The association between self-reported and clinically determined hypomanic symptoms and the onset of major mood disorders

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Background
Hypomanic symptoms may be a useful predictor of mood disorder among young people at high risk for bipolar disorder.

Aims
To determine whether hypomanic symptoms differentiate offspring of parents with bipolar disorder (high risk) and offspring of well parents (control) and predict the development of mood episodes.

Method
High-risk and control offspring were prospectively assessed using semi-structured clinical interviews annually and completed the Hypomania Checklist-32 Revised (HCL-32). Clinically significant sub-threshold hypomanic symptoms (CSHS) were coded.

Results
HCL-32 total and active or elated scores were higher in control compared with high-risk offspring, whereas 14% of high-risk

and 0% of control offspring had CSHS. High-risk offspring with CSHS had a fivefold increased risk of developing recurrent major depression ($P=0.0002$). The median onset of CSHS in high-risk offspring was 16.4 (6–31) years and was before the onset of major mood episodes.

Conclusions
CSHS are precursors to major mood episodes in high-risk offspring and could identify individuals at ultra-high risk for developing bipolar disorder.

Declaration of interest
None.

Bipolar disorder is a severe psychiatric disorder with peak onset in late adolescence and early adulthood.[1] Bipolar disorder is ranked among the top 10 medical illnesses associated with the most disability worldwide.[2] Difficulty in accurate diagnosis early in the course of illness contributes to this substantial illness burden and, in turn, worsened prognosis because of delayed and potentially harmful treatment.[3] Given the high heritability, family history is the most robust risk factor for predicting bipolar disorder and identifies a high-risk population,[4] informative for development of clinical monitoring and early intervention strategies, and research into antecedent and prodromal features. Among individuals at confirmed genetic risk, bipolar disorder typically debuts as a depressive episode, preceding the first manic episode by an average of 4 years.[5,6] However, there is substantial variability in clinical course between individuals. International research efforts have focused on identifying antecedent clinical precursors to bipolar disorder to refine risk prediction, improve early detection and prevent progression of the impairing disease.[7] However, at present, it is challenging to predict among those at confirmed familial risk who will transition to full-blown bipolar disorder and related major mood disorders.[8]

Evidence from the Flourish Canadian high-risk offspring cohort study demonstrated that non-specific psychiatric disorders precede the onset of bipolar disorder in a substantial proportion of high-risk offspring, including sleep, anxiety and minor mood disorders.[6,9] Similar findings have been reported in other independent international high-risk cohort studies.[10–12] Antecedent symptom-level psychopathology may also be evident and informative in the prediction of bipolar disorder and related major mood disorder onset. Other high-risk and clinical studies have reported associations between sub-threshold hypomanic symptoms (not meeting full DSM-IV criteria) and subsequent diagnosable episodes of (hypo)mania in offspring of a parent with bipolar disorder.[13–17]

This finding requires replication based on prospective observations and further investigation. For example, it remains unclear if sub-threshold hypomanic symptoms are more common in offspring at confirmed familial risk compared with those not at familial risk and if they have the same clinical importance in these different populations. Although hypomanic symptoms are commonly reported in general and clinical populations, not all individuals reporting these symptoms develop bipolar disorder.[18–20] Some studies using clinical and community populations report that sub-threshold hypomanic symptoms are precursors to full onset bipolar disorder in adults and predict conversion from unipolar major depressive disorder (MDD) to bipolar disorder,[21,22] whereas other studies report no progression to bipolar disorder in children and adolescents,[20] or progression only when in conjunction with other clinical predictors,[22] or when particularly persistent over adolescence.[23]

Taken together, sub-threshold hypomanic symptoms measured by several informants or clinical assessment may be useful in the prediction of bipolar disorder onset or conversion to bipolar disorder among individuals with other risk factors such as a confirmed familial risk. This study sought to determine whether self-reported hypomanic symptoms measured by the Hypomania Checklist-32 Revised (HCL-32) or clinically significant sub-threshold hypomanic symptoms (CSHS) diagnosed by a clinician are associated with the onset of bipolar disorder. In particular, our study objectives were to determine (1) if HCL-32 scores (self-rated) are correlated with clinician determined CSHS; (2) if hypomanic symptoms (self-rated and clinician determined) differentiate high-risk offspring of parents with bipolar disorder (high risk) from offspring of well parents (controls) and within those at high risk, differentiate subgroups based on the lithium response of the parent; and (3) within high risk, determine the predictive utility and timing of sub-threshold hypomanic symptoms in the onset of major mood disorders.

Method

Recruitment

Participants were high-risk and control offspring enrolled in the Flourish Canadian high-risk offspring cohort study. Recruitment and procedures for this dynamic cohort study are described in detail elsewhere.[6,24] Briefly, high-risk offspring were recruited, starting in 1996, from large multi-generational families identified through an adult patient with confirmed bipolar disorder I.[25] Probands and affected first-degree relatives with bipolar disorder I, bipolar disorder II or in a subset recurrent MDD who had children were approached for recruitment into the high-risk study given the evidence that recurrent mood disorders in relatives of patients with bipolar disorder I reflects the bipolar disorder diathesis.[26] Lithium response of probands was determined based on a validated scale and previously described clinical criteria.[27] The other parent was confirmed to have no major DSM-IV psychiatric disorders at baseline to control for assortative mating. Control offspring were recruited from schools in Ottawa from parents confirmed to have no major DSM-IV psychiatric disorders at baseline. All diagnoses in both parents were confirmed by Schedule for Affective Disorders – Present and Lifetime Version (SADS-PL),[28] semi-structured interviews by psychiatrists specialising in mood disorders, and were verified by blind consensus review with at least two additional psychiatrists.

Procedure

Consenting high-risk and control offspring were clinically assessed annually by a child and adolescent psychiatrist specialising in mood disorders using the Kiddie-SADS-PL[29] semi-structured interview. As part of the semi-structured interview, sub-threshold hypomanic symptoms were systematically documented. The operationalised criteria to confirm CSHS included (1) participant endorsed a minimum of three DSM-IV hypomanic symptoms, but did not meet full DSM-IV criteria for hypomania or bipolar disorder not otherwise specified episode based on duration or severity; (2) symptoms represented a clear change from normal functioning, endorsed by self and others that knew the person well; and (3) no evidence of major impairment. All diagnoses (including CSHS) in high-risk and control offspring were confirmed by a blind consensus review with at least two additional psychiatrists. As part of the high-risk study, during each annual research assessment remitted or well offspring completed the HCL-32.[30] Parents completed the Hollingshead socio-economic status (SES) scale,[31] which is a validated measure of SES comprising a composite score of both working spouses highest achieved education and occupation. This research was approved by the local Independent Research Ethics Board in Ottawa, Ontario.

HCL-32 first revision

The HCL-32[30] is a 32-item self-report questionnaire originally designed to assess hypomanic symptoms among patients with MDD. A score of 14 or more is considered a clinically significant level of bipolar symptoms and cut-offs of >12 and >3 have been established for active or elated and irritable or risk-taking subscales, respectively.[30] The HCL-32 has been well validated in clinical populations,[30,32] with coefficients alpha ranging between 0.8 and 0.9.[32] For this analysis, owing to the age cut-off of the HCL-32, only high-risk and control offspring aged 15 years and over were included.

Data analysis

This study involved repeated measures within individuals and interdependency among individuals because of more than one sibling in a family. Linear mixed-effect models (LMEMs) and shared frailty models were used to account for these design aspects. In particular, analyses pertaining to repeated HCL-32 continuous scores involved LMEMs. All LMEMs were adjusted for baseline age, HCL-32 assessment time and gender. A normally distributed random intercept for each individual (or each family, if multiple observations per family) was added to each LMEM which takes into account the interdependence among observations. The random intercept and residuals of fit must follow an approximately normal distribution, or the validity of the results may be compromised. Generalised linear mixed models with the logit link function were used wherever fundamental model assumptions for LMEM were not satisfied and thus the outcome had to be dichotomised (i.e. when examining HCL-32 scores using established cut-offs).

Shared frailty models, adjusted for gender were used to determine the association between CSHS and time to MDD and bipolar disorder onset. All cases in which a major depressive episode or activated episode (hypomanic, manic or mixed) occurred before the onset of CSHS or HCL-32 completion date were omitted from the analysis to ensure temporality. For individuals without any major depressive or activated episode, the observation period was censored at their age at last assessment; also age from date of birth was used as the beginning of observation period as this study uses an open, dynamic design, where participants enter the study at different times and ages. Hazard ratios and their corresponding 95% confidence intervals (CI) are reported and reflect, for example, the increase in hazard of first-onset episode of major depression or activated episode given prior CSHS compared to the absence of these symptoms. Owing to the age cut-off (≥15 years) and our dynamic study design, participants completing the HCL-32 were a subset of the entire sample; therefore, all models pertaining to the HCL-32 are of a different and smaller sample size compared with models pertaining to CSHS.

Results

Descriptive characteristics

A total of 283 high-risk and 87 control offspring were prospectively assessed as part of the Canadian Flourish high-risk offspring cohort study, and of these, 156 high-risk and 45 control offspring completed the HCL-32 at least once. In the entire sample, the mean age at last interview was 23.3 years [standard deviation (s.d.)=8.3] in high-risk and 20.5 (s.d.=4.0) in control offspring. Approximately 60.0% of high-risk and control offspring were female, and control offspring had slightly higher proportions in upper class SES Hollingshead groups compared with high-risk offspring (Table 1). Mean follow-up time in years in high-risk offspring was 6.9 (s.d.=5.4, median 7.0, range 0.0–19.8) and in control offspring was 5.5 (s.d.=3.3, median 5.0, range 0.0–10.8). The pattern of differences in demographic variables remained similar among the subset of offspring completing the HCL-32 (156 high-risk and 45 control offspring) (data not shown). At the time of this analysis, high-risk and control offspring completed up to four repeated HCL-32 measures during annual clinical visits. The mean age in years when completing the baseline HCL-32 in high-risk offspring was 24.8 (s.d.=6.2) and in control offspring was 21.0 (s.d.=2.4).

At the time of the last observation for this analysis, 21.0% (*n*=60) of high-risk offspring had a hierarchical lifetime diagnosis of MDD, 8.5% (*n*=24) bipolar disorder II and 5.6% (*n*=16) bipolar disorder I. Twenty-one per cent (*n*=59) of the high-risk offspring had a lifetime history of substance use disorder (SUD), 29% (*n*=82) anxiety disorder and 19% (*n*=55) sleep disorder at last observation with 63, 57 and 47% of these cases being comorbid with a mood disorder lifetime diagnosis, respectively. At last observation, the

Table 1 Demographic and clinical characteristics of the sample

		High-risk offspring	Control offspring	P
N		283	87	
Age at last interview, mean (s.d.)		23.31 (8.31)	20.25 (4.02)	0.001[a]
Gender, n (%)	Female	169 (59.72)	51 (58.62)	0.8554[b]
	Male	114 (40.28)	36 (41.38)	
SES, n (%)	1	1 (0.36)	0 (0.00)	0.0346[c]
	2	7 (2.52)	3 (3.45)	
	3	30 (10.79)	2 (2.30)	
	4	101 (36.33)	27 (31.03)	
	5	139 (50.00)	55 (63.22)	
Lithium response, n (%)	Responder	118 (41.84)	–	–
	Non-responder	164 (58.16)	–	
Major depression, n (%)		60 (21.20)	2 (4.30)	<0.0001[c]
Mean age onset major depression (s.d.)		17.81 (4.64)	20.22 (4.23)	0.9125[a]
Bipolar disorder I n (%)		16 (5.65)	0 (0)	–
Mean age onset bipolar disorder I (s.d.)		19.93 (5.19)	–	–
Bipolar disorder II n (%)		24 (8.48)	0 (0)	–
Mean age onset bipolar disorder II (s.d.)		20.40 (5.32)	–	–
CSHS, n (%)		40 (14.13)	0 (0.00)	–
Mean age onset CSHS (s.d.)		17.89 (5.22)	–	–

CSHS, clinical significant sub-threshold hypomanic symptoms; s.d., standard deviation; SES, socio-economic status.
a. T-test.
b. Chi-square test.
c. Fisher's exact test.

control offspring had low rates of major mood disorders as described in detail elsewhere.[6] Only two control offspring had a diagnosis of MDD (4.3%), whereas the remainder of the control offspring were unaffected for any lifetime major mood disorder (Table 1). Clinically significant sub-threshold hypomanic symptoms (CSHS) were present in 14% (40) of high-risk offspring compared with 0% of control offspring, and most of these cases (n=32, 80%) were among high-risk offspring with a diagnosed major mood disorder by last observation. The median age at onset of CSHS in high-risk offspring was 16.4 years (range=6.0–30.7). Among those high-risk offspring with CSHS (n=40) and who developed a major mood disorder, the median ages at onset for these hierarchical lifetime diagnoses were 16.8 years for MDD, 18.4 years for bipolar disorder I and 21.0 years for bipolar disorder II (Fig. 1).

HCL-32 scores in high-risk and control offspring

Adjusted HCL-32 total scores were significantly higher in control compared with high-risk offspring (P=0.0165). Active or elated and irritable or risk-taking subscale scores were analysed using established cut points (>12 and >3) as the residuals were not normally distributed. Control offspring met criteria for active or elation significantly more than high-risk offspring (P=0.0176), whereas irritability or risk taking was not significantly different between the groups (P=0.9087) (Table 2). We included a variable indicating the presence of diagnosable (hypo)mania before completing the baseline HCL-32 measure in high-risk offspring into each model with HCL-32 total scores, active or elated and irritable or risk-taking subscale cut-offs as the outcome, and after the inclusion of this variable, the group differences in HCL-32 total scores and the active
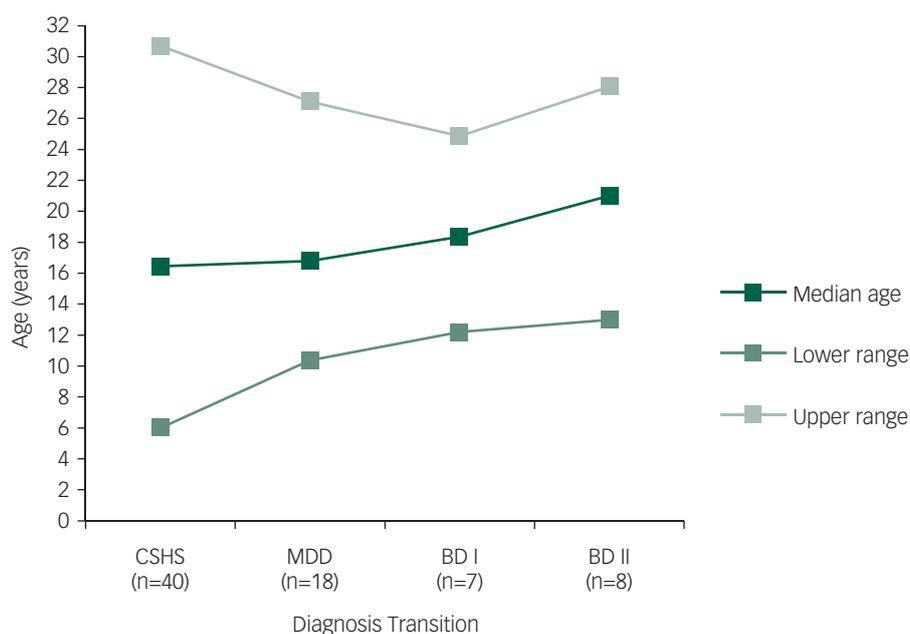

Fig. 1 Median ages of onset of clinically significant sub-threshold hypomanic symptoms (CSHS), major depressive disorder (MDD) and bipolar disorder I and II in the 40 high-risk offspring with CSHS and subsequent onset of MDD, bipolar disorder I or bipolar disorder II.

Table 2	Differences in HCL-32 scores over time between high-risk and control offspring adjusted for gender, time and baseline age				
	High-risk mean (s.d.)	Control mean (s.d.)	beta[a]	s.e.	P
HCL-total	15.65 (6.06)	17.52 (5.53)	2.342[b]	0.968	0.0165
HCL-active or elated	11.29 (3.58)	12.64 (3.35)	0.915[c]	0.379	0.0176
HCL-irritability or risk taking	1.83 (2.16)	1.94 (1.83)	0.053[c]	0.465	0.9087

HCL, Hypomania Checklist; s.d., standard deviation.
a. Each row reflects a separate adjusted model.
b. Linear mixed model.
c. Generalised linear mixed model.

or elated subscale became non-significant (beta (*b*)=1.5, standard error (s.e.)=1.3, *P*=0.2312) and (*b*=1.0, s.e.=0.8, *P*=0.2265), respectively. Irritability or risk taking remained similar between the groups after including prior diagnosable (hypo)mania to the mixed model (*b*=0.2, s.e.=0.4, *P*=0.6827).

There were significant differences in the contextual questions from the HCL-32. Namely, 100% of control offspring endorsed that they experienced a high (as defined by the items from the prior question in the measure) in the past 12 months compared with 77% of high-risk offspring (*P*=0.0021). Other's reactions and comments to the offspring self-reported highs were marginally different between high-risk and control offspring (*P*=0.0595), where a large proportion of control offspring endorsed positive reactions to their highs from other people (64% compared with 38% of high-risk offspring). No control offspring endorsed negative reactions compared with 4% of high-risk offspring (Table 3).

The presence of CSHS was positively and significantly associated with HCL-32 baseline scores (*b*=3.7, s.e.=0.8, *P*=0.0000). High-risk offspring with prior CSHS reported HCL-32 total scores that were 3.7 units higher than those without CSHS. In high-risk offspring, proband lithium response was not significantly associated with repeated HCL-32 total scores (*b*=0.5, s.e.=1.2, *P*=0.6907), active or elated (*b*=0.2, s.e.=0.40, *P*=0.5168) or irritable or risk-taking subscale scores (*b*=0.1, s.e.=0.4, *P*=0.6993) after adjusting for gender, time and baseline age. Proband lithium response was also not significantly associated with CSHS in high-risk offspring (*b*=−0.1, s.e.=0.5, *P*=0.8956).

Hypomanic symptoms and the onset of MDD, bipolar disorder II and bipolar disorder I

Given the design of this dynamic cohort study (recruiting offspring from ages 5 to 25 years as they became available), there were not enough cases of diagnosable major mood disorders that occurred after the completion of the HCL-32 measure; therefore, the numbers were too low to prospectively estimate the association between HCL-32 scores and subsequent onset of major mood disorder. Mean scores in remitted or well offspring, high-risk offspring with a lifetime diagnosis of mood disorder and control offspring are presented in Table 4.

Although CSHS were not significantly associated with the subsequent lifetime diagnosis of MDD (hazard ratio=1.1, *P*=0.8647, 95% CI=0.4, 2.6), when separating out lifetime recurrent MDD from lifetime single episode MDD, CSHS were significantly associated with the development of lifetime recurrent MDD (hazard ratio 5.1, *P*=0.0002, 95% CI=2.1, 12.4) (Fig. 2). Clinically significant hypomanic symptoms were indicative of risk of the subsequent development of bipolar disorder II, however, this was not statistically significant (hazard ratio 2.0, *P*=0.2146, 95% CI=0.7, 5.7).

Discussion

The main findings from this prospective cohort study of offspring of parents with bipolar disorder compared with offspring of well parents include (1) clinically determined but not self-reported hypomanic symptoms differentiated high-risk from control offspring; (2) within high-risk offspring, there is evidence of concordance of clinically determined and self-report measures of hypomanic symptoms; and (3) hypomanic symptoms that are assessed to be of clinical importance in young people at familial risk predict onset of recurrent MDD – often heralding the onset of bipolar disorder in this population.

Self-reported hypomanic symptoms in the control offspring appeared to have a different meaning than in the high-risk offspring. This was evidenced by the paradoxical finding of higher total and active or elated HCL-32 scores in control compared with high-risk offspring, with 100% of control offspring endorsing experiencing such highs, despite 0% of clinically determined cases of bipolar disorder or CSHS and a high proportion of control offspring endorsing positive responses by other towards their reported highs. Moreover, when accounting for a prior diagnosable hypo(manic) episode in high-risk offspring, HCL-32 scores were no longer different between high-risk and control offspring and were strongly associated with prior CSHS, suggesting that self-reported hypomanic symptoms may be more clinically meaningful in offspring at confirmed familial high risk. Other studies have reported similar, contradictory findings pertaining to the HCL-32 in general population and control samples, where scores are surprisingly high (meeting the established cut-offs for possible bipolarity)[33] and sometimes higher than clinical samples of patients with bipolar disorder I and bipolar disorder II.[34]

There are a few possible explanations for this finding. First, the high-risk offspring in this sample were in clinical remission when completing self-reported measures, and therefore, their responses may look similar to control offspring responses. Second, given that the majority of high-risk offspring were exposed to some form of their parents' mood disorder[35] and 18% experienced (hypo)mania themselves, the high-risk offspring may have a different perspective or point of comparison influencing their ranking of hypo(manic) symptoms compared with control offspring. That is, the two populations may be measuring different constructs (i.e. normal mood fluctuation *v.* psychopathology). General population and control samples may exhibit different baselines for 'highs' described in the HCL-32. Despite endorsing higher HCL-32 total and active or elated scores, only one control offspring reported that their highs were equal to or longer than 4 days and no control offspring endorsed negative reactions from other people to these highs, with most reactions reported as positive. Third, other unaccounted for variables may influence HCL-32 scores and reflect hypomanic-like symptoms (particularly related to the active or elated subscale). For example, one study[36] found that intense romantic love in adolescents was associated with higher HCL-32 scores compared with adolescents not endorsing this experience.

These possible explanations of the paradoxical finding of higher HCL-32 total and active or elated subscale scores in control offspring compared with high-risk offspring do not discredit the measure's utility in clinical or high-risk populations,

Table 3 HCL-32 contextual items in high-risk and control offspring

HCL-32 item		High-risk offspring	Control offspring	P
Baseline HCL-32 age in years, mean (s.d.)		24.77 (6.16)	21.03 (2.44)	<0.0001[a]
How are you feeling today compared with your usual state? n (%)				0.0571[b]
	Much worse than usual	1 (0.65)	0 (0)	
	Worse than usual	6 (3.87)	1 (2.22)	
	A little worse than usual	21 (13.55)	0 (0)	
	Neither better nor worse than usual	90 (58.06)	32 (71.11)	
	A little better than usual	25 (16.13)	9 (20)	
	Better than usual	11 (7.10)	2 (4.44)	
	Much better than usual	1 (0.65)	1 (2.22)	
Compared to other people my level of activity, energy and mood... n (%)				0.3329[b]
	Is always rather stable and even	71 (46.10)	15 (33.33)	
	Is generally higher	34 (22.08)	15 (33.33)	
	Is generally lower	20 (12.99)	5 (11.11)	
	Repeatedly shows periods of ups and downs	29 (18.83)	10 (22.22)	
Did the questions above, which characterise a 'high', describe how you are? n (%)				0.0898[b]
	Never	18 (11.84)	1 (2.33)	
	Sometimes	95 (62.50)	26 (60.47)	
	Most of the time	39 (25.66)	16 (37.21)	
Impact of your 'highs' on various aspects of your life n (%)				0.1504[b]
	Family No impact	29 (21.64)	4 (9.52)	
	Positive	6 (4.48)	0 (0.00)	
	Negative	67 (50.00)	27 (64.29)	
	Positive and negative	32 (23.88)	11 (26.19)	
	Social No impact	15 (11.19)	2 (4.76)	0.4978[b]
	Positive	2 (1.49)	0 (0.00)	
	Negative	99 (73.88)	36 (85.71)	
	Positive and negative	18 (13.43)	4 (9.52)	
	Work No impact	23 (17.16)	6 (14.29)	0.9463[b]
	Positive	4 (2.99)	1 (2.38)	
	Negative	85 (63.43)	27 (64.29)	
	Positive and negative	22 (16.42)	8 (19.05)	
	Leisure No impact	17 (12.78)	3 (7.14)	0.5862
	Positive	0 (0.00)	0 (0.00)	
	Negative	103 (77.44)	36 (85.71)	
	Positive and negative	13 (9.77)	3 (7.14)	
Other people's reactions and comments to your 'highs' n (%)				0.0595[b]
	No reaction	33 (24.81)	7 (16.67)	
	Positive and negative	21 (15.79)	5 (11.90)	
	Negative	5 (3.76)	0 (0.00)	
	Neutral	23 (17.29)	3 (7.14)	
	Positive	51 (38.35)	27 (64.29)	
Length of your 'highs' as a rule (on the average) n (%)				0.3329[b]
	I can't judge or don't know	30 (29.13)	9 (33.33)	
	Longer than 1 month	10 (9.71)	0 (0.00)	
	Longer than 1 week	5 (4.85)	0 (0.00)	
	4–7 days	9 (8.74)	1 (3.70)	
	2–3 days	18 (17.48)	8 (29.63)	
	1 day	31 (30.10)	9 (33.33)	
Have you experienced such 'highs' in the past 12 months? n (%)				0.0021[b]
	Yes	79 (76.70)	28 (100.00)	
	No	24 (23.30)	(0.00)	
	For how many days?	66.30 (88.05)	50.65 (79.15)	0.2571[c]

HCL-32, Hypomania Checklist-32; s.d., standard deviation.
a. Kruskal–Wallis test.
b. Fisher's exact test.
c. T-test.

Table 4 HCL-32 total and subscale scores in high-risk and control offspring

	Total mean (s.d.)	Active or elated mean (s.d.)	Irritable or risk taking mean (s.d.)
High-risk (*n*=156)	15.65 (6.06)	11.29 (3.58)	1.83 (2.16)
Control (*n*=45)	17.52 (5.53)	12.64 (3.35)	1.94 (1.83)
Within high-risk only			
Unaffected (*n*=129)	15.51 (5.65)	11.50 (3.70)	1.57 (1.67)
MDD (*n*=44)	15.87 (6.09)	11.55 (3.54)	1.72 (2.08)
Bipolar disorder II (*n*=16)	18.96 (7.10)	11.80 (3.00)	3.56 (3.05)
Bipolar disorder I (*n*=12)	18.88 (6.43)	12.46 (3.0)	3.11 (3.18)

MDD, lifetime hierarchical diagnosis of major depression; s.d., standard deviation.

but warrants discretion of its use in the general population of young people, where high scores may not necessarily indicate clinically significant hypomanic symptoms, but rather a different conceptualisation of the construct of 'high mood'. These findings are specific to the HCL-32 within this study cohort and cannot extend to other measures of hypomanic symptoms (e.g. Mood Disorders Questionnaire); however, replication of these findings using other commonly used measures in patient populations could be insightful into their utility in non-clinical populations.

Although the earliest DSM-IV diagnosable hypomanic episode in this cohort so far has been at age 12.5 years, this analysis showed that CSHS are evident in high-risk children as early as 6 years of age. There are no reported cases of CSHS in our control sample. In high-risk offspring, CSHS strongly increased the hazard of developing recurrent MDD and were indicative of risk for bipolar disorder II onset – but failed to reach significance in the latter case likely due to low power. Interestingly, prior CSHS were only significantly associated with recurrent MDD, but not when cases of MDD single episode were added to the group. Moreover, CSHS manifested before the development of major mood disorders in high-risk offspring, just before the median age at onset of MDD and approximately 2 and 4.5 years before the onset of meeting lifetime diagnostic criteria for bipolar disorder I and bipolar disorder II, respectively. Taken together, this finding lends supporting evidence that CSHS predict the development of bipolar disorder in high-risk

Fig. 2 The hazard of recurrent major depression in high-risk offspring with and without prior clinically significant sub-threshold hypomanic symptoms.

offspring, as MDD is often the index mood episode of bipolar disorder, and recurrence of mood episodes has been characterised as the hallmark of bipolar disorder.[37] These findings are in agreement with other high-risk studies[13,15] and underscore the potential clinical utility of using CSHS to help predict among individuals at genetic risk, who will transition to the early stages and full onset bipolar disorder.

The following study limitations should be considered when interpreting these findings. We did not have enough cases of major mood disorder occurring before completion of the baseline HCL-32 measure, therefore were unable to estimate the association between self-reported hypomanic symptoms and first onset MDD, bipolar disorder I or bipolar disorder II. Similarly, there were not enough cases of bipolar disorder I occurring before CSHS and the number of cases of bipolar disorder II and MDD were low, limiting statistical power. The models pertaining to HCL-32 scores were in a smaller subset of the entire cohort owing to the age cut-off from the measure (15+). These missing data were not due to refusal to complete the measure, or drop out, and the subset cohort was not significantly different on key characteristics reported in Table 1 compared with the entire cohort making the likelihood of a selection bias low. However, some of these models had low power, impacting the variance, potentially making estimates appear less significant. There may have been other potential confounders not accounted for, particularly in models pertaining to self-reported hypomanic symptoms, such as positive life experiences, which may have influenced the findings. In this high-risk cohort, and others, anxiety and sleep disorders tend to onset before mood disorder and may represent an early manifestation of the bipolar disorder illness,[6] however SUDs are likely an effect modifier, where, the association between CSHS and mood disorder may be magnified among those with SUD. Unfortunately, we did not have enough cases of mood disorder to test this. Future research should explore how psychiatric comorbidity influences these associations. Some risk of retrospective recall bias is inevitable in naturalistic cohort studies using an open, dynamic design, where in some cases the outcome occurred before baseline. However, in this analysis, any instance of the outcome occurring before the completion of the HCL-32 or before CSHS were omitted from the analysis to ensure temporality, therefore, using these baselines, all data used in this analysis were prospectively captured.

These results have implications for the potential clinical utility of identifying CSHS in high-risk offspring early in development to help identify an ultra-high-risk population suitable for close monitoring and early intervention. These findings also underscore the importance of using several criteria to inform a bipolar disorder diagnosis including a detailed family history and clinical assessment with reports from multiple informants and cautions against the use of reliance on self-reported symptom level data in isolation as a predictive tool.
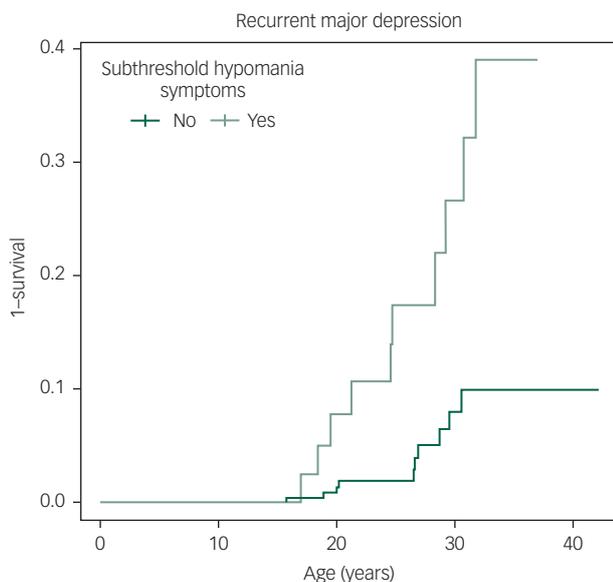
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References

1 Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 2011; **68**: 241–51.

2 Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**: 1747–57.

3 Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry* 2003; **64**: 161–74.

4 Goodwin F, Jamison R. *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression.* Oxford University Press, 2007.

5 Angst J, Gamma A. Diagnosis and course of affective psychoses: was Kraepelin right? *Eur Arch Psychiatry Clin Neurosci* 2008; **258** (suppl 2): 107–10.

6 Duffy A, Horrocks J, Doucette S, Keown-Stoneman C, McCloskey S, Grof P. The developmental trajectory of bipolar disorder. *Br J Psychiatry* 2014; **204**: 122–8.

7 Duffy A. Early identification of recurrent mood disorders in youth: the importance of a developmental approach. *Evid Based Ment Health* 2015; **18**: 7–9.

8 Duffy A. Toward a comprehensive clinical staging model for bipolar disorder: integrating the evidence. *Can J Psychiatry* 2014; **59**: 659–66.

9 Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disord* 2007; **9**: 828–38.

10 Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. *Am J Psychiatry* 2013; **170**: 542–9.

11 Shaw JA, Egeland JA, Endicott J, Allen CR, Hostetter AM. A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. *J Am Acad Child Adolesc Psychiatry* 2005; **44**: 1104–11.

12 Nurnberger JI, McInnis M, Reich W, Kastelic E, Wilcox HC, Glowinski A, et al. A high-risk study of bipolar disorder. Childhood clinical phenotypes as precursors of major mood disorders. *Arch Gen Psychiatry* 2011; **68**: 1012–20.

13 Axelson D, Goldstein B, Goldstein T, Monk K, Yu H, Hickey MB, et al. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. *Am J Psychiatry* 2015; **172**: 638–46.

14 Hafeman DM, Merranko J, Axelson D, Goldstein BI, Goldstein T, Monk K, et al. Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. *Am J Psychiatry* 2016; **173**: 695–704.

15 Egeland JA, Endicott J, Hostetter AM, Allen CR, Pauls DL, Shaw JA. A 16-year prospective study of prodromal features prior to BPI onset in well Amish children. *J Affect Disord* 2012; **142**: 186–92.

16 Correll CU, Hauser M, Penzner JB, Auther AM, Kafantaris V, Saito E, et al. Type and duration of subsyndromal symptoms in youth with bipolar I disorder prior to their first manic episode. *Bipolar Disord* 2014; **16**: 478–92.

17 Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Demeter CA, Bedoya D, et al. Early symptoms of mania and the role of parental risk. *Bipolar Disord* 2005; **7**: 623–34.

18 Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord* 2000; **2**: 281–93.

19 Carlson GA, Kelly KL. Manic symptoms in psychiatrically hospitalized children – what do they mean? *J Affect Disord* 1998; **51**: 123–35.

20 Hazell PL, Carr V, Lewin TJ, Sly K. Manic symptoms in young males with ADHD predict functioning but not diagnosis after 6 years. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 552–60.

21 Fiedorowicz JG, Endicott J, Leon AC, Solomon DA, Keller MB, Coryell WH. Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *Am J Psychiatry* 2011; **168**: 40–8.

22 Faedda GL, Marangoni C, Serra G, Salvatore P, Sani G, Vázquez GH, et al. Precursors of bipolar disorders: a systematic literature review of prospective studies. *J Clin Psychiatry* 2015; **76**: 614–24.

23 Tijssen MJA, van Os J, Wittchen H-U, Lieb R, Beesdo K, Mengelers R, et al. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. *Br J Psychiatry* 2010; **196**: 102–8.

24 Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. *J Affect Disord* 2010; **121**: 127–35.

25 Duffy A, Grof P, Grof E, Zvolsky P, Alda M. Evidence supporting the independent inheritance of primary affective disorders and primary alcoholism in the families of bipolar patients. *J Affect Disord* 1998; **50**: 91–6.

26 Blacker D, Lavori PW, Faraone SV, Tsuang MT. Unipolar relatives in bipolar pedigrees: a search for indicators of underlying bipolarity. *Am J Med Genet* 1993; **48**: 192–9.

27 Manchia M, Adli M, Akula N, Ardau R, Aubry JM, Backlund L, et al. Assessment of response to lithium maintenance treatment in bipolar disorder: a consortium on lithium genetics (ConLiGen) report. *PLoS One* 2013; **8**: e65636.

28 Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 1978; **35**: 837–44.

29 Axelson D, Birmaher BJ, Brent D, Wassick S, Hoover C, Bridge J, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. *J Child Adolesc Psychopharmacol* 2003; **13**: 463–70.

30 Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. *J Affect Disord* 2005; **88**: 217–33.

31 Hollingshead A. Commentary on the indiscriminate state of social class measurement. *Soc Forces* 1970; **49**: 563.

32 Meyer TD, Schrader J, Ridley M, Lex C. The Hypomania Checklist (HCL) – systematic review of its properties to screen for bipolar disorders. *Compr Psychiatry* 2014; **55**: 1310–21.

33 Richardson T, Garavan H. Hypomanic symptoms in female undergraduate students diagnosed with unipolar depression based on scores on the hypomania checklist. *Clin Pract Epidemiol Ment Health* 2009; **5**: 22–5.

34 Lee K, Oh H, Lee EH, Kim JH, Kim JH, Hong KS. Investigation of the clinical utility of the hypomania checklist 32 (HCL-32) for the screening of bipolar disorders in the non-clinical adult population. *BMC Psychiatry* 2016; **16**: 124.

35 Goodday S, Levy A, Flowerdew G, Horrocks J, Grof P, Ellenbogen M, et al. Early exposure to parental bipolar disorder: findings from a 16-year prospective cohort study. *Early Interv Psychiatry* 2016; **19**: pyv071.

36 Brand S, Luethi M, von Planta A, Hatzinger M, Holsboer-Trachsler E. Romantic love, hypomania, and sleep pattern in adolescents. *J Adolesc Health* 2007; **41**: 69–76.

37 Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. *Biol Psychiatry* 2000; **48**: 445–57.