Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Incidence of child and adolescent mental disorders in children aged 0-17 with familial high risk for severe mental illness - A Danish register study

Anne A.E. Thorup [a,d,f,*], Thomas Munk Laursen [b,d], Trine Munk-Olsen [b,d], Anne Ranning [c,d], Preben Bo Mortensen [b,e], Kerstin J. Plessen [a,d,f], Merete Nordentoft [c,d,f]

[a] Child and Adolescent Mental Health Center, Capital Region of Denmark, Denmark
[b] National Center for Register-Based Research, Aarhus University, Denmark
[c] Reseach Unit at Mental Health Center Copenhagen, Capital Region of Denmark, Denmark
[d] iPsych - The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Denmark
[e] Cirrau - Centre for Integrated Register-based Research at Aarhus University, Denmark
[f] University of Copenhagen, Faculty of Health and Medical Sciences, Denmark

ARTICLE INFO

Article history:
Received 16 March 2017
Received in revised form 2 November 2017
Accepted 5 November 2017
Available online xxxx

Keywords:
Familial high risk
Child and adolescent psychiatry
Schizophrenia
Bipolar disorder
Depression
Register study

ABSTRACT

Background: Offspring of parents with severe mental illness (SMI: schizophrenia, bipolar disorder or major depressive disorder) have an increased risk of developing mental disorder themselves. In childhood they may have neurodevelopmental delays, cognitive deficits and social adversities. We aimed to investigate if these individuals are more at risk of being diagnosed with a mental disorder during childhood/adolescence in a national sample.

Methods: By linking Danish registers we established a cohort consisting of all persons born to parents with SMI with those born to parents without SMI serving as a reference group. Incidence rate ratios (IRRs) for offspring diagnosed with a mental disorder by parental mental disorder were calculated.

Results: Offspring of parents with SMI showed increased IRR for all diagnoses of child and adolescent mental disorders compared to the reference group. Offspring of mothers with schizophrenia had IRR of 2.60 (CI: 2.50–2.70, N = 2550) of having any diagnoses, for children of fathers with schizophrenia IRR was 2.06 (CI: 1.97–2.16, N = 1901) and for offspring of two parents with schizophrenia IRR was 4.57 (CI: 3.94–5.31, N = 175). For individuals with a mother with bipolar disorder the IRR was 2.29 (CI: 2.09–2.50, N = 502), with a father 1.77 (CI: 1.74–1.87, N = 320), whereas the IRR was 2.96 (CI: 2.63–3.34, N = 264) if both parents had unipolar depression.

Discussion: Offspring of parents with a SMI have a higher risk of being diagnosed with any child and adolescent mental disorder. The IRRs for all diagnoses during childhood were increased by a factor 2–4. Having two ill parents increased the IRR.

1. Introduction

Individuals born to parents with a severe mental illness (SMI) like schizophrenia, bipolar disorder or major depression have an increased risk of developing a mental illness in adulthood. According to a meta-analysis 55% of all individuals with familial high risk for SMI develop some kind of mental illness across the life-span, and familial high risk for SMI increased the risk of developing a SMI by approx. 30%, which was more than twice the risk of the controls (RR 2.52) (Rasic et al., 2013). Results from Danish register studies suggest that offspring born to parents with affective or non-affective psychosis are at an increased risk during adolescence and adulthood (i.e. from age 14 and up to 28) of a range of mental disorders, particularly if both parents were affected (Dean et al., 2010; Gottesman et al., 2010). This vulnerability for mental illness may originate in both genetic and environmental factors (Uher, 2014).

Schizophrenia, bipolar disorder and major depression are among the most disabling mental illnesses, and especially individuals with schizophrenia and bipolar disorder have considerable overlapping genetic and environmental risk factors (Rasic et al., 2013; Uher, 2014). Schizophrenia and bipolar disorder are considered neurodevelopmental disorders that display signs of vulnerability already during childhood and long before their possible onset. A Danish population-based register study showed that individuals with a mental illness before age 18 had an increased risk of later schizophrenia (Maibing et al., 2015). Findings

* Corresponding author at: Research Unit at Child and Adolescent Mental Health Center, Capital Region of Denmark, Kildegårdsvej 28, opg. 15, 4. Sal, DK 2900 Hellerup, Denmark.
E-mail addresses: Anne.Amalie.Elgaard.Thorup@regionh.dk (A.A.E. Thorup), tml@econ.au.dk (T.M. Laursen), tmo@econ.au.dk (T. Munk-Olsen), Anne.Ranning@regionh.dk (A. Ranning), pbm@econ.au.dk (P.B. Mortensen), Kerstin.Jessica.Plessen@regionh.dk (K.J. Plessen), Merete.Nordentoft@dadlnet.dk (M. Nordentoft).

https://doi.org/10.1016/j.schres.2017.11.009
0920-9964/

from clinical familial high-risk studies have emphasized these children's increased vulnerability in many ways (Niemi et al., 2003). Cognitive deficits and delays in e.g. motor and language development in individuals at familial high risk for schizophrenia have been identified as an indicator of increased vulnerability (Niemi et al., 2003). For offspring of parents with bipolar disorder, neurocognitive deficits have also been reported (Balanza-Martinez et al., 2008) as well as mood and behavioral disorders (Chang et al., 2003) and childhood anxiety has been proposed as a precursor of later illness (Duffy et al., 2013). Several studies report higher frequencies of depression and anxiety among offspring of parents with depression (Olfson et al., 2003; Mattejat and Remschmidt, 2008).

From a neurodevelopmental perspective an increased risk of child or adolescent mental illness could be understood as an early manifestation of vulnerability (Howes and Murray, 2014) for SMI. However, to our knowledge, no study has investigated how familial high risk for SMI affects the children's risk of being diagnosed with a child and adolescent mental illness, i.e. a diagnosis before age 18, in a nationwide sample.

2. Aims and hypotheses

The aim of the study was to investigate if familial high risk for schizophrenia spectrum disorders, bipolar disorder or major depressive disorder increases the risk of any child or adolescent mental illness (age 0–17) compared to a reference group and further to investigate the risk of specific disorders among individuals at familial high risk for SMI.

2.1. Hypotheses

We expected individuals with familial high risk for SMI to show higher rates of any child or adolescent mental illness compared to the reference group across all three groups. Further, we expected that anxiety, mood disorders and substance abuse would show higher incidences among those predisposed to bipolar disorder and major depressive disorder (Duffy et al., 2013, 2010), whereas individuals at familial high risk for schizophrenia would display higher frequencies of attention deficits, autism, and behavioral problems (Niemi et al., 2005).

3. Method

3.1. Study population

We used data from the Danish Civil Registration System (Pedersen et al., 2006) to obtain a population based, representative cohort. This system provides data for each individual on name, sex, date of birth, address, identification of parents, and spouses among many other variables. We linked nationwide Danish registers which provide data on all residents in Denmark from 1969 with a unique identification number allowing accurate linkage of individuals across registers.

We defined three study populations based on data from The Danish Psychiatric Central Research Register (Mors et al., 2011): individuals born to one or two parents diagnosed with schizophrenia spectrum disorders (abbreviated sz in tables and figures), individuals born to one or two parents diagnosed with bipolar disorder or major depression (abbreviated mdd/bip in tables and figures) or individuals born to parents who had never been diagnosed with any of the above mentioned diseases. From 1969 to 1993 the diagnostic system used was the Danish modification of International Classification of Diseases, 8th revision (ICD-8 (World Health Organisation, 1971), and from 1994 it was the International Classification of Diseases, 10th revision, Diagnostic Criteria for Research (ICD-10-DCR (World Health Organisation, 1992)). The study population consists of all individuals in Denmark born to parents registered in the register with a diagnosis of either schizophrenia spectrum disorder (ICD-10: F 20–29, ICD 8: 295.x9, 296.89, 297.x9, 298.29–298.99, 299.04, 299.05, 299.09, 301.83), bipolar affective disorder (ICD-10: F 30–31, ICD-8: 296.19, 296.39, 298.19) or major depressive disorder and other mood disorders (ICD10: F 32–33, ICD8: 296.09, 296.29, 298.09, 300.49) and all children born to parents without any of these disorders (Table 1). Parents were classified with a mental disorder if they had been admitted to a psychiatric hospital or had received outpatient care with one of the mentioned diagnoses. Parents in the population had to be born in 1955 or later to ensure information from the registers, which started in 1969. From 1995 outpatient contacts were included in the registers, too.

3.2. Outcomes

Outcome measures were all diagnoses of child and adolescent mental disorders from age 0–17 in the cohort (Table 1). Cohort members were classified with a mental disorder if they had been admitted to an in- or outpatient treatment at a psychiatric or somatic hospital and had been given one of the outcome diagnoses. For each illness, date of onset was defined as the date of the first contact (in- or outpatient) with the diagnosis of interest. This implies that an individual can have more than one 'contact' if the individual has more than one diagnosis, but here we only look at incident diagnoses. Because a minority was treated in somatic departments, we included cases from the National Patient Register. We also included F20–29 (schizophrenia spectrum and schizoaffective disorders), and abuse F10–19 (mental and behavioral disorders due to psychoactive substance use) in the outcome measure 'any childhood psychiatric disorder' and F10 and F12 (alcohol and cannabinoids) as separate outcomes. We conducted all diagnosis-specific analyses by collapsing data from individuals with familial high risk for bipolar disorder with data from individuals with familial high risk for major depression in order to create sufficiently large categories and ensure power and called this category major depressive disorder/bipolar disorder (mdd/bip). This seems reasonable considering that both are in the F3-spectrum in ICD-10. Further, individuals with schizophrenia

Table 1
Included from ICD-10 diagnoses of child and adolescent mental disorders and corresponding ICD 8 diagnoses.

Child and adolescent mental disorders	ICD-10	ICD-8
Any child or adolescent mental disorder	F00–99	290–315
Affective	F30–39, F92.0,	296.x9 (excl. 296.89), 298.09, 298.19, 300.49, 301.19
Anxiety and OCD	F 40–48, F 93, F94	300.x9 (excl. 300.49), 305.x9, 305.68, 307.99
Eating disorders	F50	305.60, 306.50, 306.58, 306.59
Developmental disorders	F80–83	306.10-19
Autism spectrum	F84 (excl. F84.2–84.4)	299.00, 299.01, 299.02, 299.03
Attention-deficit/hyperactivity-disorder	F90 + 98.8	308.01, 308.03
Oppositional defiant disorder and conduct disorder	F91	308 (excl. 308.01 and 308.03)
Attachment disorders	F94 (excl. F94.0, ex 94.8, ex 94.9)	
Tic and Tourette's disorder	F95	306.29, 306.39
Other developmental incl. enuresis, encopresis	F 98 (excl. F98.8)	306.69–306.79, 306.09
Mental retardation	F70–79 (excl. F74, ex F78)	310–315
Psychosis	F 20–29	295.x9, 296.89,297.x9, 298.29–298.99,299.04, 299.05,299.09,301.83
Personality disorders	F 60–62	301.x9 (not 301.19), 301.80, 301.81, 301.82, 301.84
Mental and behavioral disorders due to alcohol use	F 10	291.x9, 303.x9, 303.20, 303.28, 303.90
Mental and behavioral disorders due to cannabis use	F 12	304.59

Please cite this article as: Thorup, A.A.E., et al., Incidence of child and adolescent mental disorders in children aged 0-17 with familial high risk for severe mental illness - A..., Schizophr. Res. (2017), https://doi.org/10.1016/j.schres.2017.11.009