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Research report

Environmental and familial risk factors for psychotic and non-psychotic severe depression

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ABSTRACT

Background: Severe unipolar depression can be classified as either psychotic depression (PD) or non-psychotic depression (non-PD). A number of biological and clinical differences have been detected between PD and non-PD, but it remains unknown whether risk factors for the two subtypes also differ. The aim of the present study was therefore to investigate whether a number of potential risk factors influenced the risk of developing PD and non-PD to different extents.

Methods: This is a register-based historical prospective cohort study following all 2.4 million individuals born in Denmark between 1955 and 1990. During follow-up 2183 and 9101 individuals were registered in the Danish Psychiatric Central Research Register with PD and non-PD respectively. The association between risk factors and the development of PD and non-PD was estimated by survival analysis (Poisson regression) and expressed as incidence rate ratios (IRR).

Results: The most consistent finding of the study was that of a general overlap in familial and environmental risk factors for PD and non-PD. However, a parental history of bipolar disorder was a risk factor for PD (mother, IRR=1.66, $p=0.003$. Father, IRR=1.56, $p=0.040$) and not for non-PD (mother, IRR=0.92, $p=0.430$. Father, IRR=1.08, $p=0.552$). Conversely, a positive family history of schizophrenia was associated with neither PD nor non-PD

Limitations: Diagnoses were assigned as part of routine clinical practice.

Conclusion: Our findings justify the distinction between PD and non-PD in the current diagnostic manuals. Furthermore, the fact that parental bipolar disorder and not schizophrenia was a risk factor for PD supports the Kraepelinian dichotomy.

1. Introduction

Severe unipolar depression is subdivided into psychotic severe depression (PD) and non-psychotic severe depression (non-PD) in both the Diagnostic and Statistical Manual of mental disorders, 4th revision (DSM-IV) (American Psychiatric Association, 2000) and the International Classification of Disease, 10th edition (ICD-10) (World Health Organization, 1993). There have been reported a number of significant differences between the two subtypes (Ostergaard et al., 2012b, 2013). First and foremost, patients with non-PD and PD display different symptom profiles beyond merely psychotic features (Maj et al., 2007; Ostergaard et al., 2012a). Furthermore, in comparison with non-PD, PD is associated with more pronounced hypothalamo–pituitary–adrenal axis dysregulation (Nelson and Davis, 1997; Posener et al., 2000), decreased activity of dopamine beta-hydroxylase (Meltzer et al., 1976; Meyers et al., 1999), increased relapse rate (Johnson et al., 1991), higher risk of conversion to bipolar disorder (Akiskal et al., 1983; Strober and Carlson, 1982), more severe psychosocial impairment (Coryell et al., 1996; Rothschild et al., 1993b), and increased mortality (Vythilingam et al., 2003). Regarding treatment, PD responds poorly to treatment with placebo (Spiker and Kupfer, 1988) and tricyclic antidepressants (Chan et al., 1987; Glassman and Roose, 1981), but favorably to electroconvulsive therapy (ECT) (Loo et al., 2010; Petrides et al., 2001) when compared to non-PD (Leadholm et al., 2012; Schatzberg and Rothschild, 1992).

In a number of epidemiological studies our group has investigated risk factors for mental disorders based on linkage between the Danish national registers. Among the most well established risk factors are: family history of mental disorder, birth weight/gestational age, place of birth, maternal/paternal age at birth and loss of a family member (Gottesman et al., 2010; Laursen et al., 2005; Laursen et al., 2007; Mortensen et al., 1999, 2010; Pedersen

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and Mortensen, 2001a; Tsuchiya et al., 2005). A *history of mental disorders among mother/father/siblings* is associated with increased risk of a wide range of mental disorders not confined to the particular disorder of the relative (Gottesman et al., 2010; Mortensen et al., 2010; Pedersen and Mortensen, 2001a), e.g. having a parent/sibling with schizophrenia or bipolar disorder also increases the risk for schizoaffective disorder in the offspring (Laursen et al., 2005). The *place of birth* is a proxy for the level of urbanicity during upbringing and has been shown to be a strong "dose–response" risk factor for schizophrenia with progressively higher levels of urbanicity leading to progressively higher likelihood of developing this disorder (Pedersen and Mortensen, 2001b). However, place of birth is only a modest/weak risk factor for bipolar disorder and unipolar depression, without the dose–response relationship operating in relation to schizophrenia (Laursen et al., 2007; Marcelis et al., 1998; Mortensen et al., 1999). *Birth weight/gestational age* also affects the risk of mental disorders. Being born small for gestational age conveys a considerable risk for bipolar/schizoaffective disorder, but appears to affect the risk of unipolar depression and schizophrenia to a much lesser extent (Cannon et al., 2002; Laursen et al., 2007). The *maternal/paternal age at birth* has opposite effects on the risk of mental disorders. While high paternal age at birth has been associated with a significantly increased risk of bipolar/schizoaffective disorder and schizophrenia in the offspring (Byrne et al., 2003; El-Saadi et al., 2004; Laursen et al., 2007), younger maternal age at the time of birth appears to increase the risk of psychotic disorders (El-Saadi et al., 2004). Finally, *loss of a relative* increases the risk for the entire spectrum of mental disorders from depression to schizophrenia, particularly if the cause of death is "unnatural" (suicide, homicide or accident) (Agid et al., 1999; Laursen et al., 2007; Tsuchiya et al., 2005).

Given the many distinctions between PD and non-PD it seems intuitive that the risk factors for developing the two subtypes would also differ significantly. However, no population-based studies have investigated how known risk factors for affective and psychotic disorders contribute to the development of PD and non-PD respectively. Therefore, the present study aimed to establish the extent to which a number of familial and early environmental risk factors influence the risk of developing PD and non-PD.

2. Methods

2.1. Design

This is a population-based historical prospective cohort study in the country of Denmark. Data was obtained by register linkage via the unique personal registration numbers, which are assigned to all Danes at the time of birth (Pedersen, 2011). A cohort consisting of all individuals born in Denmark between January 1st 1955 and December 31st 1990 who were alive at 20 years of age, was established through the Danish Civil Registration System (Pedersen, 2011). Mothers, fathers and siblings to all subjects in the cohort were identified through the same register. Data regarding mental disorders among subjects and their relatives was extracted from the Danish Psychiatric Central Research Register (DCPRR), which contains electronic data on all psychiatric diagnoses assigned in relation to admissions to psychiatric hospitals in Denmark since 1969 (Mors et al., 2011). Diagnoses were registered according to the 8th International Classification of Diseases (ICD-8) (Danish National Board of Health, 1971) until January 1st 1994, when the ICD-8 was replaced by the ICD-10. The diagnoses are assigned at discharge by the treating psychiatrist as part of routine clinical practice. Data from outpatients and contacts with psychiatric emergency rooms were included in the DPCRR from January 1st 1995. Treatment in Danish hospitals is financed through taxes and is free of charge for all residents. There are no private psychiatric in-patient facilities in Denmark ensuring that all psychiatric admissions are represented in the DPCRR. The use of the Danish national registers for linkage studies in psychiatric research is well established (Munk-Jorgensen and Ostergaard, 2011).

2.2. Follow-up

For each subject follow-up began on their 20th birthday or on January 1st 1995 (whichever came last) and ended at the occurrence of the first of the following events: a diagnosis of PD or non-PD, emigration, death or December 31st 2010 (whichever came first). Cases of PD and non-PD were defined as subjects assigned with an ICD-10 diagnosis of PD (F32.3 and F33.3) or non-PD (F32.2 and F33.2) registered in the DCPRR between January 1st 1995 and December 31st 2010. Consequently, the age of the cohort members at the end of follow-up ranged from 20 to 56 years. In order to avoid bias due to the inclusion of subjects with schizophrenia, schizoaffective- or bipolar disorder, likely to be misdiagnosed as unipolar psychotic depression, all individuals registered with ICD-8/ ICD-10 diagnoses of these three disorders prior to the diagnosis of PD/non-PD were censored at the time of this registration.

2.3. Assessment of risk factors

History of mental disorders among mother/father/siblings: These variables were based on diagnoses registered in the DPCRR. The following eight categories were considered for the fathers, mothers and siblings (all siblings were pooled) of the cohort members (ICD-8/ ICD-10): schizophrenia (295 (excl. 295.7)/ F20), schizoaffective disorder (295.7, 296.8/ F25), bipolar disorder (296 (excl. 296.0, 296.2, 296.8), 298.1/ F30, and F31), other psychotic disorders (297, 298.2, 298.3, 298.8, 298.9, 301.83, 301.84/ F21, F22, F23, F24, F28, and F29), non-psychotic depression (296.0, 296.2, 298.0, 300.4/ F32, F33 (excl. F32.3, and F33.3)), psychotic depression (F32.3, F33.3), other mental disorders (any other diagnosis registered in the DPCRR) and any mental disorders (any diagnosis registered in the DPCRR). The categories are not mutually exclusive, i.e. family members can appear within more than one diagnostic group in the analysis. *Place of birth:* the place of birth was assessed through the Danish Civil Registration System (Pedersen, 2011) and classified into 5 categories according to the degree of urbanization: capital, suburb of the capital, provincial city with more than 100,000 inhabitants, provincial town with between 10,000 and 100,000 inhabitants, or rural area as described in detail elsewhere (Pedersen and Mortensen, 2001b). *Born in Aarhus:* Based on a previous study detecting an association between being born in the city of Aarhus, the second largest Danish city with a population of approximately 300.000, and later diagnoses of bipolar disorder (Pedersen and Mortensen, 2006c), we included a dichotomous variable defined by whether subjects were born in Aarhus or not. *Gestational age and birth weight*: information on gestational age and birth weight was extracted from the Danish Medical Birth Registry (Knudsen and Olsen, 1998). Since this registry only contains electronic data on births in Denmark from January 1st 1973 and onwards, the potential risk of developing PD and non-PD inferred by gestational age and birth weight was assessed based on a sub-cohort consisting of individuals born between January 1st 1973 and December 31st 1990 who were alive at 20 years of age. Gestational age was divided into the following strata: birth $\leq$ week 34, within week 35–36 and birth $\geq$ week 37. The birth weight was stratified as follows: $<$ 2700 g, 2700–2999, 3000–3299, 3300–3599, 3600–3999 and $\geq$ 4000 g. *Small for gestational age*: Being