Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis

Aswin Ratheesh [a,b,*], Susan M. Cotton [a,b], Christopher G. Davey [a,b], Ashleigh Lin [c], Stephen Wood [a,b,d], Hok Pan Yuen [a,b], Andreas Bechdolf [e], Patrick D. McGorry [a,b], Alison Yung [f], Michael Berk [a,g,h], Barnaby Nelson [a,b]

[a] Orygen, the National Centre of Excellence in Youth Mental Health, Melbourne, Australia
[b] Centre for Youth Mental Health, University of Melbourne, Australia
[c] Telethon Kids Institute, The University of Western Australia, Perth, Australia
[d] School of Psychology, University of Birmingham, UK
[e] Vivantes Hospital am Urban and Vivantes Hopital im Friedrichshain, Charite Medical University, Berlin, Germany
[f] Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[g] Florey Institute of Neuroscience and Mental Health, Melbourne, Australia
[h] Deakin University, IMPACT Strategic Research Centre, Barwon Health, Geelong, Australia

ARTICLE INFO

Article history:
Received 8 January 2017
Received in revised form 18 March 2017
Accepted 17 April 2017
Available online xxxx

Keywords:
Mania
Psychosis
At-risk
Bipolar disorder
Subthreshold
Antidepressants

ABSTRACT

Introduction: Psychosis and mania share conceptual, genetic and clinical features, which suggest the possibility that they have common antecedents. Participants identified to be at-risk for psychosis might also be at-risk for mania. We aimed to identify the rate and predictors of transition to mania in a cohort of youth with clinical or familial risk for psychosis.

Methods: Among a cohort of 416 young people with an at-risk mental state for psychosis defined using the Ultra-High-Risk (UHR) criteria, 74.7% were followed up between 5 and 13 years from their baseline assessment. We undertook a matched case-control examination of those who developed mania over the follow-up period compared to those who did not develop mania or psychosis. Transition to mania was determined using either a structured clinical interview, or diagnoses from a state-wide public mental health contact registry. Clinical characteristics and risk factors were examined at baseline using information from structured interviews, clinical file notes, rating scales and unstructured assessments.

Results: Eighteen participants developed mania (UHR-Manic transition or UHR-M, 4.3%). In comparison with participants matched on age, gender and baseline-study who developed neither mania nor psychosis, more UHR-M participants had subthreshold manic symptoms or were prescribed antidepressants at baseline. They also had lower global functioning.

Discussion: In addition to the UHR criteria, features such as subthreshold manic symptoms and antidepressant use may help identify at-risk groups that predict the onset of mania in addition to transition to psychosis. Presence of manic symptoms may also indicate syndrome specificity early in the prodromal phase.

1. Introduction

Prediction of the onset of mania may assist in prevention efforts and help to decrease the disability associated with this disorder (Bechdolf et al., 2012). Early or preventive interventions (Berk et al., 2007b) may also help prevent the possible decline in neurocognition (Lewandowski et al., 2011) or the risk of recurrence (Gignac et al., 2015) associated with onset of one or more manic episodes. Hence, methods to define clinical at-risk stages for bipolar disorder (BD) before the onset of frank manic episodes are important. Several findings point to a relationship between psychotic symptoms and risk of development of BD. These include the genetic overlap between schizophrenia and BD (Smoller, 2013), common therapeutic agents and the common structural and functional brain changes, cognition and peripheral markers (Clementz et al., 2016) seen across the two disorders. Psychosis-at-risk samples may, thus, represent one of the common at-risk stages for BD, or more specifically, mania.

Previous studies in at-risk cohorts for psychosis (Olvet et al., 2010) have been limited by the lack of information on characteristics such as sub-threshold mood symptoms, which may represent a useful risk

* Corresponding author at: Orygen, the National Centre of Excellence in Youth Mental Health, 35 Poplar Road, Parkville, VIC 3052, Australia.
E-mail address: aswin.ratheesh@orygen.org.au (A. Ratheesh).

http://dx.doi.org/10.1016/j.schres.2017.04.036
0920-9964/

identification approach prior to the onset of mania (Berk et al., 2007a). A meta-analysis of transition from at-risk cohorts (Fusar-Poli et al., 2013) identified that 6% developed BD, but no specific predictors of transition to BD were identified. Those who developed a broader group of affective psychoses had a lower mean age at baseline and were less likely to be identified using 'basic symptoms'. Further characterisation of pre-manic states may help identify a sub-group of participants within psychosis-at-risk clinical services. Additionally, such characteristics may add to the understanding of clinical prodromal characteristics for manic episodes. Several such characteristics have been identified to be predictive of later mania in longitudinal studies including the presence of a family history of bipolar disorder (Duffy et al., 2009), substance use disorders (Henquet et al., 2006), antidepressant use (Strober and Carlson, 1982), subthreshold manic symptoms (Fiedorowicz et al., 2011), anxiety symptoms (Gilman et al., 2012)and severity of depression (Holma et al., 2008). An association between these factors and later mania in psychosis-risk samples may help enrich such samples for prediction of onset of mania.

Thus, the aims of this study were: (i) to determine the proportion who transitioned to mania; and (ii) identify the clinical risk factors associated with the onset of mania, among help-seeking youth aged 15–30 years who were identified as ultra-high-risk (UHR) for psychosis. As the study was exploratory, no a-priori hypotheses were posited.

2. Method

We conducted a matched case-control examination of baseline clinical and research data within a large prospective cohort of help-seeking young people at ultra-high risk (UHR) of developing psychosis (Yung et al., 2012; Yung et al., 2004) and who were selected based on their inclusion in five research studies at baseline.

2.1. Participants

All participants were part of a cohort of 416 young people aged 15 to 30 years, were help-seeking and met criteria for being at UHR for psychotic disorder. The participants were recruited from a specialist clinic – the Personal Assessment and Crisis Evaluation (PACE) clinic – in a publicly funded youth mental health service in Melbourne, Australia. The referral characteristics of the PACE clinic (Yung et al., 2007), and the UHR features for psychosis (Yung et al., 2012), have been previously described. Briefly, all participants had one or more of the following criteria: (i) attenuated psychotic symptoms; (ii) brief limited intermittent psychotic symptoms; and/or (iii) trait vulnerability for psychotic illness (schizotypal personality disorder or history of psychosis in a first-degree relative) along with deterioration in functioning or chronic low functioning. The exclusion criteria for entry to PACE clinic included a previous psychotic episode, an organic cause for presentation, and past total antipsychotic exposure equivalent to a haloperidol dosage of more than 15 mg. A detailed description of the cohort has been previously published (Lin et al., 2015; Nelson et al., 2013). In addition, participants with full threshold BD I or II at baseline were excluded from the examination of incident mania in this study. Participants included in this study were recruited for five baseline studies focusing on: (i) prediction of onset of psychosis (Yung et al., 2003); (ii) stress-vulnerability (Thompson et al., 2007); (iii) randomized intervention of risperidone vs placebo (McGorry et al., 2002); (iv) open label intervention using lithium (Berger et al., 2012); and (v) longitudinal monitoring (Phillips et al., 2009). The lithium intervention was not aimed at (sub)threshold manic or affective symptoms, but was an open label intervention for attenuated psychotic symptoms related to UHR status (Berger et al., 2012). Thus, these studies represent a sub-proportion of young people referred to the PACE clinic and who consented to research studies at the clinic. Assessments in these studies were conducted by trained research assistants. The studies associated with this project were approved by the Melbourne Health Human Research Ethics Committee, and all participants provided written informed consent.

2.2. Baseline measures and risk variables

The baseline data on subthreshold symptoms, use of substances or antidepressants and family history were extracted by the first author (AR, a consultant psychiatrist) from a number of sources including: (i) the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P, First et al., 1997), including additional notes made by baseline assessors; (ii) Family Interview for Genetic Studies (FIGS, Maxwell, 1992); and (iii) patients' clinical files. In case of discrepancies across these sources, these were resolved using clinical judgment of the first author. BD I or II at baseline were excluded as possible diagnoses for all participants in the current study using SCID-I/P.

The clinical risk factors examined at baseline included:

i. *subthreshold manic symptoms*, defined as two or more mania symptoms at threshold/sub-threshold severity (rated 2 or 3 on the SCID-I/P) coded within the Current or Past section of mania or hypomania in SCID-I/P;
ii. *depression* documented in SCID-I/P as major depressive episodes or minor depressive episodes;
iii. *family history* of bipolar disorder, schizophrenia and/or psychotic disorders, and depression among first or second degree relatives. This was examined first in the ratings on the FIGS and if this information was not available, then by examining the assessment proforma in clinical files;
iv. *substance use,* primarily alcohol, cannabis and stimulants, as recorded in the Substance Use Questionnaire (Phillips et al., 2002). This instrument provided details on the ratings of frequency of use in the 'previous month' or 'lifetime before'. This was supplemented by information from clinical records. Cannabis or alcohol use was defined as more than once monthly use, as a categorical variable of 'lifetime use';
v. *symptom severity* measured using the Brief Psychiatric Rating Scale - total score ((BPRS, Overall and Gorham, 1962)), Scale for Assessment of Negative Symptoms ((SANS, Andreasen, 1984)), Hamilton Rating Scale for Depression ((HRSD, Hamilton, 1960)), and the Comprehensive Assessment of At-Risk Mental States ((CAARMS, Yung et al., 2005));
vi. *functioning* as measured by the Global Assessment of Functioning scale ((GAF, Endicott et al., 1976)) and Heinrichs Quality of Life Scale ((QLS, Heinrichs et al., 1984)).
vii. *medication use* as described in clinical files. A participant was considered to have had significant medication exposure if the clinical note indicated prescription of these medications on at least two occasions without documented non-compliance to this medication.

2.3. Follow-up

Among the participants initially assessed between 1993 and 2006, 74.8% (311) were followed up between 5 and 13 years later. The participants included in the study were followed up in two waves; first from October 2007 to May 2009 and the second from August 2012 to December 2013. In each follow-up wave, we contacted the participants and reassessed them using the SCID-I/P via face-to-face (64.4%) or telephone interviews (9.6%). If the participants could not be contacted, the state-wide mental health registry was examined to determine if there had been contact with public mental health services and the diagnoses provided if such contact had occurred. Given the accessibility of public mental health services for significant episodes of mental illness in Victoria, requirements of the local mental health legislation, limits of private practice services in Australia, and the high reliability of clinical diagnoses of BD I disorder diagnoses in general (Regier et al., 2013;

Please cite this article as: Ratheesh, A., et al., Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.04.036

Taiminen et al., 2001), it was considered that recorded manic episodes in the state-wide mental health registry were likely to be accurate.

Two subgroups were derived from the cohort of participants who were followed up. The first subgroup was those who later developed a manic episode after the baseline assessment according to DSM IV (American Psychiatric Association, 1994) criteria or equivalent (termed UHR –Manic transition or UHR-M). The second subgroup comprised participants individually matched on age and gender but who did not develop mania *or* threshold psychosis over the follow-up period (UHR- Non-transitioned or UHR-NT). Threshold psychosis was defined as a week or more of one or more positive psychotic symptom at full severity/intensity, as per previous research (Nelson et al., 2013).

2.4. Matching

For each included participant who developed mania, a control participant was chosen by serially selecting the next participant in the individual baseline study on the basis of their gender being the same and their baseline age being no more than 3 years apart. When participants were prescribed lithium or risperidone as part of the baseline study, the medication prescribed was also matched. Participants with baseline diagnosis of BD I or II were excluded.

2.5. Analyses

Baseline information was described using basic descriptive and inferential statistics. The included participants were compared with those who were not included using Mann Whitney *U* tests and chi-square (χ^2) tests. Due to the relatively small numbers of participants in individual groups, parametric assumptions were not met. Within the included sample ($n = 36$), we performed McNemar's tests for categorical variables and Wilcoxon signed rank tests for continuous variables to compare the baseline differences between the group that developed mania and those who did not. Effect sizes were calculated as the *r* score for the Wilcoxon-test obtained by dividing the z score by the square root of the total number of observations (Pallant, 2007). For categorical variables, Odds Ratios (OR) were determined as ratios of discordant pairs when cell numbers permitted the same.

3. Results

Eighteen participants developed mania over the follow up period (4.3%, UHR-M). The same number of individually matched participants was selected (UHR-NT). The sample that was included in the current analyses ($n = 36$) did not differ from those who were not included ($n = 380$) based on their age ($z = -1.5$, $p = 0.12$), gender ($\chi^2 = 0.88$, $df = 1$, $p = 0.35$) or baseline educational status ($\chi^2 = 6.75$, $df = 5$, $p = 0.24$).

The mean length of follow-up for the included participants was 9.6 years ($SD = 2.2$) and did not differ significantly between UHR-M and UHR-NT ($p = 0.92$) groups (Table 1). One participant developed BD I within 6 months from baseline assessment but completed suicide in the month after this follow-up assessment. It should be noted that the UHR-M sample had a high rate of transition to psychosis (77%) as operationally defined using the CAARMS, but only 22% developed sufficient psychotic symptoms to merit a schizoaffective diagnosis on SCID. One third of the participants ($n = 12$) had information on family history available from FIGS, one participant had no family history information available and the remaining participants ($n = 23$) had their family history information collected from clinical file notes. Three participants had file information regarding family members with depressive symptoms that did not allow an estimation of whether these participants had a family history of depression or not.

More than half of those who later developed mania had subthreshold manic symptoms at baseline. The prevalence of subthreshold manic symptoms was statistically significantly greater among the UHR-M group than that in the UHR-NT group. Similarly, the prevalence of antidepressant prescription for the UHR-M group (76.47%) at baseline was nearly double that of the UHR-NT group (38.46%). Those who later developed mania also had significantly lower GAF scores at baseline (Table 2).

No participant was recorded as having used prescribed psychostimulant medication. At baseline, the prevalence of daily cannabis use in the previous month was not different between those who later developed mania (50%) and those who did not (42.86%). Relatively few participants (twelve) were reliably assessed as having minor depression in the absence of major depression or prior to the onset of major depression from case records or from SCID notes. The different domains of CAARMS were not different across the two groups, including those of energy or the quality of emotions measured in terms of their frequency or intensity of symptoms.

*OR*s could not be computed for the significantly different variables between groups such as subthreshold manic symptoms and antidepressant use due to low cell numbers (zero pairs). The difference in global functioning ($r = 0.34$, $p = 0.04$) and severity of depression ($r = 0.29$, $p = 0.31$) between the two groups was of small effect.

Although there was no association between rates of antidepressant use and subthreshold mania symptoms among all participants at baseline, whether such sub-threshold mania symptoms were in the context of antidepressant use could not be established. This was primarily because the information on subthreshold mania symptoms was mostly obtained from SCID-I/P notes and antidepressant use mostly obtained from clinical files. However, there was a significant relationship at a trend level between the baseline severity of depression and the use of antidepressants at baseline ($U = 45.5$, $Z = -1.92$, $p = 0.055$). Sensitivity analyses excluding participants exposed to lithium at baseline identified that the significant associations between subthreshold manic

Table 1
Descriptive characteristics of participants who developed mania (UHR M, $n = 18$) and those who did not transition to psychosis or mania (UHR NT, $n = 18$) at follow-up.

Characteristic		Developed mania (UHR M) ($n = 18$)	Did not develop mania or psychosis (UHR NT) ($n = 18$)
Age at assessment, in years	M ± SD	28.19 ± 4.91	28.77 ± 5.06
Gender, male	% (*n*)	55.56 (10)	55.56 (10)
Length of follow-up, years	M ± SD	9.50 ± 2.38	9.66 ± 2.16
Diagnostic ascertainment of mania			
Structured assessment	% (*n*)	88.89 (16)	55.56 (10)
State-wide registry diagnosis	% (*n*)	12.11 (2)	44.44 (8)
Primary diagnosis on follow-up	*n*	Bipolar I disorder ($n = 14$) Schizoaffective disorder-manic type ($n = 4$)	Major depressive disorder ($n = 8$) Substance use disorder ($n = 2$) Anxiety disorder ($n = 2$) Brief psychotic disorder ($n = 1$) Dissociative disorder ($n = 1$) No formal diagnosis ($n = 4$)
Transition to psychosis threshold	% (N)	77.78 (14)	0.00 (0)

Please cite this article as: Ratheesh, A., et al., Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.04.036

Table 2
Baseline characteristics of youth who later developed manic episodes compared to a subgroup who did not develop mania or threshold psychosis (N = 36).

Characteristic	Measure	N (pairs)	Developed mania (UHR-M)*	Did not develop mania or psychosis (UHR-NT)#	Test statistic	*p*-Value
Age at baseline	*M* (*SD*)	18	19.89 ± 3.89	19.39 ± 3.48	Z = −0.28	0.777
Symptom domains						
Subthreshold manic symptoms	% (*n*)	14	58.82 (10)	0 (0)	–	**0.008**
Major depressive episodes	% (*n*)	14	76.47 (13)	54.54 (6)	–	0.375
Cannabis use- lifetime	% (*n*)	13	64.70 (11)	64.28 (9)	–	1.000
Antidepressant use- lifetime	% (*n*)	12	76.47 (13)	38.46 (5)	–	**0.031**
Family history						
Family history of bipolar disorder	% (*n*)	17	23.52 (4)	0 (0)	–	0.125
Family history of major depression	% (*n*)	14	6.67 (1)	25.00 (4)	–	0.375
Family history of schizophrenia spectrum disorder	% (*n*)	17	50.00 (9)	35.29 (6)	–	0.754
Family history of bipolar or a psychotic disorder	% (*n*)	17	55.56 (10)	35.29 (6)	–	0.549
Functioning						
Global assessment of Functioning	*M* (*SD*)	18	55.56 ± 9.02	62.33 ± 12.33	Z = −2.04	**0.041**
Heinrichs Quality of Life Scale	*M* (*SD*)	18	84.17 ± 33.38	82.06 ± 22.79	Z = −0.61	0.542
Symptom severity						
Scale for Assessment of Negative Symptoms	*M* (*SD*)	18	17.50 ± 10.59	13.94 ± 9.67	Z = −0.96	0.338
Brief Psychiatric Rating Scale total	*M* (*SD*)	18	45.72 ± 7.81	45.72 ± 10.03	Z = −0.02	0.981
Hamilton Anxiety Rating Scale	*M* (*SD*)	11	17.64 ± 9.27	14.18 ± 8.72	Z = −0.98	0.327
Hamilton Depression Rating Scale	*M* (*SD*)	12	25.00 ± 15.69	18.25 ± 12.81	Z = −1.02	0.307

*: UHR Mania; # UHR-Non-Transitioned; p values in bold represent p < 0.05.

symptoms and antidepressant use with later mania remained while the relationship with lower functioning was no longer significant.

4. Discussion

In our long-term follow-up study of youth identified to be at risk for psychosis at baseline, the proportion making a transition to mania over the 5 to 13-year follow-up period was low, but those who developed mania had a greater baseline prevalence of subthreshold manic symptoms, antidepressant use and had lower functioning.

The identification of subthreshold manic symptoms in the pre-diagnostic stages of those who later developed mania may indicate that disorder-specific symptoms may occur early in the prodromal phase. Pragmatically, the association with subthreshold manic symptoms points to the utility of the prodromal approach for mania as outlined in staging models for severe mental disorders (Scott et al., 2013). Previous prospective studies (Birmaher et al., 2006; Tijssen et al., 2010) have also identified the occurrence of subthreshold manic symptoms prior to threshold manic episodes. The higher prevalence of antidepressant use may point to their potential contribution in switch from depression to mania (Tondo et al., 2010). Alternatively, this may also indicate that persons with greater severity of depression are more likely to be prescribed antidepressant medication, as in the current study and consistent with clinical practice guidelines. Greater severity of depression has been previously associated with transition to mania among adolescents (Strober and Carlson, 1982).

The lower functioning in the UHR-M group may not be specific for transition to mania but that of the incipient risk of transition to psychosis (Nelson et al., 2013; Thompson et al., 2011), which occurred in most the UHR-manic sample, or that of poorer outcomes in general. Pragmatically, lower functioning could be a marker of greater risk of transition to BD with psychosis, as outlined in staging models for BD (Duffy, 2014). In the model proposed by Duffy, lower functioning among persons who later develop BD may be relatively specific to those who develop psychotic mania, as opposed to classical lithium-responsive mania. This has been supported to some degree also by the finding of lower psychosocial functioning among those with BD and comorbid psychosis in the months following an acute mood episode compared to those who did not suffer from psychosis (Levy et al., 2013).

One previous study had identified anxiety disorders at baseline as being associated with transition to BD with psychotic features (Correll et al., 2008) in a smaller cohort of persons with at-risk mental state on follow-up. Although the current study did not identify the presence of anxiety disorders using the SCID, the baseline severity of anxiety was not significantly different between groups.

4.1. Limitations

The small number of conversions to mania in the cohort limited the power to detect smaller differences between groups. However, the small number of conversions to mania is itself indicative of the possibility that samples with standard UHR criteria for psychoses may be relatively less useful in prevention paradigms for mania. This may be consistent with the low rate of incident BD reported in a large cohort of UHR participants from North America, though the length of follow-up in that study was lower (Webb et al., 2015). The confounding effect of the risk for psychosis in the sample is also an important consideration. A comparison group that later developed schizophrenia may have facilitated examination of factors more specific for BD in this study. However, given the high genetic and/or clinical loading for psychosis at baseline for all participants, as well as the large proportion that also transitioned to psychosis by follow-up, it was not possible to parse out the risk associated with psychosis in the current sample. Determination of diagnosis of eight control participants and two manic participants using non-interview based means (i.e., mental health registries) may be another limitation. However, it is unlikely that significant episodes of mania were missed, as these usually lead to contact with public mental health services. The lack of availability of some data particularly with respect to temporal sequences of onset of mania, psychosis and substance use limits the ability of the study to control for these confounding variables or to perform sub-group analyses based on ages of onset. However, substance-induced manic episodes were excluded using SCID interviews. Additionally, it is also possible that participants with missing data were more likely to have poorer outcomes (Allott et al., 2006). However, the identification of participants from statewide registries of mental health contact may have accounted for this to some degree. Lack of blinding and or extraction of data by independent raters may have increased the risk of observation and expectancy bias. Lastly, the study results may only be generalizable to clinically help-

Please cite this article as: Ratheesh, A., et al., Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.04.036

seeking youth and not to population samples. For population-based samples, there is a need for briefer and simpler measures of risk and outcomes.

4.2. Significance for pre-onset identification and interventions

This study validates the sub-threshold symptom approach in predicting the onset of mania. The identified characteristics may help improve risk prediction tools (Bechdolf et al., 2010; Correll et al., 2014) for the onset of mania among help-seeking young people with an at-risk mental state for psychosis but possibly also other help-seeking young people with clinical symptoms, distress or family history. The Bipolar At-Risk (BAR) criteria are an example of such a risk prediction tool (Bechdolf et al., 2010), which have been associated with prospective transition risks of 11% within one year of follow-up (Bechdolf et al., 2014). These criteria incorporate concepts of subthreshold mania, cyclothymic features, depression and genetic risk among youth at a similar age group as those with UHR criteria. Incorporation of reduced functioning in such criteria may be important given the association with transition to mania and/or psychosis. This finding also points to the possible trans-diagnostic significance of deterioration in functioning prior to the onset of severe mental disorders. The trans-diagnostic enriching of these disorders is also indicated by the finding that those with UHR criteria and baseline BD were at a greater risk of transition to psychosis in short to medium term follow-up (Salokangas et al., 2012), a finding that was not identified with non-bipolar depressive mood disorders or anxiety disorders. The association with antidepressant use may be of clinical relevance in considering the risks of prescription of these medications for help-seeking young people when other risk factors of latent bipolarity such as subthreshold manic symptoms or family history of severe mental disorders are present. Future well-powered cohort studies with cross-diagnostic outcomes will help clarify the predictive power of these risk factors.

Contributors

AR, BN, SC, CD and MB developed the protocol. AR collected additional data and prepared the initial draft. AR, HY and SC performed statistical analysis. AY, SW, AL, PM and AB contributed to the study conceptualization and manuscript preparation.

Conflicts of interest

This study was supported by National Health and Medical Research Council (NHMRC) program grants (350241 and 566529) to Drs. Yung, Wood, and McGorry, by the Colonial Foundation, and by an unrestricted research grant from Janssen-Cilag. No funding source played any role in the collection, analysis, interpretation, or publication of data.

CD is supported by a National Health and Medical Research Council of Australia (NHMRC) Career Development Fellowship (1061757). PM currently receives research support from the NHMRC and the Colonial Foundation. He has also received grant funding from NARSAD and unrestricted research funding from Astra Zeneca, Eli Lilly, Janssen-Cilag, Pfizer, and Novartis, as well as honoraria for educational activities with Astra Zeneca, Eli Lilly, Janssen-Cilag, Pfizer, Bristol Myer Squibb, Roche and the Lundbeck Institute. MB is supported by a NHMRC Senior Principal Research Fellowship (1059660) and receives grant funding from Deakin University, CRC for Mental Health, NIH, NHMRC, Stanley Medical Research Insitute, CRE in Clinical Research, Meat and Livestock Australia, University of British Colombia, National Natural Science Foundation of China. MB has received personal fees from Janssen, Lundbeck, Astra Zeneca, Servier, Glax-Smithkline and Lilly Pharmaceuticals and has pending patents for NAC and related compounds. AY has received an unrestricted research grant from Janssen-Cilag and honoraria from Janssen-Cilag. She has received funding from the National Health and Medical Research Council (NHMRC) (grants 350241 and 566529), an NHMRC Senior Research Fellowship, the Brain and Behavior Research Foundation (formerly NARSAD), and the Colonial Foundation. SW was supported by NHMRC Career Development Awards. BN was supported by a Ronald Phillip Griffith Fellowship and an NHMRC Career Development Fellowship. AL is supported by an NHMRC Early Career Fellowship (1072593). SMC is supported by an NHMRC Career Development Fellowship. AR, AB and HY have no conflicts to declare.

Role of funding source

No funding source played any role in the collection, analysis, interpretation, or publication of data.

Acknowledgements

None.

References

Allott, K., Chanen, A., Yuen, H.P., 2006. Attrition bias in longitudinal research involving adolescent psychiatric outpatients. J. Nerv. Ment. Dis. 194 (12), 958–961.
American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. fourth ed. (Washington, D.C.).
Andreasen, N.C., 1984. Scale for the Assessment of Negative Symptoms (SANS) University of Iowa (Iowa City).
Bechdolf, A., Nelson, B., Cotton, S.M., Chanen, A., Thompson, A., Kettle, J., Conus, P., Amminger, G.P., Yung, A.R., Berk, M., McGorry, P.D., 2010. A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults. J. Affect. Disord. 127 (1–3), 316–320.
Bechdolf, A., Ratheesh, A., Wood, S.J., Tecic, T., Conus, P., Nelson, B., Cotton, S.M., Chanen, A.M., Amminger, G.P., Ruhrmann, S., Schultze-Lutter, F., Klosterkotter, J., Fusar Poli, P., Yung, A.R., Berk, M., McGorry, P.D., 2012. Rationale and first results of developing at-risk (prodromal) criteria for bipolar disorder. Curr. Pharm. Des. 18 (4), 358–375.
Bechdolf, A., Ratheesh, A., Cotton, S.M., Nelson, B., Chanen, A., Betts, J., Bingmann, T., Yung, A., Berk, M., McGorry, P., 2014. The Predictive Validity of Bipolar At-risk (Prodromal) Criteria in Help Seeking Adolescents and Young Adults: A Prospective Study Bipolar Disorders.
Berger, G.E., Wood, S.J., Ross, M., Hamer, C.A., Wellard, R.M., Pell, G., Phillips, L., Nelson, B., Amminger, G.P., Yung, A.R., Jackson, G., Velakoulis, D., Pantelis, C., Manji, H., McGorry, P.D., 2012. Neuroprotective effects of low-dose lithium in individuals at ultra-high risk for psychosis. A longitudinal MRI/MRS study. Curr. Pharm. Des. 18 (4), 570–575.
Berk, M., Conus, P., Lucas, N., Hallam, K., Malhi, G.S., Dodd, S., Yatham, L.N., Yung, A., McGorry, P., 2007a. Setting the stage: from prodrome to treatment resistance in bipolar disorder. Bipolar Disord. 9 (7), 671–678.
Berk, M., Hallam, K., Lucas, N., Hasty, M., McNeil, C.A., Conus, P., Kader, L., McGorry, P.D., 2007b. Early intervention in bipolar disorders: opportunities and pitfalls. Med. J. Aust. 187 (7 Suppl), S11–S14.
Birmaher, B., Axelson, D., Strober, M., Gill, M.K., Valeri, S., Chiappetta, L., Ryan, N., Leonard, H., Hunt, J., Iyengar, S., Keller, M., 2006. Clinical course of children and adolescents with bipolar spectrum disorders. Arch. Gen. Psychiatry 63 (2), 175–183.
Clementz, B.A., Sweeney, J.A., Hamm, J.P., Ivleva, E.I., Ethridge, L.E., Pearlson, G.D., Keshavan, M.S., Tamminga, C.A., 2016. Identification of distinct psychosis biotypes using brain-based biomarkers. Am. J. Psychiatry 173 (4), 373–384.
Correll, C.U., Smith, C.W., Auther, A.M., McLaughlin, D., Shah, M., Foley, C., Olsen, R., Lencz, T., Kane, J.M., Cornblatt, B.A., 2008. Predictors of remission, schizophrenia, and bipolar disorder in adolescents with brief psychotic disorder or psychotic disorder not otherwise specified considered at very high risk for schizophrenia. J. Child Adolesc. Psychopharmacol. 18 (5), 475–490.
Correll, C.U., Olvet, D.M., Auther, A.M., Hauser, M., Kishimoto, T., Carrion, R.E., Snyder, S., Cornblatt, B.A., 2014. The bipolar prodrome symptom interview and scale-prospective (BPSS-P): description and validation in a psychiatric sample and healthy controls. Bipolar Disord. 16 (5), 505–522.
Duffy, A., 2014. Toward a comprehensive clinical staging model for bipolar disorder: integrating the evidence. Can. J. Psychiatr. 59 (12), 659–666.
Duffy, A., Alda, M., Hajek, T., Grof, P., 2009. Early course of bipolar disorder in high-risk offspring: prospective study. Br. J. Psychiatry J. Ment. Sci. 195 (5), 457–458.
Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33 (6), 766–771.
Fiedorowicz, J.G., Endicott, J., Leon, A.C., Solomon, D.A., Keller, M.B., Coryell, W.H., 2011. Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. Am. J. Psychiatry 168 (1), 40–48.
First, M.B., Spitzer, R.L., Gibbon, M., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders-Research Version, Patient Edition (SCID-I/P). Biometrics Research Department, New York State Psychiatric Institute, New York, NY.
Fusar-Poli, P., Bechdolf, A., Taylor, M.J., Bonoldi, I., Carpenter, W.T., Yung, A.R., McGuire, P., 2013. At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. Schizophr. Bull. 39 (4), 923–932.
Gignac, A., McGirr, A., Lam, R.W., Yatham, L.N., 2015. Recovery and recurrence following a first episode of mania: a systematic review and meta-analysis of prospectively characterized cohorts. J. Clin. Psychiatry 76 (9), 1241–1248.
Gilman, S.E., Dupuy, J.M., Perlis, R.H., 2012. Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions. J. Clin. Psychiatry 73 (6), 829–836.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Heinrichs, D.W., Hanlon, T.E., Carpenter Jr., W.T., 1984. The quality of life scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr. Bull. 10 (3), 388–398.
Henquet, C., Krabbendam, L., de Graaf, R., ten Have, M., van Os, J., 2006. Cannabis use and expression of mania in the general population. J. Affect. Disord. 95 (1–3), 103–110.
Holma, K.M., Melartin, T.K., Holma, I.A., Isometsa, E.T., 2008. Predictors for switch from unipolar major depressive disorder to bipolar disorder type I or II: a 5-year prospective study. J. Clin. Psychiatry 69 (8), 1267–1275.
Levy, B., Medina, A.M., Weiss, R.D., 2013. Cognitive and psychosocial functioning in bipolar disorder with and without psychosis during early remission from an acute mood episode: a comparative longitudinal study. Compr. Psychiatry 54 (6), 618–626.
Lewandowski, K.E., Cohen, B.M., Ongur, D., 2011. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychol. Med. 41 (2), 225–241.
Lin, A., Wood, S.J., Nelson, B., Beavan, A., McGorry, P., Yung, A.R., 2015. Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. Am. J. Psychiatry 172 (3), 249–258.

Maxwell, M.E., 1992. Family interview for genetic studies: a manual for FIGS. Clinical neurogenetic Branch, Intramural Research Program; NIMH.
McGorry, P.D., Yung, A.R., Phillips, L.J., Yuen, H.P., Francey, S., Cosgrave, E.M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adlard, S., Jackson, H., 2002. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch. Gen. Psychiatry 59 (10), 921–928.
Nelson, B., Yuen, H.P., Wood, S.J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D.L., Brewer, W.J., Francey, S.M., Amminger, G.P., Thompson, A., McGorry, P.D., Yung, A.R., 2013. Long-term follow-up of a group at ultra-high risk ("prodromal") for psychosis: the PACE 400 study. JAMA Psychiat. 70 (8), 793–802.
Olvet, D.M., Stearns, W.H., McLaughlin, D., Auther, A.M., Correll, C.U., Cornblatt, B.A., 2010. Comparing clinical and neurocognitive features of the schizophrenia prodrome to the bipolar prodrome. Schizophr. Res. 123 (1), 59–63.
Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.
Pallant, J., 2007. SPSS Survival Manual: A Step by Step Guide to Data Analysis Using SPSS for Windows Version 15. third ed. Open University Press Milton Keynes, UK.
Phillips, L.J., Curry, C., Yung, A.R., Yuen, H.P., Adlard, S., McGorry, P.D., 2002. Cannabis use is not associated with the development of psychosis in an 'ultra' high-risk group. Aust. N. Z. J. Psychiatry 36 (6), 800–806.
Phillips, L.J., Nelson, B., Yuen, H.P., Francey, S.M., Simmons, M., Stanford, C., Ross, M., Kelly, D., Baker, K., Conus, P., Amminger, P., Trumpler, F., Yun, Y., Lim, M., McNab, C., Yung, A.R., McGorry, P.D., 2009. Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: study design and baseline characteristics. Aust. N. Z. J. Psychiatry 43 (9), 818–829.
Regier, D.A., Narrow, W.E., Clarke, D.E., Kraemer, H.C., Kuramoto, S.J., Kuhl, E.A., Kupfer, D.J., 2013. DSM-5 field trials in the United States and Canada, part II: test-retest reliability of selected categorical diagnoses. Am. J. Psychiatry 170 (1), 59–70.
Salokangas, R.K.R., Ruhrmann, S., Graf Von Reventlow, H., Heinimaa, M., Svirskis, T., Luutonen, S., Juckel, G., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Klosterkotter, J., 2012. Axis i diagnoses and transition to psychosis in clinical high-risk patients. Eur. Psychiatry 27.
Scott, J., Leboyer, M., Hickie, I., Berk, M., Kapczinski, F., Frank, E., Kupfer, D., McGorry, P., 2013. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. Br. J. Psychiatry 202, 243–245.
Smoller, J.W., 2013. Disorders and borders: psychiatric genetics and nosology. Am. J. Med. Genet. B Neuropsychiatr. Genet. 162 (7), 559–578.
Strober, M., Carlson, G., 1982. Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three- to four-year prospective follow-up investigation. Arch. Gen. Psychiatry 39 (5), 549–555.
Taiminen, T., Ranta, K., Karlsson, H., Lauerma, H., Leinonen, K.M., Wallenius, E., Kaljonen, A., Salokangas, R.K., 2001. Comparison of clinical and best-estimate research DSM-IV diagnoses in a Finnish sample of first-admission psychosis and severe affective disorder. Nord. J. Psychiatry 55 (2), 107–111.
Thompson, K.N., Phillips, L.J., Komesaroff, P., Yuen, H.P., Wood, S.J., Pantelis, C., Velakoulis, D., Yung, A.R., McGorry, P.D., 2007. Stress and HPA-axis functioning in young people at ultra-high risk for psychosis. J. Psychiatr. Res. 41 (7), 561–569.
Thompson, A., Nelson, B., Yung, A., 2011. Predictive validity of clinical variables in the "at risk" for psychosis population: international comparison with results from the North American Prodrome Longitudinal Study. Schizophr. Res. 126 (1–3), 51–57.
Tijssen, M.J., van Os, J., Wittchen, H.U., Lieb, R., Beesdo, K., Mengelers, R., Wichers, M., 2010. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. Br. J. Psychiatry J. Ment. Sci. 196 (2), 102–108.
Tondo, L., Vazquez, G., Baldessarini, R.J., 2010. Mania associated with antidepressant treatment: comprehensive meta-analytic review. Acta Psychiatr. Scand. 121 (6), 404–414.
Webb, J.R., Addington, J., Perkins, D.O., Bearden, C.E., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Heinssen, R.K., Seidman, L.J., Tarbox, S.I., Tsuang, M.T., Walker, E.F., McGlashan, T.H., Woods, S.W., 2015. Specificity of incident diagnostic outcomes in patients at clinical high risk for psychosis. Schizophr. Bull. 41 (5), 1066–1075.
Yung, A.R., Phillips, L.J., Yuen, H.P., Francey, S.M., McFarlane, C.A., Hallgren, M., McGorry, P.D., 2003. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr. Res. 60 (1), 21–32.
Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D., 2004. Risk factors for psychosis in an ultra-high-risk group: psychopathology and clinical features. Schizophr. Res. 67 (2–3), 131–142.
Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust. N. Z. J. Psychiatry 39 (11 – 12), 964–971.
Yung, A.R., McGorry, P.D., Francey, S.M., Nelson, B., Baker, K., Phillips, L.J., Berger, G., Amminger, G.P., 2007. PACE: a specialised service for young people at risk of psychotic disorders. Med. J. Aust. 187 (7 Suppl), S43–S46.
Yung, A.R., Fusar-Poli, P., Nelson, B., 2012. The ultra-high risk approach to define psychosis risk. Curr. Pharm. Des. 18 (4), 346–350.

Please cite this article as: Ratheesh, A., et al., Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.04.036