Appendix 1: STROBE checklist and study design.

a) STROBE checklist

STROBE Statement—Checklist of items for inclusion in reports of cohort studies

	Item No	Recommendation	PAGE
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4, Appendix 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3, Appendix 1
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(b)For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4 & APPENDIX 2
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4, APPENDIX 1
Bias	9	Describe any efforts to address potential sources of bias	Appendix 2
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5, Appendix 3
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5, Appendix 3
		(b) Describe any methods used to examine subgroups and interactions	5, Appendix 3
		(c) Explain how missing data were addressed	5, Appendix 3
		(d) If applicable, explain how loss to follow-up was addressed	5, Appendix 3
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	05-Jun
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	Appendix 2, 3
		(c) Summarize follow-up time (e.g., average and total	3, Appendix 1

		amount)	
Outcome data	15	Report numbers of outcome events or summary measures over time	3, Appendix 1
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(b) Report category boundaries when continuous variables were categorized	5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	05-Jun
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	05-Jun
Discussion			
Key results	18	Summarize key results with reference to study objectives	06-Aug
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	06-Aug
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	06-Aug
Generalizability	21	Discuss the generalizability (external validity) of the study results	06-Aug
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3-4, Appendix 1

b) Study design

Young persons aged 16 to 25 currently accessing health services for a mood problem. In Newcastle, they may be in contact with primary care, CAMHS, EIP, child liaison (DSH), Youth Drug & Alcohol Services, adult psychiatry (CMHT), adult liaison, adult substance misuse services, CAT (Crisis Assessment and Treatment), adolescent or adult inpatients, counselling, psychotherapy, CBT or specialist mood or adult ADHD services.

Our goal was to recruit a sample of about 150 young people (about 100 from secondary care and 50 from primary care) with a recent history of depression (subthreshold or clinically diagnosed) and/or subthreshold/attenuated or brief hypomanic symptoms (i.e. do not meet diagnostic criteria for hypo/mania) occurring up to 2 years prior to recruitment), and monitoring progress through a reliable and well validated structured clinical interview over the course of 12 months. Any study participant could decide to withdraw from the study at any time. If a participant dropping out of all aspects of the study was “replaced” by an additionally recruited participant.

The secondary/tertiary care subsample represents the ultra-high-risk group, whilst the primary care subgroup will be identified through screening of GP data records. In the current study, individuals attending primary care or receiving inpatient care were excluded. (The primary care project will be studied at a later date).

Potential participants were initially identified by the clinician team and then contacted by their clinician to gauge their interest in the study, providing information and a contact sheet (for further information), as well as a consent form if they wish to take part. Those individuals who completed this process were then approached by a researcher to organize the assessment interviews.

Participants were asked to attend three separate interview sessions: Baseline 1, Baseline 2, and Follow-up. At Baseline 1, participants were first asked to complete some screening measures identified by a systematic

literature review including the General Behavior Inventory (GBI), the Hypomanic Checklist (HCL-32), Mood Disorder Questionnaire (MDQ), the Inventory to Diagnose Depression Lifetime Version (IDDL), the Centre for Epidemiological Studies Depression Scale (CES-D), and the Alcohol Use Disorders Identification Test (Audit). Minor adaptations have been made with respect to wording or layout of the HCL-32, MDQ, and IDDL based on feedback from people in this age group we had obtained in a prior pilot study next, participants completed the Structured Clinical Interview for DSM-IV-TR (with 'skip' questions removed). Afterwards participants completed a range of short questionnaires including EuroQOL, The World Health Organization adult ADHD self-report scale (ASRS), and the Health Survey.

In total, Baseline 1 took approximately three and a half hours to complete. Though lengthy, consultation with potential participants and the Steering Group Committee (SGC) suggested that this length of time would be acceptable for participants in this age range and would not be too demanding.

Baseline 2 interviews were held between two and six weeks after Baseline 1 to assess stability of the measures. The interval of 2 to 6 weeks was chosen to suit the participant's schedule, and to give an adequate period of time between repeating measures to estimate test-retest reliability. At Baseline 2, participants again completed HCL-32, MDQ, IDDL, CES-D, and the Health Survey. Participants were also be asked to complete the Structured Clinical Interview for DSM-IV-TR II, to assess personality and interpersonal functioning. In total, Baseline 2 took approximately two and a half hours to complete.

The follow-up interview was held 12 months after the Baseline 1 interview. At follow-up, participants were asked to complete the SCID-I again focusing on problems and symptoms occurring within the last 12 months. Participants also completed the Client Service Receipt Inventory (CSRI) for the same time period, and the EuroQoL. If participants preferred not to participate in the follow-up interview, or were unavailable, data from clinical case records regarding diagnosis and treatment were retrieved. (Testing of a subset of data recordings demonstrated a high level of agreement between case note recordings versus SCID diagnosis of hypo/mania (kappa .91). If there were any uncertainties regarding the diagnosis of hypo/mania, it was assumed the BAR presentation had not developed into BD-I or II.

Participants were reimbursed for their travel expenses, and for subsistence for each visit. With ethical approval, a further £10 Amazon.co.uk voucher was given to participants who complete the follow-up interview as a token of gratitude (for time, etc.). However, it was emphasized that this was related to their participation in the project not for engagement with their clinical team.

To summarize the data collection-

1. Baseline 1 Interview

General Behavior Inventory (GBI) [1].

Hypomanic Checklist (HCL-32) [2].

Mood Disorder Questionnaire (MDQ) [3].

Inventory to Diagnose Depression Lifetime Version (IDDL) [4].

Centre for Epidemiological Studies Depression Scale (CES-D) [5].

Alcohol Use Disorders Identification Test (AUDIT) [6].

Structured Clinical Interview for DSM-IV TR I (SCID-I)

Family History Screen [7].

EuroQOL [8].

The World Health Organization adult ADHD self-report scale (ASRS) [9].

Health Survey

Total: 3 ½ hours

2. Baseline 2 Interview (2-6 weeks later)

Hypomanic Personality Scale (HPS) [10].

HCL-32

MDQ

IDDL

CES-D

Health Survey

Structured Clinical Interview for DSM-IV TR II (SCID II)

Total: 2 ½ hours

3. Follow-up Interview (12 months after Baseline 1)

SCID I

Client Service Receipt Inventory (CSRI) [11]

EuroQOL

Total: 2 hours

Data Handling

Data were anonymized and entered in a numerically coded electronic dataset by researchers who were blinded to the risk status and /or clinical outcomes of the individuals. All data were treated as confidential and managed in accordance with the Data Protection Act 1998.

Appendix 2: Operationalization of BAR criteria**.**

Below, we report the operationalization of the BAR criteria that have been shown to have clinical utility (Scott et al., 2017) and/or represent a potentially important additional criterion (e.g. cyclothymia with genetic risk) that have been examined in recent publications.

Original BAR criteria Bechdolf et al., 2010; ibid, 2014)

I. Aged between 15 and 25 years,

and

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

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-h 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.

Additional criteria from Extended BAR Criteria [12]

Additional Risk Factors-

After examining five additional putative risk factors for early transition to BD. The following items met criteria for clinical utility:

- Evidence of psychotic symptoms during one or more previous episodes of mood disturbance
- Atypical depression (operationalized as anergia and/or hypersomnia)
- Probable antidepressant emergent elation: criteria were adapted from previous research (for a discussion see Brichant Petit-John et al., 2017). Namely, we regarded an individual as meeting this criterion if the mood elation or instability (i) occurred within 90 days of commencing treatment with a recognized antidepressant and (ii) was accompanied by at least one other symptom of mania. However, it is important to note, that this criterion was difficult to assess in some circumstances, and often required access to additional data records (e.g., such as free text). Given these uncertainties (and to be compatible with information recorded for Sample 2), we have reported the item as probable antidepressant emergent elation but draw attention to the fact that the reliability of the assessment of this criterion was the lowest of any variable studied.

Additional BAR criteria from SIBARS [7].

Note- we did not include some of the additional SIBARS criteria as e.g. mood instability overlaps with the initial selection criteria for inclusion of participants in our study (and with antidepressant induced elation, etc.).

Several studies have examined additional BAR criteria, many have not been replicated or been shown to have validity. However, studies of the offspring of BD parents do indicate that the combination of cyclothymia with familial risk may be an important additional BAR criterion [14,15]. As such, we included this in the current study (in fact all the cases that met this criterion also met the Depression and Genetic risk criterion). We give the operationalization below:

Cyclothymic features and Genetic risk

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 h period and at least 4 cumulative lifetime days meeting the criteria

+

Genetic Risk:

First degree relative with bipolar disorder

NB: In the current study, we found that all individuals with Cyclothymic features and Genetic risk also met criteria for Depression and Genetic risk, hence we report the group as 'Cyclothymia, Depression and Genetic risk.

Appendix 3: Statistical Analyses.

For the purposes of this study, missing continuous variables were replaced by sample means (as appropriate). Any missing ratings of BAR criteria were assumed to indicate the absence of that characteristic or outcome. Formulae for estimating other metrics were as follows:

Likelihood Ratios

The Likelihood Ratio (LR) is defined as

probability of finding in patients with target problem/probability of same finding in patients without target problem

In our study, the LR reflect is the likelihood that a specific BAR criterion would be present in a young person who experienced early transition to BD compared to the likelihood that that same finding would be found in a young person without early transition.

The positive (LR+) and negative (LR-) likelihood ratios for early transition were calculated as follows:

For each BAR criterion, we assumed that there are four possible subgroups:

group a, who are BAR positive and BD positive;

group b, who are BAR negative but BD positive;

group c, who are BAR positive but BD negative;

group d, who are BAR negative and BD negative.

Then:

LR+ = (a/(a+c)) / (b/(b+d))

LR- = (c/(a+c)) / (d/(b+d))

Using Bayes theorem, we then estimated the post-test probability of early transition, using the following formulae:

Post-test odds = pre-test odds * LR

Pre-test odds = pre-test probability / (1-pre-test probability)

Post-test probability = post-test odds / (post-test odds+1)

For example, several publications suggest that the pre-test probability was 25% for early transition to BD (i.e. this is the estimate prior to assessing any specific BAR criteria). This translates as pre-test odds of 0.33 (0.25/1-0.25), and the LR+ for a specific BAR criterion was 10, then the post-test odds can be calculated as follows:

Post-test odds = pre-test odds * LR = 0.33*10=3.3

Post-test probability = post-test odds / (post-test odds + 1) = 3.3/4.3=77%

Several websites provide online LR calculators (e.g., https://azcalculator.com/calc/likelihood-ratio.php). Likewise, switching between probability and odds can be done simply using a nomogram (such as online versions of Fagan's nomogram).

Diagnostic Odds Ratios

The Diagnostic Odds Ratio [DOR] is another summary statistic for estimating diagnostic/prognostic accuracy and allows comparison of between two or more tests. The DOR of a test is defined as the ratio of the odds of positivity in individuals with disease relative to the odds of positivity in individuals without disease, i.e.,

DOR = TP × TN/FP × FN

This can be re-written as DOR= +LR/-LR

The DOR depends significantly on the sensitivity and specificity of a test a high specificity and sensitivity [i.e., low rates of false positives and false negatives] will have a high DOR. (NB: the same DOR can be achieved with different combinations of sensitivity and specificity.

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