared with serological and DNA methodology (16).

#### The linkage

Through record linkage between the Danish Twin Register, the Danish Psychiatric Central Research Register and the Danish Civil register, a cohort of 'High-Risk' twins was identified. This linkage identified same sex twin pairs in which one twin had been treated in a psychiatric hospital setting for an affective episode (the proband) and one had not been treated for affective disorder, the high-risk healthy co-twin. Proband twins were identified as

twins who on their first admission, in the period between 1968 and 2005, were discharged from a psychiatric hospital with a diagnosis of depression or recurrent depression (ICD-8-codes: 296.09, 296.29, 296.89, 296.99; ICD-10-codes: F32–33.9) or a first diagnosis of manic mixed episode or bipolar affective disorder (ICD-8-codes: 296.19, 296.39; ICD-10-codes: F30–31.6, F34.0, F38.00). Control-twins (low-risk) were identified as twins without known personal or co-twin history of hospital contact with affective disorder, and matched on age, sex and zygosity for each high-risk twin.

#### Participants

During the recruitment period (May 2003 to September 2005) 204 high-risk and 204 low-risk twins were invited to participate in the study. A total of 408 letters containing an invitation and a return envelope were posted to the cohort. Persons who did not respond were contacted by telephone after 2 weeks. If contact was not established, a new letter, including a short questionnaire was posted. Those who did not wish to participate were asked to participate in a short telephone interview or to fill out a short questionnaire. They were asked about family history of affective disorder, education, work status, and somatic and psychiatric health. The interviewer was blinded for the risk status of the participants and did not know whether the co-twin of the participants had been admitted to a psychiatric hospital or treated in an out-patient setting or not.

#### Inclusion and exclusion criteria for high-risk and low-risk twins

**Inclusion criteria high-risk twins:** having an MZ or a DZ co-twin with a diagnosis of affective disorder (co-twin history of affective disorder) according to information from the Danish Psychiatric Central Research Register. **Exclusion criteria:** a personal history of severe to moderate depression, earlier medical treatment for an affective episode, severe organic brain disease or schizophrenia. **Inclusion criteria low-risk twins:** no family history of affective disorder among the MZ or DZ co-twin or other severe psychiatric illness (schizophrenia and affective disorders) among other first-degree relatives. **Exclusion criteria:** earlier medical treatment for an affective episode, severe organic brain disease. The control twins and their co-twins were not recorded in the Danish Psychiatric Central Research Register with a diagnosis of mania or depression. However, it is possible that they or their co-twin had received another diagnosis. If a low-risk twin

had been admitted to a psychiatric hospital they were excluded. If they at the end of the interview answered that a first-degree relative had a history of severe psychiatric illness they were reclassified to the group of twins with another family history.

The sample

As described, healthy monozygotic (MZ) and dizygotic (DZ) twins with and without at co-twin history of affective disorder were identified through nationwide registers. Accordingly, four groups were identified: (1) twins at high risk for development of affective disorder (MZ twin, co-twin affected); (2) twins at moderate risk for development of affective disorder (DZ twin, co-twin affected); (3) twins moderately protected against development of affective disorder (DZ twin, co-twin unaffected); and (4) twins at low risk for development of affective disorder (MZ twin, co-twin unaffected).

A total of 408 high-risk and low-risk twins was invited and 271 agreed to participate. Subsequently, 37 persons were excluded (mainly because of prior or current affective episode). The 234 participants were divided into groups according to risk of affective disorder as described above. Additionally, a fifth group was defined as twins having a first-degree relative other than a twin with affective disorder or schizophrenia. This group was excluded in the present study because they had a family history of mixed psychiatric disorders. Five participants did not fulfil Eysenck Personality Questionnaire (EPQ) (2.3%). Further detailed description and discussion of the study design have been presented in detail elsewhere (17).

As can be seen from Table 1, the remaining 211 participants were categorized into four groups according to their genetic liability of affective disorder: 39 high-risk MZ twins, 86 high-risk DZ-twins, 50 low-risk DZ and 36 low-risk MZ

twins. There were significant differences in age, years of education BDI 21, Anxiety<sub>14</sub> and number of lifetime subthreshold disorders (alcohol use, phobia, anxiety disorder, eating disorders, acute stress-depression/anxiety reactions). Among the 211 participants, 38 (18%) had a lifetime subthreshold disorder (alcohol use, phobia, anxiety disorder, eating disorders, and acute stress-depression/anxiety reactions). Finally, a total of 22 high-risk twins had a co-twin with bipolar disorder and 103 had a co-twin with depressive disorder.

Ethics

The Danish Ministry of Health, The Danish Ethical Committee [(KF)-12-122/99 and (KF)-01-001/02] and the Danish Data Protection Agency approved the study. The study was conducted in accordance with the latest version of the Declaration of Helsinki. All participants gave written informed consent.

Assessment

Participants were rated in a face-to-face interview using semi-structured interviews: diagnoses were made using Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1 (18). All persons with a lifetime (current or past) diagnosis of affective disorder, schizoaffective disorder or schizophrenia according to SCAN interview were excluded from the study. Participants with a lifetime subthreshold disorder defined, as non-organic, non-schizophrenic or non-affective SCAN diagnoses were included in the study. The Hamilton Depression Scale HAM-D, 17-items (19) was used to assess depressive symptoms. Furthermore, self-rating of psychopathology was assessed using Symptom Rating Scale for Depression and Anxiety including assessment of depressive symptoms using the 21-item Beck Depression Inventory

Table 1. Demographic details, BDI 21, Anxiety<sub>14</sub>, ICD 10 and recent life events and a comparison of neuroticism and extraversion scores according to risk status. Mean (SD)

	High-risk MZ	High-risk DZ	Low-risk DZ	Low-risk MZ	P-value
Number	39	86	50	36	
Sex M/F	13/26	33/53	20/31	11/25	0.80
Age	42.9 (13.9)	46.9 (12.8)	46.3 (12.4)	38.3 (13.1)	0.01
Education	12.1 (2.8)	12.0 (3.4)	13.2 (2.9)	14.2 (3.1)	0.003
BDI 21	2.8 (2.9)	2.2 (3.3)	1.0 (1.8)	1.0 (1.5)	0.003
Anxiety <sub>14</sub>	2.0 (2.5)	1.4 (2.2)	0.8 (1.8)	0.8 (1.2)	0.02
ICD 10	13	22	2	1	0.0001
Recent LE	2.7 (2.5)	2.8 (2.5)	1.4 (1.6)	1.3 (1.5)	0.0001
Neuroticism	5.5 (4.2)	5.7 (5.1)	3.4 (2.9)	4.9 (4.2)	0.02
Extraversion	14.3 (3.8)	14.5 (4.3)	15.2 (4.2)	15.6 (3.4)	0.4

Sex: M, male; F, female. Education is measured as number of years. ICD 10, number of prior or present subthreshold disorder; anxiety<sub>14</sub>, Bech's anxiety scale 14 items; BDI 21, Bech's Depression Inventory 21 items; Recent LE, life events during the recent 12 months.

(BDI 21) (20) and anxiety symptoms using the 14-item Anxiety Subscale (Anxiety<sub>14</sub>) (21).

#### Personality measure

Personality dimensions were assessed using the EPQ, Danish version. The EPQ comprises 101 items intended to measure a broad dimension of neuroticism, extroversion and psychotism (22). The Danish version of the EPQ has shown coefficient alpha values of 0.87 for neuroticism and 0.84 for extraversion (23).

#### Life events

Participants were asked about life events in the year before the interview (recent life events) and life events in their lifetime before that, using a Danish version (translated to Danish after permission from the author) of the questionnaires used by Kendler and colleagues (24) in their studies. Participants were asked about personal and network events. Nine 'personal' events (events that happened to the participant) were assessed including assault, serious marital problems, divorce/break-up, job loss, and loss of a confidant, serious illness, major financial problem, being robbed, and serious legal problems. In addition, 22 'network' events were assessed, i.e. events that occurred primarily to, or in interaction with, an individual in the participant's social network. Included were death or severe illness of the participant's spouse, child, parent, co-twin, other sibling, other relative or other individuals close to the participant and serious trouble getting along with the participant's parent, child, co-twin, sibling, in-laws, other relative, neighbour, or close friend.

#### Statistical analyses

Independent *t*-tests and analyses of variance (ANOVA) were used to compare two or three or more independent groups and Pearson's correlations were used to analyse bi-variate correlations between scores on the EPQ and continuous variables. The effect of multiple variables on measures of personality traits was analysed in multiple regression analyses with the trait score (e.g. neuroticism) as the dependent variable. Firstly, a 'simple' regression model was used including the variables sex, age and years of education as predictors. Secondly, the effects of multiple variables on the measure of personality was analysed in a complex multiple regression model adding variables of minor psychopathology (Anxiety<sub>14</sub>, BDI 21 and ICD-10 before present subthreshold disorder)

and recent life events. The level of significance was set at 5% (one-tailed). The Statistical Package for the Social Sciences was used to create a database and undertake the statistical analyses (SPSS, version 13 for Windows).

#### Results

##### Neuroticism and extraversion: correlations to other variables

The 76 male participants had significantly lower scores on neuroticism (mean 3.9, SD 4.2) compared with the 135 female participants (mean 5.7, SD 4.5) ( $t = -3.1, P = 0.002$ ). Mean score on extraversion was 14.5 (SD 4.2) in males and 14.9 (SD 3.9) in females ( $t = -0.62, P = 0.5$ ). Neuroticism correlated significantly with the number of recent life events ( $r = 0.26, P = 0.0001$ ), Anxiety<sub>14</sub> ( $r = 0.33, P = 0.0001$ ) and BDI 21 ( $r = 0.47, P = 0.0001$ ). The correlation between age and neuroticism scores ( $r = -0.07, P = 0.14$ ) and the correlation between years of education and neuroticism ( $r = -0.04, P = 0.14$ ) were not significant. Extraversion score was negatively associated with BDI 21 ( $r = -0.14, P = 0.02$ ), but not significantly correlated to recent life events ( $r = -0.04, P = 0.30$ ), Anxiety<sub>14</sub> ( $r = -0.12, P = 0.15$ ) or age ( $r = -0.18, P = 0.08$ ).

As can be seen from Table 1, analyses of variance (ANOVA) showed significant group differences on neuroticism score according to EPQ. The high-risk twins scored significantly higher on neuroticism compared with the low-risk twins. No significant differences among the four groups were observed on extroversion scores.

##### Predicting neuroticism from demographic variables

In multiple regression analyses, the association between risk status and personality score was adjusted for differences in sex, age and years of education. In this model, the association between risk status and neuroticism was marginally significant ( $B = 0.41, SD 0.22, P = 0.06$ ). Female sex was significantly associated with a higher neuroticism score ( $B = 1.56, SD 0.63, P = 0.01$ ), whereas age ( $B = -0.04, SD 0.02, P = 0.13$ ) and years of education ( $B = -0.14, SD 0.10, P = 0.18$ ) were not significantly associated with neuroticism. In a model without age and years of education, risk status ( $B = 0.45, SD 0.21, P = 0.04$ ) and female sex ( $B = 1.62, SD 0.62, P = 0.01$ ) were significantly associated with neuroticism. There was no significant effect of risk status or any other variables on extraversion (results not presented).

Predicting neuroticism from subclinical psychopathology and recent life events

In further multiple regression analyses, the covariates sex, age and years of education remained and additionally, Anxiety<sub>14</sub> score, BDI 21 score, ICD 10 (a lifetime subthreshold disorder) and the number of life events rated 12 months before the SCAN interview were included as predictors.

The results are presented in Table 2. Sex, BDI 21 score, a lifetime minor psychiatric diagnoses and life events were significantly associated with neuroticism, whereas risk status did not contribute significantly to a higher neuroticism score after covariate adjustment. Additional analyses showed that the significant association between risk status and neuroticism that was found in the described model including the demographic variables, disappeared when each of the three variables BDI 21, ICD 10 and recent life events were included in separate models. The adjusted  $R^2$  value of the model was 0.27.

As can be seen from Table 2, the variables had only small and non-significant effects on extraversion and the adjusted  $R^2$  value of the model was 0.01. The analyses were repeated excluding the 22 participants with a family history of bipolar disorder and the result remained essentially the same.

The 39 participants with a lifetime minor psychiatric diagnoses had significantly higher neuroticism scores (mean 8.1, SD 4.8) compared with the 172 participants without a subthreshold disorder (mean 4.3, SD 4.2) ( $t = -5.0, P = 0.0001$ ). Mean score on extraversion was 14.6 (SD 4.7) for the participants with a lifetime subthreshold disorder and 14.9 (SD 3.9) for those without. Excluding the 39 participants with a lifetime subthreshold disorder, no significant associations were found between risk status and neuroticism or extroversion in ANOVA analyses respectively (results not presented).

## Discussion

### Main findings

A higher level of neuroticism was observed in individuals with a genetic liability to affective disorder compared with individuals without a family history of affective disorder but the association was not unambiguous. Thus, in a multiple regression model the association between genetic liability and neuroticism was not significant. In this model, including socio-demographic variables and a measure of minor psychopathology and recent stressful life events: the level of neuroticism was correlated to female sex, to minor psychopathology and to the number of recent life events. Thus, genetic liability, neuroticism, increased prevalence of minor psychopathology and life events show a complex pattern of intercorrelations. Extraversion was only found to have a negative correlation to BDI 21 scores.

### Neuroticism and genetic liability

Twin studies utilize the fact that MZ twin pairs share all their genes, whereas DZ twins share on average half of their segregating genes (25). Kendler et al. (26) showed in a 15 months follow-up study of female twins that approximately 55% of the genetic liability of major depression appeared to be shared with neuroticism (26). The present study was not designed to replicate this study and as only the twins without affective disease were included in the present study it was not possible to replicate the findings from Kendler and colleagues. In the present study, it was possible to compare a group of individuals with a very high genetic liability to affective disorder, the high-risk MZ twins, with a group of individuals with a very low genetic liability, the low-risk MZ-twins. The hypothesis that the genetic liability would affect neuroticism

Table 2. The complex multiple regression analyses model: *B* coefficients, standard error and significance levels for neuroticism and extraversion (all participants)

Predictor variable	Neuroticism			Extraversion		
	B	SD	<i>P</i> -value	B	SD	<i>P</i> -value
Constant	1.2	2.3	0.6	17.8	2.5	0.0001
Risk	-0.2	0.2	0.3	-0.2	0.2	0.3
Sex	1.3	0.6	0.03	-0.02	0.6	1.0
Age	-0.01	0.02	0.5	-0.03	0.02	0.2
Years of education	-0.1	0.1	0.3	-0.05	0.1	0.6
ICD 10	2.0	0.8	0.01	0.2	0.8	0.8
Anxiety <sub>14</sub>	-0.2	0.2	0.3	0.06	0.8	0.8
BDI 21	0.7	0.1	0.0001	-0.2	0.2	0.1
Recent LE	0.3	0.1	0.02	-0.02	0.1	0.9

ICD 10, prior or present subthreshold disorder; Anxiety<sub>14</sub>, Bech's anxiety scale 14 items; BDI 21, Bech's Depression Inventory 21 items; Recent LE, life events during the recent 12 months.

score was only partially confirmed; as the MZ high-risk twins did not have higher neuroticism scores compared with the DZ high-risk twins (Table 1). This may be due to the fact that only participants who had not experienced an affective episode were included in the study, since those MZ twins who premorbid had a high level of neuroticism already might have experienced their first affective episode and thereby might have been excluded from the study. In addition, the age information in Table 1 suggests that some of the high-risk MZ twins may have passed the average age of onset of affective disorder. In fact, possibly the older high-risk twins may present with personality trait resilience rather than a trait risk.

#### Other studies

The tendency towards a higher level of neuroticism in the high-risk twins in the present study is in accordance with five of nine cross-sectional high-risk studies that were identified in a recent systematic review of personality traits in affective disorder (2). The remaining four studies found no differences on neuroticism or extroversion scores between first-degree relatives of probands with affective disorder compared with control persons (2). Especially, the study by Farmer et al. (27) should be accentuated, as life events and BDI score were also included in their analyses, and in accordance with our findings, the study showed no differences in neuroticism scores comparing 81 never depressed siblings of depressed patients with 105 never depressed siblings of normal controls. Thus, in the two studies adjusting for the prevalence of life events and depressive symptoms it was not demonstrated that neuroticism represented an independent trait vulnerability to depression.

#### Neuroticism, sex and psychopathology

Elevated neuroticism score in female individuals and no sex differences for extraversion have been reported previously (28). The positive relation between minor psychopathology and neuroticism scores has also been described in other studies including non-affective ill individuals with a family history of affective disorder (27, 29) and it has been established that neuroticism scales items have some overlap with the symptoms of depression (30).

The finding of an association between higher neuroticism score and the presence of a prior or actual subthreshold disorders has been showed in previous studies (31, 32). The latter study found

that high neuroticism appeared to be a broad vulnerability factor for comorbid psychiatric disorders (anxiety disorders, major depression, alcohol and drug dependence, antisocial personality disorder and conduct disorder). A study of the psychodynamic personality profile of 61 patients with a first-episode severe mental disorder did not support the hypothesis that severe mental disorders would differ from each other in terms of personality profiles (33). Another population-based longitudinal study of 4796 adults showed that neuroticism was more strongly associated with comorbid than with pure disorders (34). The results of these studies and the present study are in accordance with the conclusion from a recent review of the association between neuroticism and psychopathology that neuroticism is a non-informative marker of vulnerability to psychopathology (35).

#### Life events and neuroticism

The present study showed that recent life events or adversity were significantly and positively associated with higher neuroticism scores both in univariate and multivariate analyses. Kendler et al. (10) concluded in a follow-up study, that the impact of neuroticism on illness was greater at high levels of adversity. Another study found that independently of familial loading, life events increased the liability to mood disorder in adolescents offspring of parents with bipolar disorder (36).

As noted in the review by Ormel et al. (35) of the association on neuroticism and psychopathology, neuroticism alone is not an explanatory concept in the aetiology of psychopathology but more a measure of a persons level of distress over a period of time (35). This explanation is in accordance with the results of the present study showing an association between recent life events and higher neuroticism scores. Results from the present study suggest that the effect of genetic liability on neuroticism may be mediated through experience of an increased number of life events and a higher level of minor psychopathology but as the study is cross-sectional no conclusions about the temporal sequence of neuroticism and adverse life events can be made. Alternatively, this association between recent life events and neuroticism could be viewed as a state phenomenon or the association might be an expression of a subsyndromal affective status in the process of becoming syndromal. To be more informative, neuroticism must be studied prospectively repeating the EPQ questionnaire to be able to distinguish between trait and state properties, as planned in the present study.

### Measures

Personality trait scales lack a well-defined time frame and many items use vague definitions of frequencies, intensity and duration (e.g. sometimes, often, and rarely). Besides, neuroticism items in the EPQ can be read as an invitation to complain (e.g. Are your feelings easily hurt?, Do you often experience periods of loneliness?) (35). In adulthood, neuroticism seems to be stable over time thereby reflecting trait vulnerability (37). Nevertheless, the present study is cross-sectional and not able to distinguish state dependent properties from trait dependent properties. It is possible that and the positive correlation found between BDI 21 scores and neuroticism scores may be related to the fact that BDI scores in this non-patient population to some extent reflect variation in the trait neuroticism.

Life events were measured using a self-report questionnaire covering the 12 months before the interview. Self-rating of events may be influenced by poor recall and poor reliability (38); in the present study, the measure of life events was used as a measure of recent adversity or stress and rating of independence and magnitude (objective negative impact) of the event was not rated as done in the semi-structured Interview for Recent Life Events (39). Not rating the objective impact of the life events, the risk of measuring participant's sensitivity to life events has to be considered. Individuals with a high neuroticism score might have a proneness to experience negative life events through exposing them self to a greater number of stressful life events and through increasing their reactivity to the events (40). Thus, neuroticism may act as a confounder regarding the number of self-reported life-events. Nevertheless, the high- and low-risk twins fulfilled the same questionnaire under the same conditions, so it seems reasonable to use the number of events in the recent 12 months as an expression of adversity/stress.

### Generalizability

To generalize findings from a twin study, twins must be representative of the general population. One study concerning bipolar disorder found equal rates of bipolar disorder in twins and singletons (41). No study has investigated this issue for unipolar depression. Among the invited participants, those who agreed to participate may have been more extraverted and less anxious than those who did not want to participate. It might explain the slightly lower overall neuroticism scores found in the present study compared with another Danish

study of twins aged 18–67 years (mean score neuroticism female twins 7.3 ( $n = 219$ ) male twins 5.2 ( $n = 231$ )) (42).

Regarding the diagnosis of the probands, there are some disadvantages from using registers as pin pointed in a recent systematic review (43) of validity studies on administrative registers in psychiatric research: the diagnoses are clinical, not research diagnoses and only a few validity studies have been conducted concerning affective diagnosis. In the present study up until 1995 only hospitalized probands were included. As the diagnoses were given at the first discharge it is unknown whether the diagnosis of the proband has changed. Likely, the number of bipolar probands in the present study is underestimated, as previous studies have shown that around 10–15% of patients with an index diagnosis of depression will subsequently develop a bipolar disorder (44). In addition, there is a genetic overlap between unipolar and bipolar disorder (45). In the present study, 22 of 234 participants had a proband (their co-twin) with a diagnosis of bipolar disorder.

Finally, it is possible that seeking treatment selects parts of the population with a higher level of neuroticism and this may bias the results of the present study. The high-risk study design might select probands with affective disorder from treated populations and thereby select families with an increased rate of illness. By using register linkage, it is possible to overcome some of this selection bias, but the identification procedure of the high-risk twin is still dependent on the probands threshold to clinical referral or admission and on the validity of the diagnosis used in the register (46). Nevertheless, to identify whether neuroticism is found in non-affected family members at a higher rate than in the general population, it seems appropriate to select the more severe affected in-patients as probands.

### Future studies

Thus, the present study suggests an association between neuroticism and a high genetic liability to affective disorder, general minor psychopathology and the experience of adversity. To elucidate the complex pathway leading to onset of affective disorder, repeated measures over time of personality traits, minor psychiatric symptoms, stress exposure, stress response and genetic susceptibility have to be included. It might be that the sensitivity of risk factors such as neuroticism and life event is mediated through specific variations in genes as shown in two recent studies (47, 48).

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**Declaration of interest**

None.

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