

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

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Abstract

Background: Childhood subthreshold manic symptoms may represent a state of developmental vulnerability to Bipolar Disorder (BD) but 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 observation 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.

Keywords: Childhood, Subthreshold Manic Symptoms, CBCL-MS

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

Methods

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 of psychiatric outcomes (Nederhof et al., 2012). The flow chart of this study is illustrated in Figure 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; Ormel et al., 2015) and are summarised in the supplemental 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.

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 supplemental 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 in 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; Biederman et al., 2013; Faraone et al., 2005; Meyer et al., 2009; Uchida et al., 2014) and the CBCL-Externalizing Scale (Youngstrom et al., 2006). The CBCL-MS performs similarly to these CBCL-derived instruments (Ratheesh et al., 2015) and may have a slight advantage in identifying children with mood disorders from those with disruptive behaviors (Papachristou et al., 2016).

The general intellectual ability (IQ) of participants at age 11 years was estimated using a composite measure derived from age-standardized scores of the Vocabulary and the Block Design subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974).

Family function was assessed using the 12-item General Functioning Subscale of the McMaster Family Assessment Device (FAD-GFS) (Epstein et al., 1983). The FAD-GFS evaluates communication, problem solving, affective responsiveness, affective involvement, roles and behavior control within families; higher scores indicate greater family dysfunction.

Parental psychopathology was evaluated using the TRAILS Family History Interview (FHI) which screens for five domains of psychopathology, namely depression, anxiety, substance dependence, persistent antisocial behavior and psychosis. Those with positive TRAILS FHI screens were assessed further using detailed clinical interviews (Amone-P'Olak et al., 2011; Ormel et al., 2005). At baseline, 45.1% of the TRAILS cohort had at least one parent considered positive for psychiatric morbidity (details in the supplemental material). Although parental BD is a robust indicator of concordant offspring disorder (Duffy et al., 2010; Gottesman et al., 2010), we did not focus on individual parental diagnoses as risk elevation is not confined to concordant disorders (Dean et al., 2010). Therefore in subsequent analyses parental psychopathology was collapsed into a single variable and was considered absent or present regardless of the individual parental diagnoses. However, a supplemental sensitivity analysis was conducted to examine the effect of the different parental diagnoses (supplemental material).

Parental Socioeconomic Status (SES) at baseline was classified as low, moderate or high based on a composite index constructed by averaging, upon standardization, five indicators from the International Standard Classification of Occupation: maternal and paternal education, maternal and paternal occupation and family income (Ganzeboom and Treiman, 1996).

Diagnostic assessment of TRAILS participants at age 19 years

TRAILS participants at age 19 years were interviewed by trained lay interviewers using the World Mental Health Composite International Diagnostic Interview (CIDI) (www.hcp.med.harvard.edu/wmhcid). Diagnostic assessments were conducted blind to CBCL scores collected at baseline. The CIDI has an established role in population-based studies of affective morbidity in youth (e.g., National Comorbidity Survey Adolescent

Supplement) (Kessler et al., 2009; Merikangas et al., 2007; 2010) and yields reliable age of onset estimates (Kessler et al. 2005). In this study, we use the term Bipolar Disorder (BD) to refer collectively to BD-I, BD-II, mania and hypomania (Merikangas et al., 2007; Merikangas et al., 2010). Other disorders considered were major depressive disorder [MDD], generalized anxiety disorder [GAD], disruptive behavior disorders (oppositional defiant disorder [ODD] and conduct disorder [CD]), attention-deficit/hyperactivity disorder [ADHD], and substance use disorders [SA] (alcohol and drug abuse/dependence).

For the predictive analyses, we considered incident disorders in 1429 TRAILS participants with complete baseline and follow-up data. We included only those cases where onset occurred after participants' 12th birthday based on the TRAILS participant interview covering at age 19 years with retrospectively covered the interval period between the assessment waves. Based on this, by age 19 years there were 66 (4.6%) cases of incident BD (1.5% BD-I; 35% BD-II; 38% hypomania only; and 25.5% mania/hypomania), 46 of incident GAD (3.2%), 188 of incident MDD (13.5%) and 424 of incident SA (29.7%). The rates of SA reported here are in line with reports from other Dutch cohorts (de Graaf et al., 2012) and reflect the higher rates of substance use in the Netherlands compared to North American countries (Simons-Morton et al., 2010).

Statistical analysis

Identification of subthreshold manic symptom classes: Latent Class Analysis (LCA) was used to determine the number of participants' distinct symptom profiles (i.e., classes) according to the CBCL-MS items at age 11 years. Models with increasing number of classes were examined using a maximum likelihood estimator (MLR) with robust standard errors. Model fit was determined by three goodness of fit indices (Jung and Wickrama, 2008): (a) the Bayesian Information Criterion (BIC); lower values indicate better fit to the data, (b) the Lo-Mendell-Rubin (LMR) likelihood ratio test, which compares a model with K classes to a model with (K-1) classes, and (c) the entropy of the model; this ranges from 0 to 1 with higher entropy indicating that the latent classes are clearly distinguishable; model scores

≥0.80 were considered adequate (Ramaswamy et al., 1993). To avoid model convergence to local maxima we increased the number of starts. Upon selection of the best-fitting solution, study participants were assigned to the class for which they had the highest posterior probability of belonging. Ambiguity in class assignment was assessed based on the entropy of the selected model and the classification probabilities for the most likely latent class membership. To account for the probabilistic nature of class assignment, subsequent regression models were weighted using the inverse of an individual's posterior class probability, thereby giving more weight to participants with higher certainty of class assignment. Similarly, when performing between class-comparisons for sex, IQ, history of childhood psychopathology, family function and parental psychopathology and socioeconomic status, the means and proportions of these variables across classes were inverse-probability weighted using Rao-Scott second-order corrections of χ^2 , yielding an F statistic with adjusted degrees of freedom.

Predictive value of Class Membership: Cox proportional hazard models were initially performed to compare age and sex-adjusted hazard ratios (HR) and 95% confidence intervals (CI) between classes for incident (i.e., new-onset) BD, GAD, MDD and SA over the 8-year follow-up period. Follow-up Cox proportional hazard models expanded the adjustments to include IQ, parental SES, parental psychiatric morbidity, family function and childhood diagnoses. In the main analysis, parental psychopathology was considered present or absent regardless of the specific parental diagnosis. We also performed a supplemental sensitivity analysis to test the effect of individual parental diagnoses on the diagnostic outcomes of the TRAILS participants (supplemental material). P-values for linear trend across classes were assessed by entering the variable representing class membership as a continuous variable in the model. The level of statistical significance was set at $p < 0.004$ following Bonferroni correction. All analyses were performed using MPlus statistical package 6.0 (Muthén & Muthén, 1998-2011) and Stata/SE 14 (StataCorp, College Station, TX).

Results

Identification of subthreshold manic symptom classes: LCA identified a 3-class solution as optimal compared to other solutions based on the BIC and LMR p-value (<0.0001) (Table 1). The 4-class solution had a lower BIC value, but also lower entropy and a non-significant LMR p-value ($p=0.06$) indicating worse fit. The entropy of the selected 3-class solution was higher than 0.80 (entropy=0.83) and the average latent class probabilities for most likely class membership ranged between 91% and 95%, indicating minimal ambiguity in class assignment.

We identified an asymptomatic (normative) class, a mildly symptomatic class and a highly symptomatic class (Figure 2). The normative class ($n=916$; 47% of the cohort) included children who had on average one manic symptom (mean=1.40, SD=1.16). The mildly symptomatic class ($n=843$; 43% of the cohort) included children whose parents endorsed on average six manic symptoms (mean=5.89, SD=1.87), most commonly hyperactivity, distractibility, disrupted sleep, and over-talkativeness. The highly symptomatic class ($n=198$; 10% of the sample) included children whose parents endorsed ten manic symptoms on average (mean=10.23, SD=2.07) that included hyperactivity, impulsivity, inattention, clowning, disrupted sleep, suspiciousness, mood lability and loud speech.

Table 2 summarizes the characteristics of the sample by class membership. Participants assigned to the highly symptomatic class were more likely to be male and were also characterized by lower IQ and SES, greater family dysfunction, higher rates of parental psychiatric morbidity, as well as higher rates of childhood diagnoses of ODD, CD and ADHD (all p -values <0.001). The highly symptomatic class gave rise to 13.0% ($n=15$) of the new-onset cases of BD, while the mildly symptomatic and the normative class gave rise to 5.2% ($n=32$) and 2.7% ($n=19$) of the cases, respectively. The mean interval between the baseline assessment and the onset of BD was longer than 4 years (mean=4.46, SD=2.26), and did not differ between classes ($p=0.72$), suggesting that the classes identified are unlikely to represent early phases of syndromal conversion.

Predictive value of Class Membership: Table 3 summarizes results of the Cox proportional-hazard models performed to assess the relationship between class membership and the risk of incident psychiatric outcomes over the follow-up period. Children assigned to the mildly (HR=2.01, 95% CI 1.13-3.59) and highly symptomatic (HR=5.02, 95%CI 2.48-10.16) classes had a significantly increased sex- and age adjusted risk of BD but not of MMD, GAD or SA (Table 3). Additional Cox proportional regression models showed that the results remained significant after further adjustments for IQ, family function, parental psychopathology and socioeconomic status, and history of childhood psychiatric disorders (Table 3). In the fully adjusted models, we identified a significant linear trend across classes for BD (HR=1.93, 95%CI 1.26-2.96, p-value for linear trend=0.003). After adjusting for the number of childhood disorders at baseline the estimates for the results remained almost identical (for the linear trend across ordered categories HR=2.01, 95%CI 1.31-3.06) and highly significant (p=0.001) (Table S3).

Relative to the asymptomatic class, the sensitivity and specificity rates for BD in the highly symptomatic class were respectively 13% and 97% and in the mildly symptomatic class they were 5% and 97%. Together, the mildly and highly symptomatic classes contributed 73% of all incident BD cases. We therefore calculated their joint sensitivity and specificity for incident BD which were 6.5% and 97.2% respectively. The joint positive predictive value (PPV) was 71.2% and the negative predictive value (NPV) was 50.0%.

Discussion

In this study we (a) confirmed the latent structure of childhood subthreshold manic symptoms in the general population; (b) determined that the risk of incident BD in early adult life increases proportionally to the burden of childhood subthreshold manic symptoms; (c) demonstrated that the association between childhood subthreshold manic symptoms and BD remained significant even after adjusting for IQ, childhood psychiatric diagnoses, family dysfunction, parental psychopathology and parental socioeconomic status.

The symptom profile of the highly symptomatic class was characterized by hyperactivity, impulsivity, inattention, mood lability, increased volume and amount of speech and reduced sleep. Our findings accord with previous studies that have identified this constellation of symptoms as a subthreshold bipolar phenotype in the general population (Pan et al., 2014; Stringaris et al., 2011). Moreover, our results are in line with findings of a recent study in offspring of BD parents which examined the predictive value of dimensional symptomatic measures for new-onset bipolar spectrum disorders (Hafeman et al., 2016). Although consistent elevations in affective lability, anxiety/depression and subthreshold manic symptoms predicted new-onset bipolar spectrum disorders, not all transitions were preceded by subclinical psychopathology (Hafeman et al., 2016). Our results extend these findings by indicating that elevated childhood subthreshold manic symptoms in community samples, even if assessed at a single time-point, can be used to identify individuals at high risk of BD. Elevated childhood subthreshold manic psychopathology in this sample had a PPV of 71.2% which means that about three quarters of children presenting with these symptoms are likely to develop BD later in life.

The constellation of subthreshold symptoms that define this high-risk phenotype for BD is thought to reflect reduced control over cognition, emotion and behavior (Pan et al., 2014; Stringaris et al., 2011). As disruptive behavior disorders and ADHD are also characterized by dyscontrol symptoms (Martel et al., 2013), it is not surprising that these disorders were common in children in the mildly and highly symptomatic classes (Table 2). For BD and ADHD in particular, there is evidence of potentially overlapping etiology and pathophysiology in light of the familial co-segregation of the two disorders (Inal-Eiroglu et al., 2008; Faraone et al., 1997) and their frequent comorbidity (Skirrow et al., 2012). It has been suggested that BD could be better differentiated from ADHD by focusing on the episodicity of core manic symptoms that include elevated mood, grandiosity, elevated self-esteem and reduced need for sleep (Leibenluft & Rich, 2008; Youngstrom et al., 2010). Nonetheless, our data suggest that the predictive value of the risk stratification for BD based on subthreshold manic symptoms is largely independent from the participants' history of ADHD.

Mildly and severely elevated levels of subthreshold manic symptoms showed a high degree of predictive specificity for BD. The relationship between subthreshold manic symptoms at age 11 years and incident BD by age 19 years was independent of individual IQ (Brietzke et al., 2012), family functioning (Sullivan and Miklowitz, 2010), socioeconomic status (Smith et al., 2013), and parental psychiatric morbidity (Brietzke et al., 2012; Rasic et al., 2014) which are key risk factors for BD. However, increased deviance in these risk factors segregated with higher levels of subthreshold manic symptoms. This reinforces evidence from other studies on children at high-risk for BD that noted that multiple risk factors are likely to have an interactive adverse effect on psychological development (Miklowitz, 2015).

There are several methodological considerations relevant to this study. A particular strength is the availability of data from a representative population sample of youth (supplemental Table S1) where subthreshold manic symptoms and key risk factors were captured contemporaneously and were therefore free from recall, attribution biases or help-seeking behavior. A further strength relates to the ascertainment of clinical diagnoses with an instrument validated in population-based studies in this age group (Merikangas et al., 2010). Clinical diagnoses at age 19 years were based on information provided by study participants while the CBCL-MS ratings at age 11 years were based on parental report. The prevalence of BD in this sample was consistent with that reported in other general population studies and supports the generalizability of our findings (Merikangas et al., 2010). The classes identified are unlikely to represent early phases of syndromal conversion given the long interval (> 4years) between the baseline assessment and subsequent illness onset. The TRAILS cohort was still going through the peak period of risk for BD when assessed at age 19 years and therefore further BD cases may arise as study participants go through adulthood. We may have missed incident cases of BD through attrition as this was higher for children in the highly symptomatic class who would be more likely to develop the disorder. Parental history of BD was not captured in TRAILS and therefore could not be adjusted for in our analyses. Nevertheless, our data suggest that the risk of conversion to BD is unlikely to

be confined to those with a family history of BD, since parental psychopathology in general was more prevalent in the highly symptomatic class. We considered many but not all theoretically possible psychiatric outcomes by age 19 years so we cannot comment on whether the classes identified would have predictive value for other disorders such as schizophrenia and schizophrenia spectrum disorders. We did not have the power to examine predictors separately for BD subtypes as the number of cases was insufficient. Finally, the CBCL items do not fully capture episodicity which is considered a salient predictor of conversion to BD particularly in young people (Leibenluft & Rich, 2008; Youngstrom et al., 2010). It is therefore possible that adding more refined information about episodicity may further enhance the predictive value of the risk stratification for BD.

Conclusions

Our results provide support for population stratification in terms of risk for BD based on subthreshold manic symptoms. From a public health perspective our findings have important implications as the CBCL-MS, a simple and brief parental-report scale, appears useful in identifying a class of children at a high risk of incident BD up-to 8 years after the initial assessment. The association between class membership and risk of subsequent BD remained significant after adjusting for other childhood comorbidities and for cognitive and familial risk factors. The extracted latent classification showed a high degree of predictive specificity as class membership was not significantly associated with incident anxiety, depressive or substance abuse disorders. Additional research using well-defined large populations, from different settings, should further determine the investigations and interventions to be pursued in children presenting with subthreshold manic features.

Acknowledgements

The present study is part of the TRacking Adolescents' Individual Lives Survey (TRAILS). Participating centres of TRAILS include various departments of the University Medical Center and University of Groningen, the Erasmus University Medical Center Rotterdam, the University of Utrecht, the Radboud Medical Center Nijmegen, and the Parnassia Bavo group, all in the Netherlands. We are grateful to all adolescents, their parents and teachers who participated in this research and to everyone who worked on this project and made it possible.

Financial support

TRAILS has been financially supported by various grants from the Netherlands Organization for Scientific Research (NWO) (Medical Research Council programme grant no. GB-MW 940-38-011; ZonMW Brainpower grant no. 100-001-004; ZonMw Risk Behavior and Dependence grant no. 60-60600-97-118; ZonMw Culture and Health grant no. 261-98-710; Social Sciences Council medium-sized investment grants no. GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project grants no. GB-MaGW 452-04-314 and GB-MaGW 452-06-004; NWO large-sized investment grant no. 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013), the Dutch Ministry of Justice (WODC), the European Science Foundation (EuroSTRESS project FP-006), Biobanking and Biomolecular Resources Research Infrastructure BBMRI-NL (CP 32) and the participating universities. The funding sources had no involvement in the collection, analysis and interpretation of data, the writing of the report or in the decision to submit the article for publication.

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Table 1. *Fit Indices of 1-5 Latent Class Solutions*

	BIC	AIC	SSA-BIC	Entropy	LMR p-value
1 Class	40541.712	40340.862	40427.339		
2 Classes	36784.694	36377.415	36552.771	0.835	0.0000
3 Classes	35997.421	35383.713	35647.948	0.830	0.0000
4 Classes	35971.484	35151.346	35504.460	0.817	0.0614
5 Classes	36060.543	35033.976	35475.969	0.777	0.0262

Shaded cells indicate selected model

BIC=Bayesian Information Criterion; AIC=Akaike Information Criterion; LMR=Lo-Mendell-Rubin; SSA-BIC=Sample Size adjusted BIC

Table 2. Sample characteristics at participants' age 11 years according to latent subthreshold manic symptom profile

	Asymptomatic class (n=701; 49%)	Mildly symptomatic class (n=613; 43%)	Highly symptomatic class (n=115; 8%)	p-value ^a
Sex, n(%) Male	265 (38%)	316 (52%)	73 (63%)	<0.001
Age (M±SD)	10.57 (0.64)	10.57 (0.64)	10.60 (0.65)	0.92
CBCL-MS T scores (M±SD)	42.14 (2.73)	53.25 (4.79)	71.09 (7.12)	<0.001
Number of subthreshold manic symptoms endorsed (M±SD)	1.40 (1.16)	5.89 (1.87)	10.23 (2.07)	<0.001
IQ (M±SD)	102.00 (14.03)	99.32 (14.03)	93.86 (15.28)	<0.001
Family function (M±SD)	1.69 (0.36)	1.80 (0.34)	1.95 (0.32)	<0.001
Low parental Socioeconomic status, n(%)	106 (15%)	125 (20%)	33 (29%)	<0.001
Parental psychiatric morbidity, n(%) positive	264 (39%)	280 (46%)	73 (65%)	<0.001
History of psychiatric diagnoses received prior to baseline assessment ^b, n(%) positive	41 (6%)	82 (13%)	34 (30%)	<0.001
Prevalent morbidity according to class membership, n(%)				
Major Depressive Episode	12 (2%)	14 (2%)	6 (5%)	0.06
Generalized Anxiety Disorder	2 (0.3%)	3 (0.5%)	4 (3%)	<0.001
Substance Abuse	0 (0%)	2 (0.3%)	1 (1%)	0.12
Conduct Disorder	11 (2%)	26 (4%)	8 (7%)	0.001
Oppositional Defiant Disorder	15 (2%)	29 (5%)	15 (13%)	<0.001
ADHD	8 (1%)	25 (4%)	16 (14%)	<0.001
^a P-value adjusted for probability weight of class allocation				
^b Includes prevalent diagnoses of behavior disorders, Depression, General Anxiety Disorder or Substance Abuse received prior to the baseline assessment				
Continuous variables are presented as means (standard deviation); CBCL-MS: Child Behavior Checklist Mania-Scale; ADHD=Attention Deficit Hyperactivity Disorder				

Table 3. Hazard ratios (95% Confidence Intervals) for the associations between class membership at age 11 years and incident psychopathology over an 8-year follow up period in a general population cohort

	Mildly Symptomatic Class (n=613; 43%)			Highly symptomatic Class (n=115; 8%)		
	HR (95% CI) ^a	HR (95% CI) ^b	HR (95% CI) ^c	HR (95% CI) ^a	HR (95% CI) ^b	HR (95% CI) ^c
Incident Bipolar Disorder (n=66; 5%)	2.01 (1.13-3.59)	2.27 (1.20-4.32)	2.07 (1.08-3.96)	5.02 (2.48-10.16)	4.86 (2.10-11.27)	3.71 (1.54-8.93)
Incident Generalized Anxiety Disorder (n=46; 3%)	1.58 (0.85-2.94)	1.46 (0.74-2.89)	1.30 (0.65-2.58)	2.17 (0.78-6.06)	1.63 (0.58-4.61)	1.20 (0.43-3.33)
Incident Major Depressive Episode (n=188; 13%)	1.42 (1.05-1.92)	1.30 (0.95-1.78)	1.23 (0.89-1.69)	1.46 (0.85-2.53)	1.19 (0.67-2.10)	1.00 (0.55-1.80)
Incident Substance Abuse Disorder (n=424; 30%)	1.21 (1.00-1.48)	1.20 (0.97-1.47)	1.12 (0.91-1.38)	1.05 (0.74-1.51)	1.04 (0.71-1.52)	0.82 (0.55-1.22)

Cox proportional Hazard Models weighted for the inverse of an individual's posterior class probability

Reference is the Asymptomatic Class (n=701; 49%)

Bold indicates significant linear trend across classes adjusted for multiple comparisons (p<0.004)

^a Adjusted for age and sex at baseline

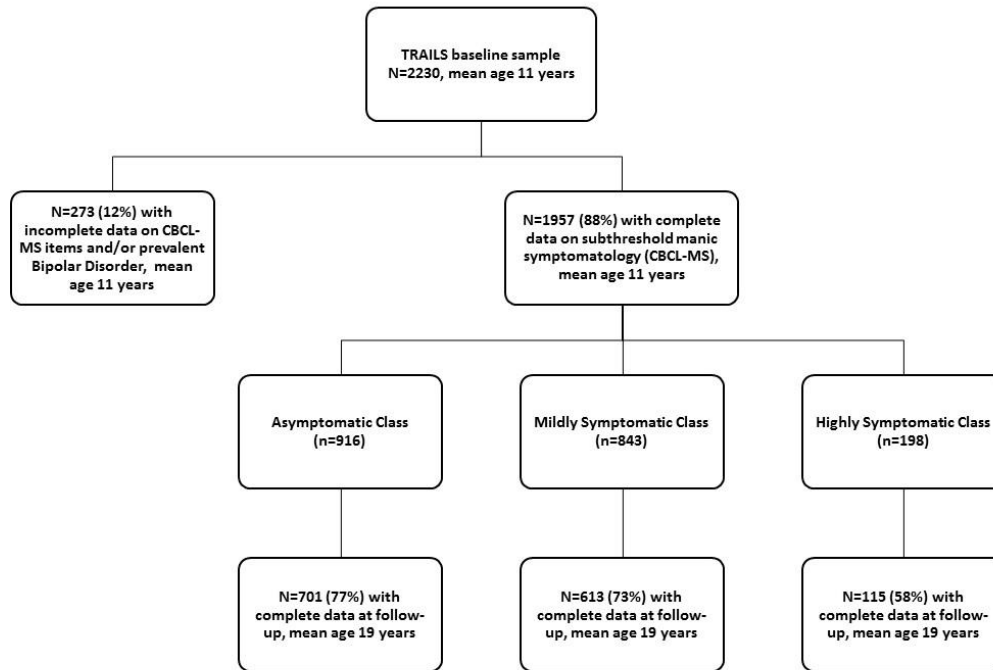
^b Further adjustments for cognitive function, family function, family history of psychopathology and socioeconomic status

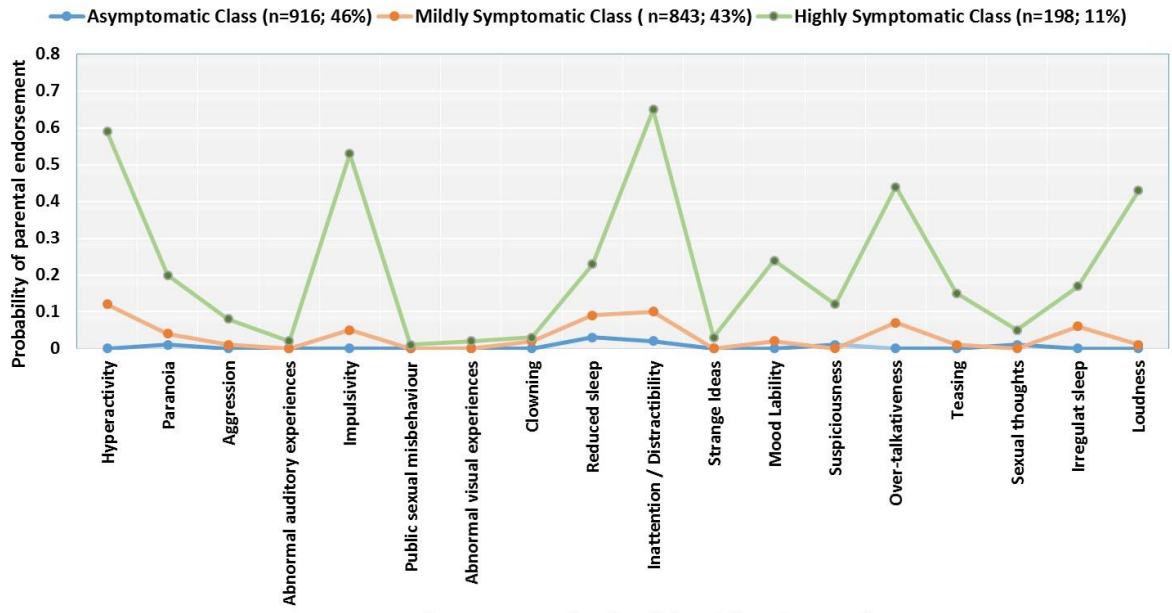
^c Further adjustments for history of conduct disorder, oppositional defiant disorder and ADHD

Figure Captions

Figure 1. Flow chart of the study

Figure 2. Subthreshold manic symptom latent profiles of 1957 TRAILS members aged 11 years





CBCL-MS items corresponding, from left to right, to item numbers 10, 34, 37, 40, 41, 59, 70, 74, 76, 78, 85, 87, 89, 93, 94, 96, 100, 104 in the CBCL 6-18