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Prospective evaluation of at-risk criteria for bipolar disorder and its implications for clinical practice

Prof. Dr. Andreas Bechdolf

Department of Psychiatry, Psychotherapy and Psychosomatic Medicine,
Vivantes Klinikum am Urban and
Vivantes Klinikum im Friedrichshain Berlin
and
Department of Psychiatry and Psychotherapy,
Charité-Universitätsmedizin Berlin,
Germany

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Breaking Boundaries
15th International Conference on Early Intervention & Prevention in Mental Health

IEPA 15

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What did we do in Early Intervention in Psychosis?

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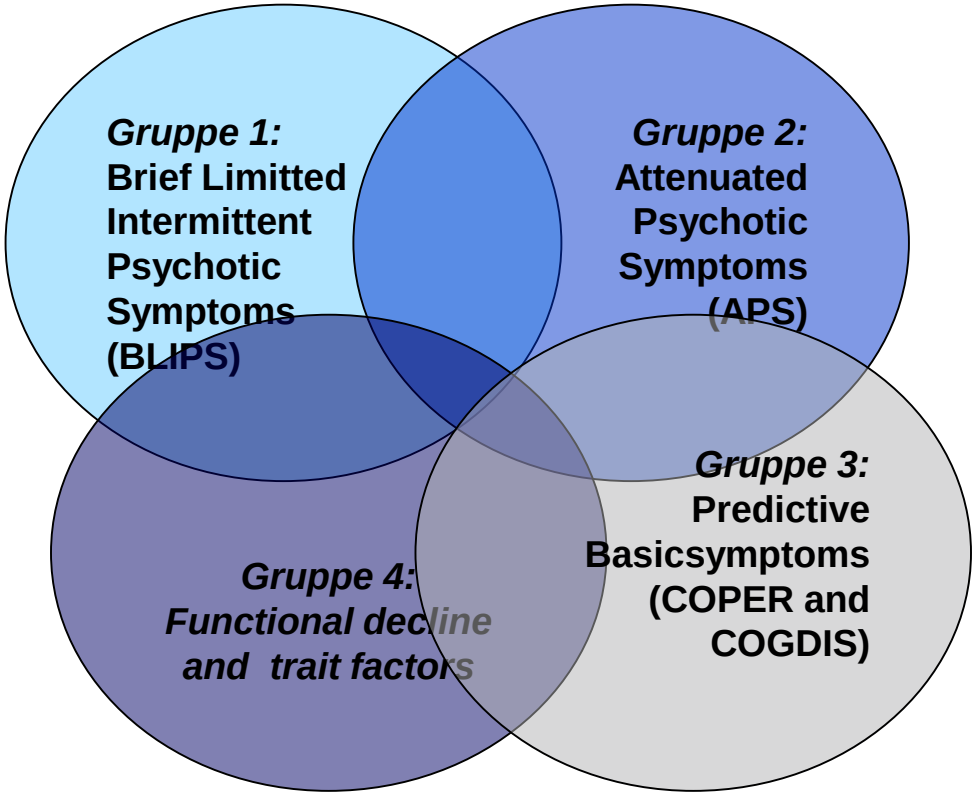
Clinical High Risk Criteria for Psychosis - CHRp

(Yung et al., 1998; Klosterkötter et al., 2001)

I. Age 15-35 years

II. At least one criteria of the four groups within the past 12 monts



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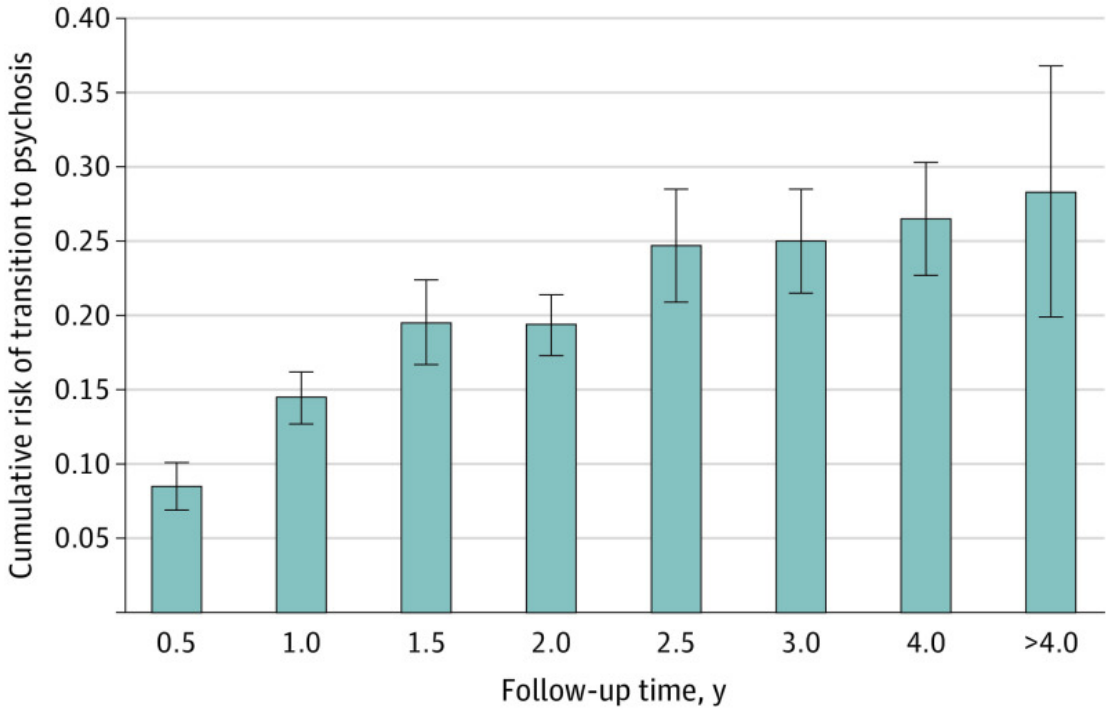
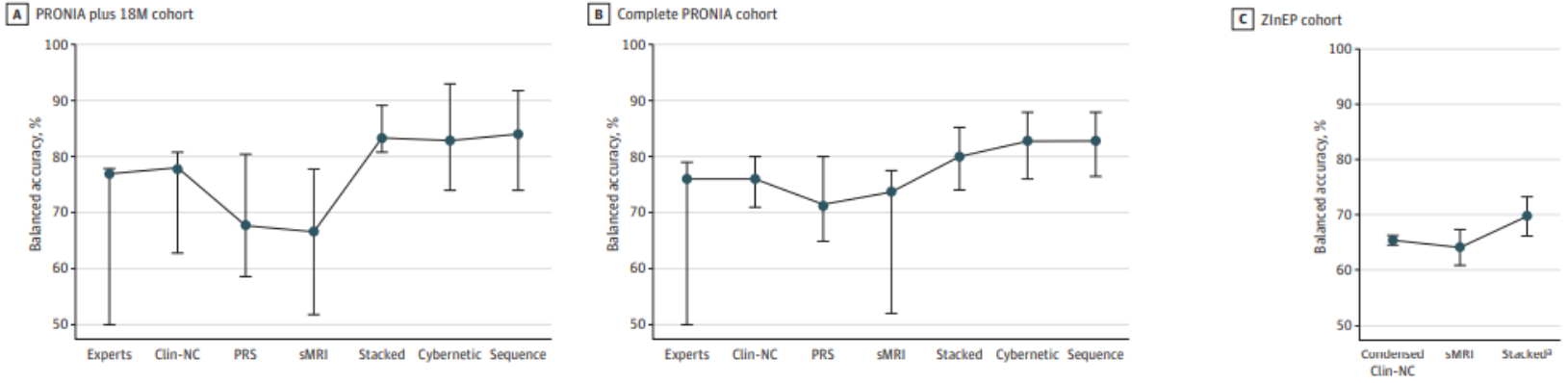
Meta-Analysis: Transition rates to psychosis in people with CHRp

(130 Studien, n= 9222, Salazar de Pablo et al., 2021)



Improve Prediction by Multimodal Machine Learning

(Koutsouleris et al., 2021)



Cohorts include patients with follow-up of 18 months or longer (PRONIA plus 18M), the complete PRONIA cohort, and the Zurich Early Recognition Program (ZInEP). Data points indicate median. The Quade test[51] was used to compare the models' median balanced accuracy (BAC) computed across the cross-validation cycle (CV_2) test data partitions. The BAC measures obtained for the ZInEP cohort (C) were produced by applying the condensed clinical-neurocognitive (Clin-NC), structural magnetic resonance imaging (sMRI)–based, and respective stacked risk calculators of the complete PRONIA sample (B) to this external sample (eFigure 2 in the Supplement). Post hoc comparisons were performed using the t distribution approximation described by Heckert and Filliben.[52] *P* values were corrected for multiple comparisons using the false discovery rate (FDR). The upper graphs represent the median BAC for each risk calculator in analyses A, B, and C along with the lower and upper quartiles of the BAC distributions (whiskers of the error bars). The lower figures show the logarithmized, FDR-corrected *P* matrix for the pairwise post hoc classifier comparisons. For an in-depth analysis of the prognostic sequence included in the risk classifier comparison, see eFigures 14 and 15 in the Supplement. The cybernetic risk calculator analyzed the combined predictions of raters, Clin-NC, polygenic risk score (PRS)–based, and sMRI-based risk calculators; the stacked risk calculator, the combined predictions of Clin-NC, PRS-based, and sMRI-based risk calculators.

[a] Indicates risk calculator encompassing the condensed Clin-NCs and sMRI-based models and specifically trained to externally validate the effect of stacking on prognostic performance in the ZInEP cohort.

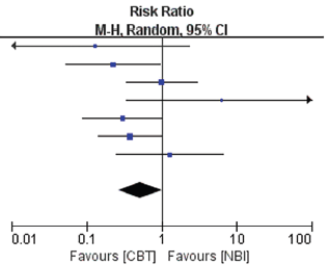
Cognitive Behavior Therapy (CBT) in young people with CHRp

Effects on transtion rates to psychosis (10 RCTs; n = 1128)

Short-term (within 6 month)

Study or Subgroup	CBT Events	CBT Total	NBI Events	NBI Total	Weight	Risk Ratio M-H, Random, 95% CI
Addington 2010	0	27	3	24	4.8%	0.13 [0.01, 2.35]
Han 2017	2	30	9	30	14.9%	0.22 [0.05, 0.94]
Morrison 2012	6	144	6	144	20.9%	1.00 [0.33, 3.03]
Stain 2016	3	30	0	27	4.8%	6.32 [0.34, 117.09]
Sun 2018 (CN)	3	55	10	55	18.3%	0.30 [0.09, 1.03]
van der Gaag 2012 (EDIE)	5	98	14	103	23.7%	0.38 [0.14, 1.00]
Yung 2011 (PACE)	4	44	2	28	12.6%	1.27 [0.25, 6.50]
Total (95% CI)		**428**		**411**	**100.0%**	**0.52 [0.26, 1.01]**
Total events	23		44			

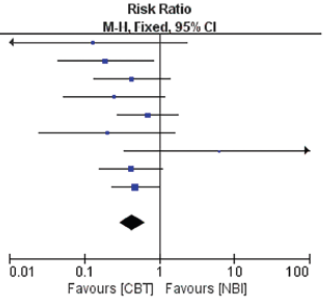
Heterogeneity: Tau² = 0.24; Chi² = 8.70, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 1.92 (P = 0.06)



Medium-term (6-12 month)

Study or Subgroup	CBT Events	CBT Total	NBI Events	NBI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Addington 2010	0	27	3	24	4.9%	0.13 [0.01, 2.35]
Bechdolf 2012	2	63	11	65	14.4%	0.19 [0.04, 0.81]
McGorry 2013 (PACE)	4	44	6	28	9.8%	0.42 [0.13, 1.37]
Morrison 2004	2	37	5	23	8.2%	0.25 [0.05, 1.18]
Morrison 2012	7	144	10	144	13.3%	0.70 [0.27, 1.79]
Pozza 2019	1	29	5	29	6.7%	0.20 [0.02, 1.61]
Stain 2016	3	30	0	27	0.7%	6.32 [0.34, 117.09]
Sun 2018 (CN)	5	55	12	55	16.0%	0.42 [0.16, 1.10]
van der Gaag 2012 (EDIE)	9	98	20	103	26.0%	0.47 [0.23, 0.99]
Total (95% CI)		**527**		**498**	**100.0%**	**0.44 [0.30, 0.64]**
Total events	33		72			

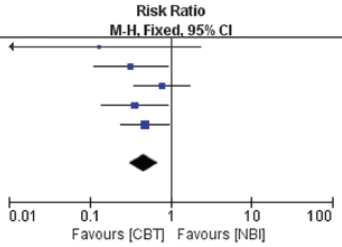
Heterogeneity: Chi² = 7.25, df = 8 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.20 (P < 0.0001)



Long-term (12-24 month)

Study or Subgroup	CBT Events	CBT Total	NBI Events	NBI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Addington 2010	0	27	3	24	5.7%	0.13 [0.01, 2.35]
Bechdolf 2012	4	63	13	65	19.7%	0.32 [0.11, 0.92]
Morrison 2012	10	144	13	144	20.0%	0.77 [0.35, 1.70]
Sun 2018 (CN)	5	55	14	55	21.6%	0.36 [0.14, 0.92]
van der Gaag 2012 (EDIE)	10	98	22	103	33.0%	0.48 [0.24, 0.96]
Total (95% CI)		**387**		**391**	**100.0%**	**0.46 [0.30, 0.69]**
Total events	29		65			

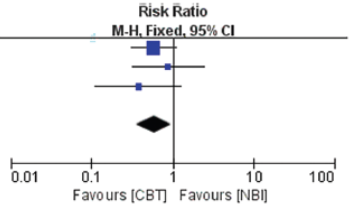
Heterogeneity: Chi² = 3.12, df = 4 (P = 0.54); I² = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)



Ultra-long-term (over 24 month)

Study or Subgroup	CBT Events	CBT Total	NBI Events	NBI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ising 2016 (EDIE)	12	98	22	103	60.2%	0.57 [0.30, 1.09]
Morrison 2007	7	37	5	23	17.3%	0.87 [0.31, 2.42]
Pozza 2019	3	29	8	29	22.5%	0.38 [0.11, 1.27]
Total (95% CI)		**164**		**155**	**100.0%**	**0.58 [0.35, 0.95]**
Total events	22		35			

Heterogeneity: Chi² = 1.09, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)



Zheng et al., 2022

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The Guardian

‘Alarming’ surge in mental ill he among young people in face of ‘unprecedented’ challenges, ex warn

Insecure employment, climate crisis and social media driving ‘dangerous’ decline, research finds

Lead researcher of the report, prof Patrick McGorry, says youth mental he serious public health problem we’ve got’. Photograph: Antonio Guillem Fern

Intergenerational inequality, unregulated social media, wag employment and the climate crisis are driving a “dangerous” and “alarming” global surge in mental ill health among youth, a consortium of health experts has warned.

There is an urgent need to address these driving factors and improve mental health treatments to stymie rates of premature death, disability and lost potential, all of which have escalated over the past two decades, the research

The Lancet Psychiatry Commissions

ational inequality, unregulated social media, wage insecurity of employment, and climate change, is ing is deep and widespread within societies. The correlated domains of distress, diagnosable des of mental ill health with a need for care, and severe, sustained, or recurrent forms of mental s are at an all-time high. Young people are showing nost serious warning signs and symptoms of a

Prof A M Chanen, M P Hamilton, Prof J Robinson, Prof L Valmaggia, Prof A Yung, Prof E Killackey); **Lusaka, Zambia** (N Dalal MD MMed); **Department of Psychology, University of Cambridge, Cambridge, UK** (Prof S-J Blakemore PhD); **School of Psychology, University**

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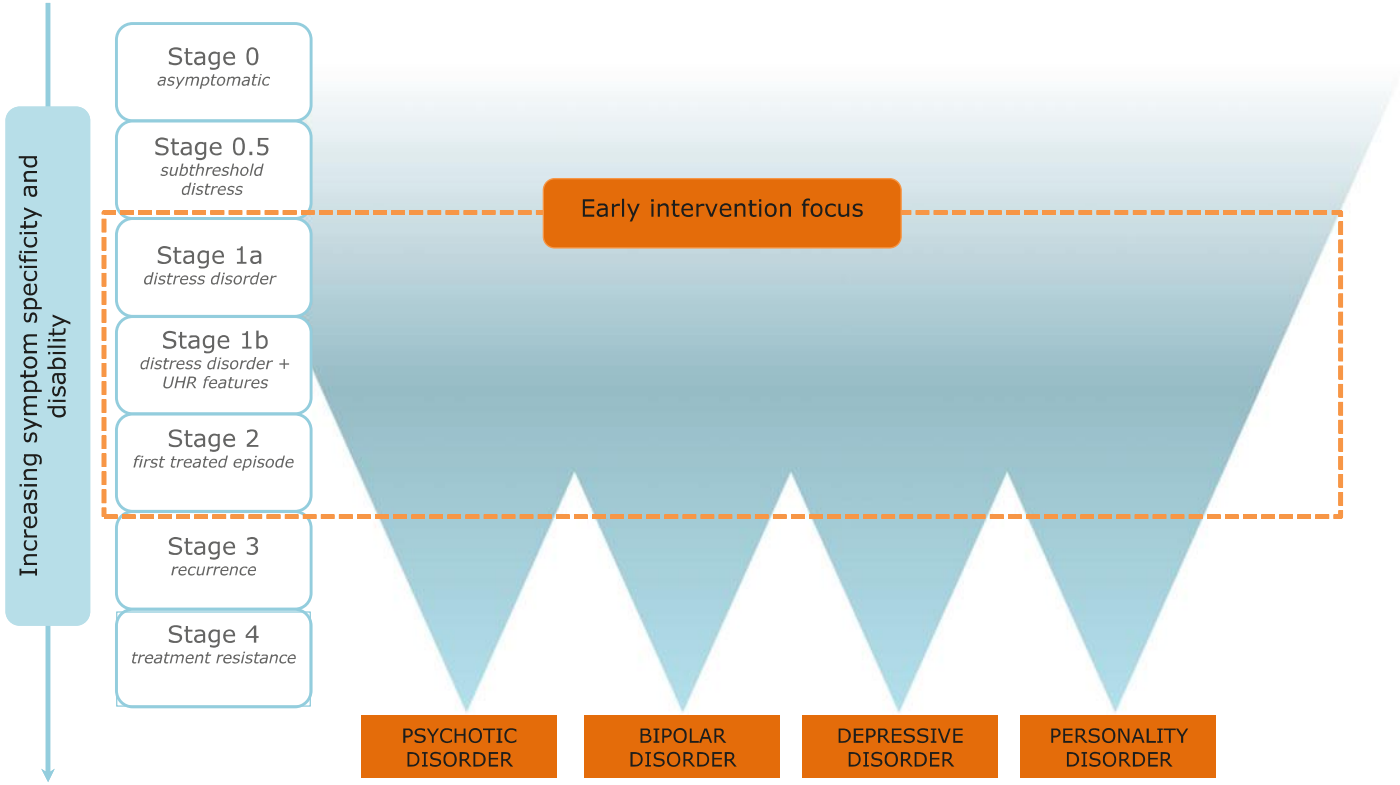
Transdiagnostic Risksyndrome

(z. B. Hartmann et al., 2017, 2021, Sha et al., 2020; Destree et al., 2024)



Health Policy

Staging 2·0: refining transdiagnostic clinical staging frameworks to enhance reliability and utility for youth mental health

Jan Scott, Frank Iorfino, William Capon, Jacob Crouse, Barnaby Nelson, Andrew M Chanen, Dominic Dwyer, Philippe Conus, Andreas Bechdolf, Aswin Ratheesh, Andrea Raballo, Alison Yung, Michael Berk, Sarah McKenna, Samuel Hockey, Alexis Hutcheon, Elizabeth Scott, Pat McGorry, Jai Shah, Ian B Hickie

Globally, 75% of depressive, bipolar, and psychotic disorders emerge by age 25 years. However, these disorders are often preceded by non-specific symptoms or attenuated clinical syndromes. Difficulties in determining optimal treatment interventions for these emerging mental disorders, and uncertainties about accounting for co-occurring psychopathology and illness trajectories, have led many youth mental health services to adopt transdiagnostic clinical staging frameworks. In this Health Policy paper, an international working group highlights ongoing challenges in applying transdiagnostic staging frameworks in clinical research and practice, and proposes refinements to the transdiagnostic model to enhance its reliability, consistent recording, and clinical utility. We introduce the concept of within-stage heterogeneity and describe the advantages of defining stage in terms of clinical psychopathology and stage modifiers. Using examples from medicine, we discuss the utility of categorising stage modifiers into factors associated with progression (ie, potential predictors of stage transition) and extension (ie, factors associated with the current presentation that add complexity to treatment selection). Lastly, we suggest how it is possible to revise the currently used transdiagnostic staging approach to incorporate these key concepts, and how the revised framework could be applied in clinical and research practice.

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Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK (Prof J Scott MD); **Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia** (Prof J Scott, F Iorfino PhD, W Capon MBMSc, J Crouse PhD, S McKenna PhD, E Scott DM, I B Hickie MD); **Orygen and Centre for Youth Mental Health, The University of Melbourne, Melbourne, VIC, Australia** (B Nelson PhD, A M Chanen PhD, D Dwyer PhD, A Ratheesh PhD, P McGorry MD); **General Psychiatry Service, Lausanne University Hospital, Lausanne, Switzerland** (P Conus MD); **Department of Psychiatry and Psychotherapy, CCM, Charité Universitatsmedizin, Berlin, Germany** (A Bechdolf PhD);

Introduction

Adolescence and early adulthood represent the peak period for the onset of major mental health problems.[1] Globally, 75% of depressive, bipolar, and psychotic disorders emerge by age 25 years, and mental disorders account for 45% of years lived with disability in people aged 10–24 years.[2] Unfortunately, it is often difficult to predict the clinical course and treatment outcomes of emerging mental disorders in individuals attending youth mental health services.[3] For example, cross-sectional and longitudinal studies in adolescence and young adulthood, have exposed substantial shortcomings regarding the reliability and validity of traditional diagnostic categories, and regarding the applicability of the accompanying treatment guidelines.[15–17] Consequently, many youth mental health services globally have moved toward transdiagnostic models of early intervention, and they advocate the use of clinical staging frameworks as a more constructive approach to classifying and understanding the multidimensional and dynamic nature of the observed clinical phenomena.[18–25]

European Commission

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Prof. Therese van Amelsvoort
(Maastricht University, UM, NL)
Prof. Andreas Bechdolf
(Charité-Universitätsmedizin, GER)
Kirsten Broekema
(European Student Organisation, AEGEE, BE)
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Dr. Covadonga Martínez Díaz-Caneja
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Prof. Patrick McGorry
(University of Melbourne, UOM, AU)
Prof. David McDaid
(London School of Economics, LSE, UK)
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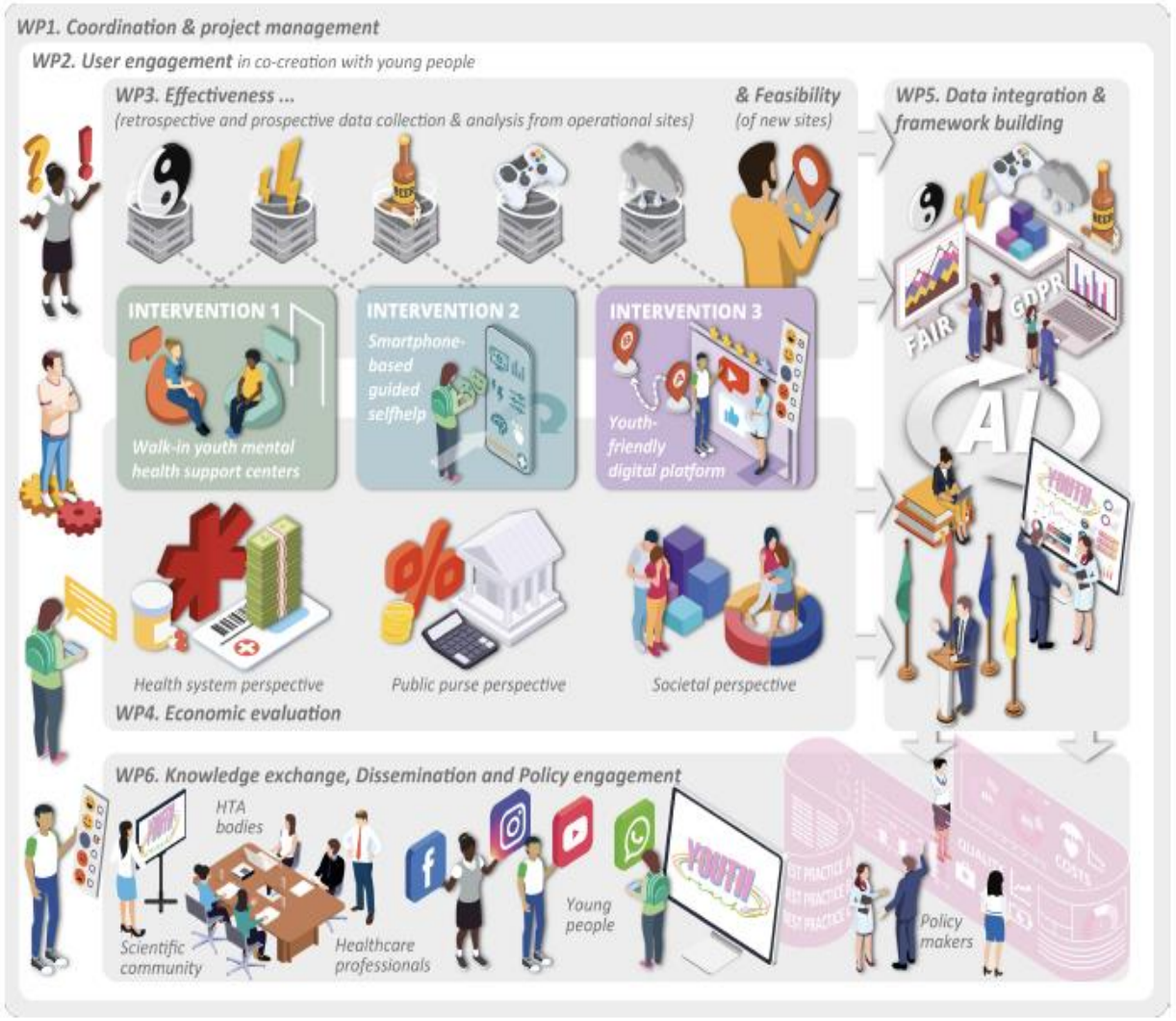
Prof. Ulrich Reininghaus
(Zentralinstitut für Seelische Gesundheit, ZISG, GER)



What can we learn from Psychosis Research for Early Intervention in Bipolar Disorder?

Arguments in support of early detection and intervention in Bipolar Disorder (BD)

- Potentially disabling and functionally impairing psychiatric disorder (e. g. Ferrari et al., 2016)
- Long duration from first onset of symptoms to initiation of specific treatment [at least 8 years on average] (Hirschfeld und Vornik, 2004, Berk et al., 2007)
- repeated mood episodes

  - lead to poor symptomatic and functional recovery (Denicoff et al, 1997; Tham et al., 1999; Quendo et al., 2000)

  - lead to structural and cognitive deteroation (Velakoulis et al.,1999, Strakowski et al., 2000; Lyoo et al., 2002; Cordoso et al., 2015)

- later episodes are more resistant to treatment than early episodes (Franchini et al., 1999; Swan et al, 1998, Scott et al., 2006; Machionatti et al., 2022)

Staging models for Bipolar Disorder

(Kapczinski et al., 2014)

Stage	Berk et al. (14, 15)	Kapczinski et al. (16)	Post (19)	Cosci and Fava (3)
0	Increased risk of mood disorder	At risk, positive family history, mood or anxiety symptoms		
1a	Mild or non-specific symptom	Well-defined periods of euthymia without symptoms	Vulnerability	Mild or non-specific symptoms/prodromal phase
1b	Prodromal features (ultra-high risk)			Cyclothymia
2	First threshold episode	Interepisodic symptoms related to comorbidities	Well-interval	Acute manifestations of major depression or mania/ hypomania
3a	Recurrence of subthreshold mood symptoms	Marked impairment in cognition or functioning	Prodrome	Residual symptoms with cognitive and functional impairment despite treatment
3b	First threshold relapse			
3c	Multiple relapses			
4	Persistent unremitting illness	Unable to live autonomously due to impairment	Illness onset	Acute episodes despite treatment
5			Episode recurrence	
6			Illness progression	
7			Treatment refractoriness	
8			End stage	

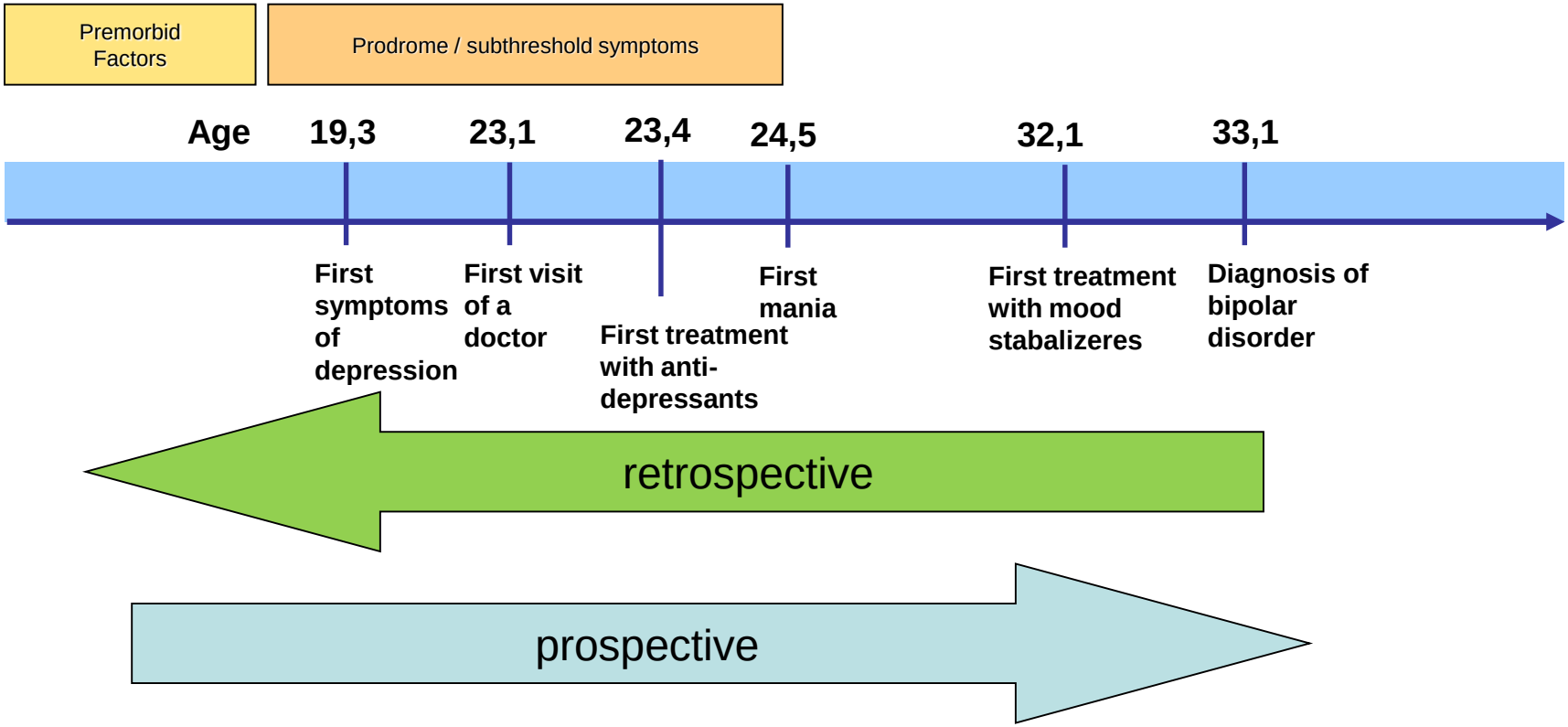
Obstacles of defining at-risk criteria for Bipolar Disorder

- Target syndrome (mania?, recurrent depression?)
- First manifestation of the disorder often is not mania
- Long latency between first episode depression and first episode mania
- Fluctuating psychopathology in general
- Sensitive and specificity of early signs

  e. g low grade depressive symptoms in young people high sensitivity but very low specifity

  Low grade mood elevation far greater specificity, but lower sensitivity
- Relatively short duration of mania prodrome

Specific At-Risk Criteria for Bipolar Disorder?



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Review

Clinical risk factors for bipol
of prospective studies

Gianni L. Faedda [a,b,c,*], Giulia Serra [d,
Gabriele Sani [d,e,i], Gustavo H. Vázque
Ross J. Baldessarini [c,f], Athanasios Ko

[a] Lucio Bini Mood Disorders Center, New York, NY, United State
[b] New York University Medical Center & Child Study Center, Ne
[c] International Consortium for Bipolar Disorder Research, McLe
[d] Centro Lucio Bini, Rome, Italy
[e] NESMOS Department (Neuroscience, Mental Health and Sensa
Sant'Andrea Hospital, Rome, Italy
[f] Department of Psychiatry, Harvard Medical School, Boston, M
[g] Section of Neurological, Psychiatric and Psychological Science
[h] Section of Psychiatry, Department of Neuroscience, University
[i] IRCCS Santa Lucia Foundation, Department of Clinical and Beh
Rome, Italy
[j] Department of Neuroscience, University of Palermo, Buenos A
[k] Centro Lucio Bini, Cagliari, Italy

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REVIEW

The Bipolar Prodrome: Meta-Analysis of Symptom Prevalence Prior to Initial or Recurrent Mood Episodes

Anna R. Van Meter, PhD, Coty Burke, BA, Eric A. Youngstrom, PhD,
Gianni L. Faedda, MD, Christoph U. Correll, MD

Objective: The aim
prevalence of sympt
bipolar disorder (BD
symptoms before
facilitate early ident

Method: Systematic
PsycINFO and Pub
studies reporting or
of symptoms before
of BD. Random effe
geographic locatio
dividuals, and stu
prevalence.

Results: In 11 studi
ing an initial mood
(range, 4.6–130 mo
subthreshold symp
episode lasted 1.0 ±
The most common
with diagnostic cri

Bipolar disorder
places a signifi
ety.[1,2] Althoug
presentations—includi
depression, brief hypo
have been described
diagnosis remains a
diagnosis has progn
frequency and severi
reducing the benefits
Bipolar disorder be
be particularly difficu
overlap with other chi
deficit/hyperactivity d
disorder (ODD), unip
onset BD may have
onset BD,[10-13] perhaps

DOI: 10.1111/bdi.12831

Check for updates

REVIEW ARTICLE

BIPOLAR DISORDERS WILEY

An International Society of Bipolar Disorders task force report: Precursors and prodromes of bipolar disorder

Gianni L. Faedda[1,2] | Ross J. Baldessarini[2,3] | Ciro Marangoni[4] | Andreas Bechdolf[5,6] | Michael Berk[7,8,9] | Boris Birmaher[10] | Philippe Conus[11] | Melissa P. DelBello[12] | Anne C. Duffy[13] | Manon H. J. Hillegers[14,15] | Andrea Pfennig[16] | Robert M. Post[17,18] | Martin Preisig[19] | Aswin Ratheesh[7,8,9] | Paola Salvatore[3,20] | Mauricio Tohen[21] | Gustavo H. Vázquez[2,22] | Eduard Vieta[23] | Lakshmi N. Yatham[24] | Eric A. Youngstrom[25] | Anna Van Meter[26,27] | Christoph U. Correll[26,27,28,29]

[1]Mood Disorders Center, New York, NY, USA

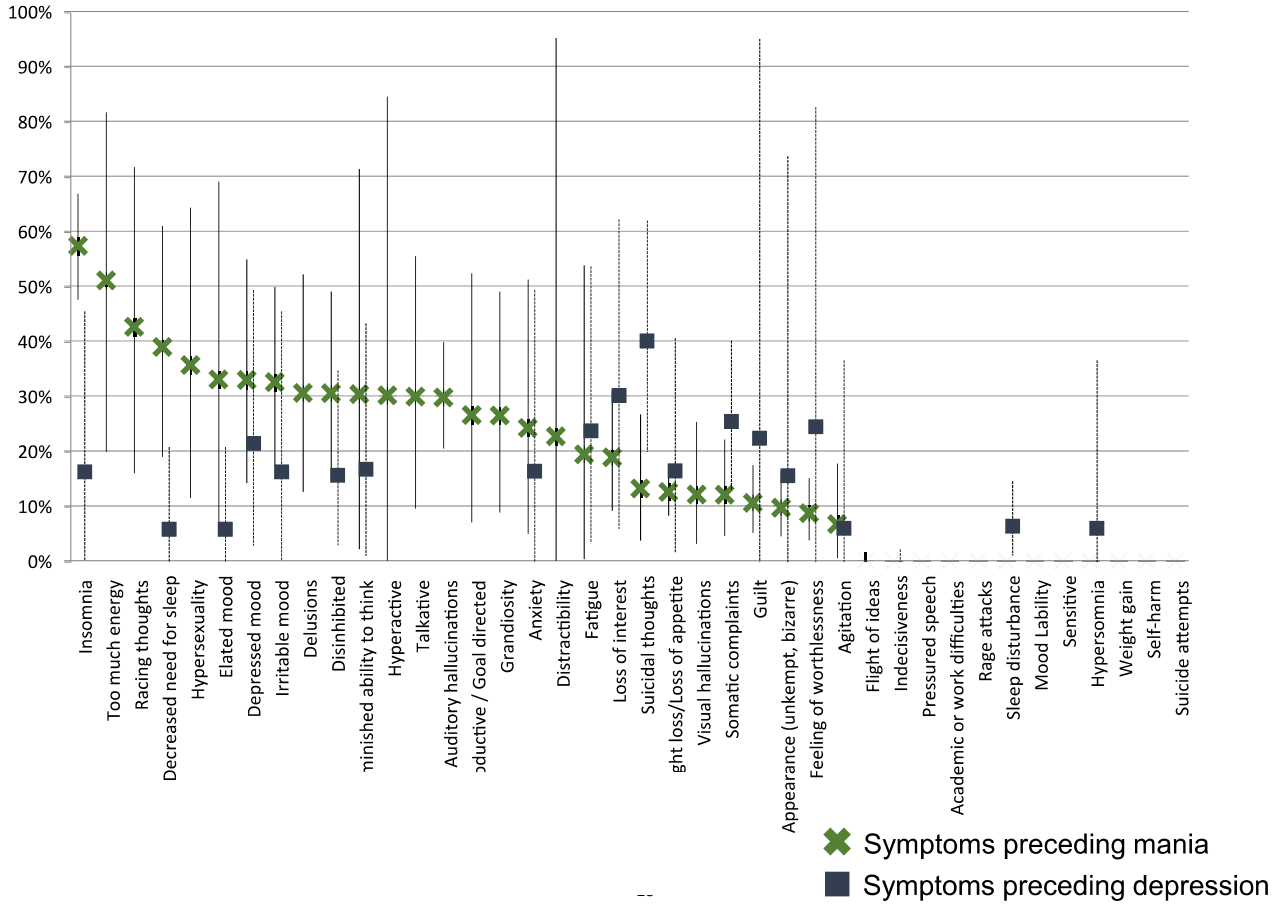
Results: Cyclothymic features, a family history of BD, retrospectively reported attenuated manic symptoms, prospectively identified subthreshold symptoms of hypomania, recurrence of depression, panic anxiety and psychotic features, have been identified as clinical precursors of BD. The prodromal symptoms like [hypo] mania often appears to be long enough to encourage early identification and timely intervention.

[13]Department of Psychiatry, Student Wellness Services, Queen's University, Kingston, ON, Canada

tes

Putative prodromal symptoms (van Meter et al., 2016)

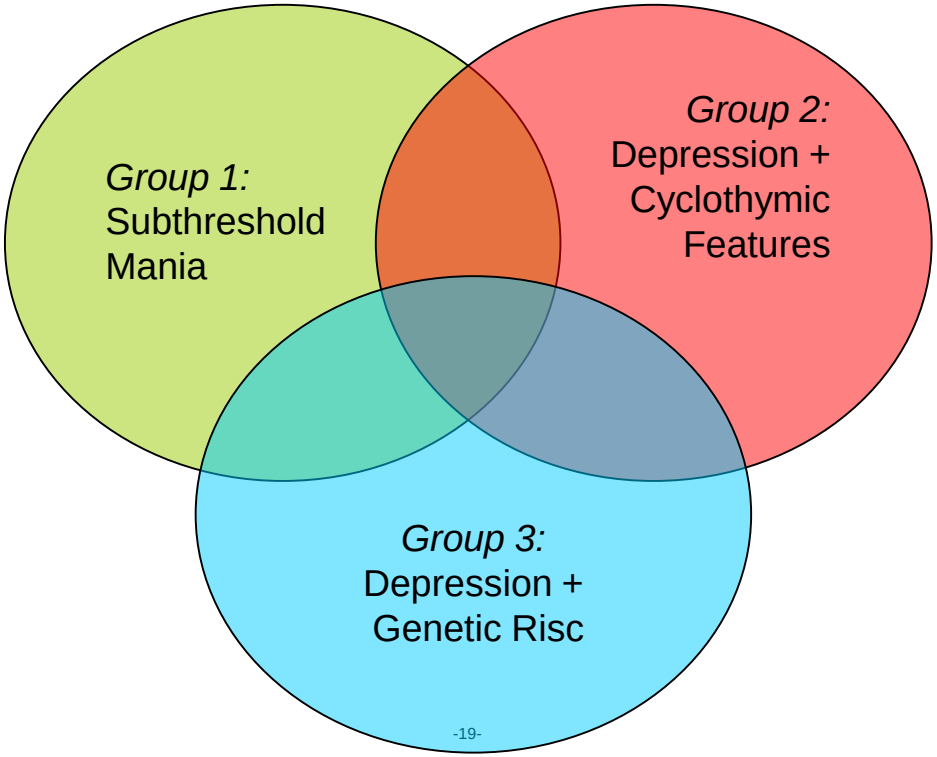
FIGURE 3 Average prevalence rate and 95% CIs for symptoms preceding recurrent manic or depressive episodes. Note: Not all symptoms were reported before both depressive and manic episode recurrences.



Bipolar At-Risk (BAR) criteria (Bechdolf et al., 2010)

I. Aged 15-25 years

II. Fulfill criteria of at least one of three groups within the last 12 months:



Bipolar At-Risk (BAR) criteria (Bechdolf et al., 2010)

Group 1: Sub-threshold mania

For at least two consecutive days but less than 4 days: period of abnormally and persistently elevated, expansive or irritable mood + at least 2 criteria from the list: (1) inflated self esteem or grandiosity, (2) decreased need for sleep (e.g. feels rested after only 3-hour sleep), (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or subjective experience that thought are racing, (5) distractibility, (6) increase goal directed activity (either socially, at work, or sexually) or psychomotor agitation.

Group 2: Depression + Cyclothymic features:

Depression

For at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation

+

Cyclothymic features

Numerous episodes with sub-threshold manic symptoms not meeting group I criteria and numerous episodes with depressive symptoms. E g. sub-threshold mania as defined in group I only for 4 h within a 24-hour period and at least 4 cumulative lifetime days meeting the criteria

Group 3: Depression + Genetic Risk:

Depression

For at least 1 week: depressed mood, or loss of interest or pleasure + at least 2 criteria from the list: (1) significant weight loss, (2) insomnia or hypersomnia nearly every day, (3) psychomotor retardation or agitation, (4) fatigue or loss of energy, (5) feelings of worthlessness or excessive or inappropriate guilt, (6) diminished ability to think or concentrate, (7) recurrent thoughts of death, recurrent suicidal ideation

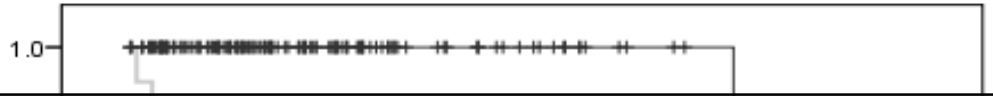
+

Genetic Risk:

First degree relative with bipolar disorder.

File audit - Conversions to first episode mania

(BAR n = 22; non-BAR n = 151)



Journal of Affective Disorders 127 (2010) 316–320

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

Brief report

A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults

Andreas Bechdolf*[,1,2], Barnaby Nelson, Sue M. Cotton, Andrew Chanen, Andrew Thompson, Jonathan Kettle, Phillippe Conus, G. Paul Amminger, Alison R. Yung, Michael Berk, Patrick D. McGorry

ORYGEN Youth Health, Department of Youth Mental Health, University of Melbourne, Australia

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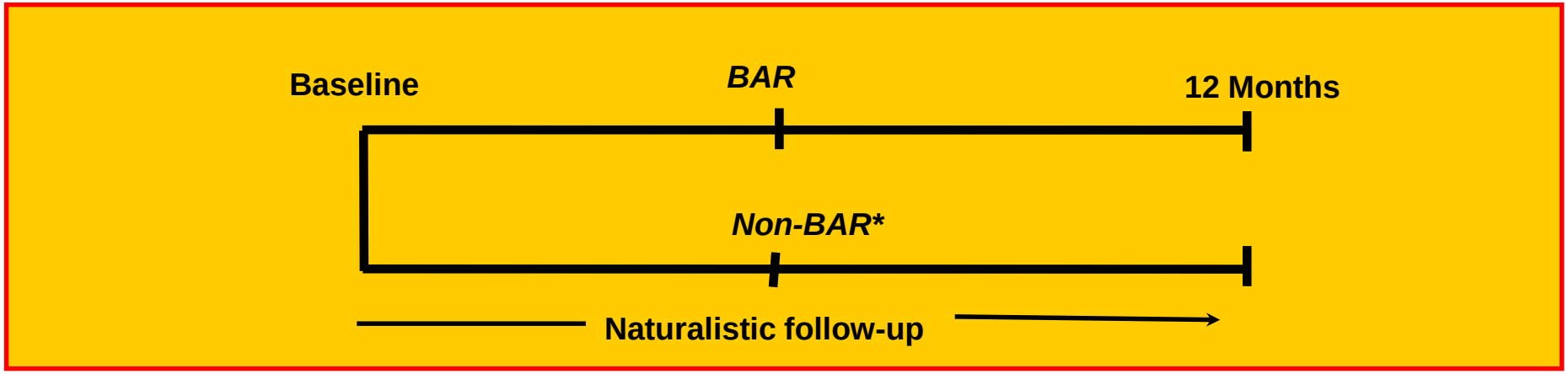
BARPS
Bipolar At Risk Prospective Study

Help seeking clients assessed at intake at Entry of ORYGEN Youth Health, Melbourne, Australia



* group-matched for gender, age, previous hospitalisations and antidepressant medication

Bechdolf et al., 2014

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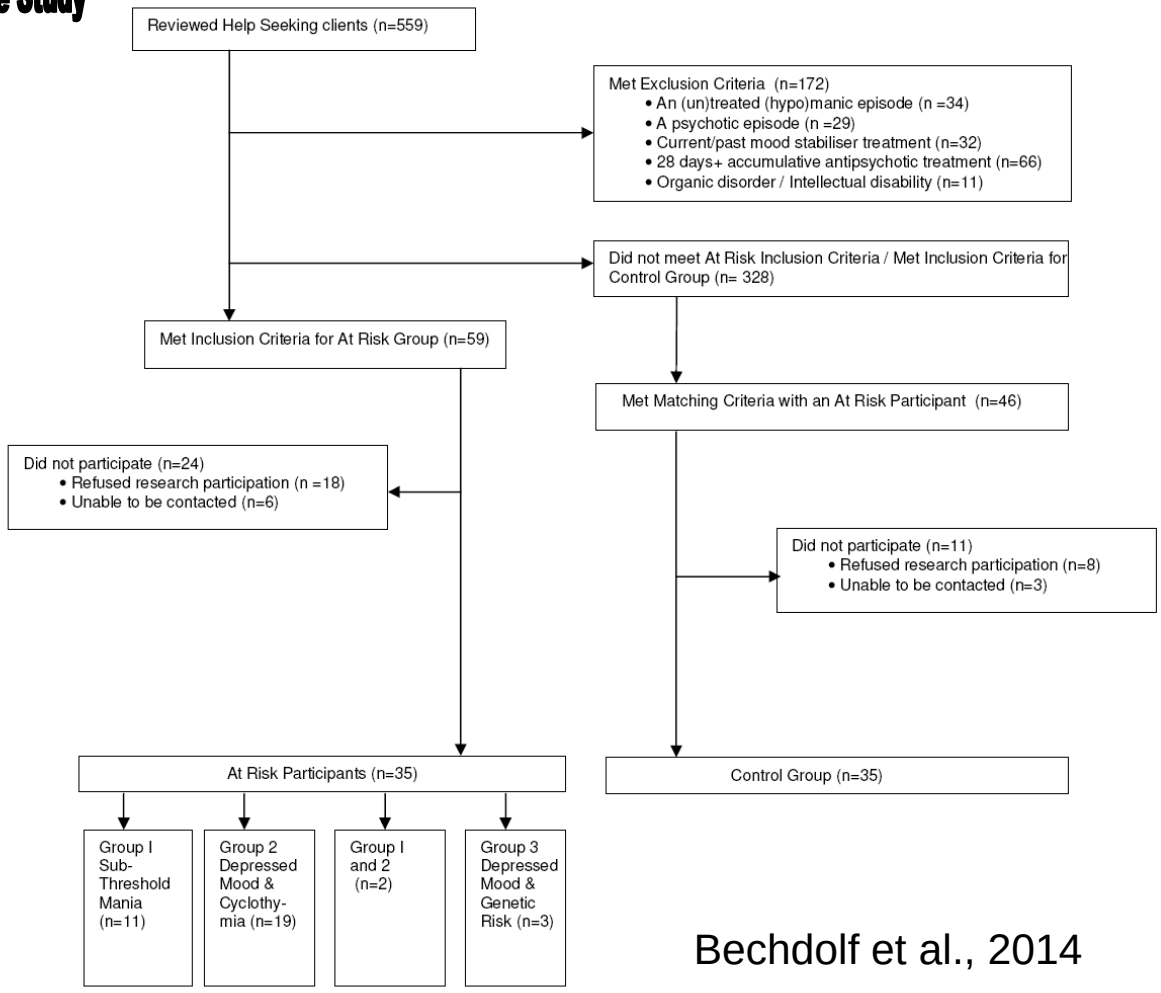
BARPS
Bipolar At Risk Prospective Study

Recruitment



Bechdolf et al., 2014

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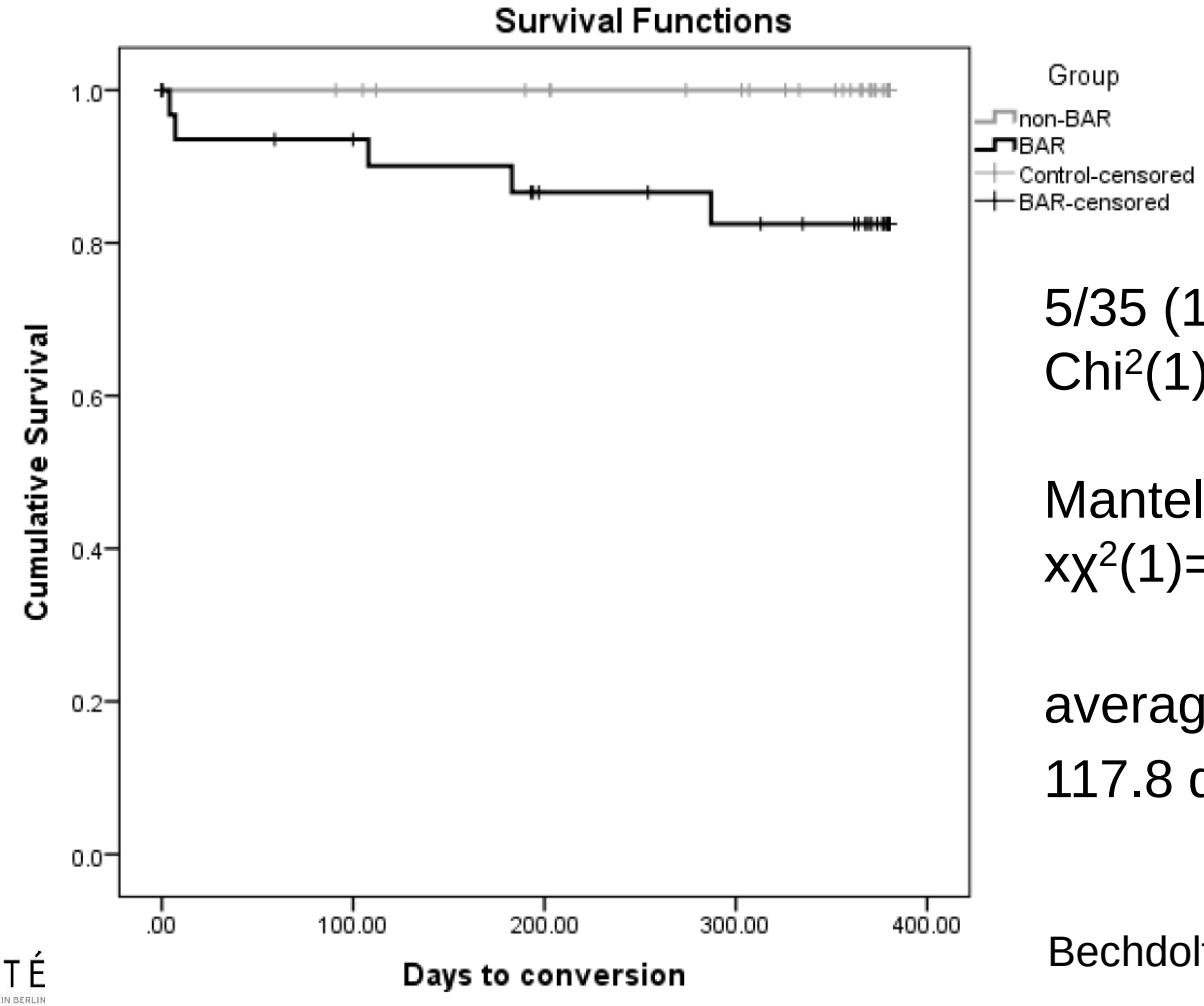
Conversion to first episode mania (BAR n=35; non-BAR n=35)



5/35 (14.3%) conversion rate
$Chi^2(1)=5.38$, $p=.020$

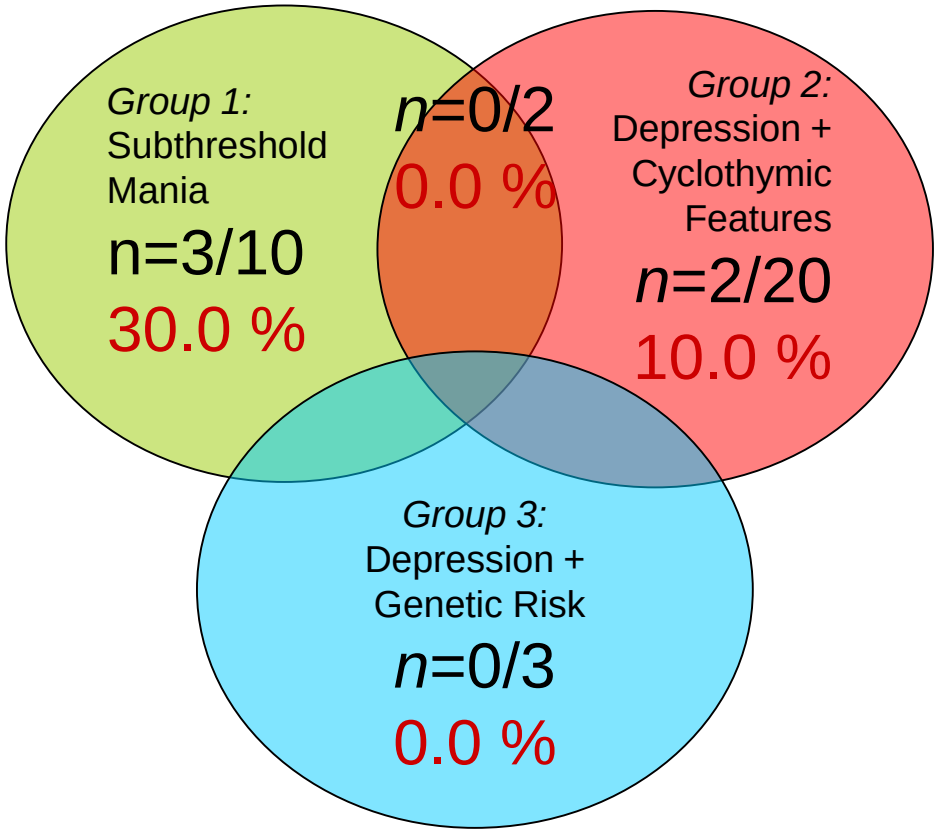
Mantel Cox Log rank
$x\chi^2(1)=6.08$, $p=.01$

average time to conversion
117.8 days

Bechdolf et al., 2014

BARPS
Bipolar At Risk Prospective Study

Conversions by BAR sub-group



Bechdolf et al., 2014

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Baseline clinical and demographic characteristics associated with onset of BD over 12 months (Ratheesh et al., 2015)

Characteristic	Sample characteristics			Comparisons			Effect size		
	Descriptive statistic	Developed BD, $N=4$	Did not develop BD, $N=48$	Test statistic	U/χ^2	Signifi-cance P	Statistic	Value	95% CI
Age at entry	M (SD)	19.5 (3.9)	19.7 (2.8)	U	92.5	0.90	AUC	0.41	0.00–0.84
Female gender	% (n)	100% (4)	83.3% (40)	χ^2	0.79	0.38	OR	1.1	1.0–1.2
Diagnosis									
Major depressive disorder	% (n)	75% (3)	64.6% (31)	χ^2	0.18	0.67	OR	1.6	0.2–17.1
Anxiety disorder	% (n)	100% (4)	77% (37)	χ^2	1.16	0.28	OR	1.1	1.0–1.2
Alcohol use disorder	% (n)	75% (3)	8% (4)	χ^2	14.1	**0.00**	OR	**33.0**	2.8–395.6
Cannabis use disorder	% (n)	25% (1)	17% (8)	χ^2	0.18	0.67	OR	1.7	0.2–18.1
Family history*									
Major depressive disorder	% (n)	67% (2)	82.5% (33)	χ^2	0.46	0.50	OR	0.4	0.03–5.4
More than 1 MDD	% (n)	67% (2)	42.5% (17)	χ^2	0.66	0.42	OR	2.7	0.2–32.3
Bipolar disorder	% (n)	0	12.5% (5)	χ^2	0.42	0.52	OR	0.9	0.8–1.0
Psychosis	% (n)	33% (1)	22.5% (9)	χ^2	0.18	0.67	OR	1.7	0.1–21.2
Any substance use disorder	% (n)	67% (2)	12.5% (5)	χ^2	6.0	**0.01**	OR	**14.0**	1.06–184.18
State and trait measures									
YMRS	M (SD)	6.8 (4.6)	6.1 (5.9)	U	80.5	0.59	AUC	0.63	0.35–0.90
MADRS	M (SD)	29.8(11.4)	21.3 (9.4)	U	49.5	0.11	AUC	**0.74**	0.42–1.00
BDRS	M (SD)	27.0 (9.7)	20.5 (10.3)	U	54.5	0.15	AUC	**0.72**	0.47–0.97
Brown ADD scale	M (SD)	74.5 (10.3)	71.6 (20.9)	U	75.5	0.80	AUC	0.50	0.31–0.69
TEMPS	M (SD)	92.3 (12.2)	100.8 (9.8)	U	45.0	0.13	AUC	0.27	0.00–0.59
Risk clusters									
Bipolar at-risk	% (n)	100% (4)	45.8% (22)	χ^2	4.3	**0.04**	OR	**1.2**	1.0–1.4
Bipolarity index total	M (SD)	27.5 (6.5)	25.6 (10.0)	U	89	0.81	AUC	0.57	0.28–0.86
UHR Psychosis#	% (n)	45.5%(10)	33.3% (1)	χ^2	0.16	0.69	OR	0.6	0.04–7.6
Quality of life									
MSQoL\widehat									
Physical	M (SD)	34.1(7.7)	44.5 (6.7)	U	15.5	**0.03**	AUC	0.13	0.00–0.36
Psychological	M (SD)	56.2 (6.0)	51.4 (10.3)	U	43.5	0.40	AUC	0.65	0.46–0.84
Life	M (SD)	42.4 (6.4)	45.3 (11.5)	U	43.0	0.39	AUC	0.35	0.13–0.57

CI—Confidence Interval, OR—Odds Ratio, AUC—Area Under the Receiver Operating Characteristic Curve, YMRS—Young Mania Rating Scale, MADRS—Montgomery Asberg Depression Rating Scale, BDRS—Bipolar Depression Rating Scale, ADD—Attention Deficit Disorder, TEMPS—Temperament Evaluation of Memphis-Pisa-San Diego Autoquestionnaire, UHR—Ultra-High Risk, MSQoL—Modular System for Quality of Life.

Data available for 25 participants.
* Data available for 43 participants.
\widehat Data available for 42 participants.

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Bipolar At-Risk Criteria: An Examination of Which Clinical Features Have Optimal Utility for Identifying Youth at Risk of Early Transition From Depression to Bipolar Disorders

Jan Scott*[,1,2], Steven Marwaha[3], Aswin Ratheesh[4,5], Iain Macmillan[6], Alison R. Yung[7,8], Richard Morriss[9], Ian B. Hickie[10], and Andreas Bechdolf[4,11,12]

[1]Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK; [2]IPPN, King's College, London, UK; [3]Division of Health Sciences, Warwick Medical School, The University of Warwick, Coventry, UK; [4]Orygen, the National Centre of Excellence in Youth Mental Health, Parkville, Australia; [5]Centre for Youth Mental Health, University of Melbourne, Parkville, Australia; [6]Early Intervention in Psychosis Service, NTW NHS Trust, Newcastle upon Tyne, UK; [7]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; [8]Greater Manchester West NHS Mental Health Foundation Trust, Manchester, UK; [9]Institute of Mental Health, University of Nottingham, Nottingham, UK; [10]Brain and Mind Centre, The University of Sydney, Sydney, Australia; [11]Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; [12]Department of Psychiatry, Psychotherapy and Psychosomatics, Vivantes Klinikum am Urban and Vivantes Klinikum im Friedrichshain, and Academic Hospital of Charity Medicine, Berlin, Germany

*To whom correspondence should be addressed; Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE4 6BE, UK; tel/fax: +44-191-2563209, e-mail: jan.scott@newcastle.ac.uk

Background: **A clinical and research challenge is to identify which depressed youth are at risk of “early transition to bipolar disorders (ET-BD).” This 2-part study (1) examines the clinical utility of previously reported BD at-risk (BAR) criteria in differentiating ET-BD cases from unipolar depression (UP) controls; and (2) estimates the Number Needed to Screen (NNS) for research and general psychiatry settings.** ***Methods:*** **Fifty cases with reliably ascertained, ET-BD I and II cases were matched for gender and birth year with 50 UP controls who did not develop BD over 2 years. We estimated the clinical utility for finding true cases and screening out non-cases for selected risk factors and their NNS. Using a convenience sample (*N* = 80), we estimated the NNS when adjustments were made to account for data missing from clinical case notes.** ***Results:*** **Sub-threshold mania, cyclothymia, family history of BD, atypical depression symptoms and probable antidepressant-emergent elation, occurred significantly more frequently in ET-BD youth. Each of these “BAR-Depression” criteria demonstrated clinical utility for** [...] **of ET-BD instruments should distinguish which criteria have clinical utility for case finding vs screening.**

Key words: screening/case finding/youth/bipolar disorder/ultra-high risk/at-risk criteria/validity/clinical utility index/number needed to screen

Introduction

Globally, the peak age at onset (AAO) of severe mental disorders such as bipolar disorders (BD) and psychotic disorders is late adolescence and early adulthood.[1–3] Since the turn of the century, researchers have begun to identify subgroups of help-seeking youth who are at ultra-high risk (UHR) of early transition from a late prodromal stage to a first episode of psychosis (FEP). The risk of transition varies between about 15% and 35% over 12–24 months, but it can be predicted by UHR criteria, namely the presence of a combination of a limited set of state, trait, and familial characteristics.[4,5] Furthermore, these features can be incorporated into screening tools that can be applied

Table 2. Prevalence and Performance of Each Putative Risk Factors for Bipolarity in Differentiating Between Cases With ET-BD and Controls With UP

	ET-BD (N = 50)	UP (N = 50)	OR (95% CI)	Clinical Rule in Accuracy (CUI+)	Clinical Rule Out Accuracy (CUI−)	Overall Clinical Utility[a]
Bipolar at-risk criteria[b]						
Cyclothymia	39	10	14.2 (5.4, 37.2)	Good	Good	Case finding and screening
Sub-threshold mania	26	3	16.9 (4.7, 61.8)	Moderate	Good	Screening
Family history of BD	12	2	7.6 (1.6, 35.9)	Poor	Good	Screening
Additional risk factors[c]						
Probable antidepressant-emergent elation	21	8	3.4 (1.2, 4.9)	Fair	Good	Screening
Atypical depression	25	4	11.5 (3.6, 36.7)	Fair	Good	Screening
Psychomotor retardation	6	2	2.6 (0.5, 13.6)	Poor	Moderate	—
Psychotic mood episode	6	1	6.7 (0.8, 57.7)	Poor	Moderate	—
Family history of other mood disorders and/or ASUD	22	14	2.0 (0.9, 4.64)	Fair	Moderate	—
Multi-generational family history of mood disorders	3	0	3.1 (0.3, 31.1)	Poor	Moderate	—

ET-BD = Early Transition to Bipolar Disorder; UP = unipolar depression

Scott et al., 2017

Semistructured Interview for Bipolar At Risk States, SIBARS

(Fusar-Poli et al., 2018)

Age 15–35, not meeting any of the exclusion criteria and meeting at least one of the following:

GROUP 1: SUB THRESHOLD MANIA
Subthreshold intensity of the Subtreshold Mania scale (SIBARS 1):
Severity score of 3–4 PLUS Frequency score of 3–6
Subthreshold frequency of the Subtreshold Mania scale (SIBARS 1):
Severity score of 5–6 PLUS Frequency score of ≤ 3
PLUS
Symptoms should not have been present for more than 4 days

Group 2: DEPRESSION + CYCLOTHYMIC FEATURES
Depression:
Subthreshold intensity of the Depression scale (SIBARS 2):
Severity score of 3–5 PLUS Frequency score of 3–6
Subthreshold frequency of the Depression scale (SIBARS 2):
Severity score of 6 PLUS Frequency score of ≤ 3
Cyclothymic features:
Total score on the Cyclothymic Features rating (SIBARS 3):
Score ≥ 11

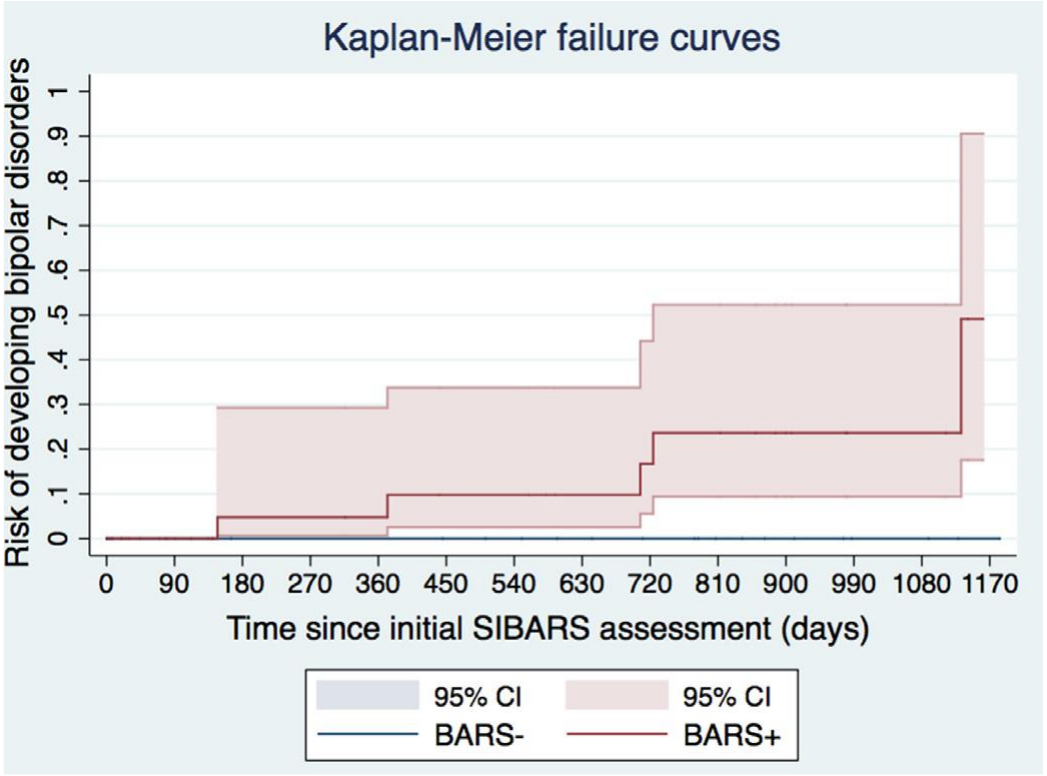
Group 3: DEPRESSION + GENETIC RISK
Genetic Risk:
First degree relative with bipolar disorder *(SIBARS 4)*
PLUS
Depression:
Subthreshold intensity of the Depression scale (SIBARS 2):
Severity score of 3–5 PLUS Frequency score of 3–6
Subthreshold frequency of the Depression scale (SIBARS 2):
Severity score of 6 PLUS Frequency score of ≤ 3

Group 4: CYCLOTHYMIC FEATURES + GENETIC RISK
Genetic Risk:
First degree relative with bipolar disorder *(SIBARS 4)*
PLUS
Cyclothymic features:
Total score on the Cyclothymic Features rating (SIBARS 3):
Score ≥ 11

Group 5: SUBTHRESHOLD MIXED EPISODE:
Subtreshold mania:
Subthreshold intensity of the Subtreshold Mania scale (SIBARS 1):
Severity score of 3–4 PLUS Frequency score of 3–6
Subthreshold frequency of the Subtreshold Mania scale (SIBARS 1):
Severity score of 5–6 PLUS Frequency score of ≤ 3
PLUS
Depression:
Subthreshold intensity of the depression scale (SIBARS 2):
Severity score of 3–5 PLUS Frequency score of 3–6
Subthreshold frequency of the depression scale (SIBARS 2):
Severity score of 6 PLUS Frequency score of ≤ 3
PLUS
Symptoms should not have been present for more than 4 days

Group 6: MOOD SWINGS:
Severity score of 3–6 *of the mood swings scale (SIBARS 5)*
PLUS
Frequency score of 3–6 *of the mood swings scale (SIBARS 5)*

Retrospective Evaluation of BARS criteria (n = 71, Fusar-Poli et al., 2018)

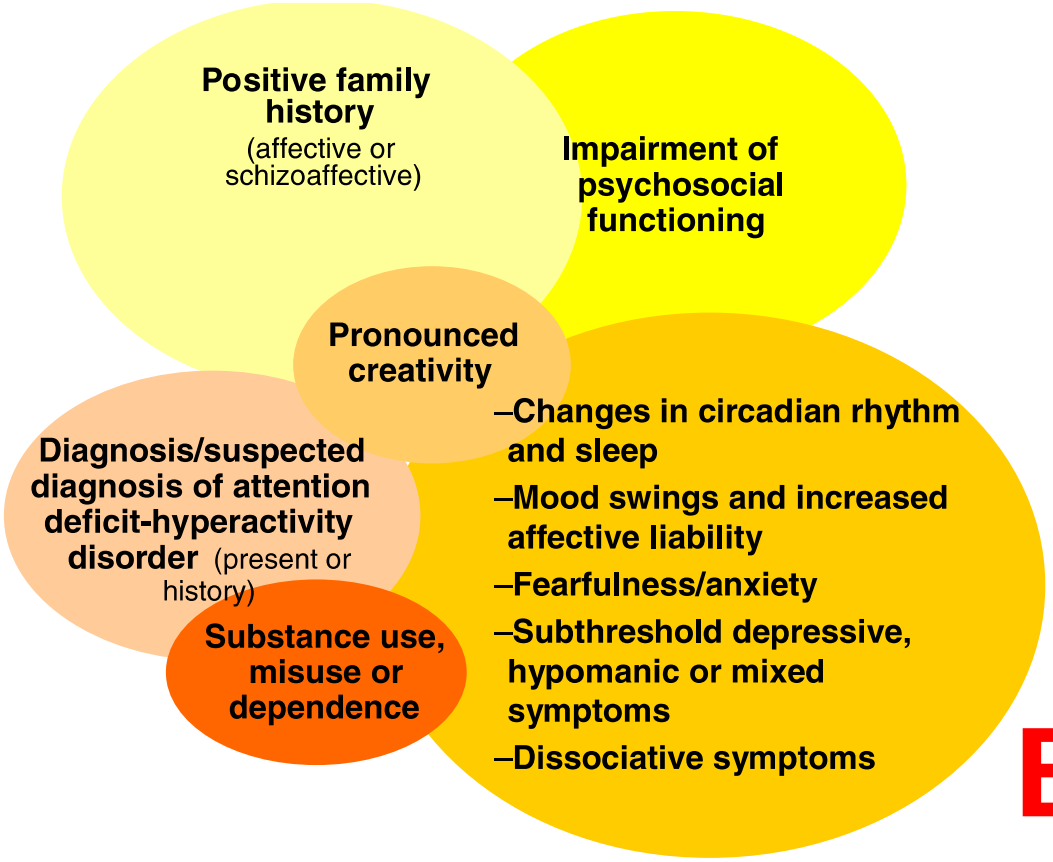


5 conversions to BD in BARS+
0 conversions to BD in BARS-

Fig. 1. Kaplan-Meier failure curves for the SIBARS interview in individuals accessing CHR-P services ($n = 71$). There were 18 individuals at risk at 6 months, 17 at 12 months, and 11 at 24 months in the BARS- group and 21 individuals at risk at 6 months, 19 at 12 months, and 12 at 24 months in the BARS + group. Estimates beyond this timepoint are plotted but should be considered cautiously.

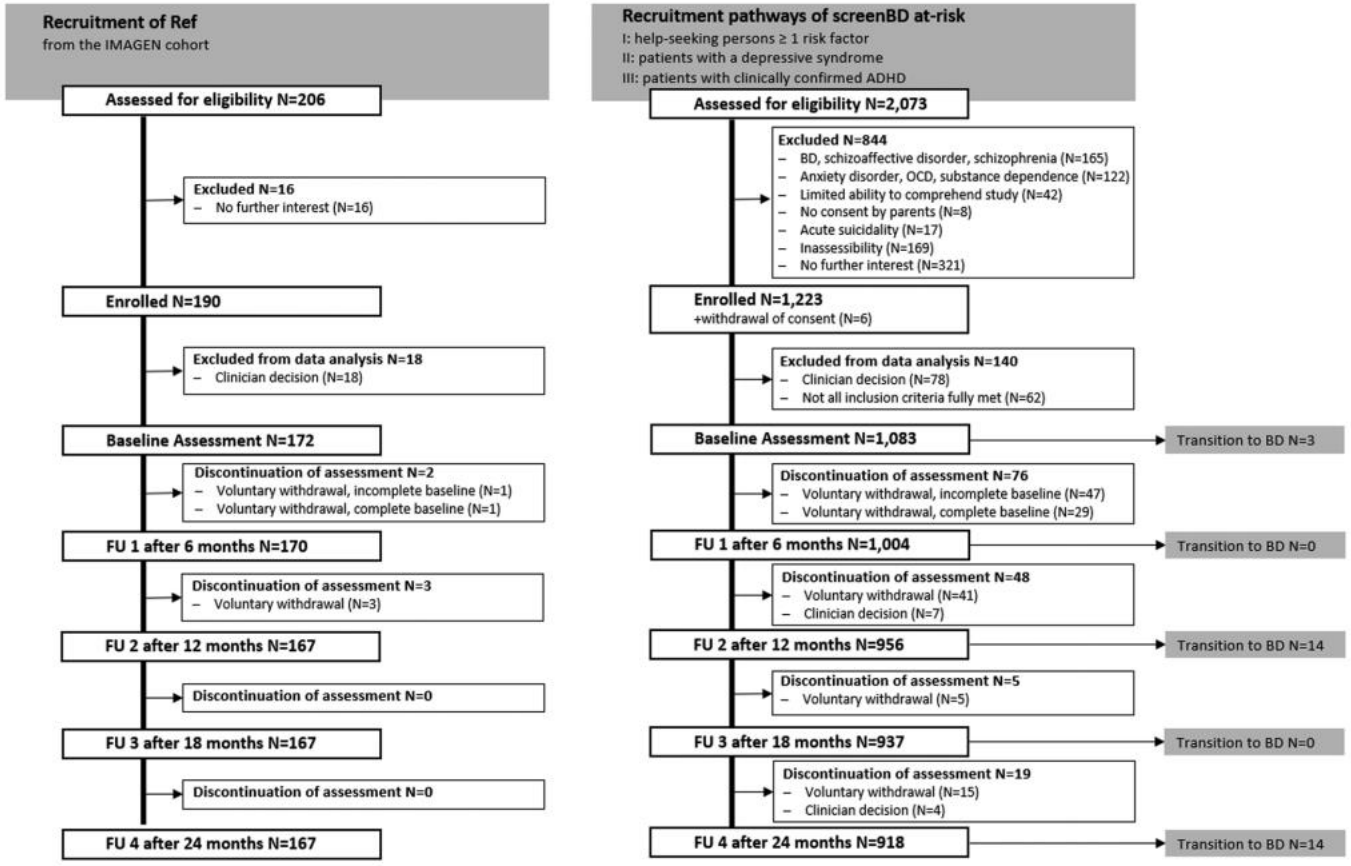
Early Phase Inventory for bipolar disorders – EPIbipolar

(Leopold et al., 2012; Pfennig et al., 2019)



BipoLife

Two-year findings from the multicenter prospective, naturalistic Early-BipoLife study



Martini,….,Pfennig, 2024

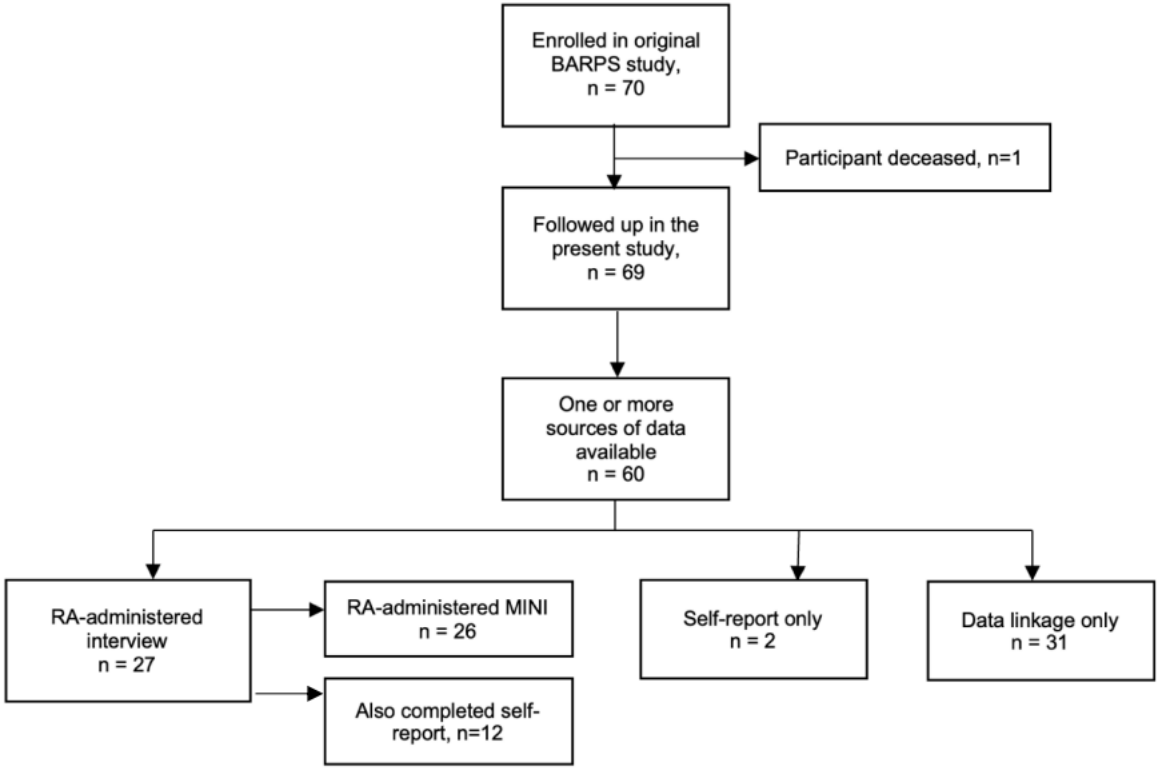
Transition rates in screenBD at-risk (N = 1083) and Ref (n=172)

	screenBD at-risk (*N* = 1083)	
	N	Converter Rate
Total transition rate screenBD at-risk	**1083**	**31 (2.9 %)**
Total transition rate in Ref	**172**	**0 (0.0 %)**
Patients with positive family history of BD (EPI*bipolar*)	83	5 (6.0 %)
Help-seeking patients with ≥ **1 potential *risk factor*** (recruitment pathway I)	433	13 (3.0 %)
Patients with major depressive disorder/ **depressive syndrome** (recruitment pathway II)	540	17 (3.1 %)
Patients with ADHD (recruitment pathway III)	110	1 (0.9 %)
Persons with high risk in Early Detection Instruments		
EPI*bipolar* (high risk)	384	18 (4.7 %)
BPSS-FP (any risk syndrome)	258	17 (6.6 %)
BARS criteria (any risk group)	713	23 (3.2 %)

BD: bipolar disorder, EPI*bipolar*: Early Phase Inventory for bipolar disorders, ScreenBD at-risk: help-seeking participants who positively screened for a potentially increased risk for BD at baseline, ADHD: attention deficit/hyperactivity disorder, BAR: Bipolar At-Risk, BARS: extended BAR, BPSS-FP: Bipolar Prodrome Symptom Scale-Full Prospective.
N: number of participants,%: percentage of participants.

Martini,….Pfennig, 2024

Flow diagram of 10 -13 Years BARPS Follow-up



BARPS: Bipolar At-Risk Prospective Study, RA: Research Assistant; MINI: Mini International Neuropsychiatric Interview

Rathesh,… ,Bechdolf, 2023

Clinical, Demographic and Treatment Characteristics of participants characteristics over the 10 to 13 years follow-up

Characteristic	Participants, No/total No. (%)				
	BAR (n = 28)	Non-BAR (n = 32)	χ^2	*P* value	Cramer *V*
Age at end of follow-up, mean (SD), y	33.27 (3.06)	32.50 (2.71)	530.0[a]	.33	−0.12[b]
Gender					
Female	24/28 (85.7)	25/32 (78.1)	NA[c]	.67	0.10
Male	4/28 (14.3)	6/32 (18.8)	NA	NA	NA
Nonbinary	0	1/32 (3.1)	NA	NA	NA
Country of birth					
Australian	25/28 (89.3)	27/32 (84.4)	NA[c]	.86	0.07
Other					
All	3/28 (10.7)	5/32 (15.6)	NA	NA	NA
Eritrea	0	1/32 (3.1)	NA	NA	NA
India	2/28 (7.1)	0	NA	NA	NA
Indonesia	0	1/32 (3.1)	NA	NA	NA
Malaysia	1/28 (3.6)	0	NA	NA	NA
Sri Lanka	0	2/32 (6.3)	NA	NA	NA
Vietnam	0	1/32 (3.1)	NA	NA	NA
In a relationship	8/14 (57.1)	8/13 (61.5)	2.38	.67	0.04
Completed tertiary education	7/11 (63.6)	3/9 (33.3)	NA[c]	.37	0.30
Currently unemployed	2/13 (13.4)	3/14 (21.43)	NA[c]	.64	0.08
Diagnosis					
MINI					
Major depressive disorder, lifetime	8/12 (75.0)	14/14 (100)	NA[c]	.03	0.39
Psychotic symptoms or disorder	4/12 (25.0)	2/14 (14.3)	NA[c]	.64	0.14
Linkage data[d]					
Depressive disorder	20/25 (80.0)	26/30 (86.7)	0.44	.51	0.09
Borderline personality disorder	14/25 (56.0)	13/30 (43.3)	0.88	.35	0.13
Other personality disorder	7/25 (28.0)	5/30 (16.7)	1.03	.31	0.14
Anxiety disorder	9/25 (36.0)	12/30 (40.0)	0.09	.76	0.04
Stress-related disorder	9/25 (36.0)	9/30 (30.0)	0.22	.64	0.06
Substance use-related diagnosis[e]	10/25 (40.0)	7/30 (23.3)	1.77	.18	0.18
Treatment					
Counselling or therapy	11/13 (84.6)	11/14 (78.6)	NA[c]	>.99[f]	0.08
Mood stabilizer prescribed	6/11 (54.6)	2/11 (18.2)	NA[c]	.18[f]	0.38
Other medication prescribed	11/13 (84.6)	11/11 (100)	NA[c]	.48	0.28
Engaged with tertiary mental health care service	7/13 (23.1)	2/14 (28.6)	NA	>.99[f]	0.11
Engaged with psychologist	12/13 (92.3)	10/14 (71.4)	NA	.33	0.30

Abbreviation: MINI, Mini International Neuropsychiatric Interview; NA, not applicable.

[a] Mann-Whitney *U* statistic.

[b] Pearson *r*.

[c] Fisher exact test used.

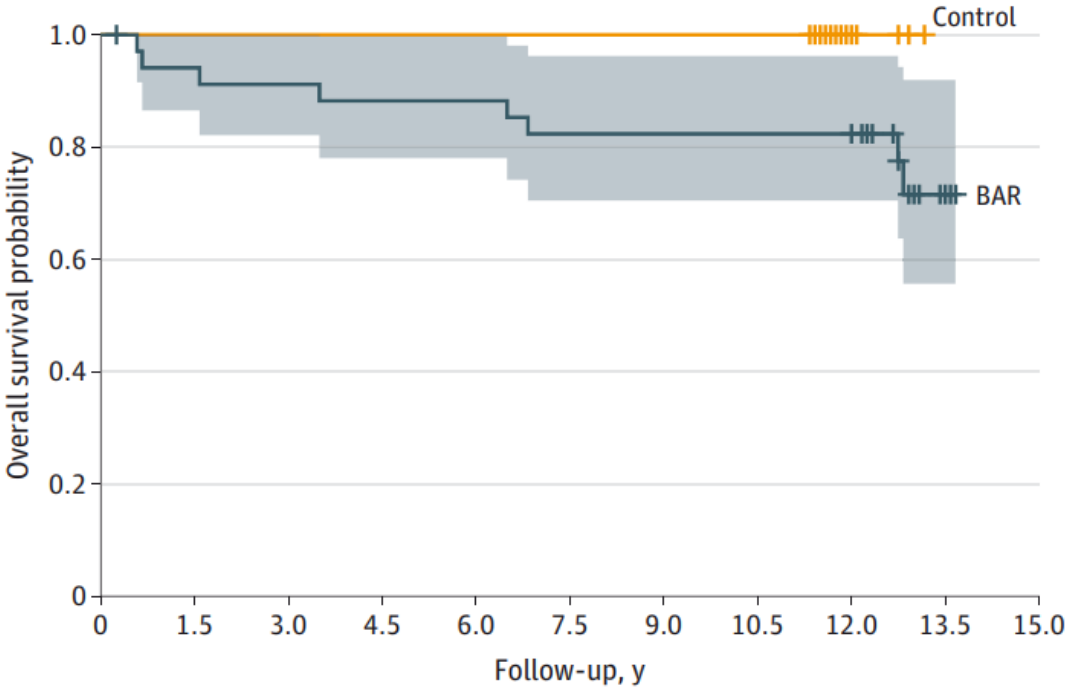
[d] Any diagnosis recorded.

[e] Other than tobacco.

[f] Two-sided Fisher exact test performed when the expected cell number was less than 5.

Rathesh,… ,Bechdolf, 2023

Kaplan Meyer estimates for transition to BD for BAR and Non-BAR at 10 to 13 year follow-up



No. at risk										
Control	35	35	35	35	35	35	35	35	10	0
BAR	35	32	31	30	30	28	28	28	28	6

28.6 % vs. 0.0 %, p<0.001

Rathesh,… ,Bechdolf, 2023

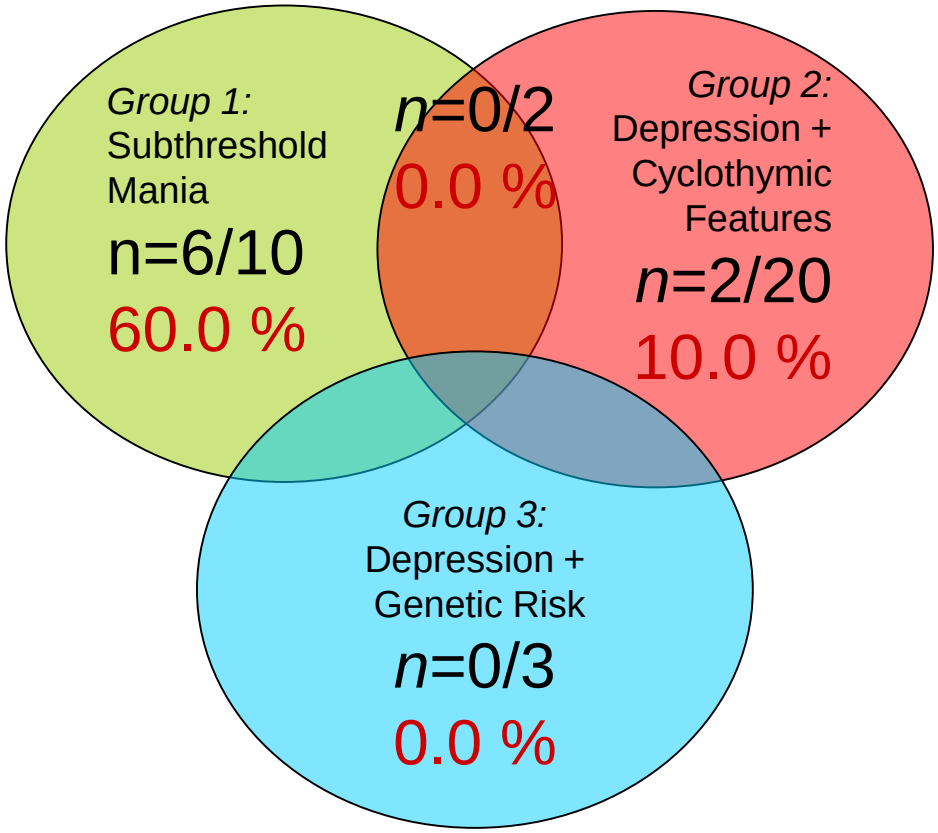
BD diagnosis at follow up and data sources providing information for consensus

Final diagnoses based on all data		Data availability across time points and sources			
		12-month follow up	10-13 year follow up		
Consensus diagnosis between 1-13 years of follow up	**N**	**LIFE**	**MINI**	**Online self-reports**	**Data linkage**
Bipolar I	1	0	0	0	1
Bipolar II	7	2	5	4	6
Schizoaffective	1	0	0	0	1
Subthreshold BD	3	0	3	1	3
No BD	48	2	18	12	44

BD: Bipolar disorder
LIFE: Longitudinal Interval Follow-up Evaluation
MINI: Mini International Neuropsychiatric Interview

Note: Out of four participants with a 12-month diagnosis of BD II, two were re-interviewed using the MINI where they reported symptoms or functional change indicating that they were sub-threshold for BD. Therefore, they were considered not to have a long-term diagnosis of BD.

Conversions by BAR sub-group



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Interventions in People At-Risk of Bipolar Disorder ?

Review

Early intervention for people at high risk of developing bipolar disorder: a systematic review of clinical trials

Gayatri Saraf, Ehsan Moazen-Zadeh, Jairo Vinicius Pinto, Kimia Ziafat, Ivan J Torres, Muralidharan Kesavan, Lakshmi N Yatham

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Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada (G Saraf MD, E Moazen-Zadeh MD, JV Pinto MD, K Ziafat BSc, Prof I J Torres PhD, Prof L N Yatham MBBS); British Columbia Mental Health and Substance Use Research Institute, Vancouver, BC, Canada (Prof I J Torres); Addiction Institute of Mount Sinai, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA (E Moazen-Zadeh MD); Department of Psychiatry, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil (JV Pinto); and National Institute of Mental Health and Neuro Sciences, Bengaluru, India (Prof M Kesavan MD)

Early intervention approaches are built on the premise of preventing disability, burden, and cognitive sequelae caused by bipolar disorder. The objective of this systematic review was to characterise the effectiveness of all the available psychological and pharmacological treatments for early intervention in people at high risk of developing bipolar disorder. The study was registered with PROSPERO (CRD42019133420). We did a systematic search to identify studies published in ten databases up to March 27, 2020. Randomised controlled trials and cohort studies that assessed the effect of pharmacological or psychological interventions in people at high risk of developing bipolar disorder were included. Studies of first episodes of mania were excluded. Eligible papers were assessed for quality and data were extracted. The primary outcomes were change in manic and depressive symptoms from baseline to endpoint. Of the 2856 citations retrieved by our search, 16 studies were included; five evaluated pharmacotherapeutic strategies (three randomised controlled trials and two open-label studies), ten assessed psychotherapeutic strategies (four randomised controlled trials and six open-label studies), and one randomised controlled trial assessed combination therapy; these 16 trials included a total of 755 participants at high risk of developing bipolar disorder. Quality assessment indicated fair to good quality for open-label studies, and a high risk of bias in four randomised controlled trials. Among the pharmacotherapeutic interventions, there is preliminary support for the efficacy of aripiprazole in reducing mood symptoms in people at high risk of developing bipolar disorder. Psychological interventions were effective for various outcomes. There was substantial methodological heterogeneity across studies. This systematic review underscores the need for multicentre, prospective, methodologically homogeneous studies evaluating conversion to bipolar disorder as an outcome measure.

Introduction

Bipolar disorder is a highly heritable, disabling, and functionally impairing psychiatric disorder, with a typical trajectory of undiagnosed and untreated illness over a substantial period of time, causing long-term distress and morbidity.[1] To reduce and prevent the morbidity and

Several attempts have been made to define at-risk groups, and clinical, endophenotypic, and genetic approaches have been described.[14] The offspring of individuals with bipolar disorder are at high risk, given the heritability of the disorder.[15] Evidence also suggests that a family history of bipolar disorder is associated with

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Pharmacological interventions (RCTs only)

	Study definition of high risk			Intervention	Outcomes	Sample size	Study design and duration	Main findings
	Participant diagnosis	Age	Family history					
Pharmacological interventions								
Geller et al (1998)[38]	Major depressive disorder lasting ≥ 2 months and CDRS score ≥40	6–12 years	Bipolar disorder type I or mania in first-degree or second-degree relatives, or multigenerational history	Lithium	KSADS and Children's Global Assessment Scale	30 (17 lithium group, 13 placebo group)	Randomised controlled trial; 6 weeks	Lithium was not significantly more efficacious than placebo for major depressive disorder in children with family history predictors of future bipolar disorder
Findling et al (2007)[39]	Cyclothymia or bipolar disorder not otherwise specified and Young Mania Rating Scale score ≥ 13 during a period lasting at least 4 h within the past 2 months	5–17 years	At least one biological parent with bipolar disorder	Valproate	Time to discontinuation for any reason or because of a mood-related event; change in scores for Young Mania Rating Scale, Children's Depression Rating Scale Revised, and Children's Global Assessment Scale	56 (29 valproate group, 27 placebo group)	Randomised controlled trial; 5 years	No significant differences in time to discontinuation for any reason or because of a mood related event; improvement noted in all rating scales, but no treatment effect compared with placebo; no significant differences in adverse events
Findling et al (2017)[40]	Cyclothymia or bipolar disorder not otherwise specified	5–17 years	Parent with bipolar disorder and first-degree or second-degree relative with a mood disorder	Aripiprazole	Young Mania Rating Scale, Clinical Global Impression-Severity, Children's Global Assessment Scale, Children's Depression Rating Scale Revised, and DSM-IV ADHD Rating Scale	62 (31 aripiprazole group, 31 placebo group)	Randomised controlled trial; 12 weeks	Aripiprazole was significantly superior to placebo in improving mood, ADHD, and functioning scores; adverse events were mild and transient, with patients in the aripiprazole group more likely to have emesis, increased appetite, coughing, and weight gain compared with the placebo group, but these did not lead to discontinuation

Psychological interventions (RCTs only) I

	Study definition of high risk			Intervention	Outcomes	Sample size	Study design and duration	Main findings
	Participant diagnosis	Age	Family history					
Psychological interventions								
Miklowitz et al (2013)[45]	Lifetime diagnosis of bipolar disorder not otherwise specified, major depressive disorder, or cyclothymic disorder, plus Young Mania Rating Scale score >11, or Children's Depression Rating Scale Revised score >29	9–17 years	At least one first-degree relative with bipolar disorder type I or II	Family-Focused Therapy High Risk protocol	Young Mania Rating Scale, Children's Depression Rating Scale Revised, and Adolescent Longitudinal Interval Follow Up Evaluation	40 (21 Family-Focused Therapy High Risk protocol group, 19 enhanced care group)	Randomised controlled trial; 4 months	Youths in Family-Focused Therapy High Risk group had more rapid recovery from their initial mood symptoms, more weeks in remission, and a more favorable trajectory of Young Mania Rating Scale scores during 1 year than youths in the enhanced care group; treatment effect was greater among youths from families with high-expressed emotion than with low-expressed emotion
Goldstein et al (2018)[46]	None stated	12–18 years	At least one biological parent with bipolar disorder	Interpersonal and social rhythm therapy plus data-informed referral vs data-informed referral alone	Strengths and Difficulties Questionnaire, Mood and Feelings Questionnaire-Child, Child Mania Rating Scale; sleep quality	42 (21 interpersonal and social rhythm therapy plus data-informed referral group, 21 data-informed referral group)	Randomised controlled trial; 6 months	No significant differences between groups in self-reported and parent-reported mood and non-mood psychiatric symptoms; the interpersonal and social rhythm therapy plus data-informed referral group was significantly less likely to develop subthreshold hypomania or mania during follow-up than the data-informed referral group

Psychological interventions (RCTs only) II

	Study definition of high risk			Intervention	Outcomes	Sample size	Study design and duration	Main findings
	Participant diagnosis	Age	Family history					
Psychological interventions								
Miklowitz et al (2020)[44]	Lifetime DSM-IV or DSM-5 criteria for unspecified bipolar disorder, or major depressive disorder and a previous period of 1 week with Young Mania Rating Scale score >11 or 2 weeks with Children's Depression Rating Scale Revised score >29	9–17 years	At least one first-degree or second-degree relative with a lifetime history of bipolar disorder type I or II	Family-focused therapy vs enhanced care	Adolescent Longitudinal Interval Follow up Evaluation and Psychiatric Status Ratings Scales	127 (61 family-focused therapy group, 66 enhanced care group)	Randomised controlled trial; 4 months	No differences between groups in time to recovery from pretreatment symptoms; family-focused therapy was associated with longer intervals to depressive episodes compared with enhanced care
Leopold et al (2020)[45]	Subthreshold bipolar symptoms beginning or worsening in the past 12 months	15–30 years	First-degree or second-degree relatives with affective disorders, or schizoaffective disorders, or both	Group cognitive behavioural therapy vs unstructured group meetings	Hamilton Depression Rating Scale, Young Mania Rating Scale, Early Phase Inventory for bipolar disorders; Bipolar Prodrome Symptom Scale-Prospective, and mini version of the International Classification of Functioning	75 (38 group cognitive behavioural therapy, 37 unstructured group meetings)	Randomised controlled trial; 14 weeks	No significant group differences in terms of improvement in affective symptoms and psychosocial functioning, which improved significantly at week 14 in both groups
Fristad et al (2015)[41]	Cyclothymia or bipolar disorder not otherwise specified	7–14 years	None stated	Omega-3 plus IFPEP vs omega-3 plus active monitoring vs placebo plus IFPEP vs placebo plus active monitoring	KSADS Depression Rating Scale, Children's Depression Rating Scale, Young Mania Rating Scale, and KSADS Mania Rating Scale	23 (5 omega-3 plus IFPEP group, 5 omega-3 plus active monitoring group, 7 placebo plus IFPEP group, 6 placebo plus active monitoring group)	Randomised controlled trial; 12 weeks	Omega-3 plus IFPEP reduced depressive symptoms but not manic symptoms; effect size for IFPEP on child depression compared with active monitoring ranged from medium (Cohen's d=0·63 for Children's Depression Rating Scale Revised) to large (Cohen's d=1·24 for KSADS Depression Rating Scale); effect size of omega-3 on depression was medium (Cohen's d=0·48 for KSADS Depression Rating Scale)

IFPEP=individual family psychoeducational psychotherapy

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DOI: 10.1111/bdi.12894

ORIGINAL ARTICLE

BIPOLAR DISORDERS WILEY

Efficacy of cognitive-behavioral group therapy in patients at risk for serious mental illness presenting with subthreshold bipolar symptoms: Results from a prespecified interim analysis of a multicenter, randomized, controlled study

Karolina Leopold[1,2] | Michael Bauer[1] | Andreas Bechdolf[2,3] | Christoph U. Correll[4,5,6,7] | Martin Holtmann[8] | Georg Juckel[9] | Martin Lambert[10] | Thomas D. Meyer[11] | Steffi Pfeiffer[1] | Sarah Kittel-Schneider[12,13] | Andreas Reif[12,13] | Thomas J. Stamm[14,15] | Maren Rottmann-Wolf[1] | Josephine Mathiebe[1] | Eva L. Kellmann[1] | Philipp Ritter[1] | Seza Krüger-Özgürdal[9] | Anne Karow[10] | Lene-Marie Sondergeld[14,15] | Veit Roessner[16] | Cathrin Sauer[1] | Andrea Pfennig[1]

[1]Department of Psychiatry and Psychotherapy, Carl Gustav Carus University Hospital, Technische Universität Dresden, Dresden, Germany
[2]Department of Psychiatry, Psychotherapy and Psychosomatics, Vivantes Klinikum Am Urban, Berlin, Germany
[3]Department of Psychiatry and Psychotherapy, University Hospital Cologne, University Cologne, Köln, Germany
[4]Psychiatry and Molecular Medicine Hofstra Northwell School of Medicine, Hempstead, NY, USA
[5]Center for Psychiatric Neuroscience Feinstein Institute for Medical Research, Manhasset, NY, USA
[6]Department of Psychiatry, Recognition and Prevention (RAP) Program, The Zucker Hillside Hospital, Long Island, USA
[7]Department of Child and Adolescent Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Berlin, Germany
[8]Department of Child and Adolescent Psychiatry and Psychotherapy, LWL-University Hospital Hamm, Ruhr-University, Bochum, Germany
[9]Department of Psychiatry and Psychotherapy, LWL- University Hospital Bochum, Ruhr-University, Bochum, Germany
[10]Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[11]Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas HSC at Houston, Houston, TX, USA
[12]Department of Psychiatry and Psychotherapy, University Hospital Würzburg, Würzburg, Germany
[13]Department of Psychiatry, Psychosomatics and Psychotherapy, University Hospital, Frankfurt, Germany
[14]Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Berlin, Germany

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Inclusion criteria

- Age 15 to 30 years
- Positive family history for affective and/or schizoaffective disorders (first or second degree relatives)
- Reduction in psychosocial functioning (coping with demands of daily living) in the last 12 months versus before (measured by SIS)
- Subthreshold bipolar symptoms beginning or worsening in the last 12 months (measured by EPI*bipolar* and BPSS-P):

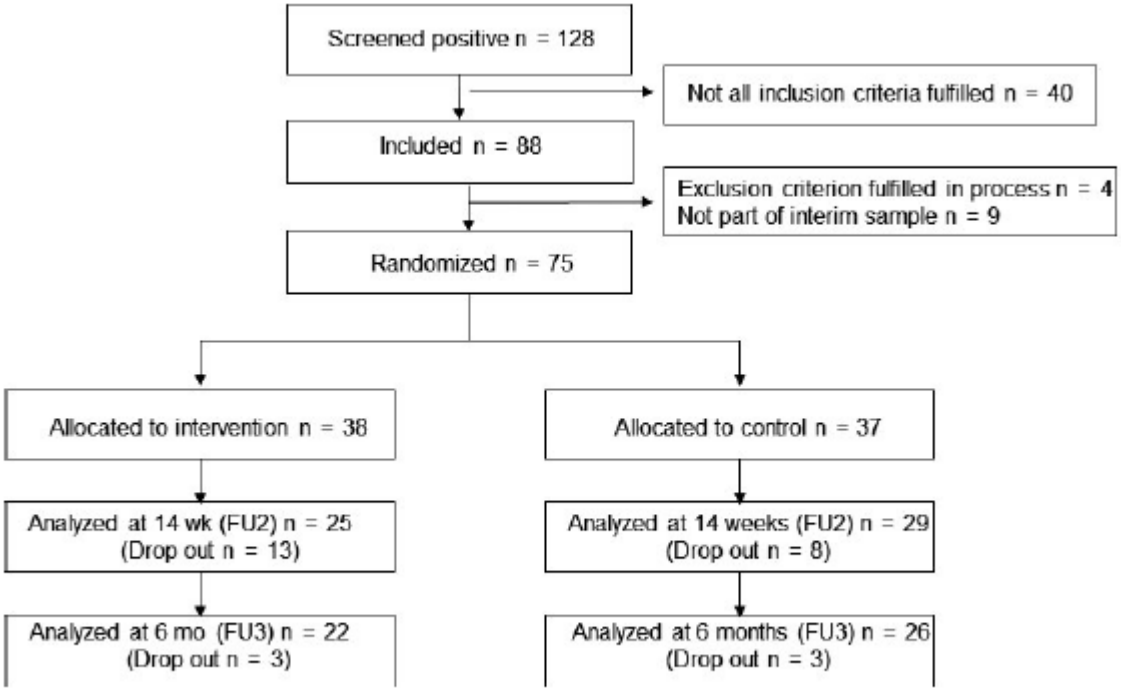
  a. Subthreshold mania and/or
  b. At least subthreshold depression with cyclothymic features and/or
  c. Cyclothymic features.

Intervention: CBT Group intervention - 14 weeks

(BEst (be)for(e) bipolar)

Session number	Topic/intervention
1	Confidence-building measures and rules
2	Psychoeducation about mental illnesses and BD in particular
3	Principles of Cognitive behavioral therapy
4	Psychoeducation about mood swings, identification, and training of coping strategies
5	Principles and exercises of mindfulness-based therapy
6	Problem-solving strategies and cognitive strategies
7	Psychoeducation about sleep disturbances and sensitization for a balanced life rhythm
8	Stress management
9,10, 11, 12	Identification of critical behaviors, reconceptualization, skills acquisition, consolidation and application training, and exercises of mindfulness-based therapy
13	Handling of early warning signs and crisis planning
14	Evaluation and Feed back

Consort


Screened positive n = 128
Not all inclusion criteria fulfilled n = 40
Included n = 88
Exclusion criterion fulfilled in process n = 4
Not part of interim sample n = 9
Randomized n = 75
Allocated to intervention n = 38
Allocated to control n = 37
Analyzed at 14 wk (FU2) n = 25
(Drop out n = 13)
Analyzed at 14 weeks (FU2) n = 29
(Drop out n = 8)
Analyzed at 6 mo (FU3) n = 22
(Drop out n = 3)
Analyzed at 6 months (FU3) n = 26
(Drop out n = 3)

Results (n= 75, Leopold et al., 2020)

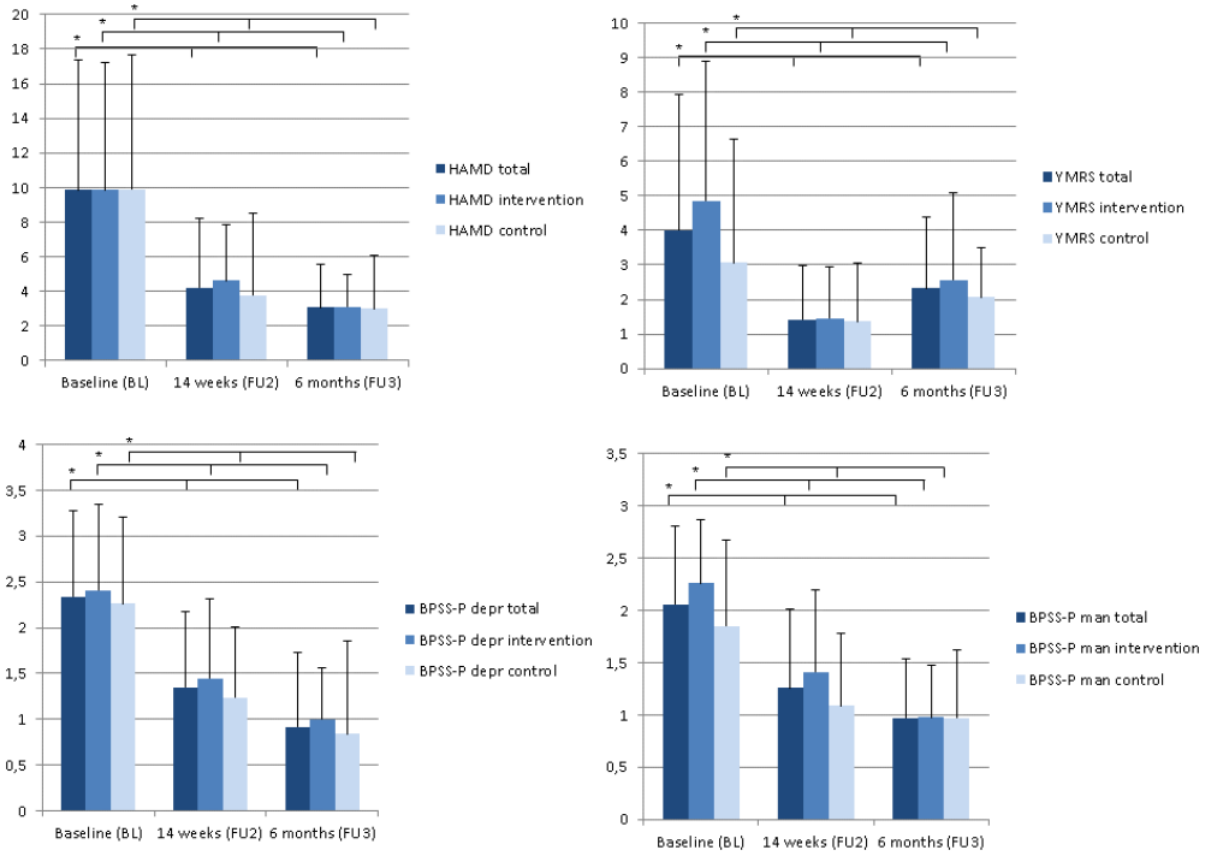


FIGURE 2 Development of affective symptomatology over time. Development of depressive (HAMD score, upper left) and manic (YMRS score, upper right) symptom severity as well as BPSS-P depressive (lower left) and (hypo)manic (lower right) feature severity. Total scores are depicted in dark blue, that of the intervention group in middle blue and that of the control group in light blue. Abbreviations: BL: Baseline, FU2: follow-up at end of intervention (14 weeks), FU3: follow-up at 6 months. BPSS-P depr: BPSS-P depressive features, BPSS-P man: BPSS-P manic features *: P < .001 in total sample, intervention and control group for BL compared to FU2 and for development over the three time points from BL via FU2 to FU3. No significant differences between intervention and control group. Note that higher scores depict higher severity

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Qualitative Paper

"It felt very special, it felt customised to me"—A qualitative investigation of the experiences of participating in a clinical trial of CBT for young people at risk of bipolar disorder

Wendy Theresa Jones[1,2]*, Sarah Peters[2], Rory Edward Byrne[1,2], David Shiers[1,2,3], Heather Law[1,2,4] and Sophie Parker[1,2,4]

[1]The Psychosis Research Unit, Greater Manchester Mental Health NHS Foundation Trust, UK
[2]Division of Psychology and Mental Health, University of Manchester, UK
[3]Primary Care and Health Sciences, Keele University, UK
[4]Youth Mental Health Research Unit, Greater Manchester Mental Health NHS Foundation Trust, UK

Objectives. The Bipolar at Risk Trial (BART) was a feasibility randomized controlled trial investigating cognitive behavioral therapy (CBT) compared with treatment as usual (TAU) in young people at high risk of developing bipolar disorder (BD). This qualitative study aimed to investigate participants' experiences of trial involvement, and the acceptability of CBT for this population.

Design. Participants were those identified as being at risk of bipolar disorder, determined by current symptoms or family history. A purposive sample of twenty-one participants from both the intervention and TAU arms of the trial was recruited.

Methods. Twenty-one semi-structured interviews were conducted by service user researchers (13 participants had received therapy and 8 TAU). Interviews were audio recorded with consent from participants and transcribed verbatim. NVivo 11 Pro software was used to conduct an inductive thematic analysis.

Results. Super-ordinate themes were "adaptability and flexibility," "feeling understood and valued," and "relevance of study and intervention" which had two sub-themes —"value of the trial therapy" and "acceptability of trial processes." Participating in the trial and having therapy enabled participants to feel understood and valued by research assistants (RAs) and therapists. Participants viewed therapy as relevant to their current concerns and valued adaptability and flexibility of RAs and therapists.

Conclusions. Findings highlight the importance and value of flexibility, adaptability, and understanding in relationships between participants and trial staff. Findings also indicate

Summary

- More complex symptomatic course in BD compared to psychosis
- Prediction more complex
- Probably longer follow-ups needed
- BAR (at long term follow-up) present with clinical relevant transition rates
- Replication in bigger samples needed
- At this stage no clinical recommendation possible
- First results of a RCT of CBT in BAR available (Sophie Parker, Manchester, UK)

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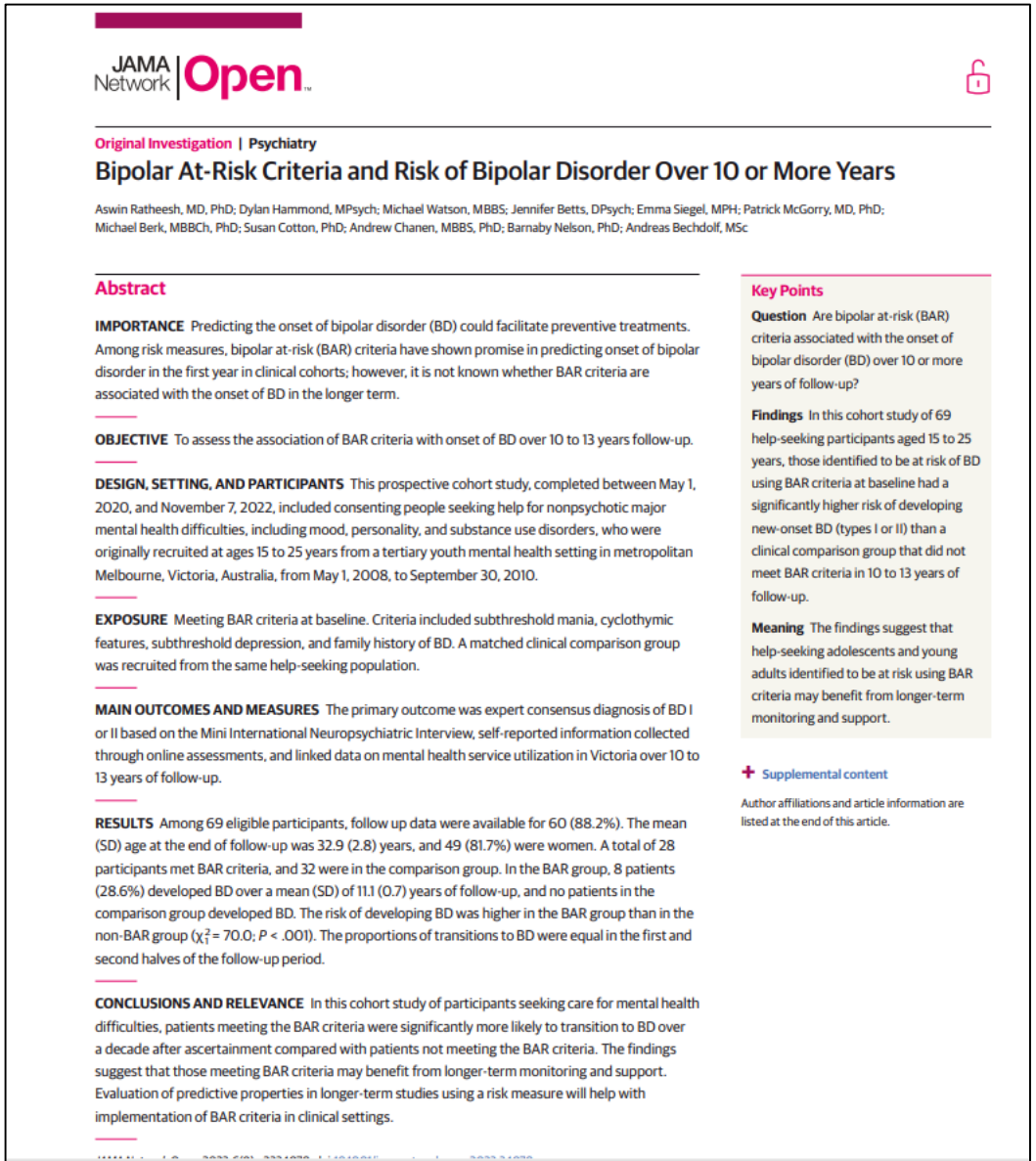

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Bipolar At-Risk Criteria and Risk of Bipolar Disorder Over 10 or More Years

Aswin Ratheesh, MD, PhD; Dylan Hammond, MPsych; Michael Watson, MBBS; Jennifer Betts, DPsych; Emma Siegel, MPH; Patrick McGorry, MD, PhD; Michael Berk, MBBCh, PhD; Susan Cotton, PhD; Andrew Chanen, MBBS, PhD; Barnaby Nelson, PhD; Andreas Bechdolf, MSc

Abstract

IMPORTANCE Predicting the onset of bipolar disorder (BD) could facilitate preventive treatments. Among risk measures, bipolar at-risk (BAR) criteria have shown promise in predicting onset of bipolar disorder in the first year in clinical cohorts; however, it is not known whether BAR criteria are associated with the onset of BD in the longer term.

OBJECTIVE To assess the association of BAR criteria with onset of BD over 10 to 13 years follow-up.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study, completed between May 1, 2020, and November 7, 2022, included consenting people seeking help for nonpsychotic major mental health difficulties, including mood, personality, and substance use disorders, who were originally recruited at ages 15 to 25 years from a tertiary youth mental health setting in metropolitan Melbourne, Victoria, Australia, from May 1, 2008, to September 30, 2010.

EXPOSURE Meeting BAR criteria at baseline. Criteria included subthreshold mania, cyclothymic features, subthreshold depression, and family history of BD. A matched clinical comparison group was recruited from the same help-seeking population.

MAIN OUTCOMES AND MEASURES The primary outcome was expert consensus diagnosis of BD I or II based on the Mini International Neuropsychiatric Interview, self-reported information collected through online assessments, and linked data on mental health service utilization in Victoria over 10 to 13 years of follow-up.

RESULTS Among 69 eligible participants, follow up data were available for 60 (88.2%). The mean (SD) age at the end of follow-up was 32.9 (2.8) years, and 49 (81.7%) were women. A total of 28 participants met BAR criteria, and 32 were in the comparison group. In the BAR group, 8 patients (28.6%) developed BD over a mean (SD) of 11.1 (0.7) years of follow-up, and no patients in the comparison group developed BD. The risk of developing BD was higher in the BAR group than in the non-BAR group ($\chi^2_1 = 70.0$; $P < .001$). The proportions of transitions to BD were equal in the first and second halves of the follow-up period.

CONCLUSIONS AND RELEVANCE In this cohort study of participants seeking care for mental health difficulties, patients meeting the BAR criteria were significantly more likely to transition to BD over a decade after ascertainment compared with patients not meeting the BAR criteria. The findings suggest that those meeting BAR criteria may benefit from longer-term monitoring and support. Evaluation of predictive properties in longer-term studies using a risk measure will help with implementation of BAR criteria in clinical settings.

Key Points

Question Are bipolar at-risk (BAR) criteria associated with the onset of bipolar disorder (BD) over 10 or more years of follow-up?

Findings In this cohort study of 69 help-seeking participants aged 15 to 25 years, those identified to be at risk of BD using BAR criteria at baseline had a significantly higher risk of developing new-onset BD (types I or II) than a clinical comparison group that did not meet BAR criteria in 10 to 13 years of follow-up.

Meaning The findings suggest that help-seeking adolescents and young adults identified to be at risk using BAR criteria may benefit from longer-term monitoring and support.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

andreas.bechdolf@vivantes.de

andreas.bechdolf@charite.de

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