Journal of Psychiatric Research 47 (2013) 565–571

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

# Risk markers for affective disorder, a seven-years follow up study of a twin cohort at low and high risk for affective disorder

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ARTICLE INFO

*Article history:*
Received 11 October 2012
Received in revised form
28 December 2012
Accepted 14 January 2013

*Keywords:*
Onset mood disorders
Depressive symptoms
Life events
Prediction

ABSTRACT

This study aims to investigate whether: familial history of affective disorder, subclinical depressive symptoms and life events (LEs) are predictive of a later development of mood disorder (onset). In a high-risk study, 234 healthy monozygotic and dizygotic twins with and without a co-twin history of affective disorder (high and low risk twins, respectively) were identified through nationwide registers and assessed from 2002 to 2005. Participants were followed longitudinally at 6-months intervals for up to nine years and finally reassessed with a personal interview to obtain information on whether they had an onset. During the follow-up period (mean time 7.0 years), 36 participants (15.4%) developed onset. Onset was significantly associated with risk status (Hazard ratio (HR) = 1.38, 95% CI 1.08–1.76), female sex, HR = 2.70, 95% CI 1.19–6.97, age HR = 0.97, 95% CI 0.93-0.99), and also with baseline Hamilton 17 score (HR = 1.30, 95% CI 1.13–1.48), Becks Depression Inventory 21 (HR = 1.14, 95% CI, 1.05–1.24) and neuroticism (HR = 1.08, 95% 1.02–1.12). Finally, the experience of LEs lifetime before baseline predicted onset (HR = 1.20, 95% CI 1.01–1.46) and the experience of LEs during follow-up also predicted onset (HR = 1.06, 95% CI 1.01–1.11). These findings suggest that young individuals at familial risk of affective disorders are at enhanced risk of onset and at further risk when having female sex and more subclinical depressive symptoms at baseline. Further, they seem to experience more LEs and to be more vulnerable to these.



## 1. Background

Unipolar and bipolar disorders are characterised by complex phenotypes, overlapping symptoms and high comorbidity and may result from an interaction between genetic liability, distress and environmental risk (Kendler et al., 1995; Farmer et al., 2005). A better understanding and a potential better treatment of mood disorders necessitate investigation of factors related to illness. Unipolar and bipolar disorder both have a substantial genetic contribution and seem to develop in characteristic clinical stages (Hetrick et al., 2008), which highlights the importance of prospective studies of individuals at family risk for affective disorder. Further, high-risk studies can provide insight into the inherited vulnerability, influence of other risk factors, determination of intermediate causal pathways and identification of prodromal stages without the confounding effects of the changes associated with the burden of the illness (Duffy et al., 2011).

It is well established that a family history of affective disorder is a predictor of depression (Mortensen et al., 2003; Merikangas and Low, 2004). The risk of developing affective disorder is increased two-to-three fold for first-degree relatives of patients with affective disorders (Weissman et al., 1984; Blehar et al., 1988; Sullivan et al., 2000; Gottesman et al., 2010). It is also established that previous experience of severe life events (LEs) is a strong predictor of onset of depression (Kendler et al., 1995; Saveanu and Nemeroff, 2012). Further the personality trait neuroticism, which refers to emotional instability, vulnerability to stress and a proneness to anxiety (Eysenck, 1970), is associated with risk of depression both cross sectionally and prospectively (Christensen and Kessing, 2006). Finally stressful LEs and neuroticism may have an additive effect by increasing the overall risk of affective disorder (Kendler et al., 2004; Vinberg et al., 2007). Previous findings are mainly based on cross sectional data and there is a lack of longitudinal studies assessing the predictive effects of these risk factors. It has never been investigated in a high risk study whether discrete subclinical symptoms predict onset of psychiatric illness.

The purpose of the present high-risk study is to explore risk factors that may lead to onset of affective disorder prospectively. In the cross-sectional part of the study we showed that healthy high-risk individuals (with a co-twin with affective disorder) presented higher rates of subclinical affective symptoms and minor psychopathology in comparison with healthy low-risk individuals (with

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http://dx.doi.org/10.1016/j.jpsychires.2013.01.013

no co-twin-history of psychiatric disorder) (Christensen et al., 2007). There was also a positive association between neuroticism and the number of LEs one year before baseline in the high risk group (Vinberg et al., 2007). However, it is not possible from the previous cross-sectional studies to determine whether subclinical psychopathology predict development of affective disorder on the syndrome level.

The aim of the present study was to investigate whether onset of affective disorder is predicted by family disposition for affective disorder, subclinical psychopathology, neuroticism, LEs, gender and age.

## 2. Materials and methods

### 2.1. Design

The present study sample is part of an on-going high-risk study elucidating risk factors of affective disorder. Healthy monozygotic (MZ) and dizygotic (DZ) twins with and without at co-twin history of affective disorder were identified through nationwide registers. Two risk groups were identified: the high-risk group: twins at risk of development of affective disorder (DZ or MZ twin, index co-twin affected), the low-risk group (control group): twins at low risk for development of affective disorder (DZ or MZ twin, index co-twin not affected). If the low-risk twins, at assessment baseline, at the end of the interview answered that a first degree relative had a history of severe psychiatric disorder they were reclassified to a group of twins with another family history and followed as high-risk twins (Christensen et al., 2007).

### 2.2. The registers

The Danish Civil Registration System assigns a unique personal identification number to all Danish residents. 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 since 1995 outpatient hospital contacts in Denmark for the country's 5.3 million inhabitants (Munk-Jorgensen and Mortensen, 1997; Mors et al., 2011). From April 1969 to December 1993, diseases were classified according to the International Classification of Diseases,"8th" revision (ICD-8) (WHO, 1974) and from January 1994 according to the International Classification of Diseases, "10th" revision (ICD-10) (WHO, 1993). The Danish Twin Registry was initiated in 1953 and contains information on 75,000 twin pairs born from 1870 to 2003 (Harvald et al., 2004).

### 2.3. The linkage

Through record linkage between the Danish Twin Register, the Danish Psychiatric 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 index twin) and the co twin had not been treated for affective disorder (the healthy high-risk co-twin). Probands/index 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, ICD-10-codes: F32–33.9) or a first diagnosis of manic or mixed episode or bipolar affective disorder (ICD-8-codes: 296.19, 296.39; ICD-10-codes: F30–31.6, F38.00). Further, the reclassified group of twins with another family history of severe psyhiatric disorder was followed as high-risk twins ($n = 18$). The control-twins (low-risk) were identified as one twin from a twin pair where the co-twin had no known personal history (the index control twin) of hospital contact due to affective/psychiatric disorder, and matched on age, sex and zygosity for each high-risk twin.

### 2.4. Ethics

The Danish Ministry of Health, the Danish Scientific Ethic Committee ((KF)-12-122/99 and (KF)-01-001/02) and the Data Inspection Agency approved the study. The study was conducted in accordance with the latest version of the Declaration of Helsinki. All procedures were carried out with the adequate understanding and written informed consent of the participants.

### 2.5. Sample at baseline

In total, 204 high-risk and 204 low-risk twins were invited to participate in the study. A total of 271 twins agreed to participate and subsequently, 37 twins 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. Participants and non-participants at base-line are described in detail elsewhere (Christensen et al., 2007). These 234 participants have been followed every 6-month since baseline.

### 2.6. Assessment baseline

Participants were rated in a face-to-face interview using semi-structured interviews: diagnoses were obtained using Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1 (WHO, 1999). 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. At the end of the interview, participants were interviewed about lifetime family psychiatric history of first-degree relatives (their biological parents, co-twin, siblings and offspring) based on the Brief Screening for Family Psychiatric History questionnaire described by Weissman et al. (2000). Low-risk twins, who had another first generation family history of affective disorder or schizophrenia, were followed as high-risk participants. Further self-rating of psychopathology was assessed using the 21-item Beck Depression Inventory, BDI 21, using the recommended cut off score 11 (Beck et al., 1961).

### 2.7. Personality measure

Personality dimensions were assessed using the Eysenck Personality Questionnaire (EPQ), Danish version. The EPQ comprises 101 items intended to measure a broad dimension of neuroticism, extroversion and psychotism (Eysenck, 1975). The Danish version of the EPQ has shown coefficient alpha values of 0.87 for neuroticism (Mortensen et al., 1996).

### 2.8. Life events

Participants were asked about: 1) At baseline severe LEs in their lifetime before (prior LEs) using a Danish version (translated to Danish after permission from the author) of the questionnaires developed by Kendler et al. (1993). The participant fulfilled ten questions concerning severe LEs lifetime before. These ten items included severe previous LEs (sexual assault or rape, other physical assault, life-threatening accident. life-threatening illness, unexpected death of loved one, abortion, broken engagement/marital separation, miscarriage or stillbirth, prolonged life-threaten illness of loved one, major property loss). 2) During follow-up all participants were asked, once a year, to full fill Kendlers life event