

Definition of Subthreshold Clinically Significant Symptoms

Clinically significant subthreshold hypomanic symptoms: participant endorsed a minimum of three DSM-IV hypomanic symptoms but did not meet full criteria for a hypomanic or bipolar disorder not otherwise specified episode based on duration or severity; ii) symptoms represented a clear change from normal functioning, endorsed by self and others that knew the person well; and iii) no evidence of major impairment.

Clinically significant subthreshold depressive symptoms: participant endorsed a minimum of three DSM-IV depressive symptoms one of which included depressed mood but did not meet full criteria for a major depressive episode or depression not otherwise specified based on duration or severity; (ii) symptoms represented a clear change from normal functioning, endorsed by self and others that knew the person well; and (iii) no evidence of major impairment.

Clinically significant subthreshold anxiety symptoms: participant endorsed a minimum of three DSM-IV anxiety symptoms one of which was feeling anxious but did not meet full criteria for an anxiety disorder or anxiety not otherwise specified based on duration or severity; (ii) symptoms represented a clear change from normal functioning, endorsed by self and others that knew the person well; and (iii) no evidence of major impairment.

Clinically significant subthreshold sleep symptoms: participant endorsed a minimum of three DSM-IV sleep symptoms but did not meet full criteria for a sleep disorder diagnosis based on duration or severity; (ii) symptoms represented a clear change from normal functioning, endorsed by self and possibly by others that knew the person well; and (iii) no evidence of major impairment.

Clinically significant subthreshold substance use symptoms: participant endorsed a minimum of three DSM-IV substance abuse symptoms, but did not meet full criteria for a substance use disorder diagnosis; (ii) symptoms were a concern to self and/or others who knew the person well; (iii) no evidence of major impairment.

Psychotic sub-threshold symptoms: participant endorsed hallucinations or delusions on assessment, but did not meet criteria for a psychotic episode; and (ii) presence of psychotic symptoms confirmed on blind consensus review of all available clinical and research information.

SUPPLEMENTARY TABLES

TABLE S1. Descriptive characteristics of the affected parents

	Lithium Responders (n=45)	Lithium Non-Responders (n=71)	p
Age of affected parent at recruitment			
Mean Years (SD)	48.29 (6.62)	46.53 (7.12)	0.1884 ^a
Age of parent illness onset			
Mean Years (SD)	27.82 (9.29)	24.63 (10.16)	0.0930 ^a
Sex of affected parent			
Male n(%)	24 (53.3)	30 (42.3)	0.2437 ^b
Female n(%)	21 (46.7)	41 (57.8)	
Affected parent lifetime mood diagnosis n(%)			
BPI	20 (44.4)	28 (39.4)	0.1193 ^b
BPII	14 (31.1)	34 (47.9)	
Depressive Disorder ^c	11 (24.4)	9 (12.7)	
Affected parent comorbidity^d			
Yes n(%)	10 (25.0)	27 (45.8)	0.0361^b
No n(%)	30 (75.0)	32 (54.2)	
Substance use disorders			
Yes n(%)	5 (12.5)	19 (32.8)	0.0219^b
No n(%)	35 (87.5)	39 (67.2)	
Anxiety disorders			
Yes n(%)	5 (12.5)	16 (27.6)	0.0736 ^b
No n(%)	35 (87.5)	42 (72.4)	
Parent lifetime hospitalization			
Yes n(%)	24 (60.0)	32 (53.3)	0.5106 ^b
No n(%)	16 (40.0)	28 (46.7)	
Parent lifetime psychotic features in mood episodes			
Yes n(%)	11 (24.4)	33 (46.5)	0.0172^b
No n(%)	34 (75.6)	38 (53.5)	

Affected parent clinical course			
Episodic Fully remitting n(%)	33 (73.3)	11 (15.5)	<0.0001 ^{b*}
Episodic with residual symptom n(%)	10 (22.2)	44 (62.0)	
Chronic/chronic fluctuating n(%)	2 (4.4)	16 (22.5)	

^a t-test; ^b Chi-square test; ^c sibling of the bipolar proband; ^d any lifetime diagnosis

TABLE S2. Polarity of first five mood episodes in high-risk offspring with lifetime bipolar diagnosis comparing between Lithium responsive (LiR) vs Lithium non-responsive (LiNR) subgroups

	LiR offspring	LiNR offspring	p
Episode 1			1.000
Activated n (%)	2 (12.50)	3 (12.00)	
Depressive n(%)	14 (87.50)	22 (88.00)	
Episode 2			0.743
Activated n (%)	9 (56.25)	10 (45.45)	
Depressive n(%)	7 (43.75)	12 (54.55)	
Episode 3			0.234
Activated n (%)	2 (16.67)	7 (41.18)	
Depressive n(%)	10 (83.33)	10 (58.82)	
Episode 4			0.074
Activated n (%)	1 (11.11)	7 (53.85)	
Depressive n(%)	8 (88.89)	6 (46.15)	
Episode 5			0.559
Activated n (%)	1 (14.29)	3 (42.86)	
Depressive n(%)	6 (85.71)	4 (57.14)	

Activated: DSM-IV manic/hypomanic episodes; Depressive: DSM-IV major depression

TABLE S3. The influence of clinically significant subthreshold symptoms and sex on the transition through clinical stages of emergent bipolar disorder in high-risk offspring

	Well→Stage 1 Non-Mood Disorders		Stage 1→Stage 2 Minor Mood & Adjustment disorders		Stage 2→Stage 3 Depressive Disorders		Stage 3→Stage 4† Bipolar Disorders	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Sub-threshold Anxiety	1.016 (0.410, 2.514)	0.973	2.035 (0.844, 4.902)	0.113	0.747 (0.291, 1.917)	0.544	0.637 (0.196, 2.072)	0.453
Sub-threshold Sleep	2.606 (1.066, 6.372)	0.036*	0.756 (0.095, 6.022)	0.791	0.651 (0.224, 1.891)	0.430	1.505 (0.062, 36.604)	0.802
Sub-threshold Depression	1.373 (0.536, 3.519)	0.509	1.645 (0.557, 4.857)	0.368	1.078 (0.309, 3.761)	0.907	1.025 (0.333, 3.155)	0.965
Sub-threshold Activation	0.697 (0.145, 3.341)	0.652	0.604 (0.063, 5.749)	0.661	0.898 (0.257, 3.137)	0.866	1.260 (0.536, 2.964)	0.596
Sub-threshold Substance Abuse	0.897 (0.197, 4.071)	0.888	1.813 (0.340, 9.675)	0.486	1.371 (0.437, 4.307)	0.589	1.516 (0.492, 4.675)	0.469
Sex (female)	1.295 (0.914, 1.834)	0.146	0.416 (0.230, 0.750)	0.004*	0.333 (0.154, 0.720)	0.005*	0.718 (0.270, 1.910)	0.507
Psychotic symptoms	2.863 (0.919, 8.923)	0.070	--&	--	--&	--	3.364 (1.340, 8.444)	0.010*

†Due to low numbers of transitions into Stage 4, Firth's correction was used

&Non-estimable

SUPPLEMENTARY FIGURES

FIGURE S1A. Cumulative incidence of anxiety disorder in high-risk offspring compared to controls

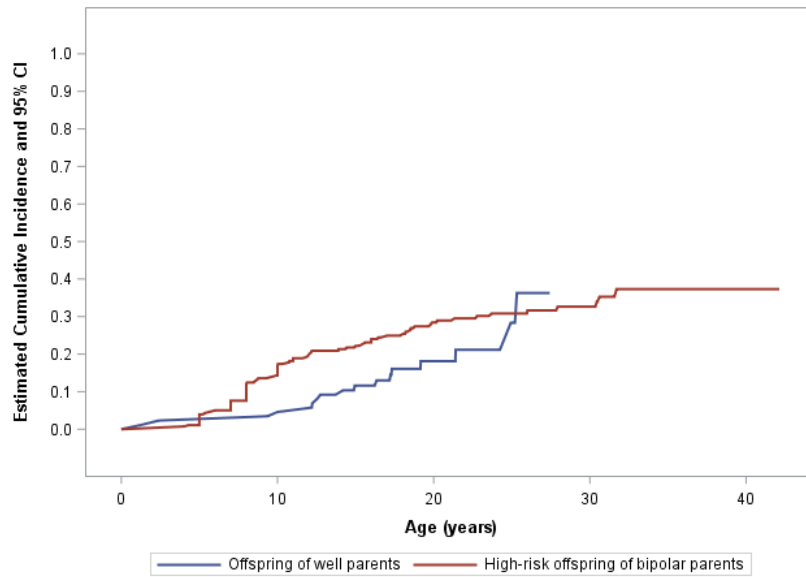


FIGURE S1B. Cumulative incidence of substance use disorder in high-risk offspring compared to controls

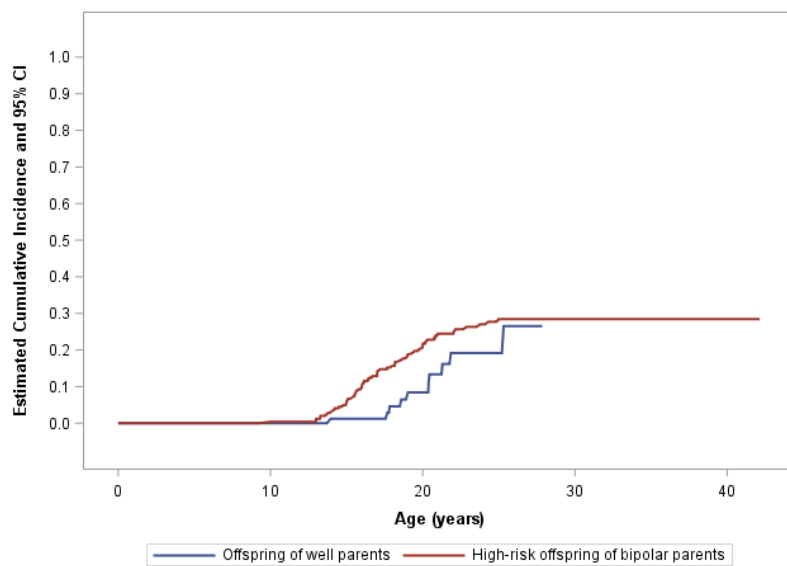
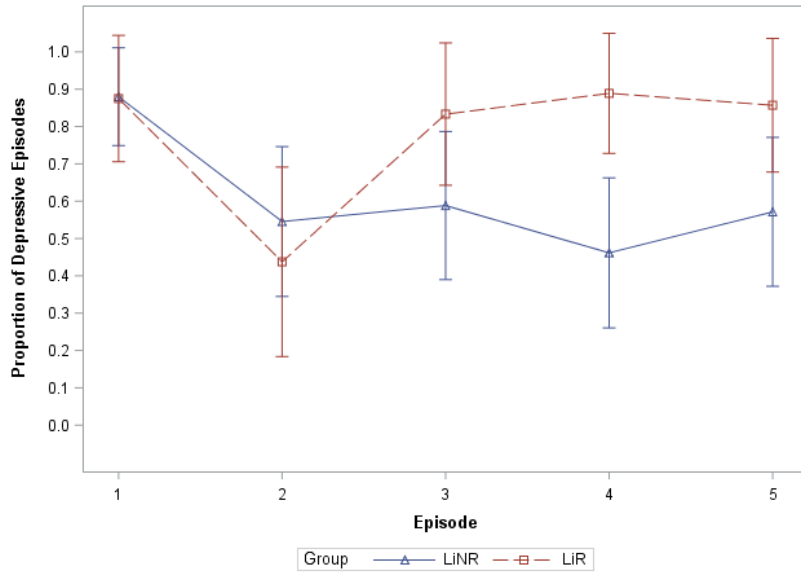
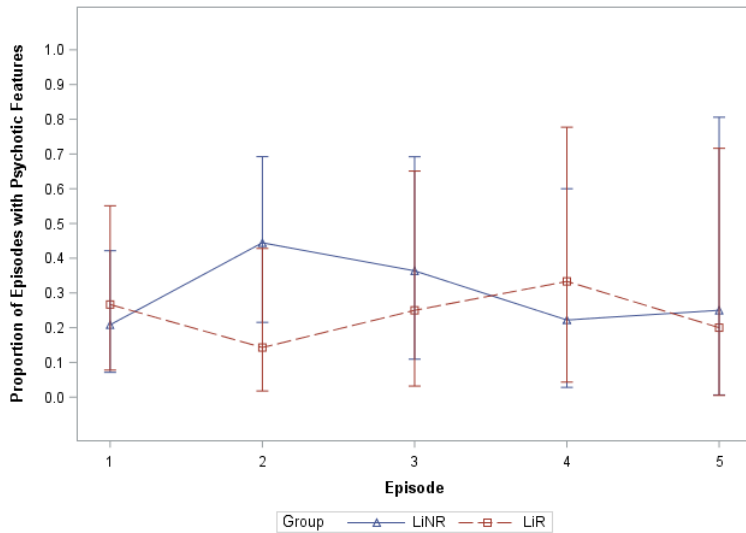


FIGURE S2A. Proportion of first mood episodes that were depressive in the early course of bipolar disorder in offspring of lithium responsive parents (LiR) and lithium non-responsive parents (LiNR)



*From a GLMM LiR group has increased odds of episodes being depressive compared to LiNR group

FIGURE S2B. Proportion of first mood episodes with psychotic features in the early course of BD in offspring of lithium responder (LiR) and lithium non-responder (LiNR) BD parents



From a GLMM there was marginal evidence of statistical significance for episode two ($p=0.053$)

FIGURE S3A. Age distribution of high-risk and control offspring at recruitment

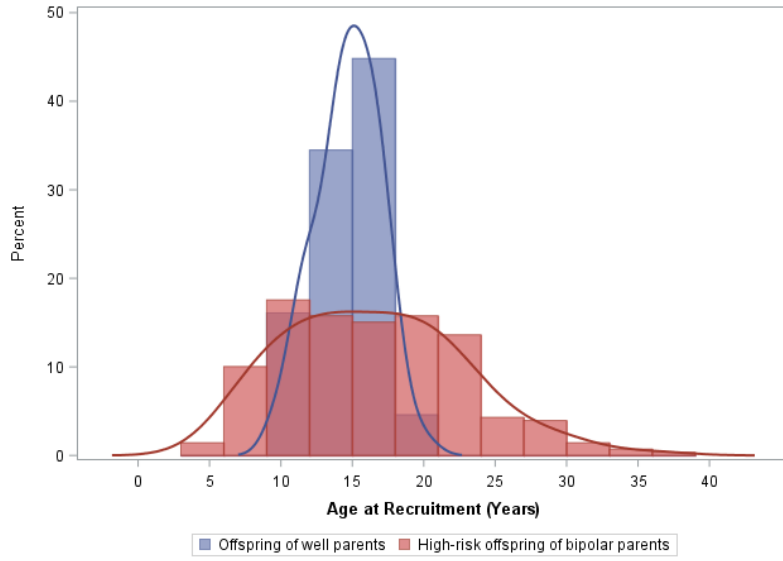


FIGURE S3B. Age distribution of high-risk and control offspring at last assessment

