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Research paper

The predictive value of childhood subthreshold manic symptoms for adolescent and adult psychiatric outcomes

Efstathios Papachristou[a], Albertine J. Oldehinkel[b], Johan Ormel[b], Dennis Raven[b], Catharina A. Hartman[b], Sophia Frangou[c,*,1], Abraham Reichenberg[c,d,1]

[a] Department of Primary Care and Population Health, University College London, London, UK
[b] Interdisciplinary Center Psychopathology and Emotion Regulation, University Medical Center Groningen, University of Groningen, The Netherlands
[c] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA
[d] Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, USA

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ABSTRACT

Background: Childhood subthreshold manic symptoms may represent a state of developmental vulnerability to Bipolar Disorder (BD) and may also be associated with other adverse psychiatric outcomes. To test this hypothesis we examined the structure and predictive value of childhood subthreshold manic symptoms for common psychiatric disorders presenting by early adulthood.

Methods: Subthreshold manic symptoms at age 11 years and lifetime clinical outcomes by age 19 years were ascertained in the TRacking Adolescents' Individual Lives Survey (TRAILS), a prospective Dutch community cohort. We used latent class analysis to identify subthreshold manic symptom profiles at baseline. The association between class membership and subsequent clinical diagnoses of BD (comprising BD-I, BD-II, mania and hypomania), depressive, anxiety and substance abuse disorders was determined using Cox proportional-hazard ratio (HR) models.

Results: At age 11 years, we identified a normative (n=916; 47%), a mildly symptomatic (n=843; 43%) and a highly symptomatic class (n=198; 10%). Referenced to the normative class, the sex- and age-adjusted risk of new-onset BD by the age of 19 years was significantly increased in the mildly (HR=2.01, 95%CI 1.13–3.59) and highly symptomatic classes (HR=5.02, 95%CI 2.48–10.16). These estimates remained significant after further adjustments for cognitive and family function, parental socioeconomic status, parental psychiatric morbidity, and comorbid disorders at baseline (p-value for linear trend across classes < 0.01). Class membership did not show significant associations with incident depressive, anxiety and substance abuse disorders in the fully adjusted regression models.

Limitations: The period of risk for adult-onset BD extends beyond the observational period of the study.

Conclusions: Elevated childhood subthreshold manic symptoms are associated with increased risk of BD by early adulthood and are therefore a potentially useful phenotype for the early identification of at-risk individuals.

1. Introduction

Emphasis on early intervention has shifted attention to defining the evolution of childhood psychiatric symptoms and ascertaining their relationship to adult diagnoses (Insel, 2007). The current study focuses on bipolar disorder (BD), which remains relatively understudied despite ranking amongst the leading causes of disability-adjusted life years in adolescents and young adults (Murray and Lopez, 1996).

Evidence from prospective evaluations of offspring of at least one BD parent suggests that attenuated manic symptoms frequently predate syndromal onset (Axelson et al., 2015; Hafeman et al., 2016; Malhi et al., 2014). However, in general population cohorts, the relationship between subthreshold symptoms and clinical outcomes has modest contemporaneous specificity and predictive value. This is because childhood subthreshold manic symptoms in the general population are common (5–25%) (Shankman et al., 2009; Tijssen et al., 2010a), they are present in children with a variety of disruptive disorders, and are associated with multiple adult diagnoses, most

* Corresponding author.
E-mail address: sophia.frangou@mssm.edu (S. Frangou).
[1] Joint senior authors.

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commonly BD, anxiety, depression and substance abuse disorders (Brietzke et al., 2012; Duffy, 2012; Faedda et al., 2015; Tijssen et al., 2010b; 2010c).

An alternative perspective is to focus on stratifying individuals into homogeneous classes based on their subthreshold manic symptom profiles. Using this approach, two independent general population studies of British (5–16 years) and Brazilian (6–12 years) children have reported the presence of subgroups with minimal, moderate and high levels of subthreshold manic symptoms (Pan et al., 2014; Stringaris et al., 2011). However, the predictive value of such stratification has yet to be tested. To address this critical knowledge gap, we examined data from the TRacking Adolescents' Individual Lives Survey (TRAILS), a large representative cohort of Dutch children that were prospectively assessed at age 11, 13, 16 and 19 years. Data from TRAILS participants at age 11 years were used to classify the sample based on patterns of co-occurring subthreshold manic symptoms. This classification was then tested with respect to its predictive value for BD and other psychiatric conditions associated with affective morbidity, namely depressive, anxiety and substance abuse disorders, with onset between ages 12–19 years.

To determine the independent predictive value of this risk stratification, we adjusted for key risk factors associated with psychopathology; these included general cognitive ability (Brietzke et al., 2012), family functioning (Sullivan and Miklowitz, 2010), socioeconomic status (Smith et al., 2013), parental psychiatric morbidity (Brietzke et al., 2012; Rasic et al., 2014), and childhood disruptive behavior disorders including ADHD (Chen et al., 2015).

2. Methods

2.1. TRAILS cohort

The study sample was drawn from the TRAILS (www.trails.nl) general population cohort of individuals born in the northern Netherlands between 1 October 1989 and 30 September 1991. Cohort members were assessed at baseline when aged 11 years (n=2230) and then at ages 13 (n=2149), 16 (n=1816) and 19 years (n=1881). The retention rate over the 8-year follow-up period was 84. 3% which is high for longitudinal studies examining psychiatric outcomes (Nederhof et al., 2012). The flow chart of this study is illustrated in Fig. 1. TRAILS members lost to attrition by age 19 years were predominantly male from a lower socioeconomic background and with worse cognitive function ($p < 0.001$), but did not differ in terms of family functioning (p=0.15) or parental psychiatric morbidity (p=0.18) from the rest of the cohort. Behavioral assessments were undertaken at age 11, 13 and 16 years and formal lifetime psychiatric diagnoses were ascertained at age 19 years according to the TRAILS data collection protocol. Details of the TRAILS design, sampling and weighted prevalence rates of psychiatric disorders have already been published (Nederhof et al., 2012; Oldehinkel et al., 2015; Ormel et al., 2012, 2015) and are summarised in the Supplementary material.

In this study, to derive classes based on subthreshold manic symptoms, we used baseline data from 1957 TRAILS participants (mean age=11.10 age, SD=0.55) for whom all relevant information was complete. To estimate the predictive value of class membership we used data from 1429 TRAILS participants (mean age=19.08 years, SD=0.60) for whom there was complete information available both at baseline and at follow-up. The mean interval period between assessments was 8.43 years (SD=0.55).

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The experimental protocol was approved by the Dutch Central Committee on Research Involving Human subjects (CCMO). Permission to use anonymized data from the TRAILS was granted by the study management committee.

2.2. Baseline assessments of TRAILS participants at age 11 years

Subthreshold manic symptoms at age 11 years were measured using the Child Behavior Checklist-Mania Scale (CBCL-MS) (Table S2). The CBCL-MS comprises 19 items from the CBCL (Achenbach, 1991) that were selected to map onto the core and extended symptom domains for mania (detailed in Supplementary material). The CBCL-MS shows temporal stability (Papachristou et al., 2013) and construct validity in community (Papachristou et al., 2013; Zappitelli et al., 2015) and clinical samples (Papachristou et al., 2016). Two other CBCL-derived instruments have been used to capture subthreshold manic symptoms, namely the CBCL-Dysregulation Profile (CBCL-DP) (Biederman et al., 2009, 2013; Faraone et al., 2005; Meyer et al.,

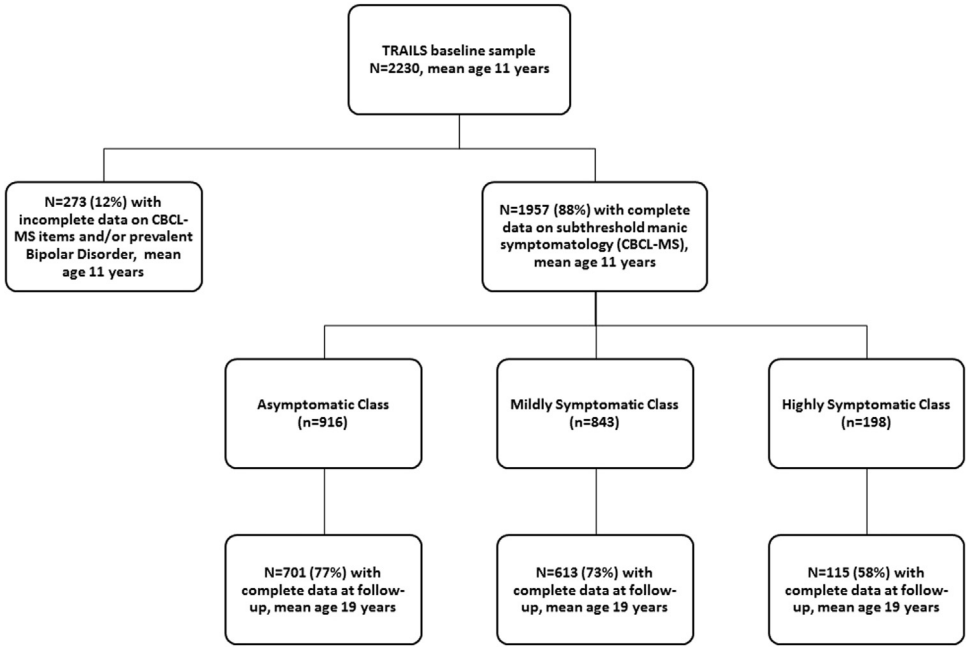

Fig. 1. Flow chart of the study.