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Highlights:

- 28% of Stage 1b (CHARMS+) individuals transitioned to a Stage 2 disorder by 12-month follow-up.
- The Stage 1b (CHARMS+) group had more severe symptoms at follow-up than the CHARMS- group.
- 96% of Stage 2 transitions were initially to severe depression.
- Meeting criteria for multiple CHARMS subgroups was associated with higher transition risk.
- The strongest baseline predictor of transition was severity of depressive symptoms.
- The CHARMS criteria identified a group of individuals at-risk of imminent onset of severe mental disorder, particularly severe depression.

Transdiagnostic Risk Identification: A Validation Study of The Clinical High At Risk Mental State (CHARMS) Criteria

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ABSTRACT

A set of clinical criteria, the Clinical High At-Risk Mental State (CHARMS) criteria, have been developed to identify symptomatic young people who are at-risk of disorder progression. The current study aimed to validate the CHARMS criteria by testing whether they prospectively identify individuals at-risk of progressing from attenuated symptomatology to a first episode of serious mental disorder, namely first episode psychosis, first episode mania, severe major depression, and borderline personality disorder. 121 young people completed clinical evaluations at baseline, 6- and 12-month follow-up. The Kaplan-Meier method was used to assess transition rates. Cox regression and LASSO were used to

examine baseline clinical predictors of transition. Linear mixed effects modelling was used to examine symptom severity. 28% of CHARMS+ individuals transitioned to a Stage 2 disorder by 12-month follow-up. The CHARMS+ group had more severe symptoms at follow-up than the CHARMS- group. 96% of Stage 2 transitions were initially to severe depression. Meeting criteria for multiple CHARMS subgroups was associated with higher transition risk: meeting one at-risk group = 24%; meeting two at-risk groups = 17%, meeting three at-risk groups = 55%, meeting four at-risk groups = 50%. The strongest baseline predictor of transition was severity of depressive symptoms. The CHARMS criteria identified a group of individuals at-risk of imminent onset of severe mental disorder, particularly severe depression. Larger scale studies and longer follow-up periods are required to validate and extend these findings.

1. INTRODUCTION

The ultra-high risk (UHR) for psychosis risk identification approach has shown utility in identifying symptomatic young people at-risk of developing a psychotic disorder (Yung & McGorry 1996; Fusar-Poli et al., 2013; Fusar-Poli et al., 2020). However, longitudinal studies indicate that the UHR criteria capture risk not only for psychosis but also for a range of other persistent and incident psychiatric disorders (Fusar-Poli et al., 2012; Fusar-Poli et al., 2013; Lin et al., 2015; Hartmann et al., 2019), suggesting the possibility of a shared early pathway or pluripotent at-risk state for psychiatric disorders (McGorry 2013; McGorry 2014; McGorry et al., 2018). This is consistent with research showing the heterotypic course and

diagnostic instability of mental disorders (Plana-Ripoll et al., 2019; Caspi et al., 2020) and that mental (ill)health involves highly dynamic processes (Nelson et al., 2017). Additionally, the currently defined at-risk criteria are limited by the fact that they do not capture all individuals who will eventually develop a homotypic stage 2 disorder (Schultze-Lutter et al., 2015; Shah et al. 2017). Apart from the common transdiagnostic course of psychiatric disorders, statistical power for case identification is also increased by broadening the scope to include a range of diagnostic outcomes of interest due to the higher combined incidence rates, as opposed to focusing on one relatively low-incidence disorder, such as psychotic disorders (Cuijpers 2003).

This background suggests that it may be useful for early identification of risk for serious mental disorders to broaden the UHR for psychosis approach to a more encompassing transdiagnostic risk identification approach (McGorry et al., 2018). This aligns with the transdiagnostic clinical staging model of mental disorders, which is based on a continuum of illness defined according to stages based on severity and extension of symptoms, from Stage 0 (no current symptoms), to Stage 1a (help-seeking with distress), to Stage 1b (attenuated symptoms across syndromes), to Stages 2 to 4 (full threshold disorder with fluctuating severity and recurrence of symptoms) (McGorry & Hickie 2019; Shah et al., 2020). The clinical staging model posits that identifying and treating early stages could allow modification of the trajectory and progression to more serious stages of illness (McGorry & Mei 2021). It allows for tailored and proportionate intervention according to illness stage, providing more personalised care to young people presenting with sub-threshold symptomatology (Cross et al., 2014; Iorfino et al., 2019). The clinical staging model ultimately aims to improve assessment, prevention, and treatment of mental disorders, as well as guide pathoaetiological research (McGorry & Mei 2021).

The clinical staging model is consistent with other approaches in the field including: the Research Domain Criteria (RDoC) framework, which aims to recast the classification of mental disorders based on better clinical and neurobiological phenotyping (Insel et al., 2010); the Hierarchical Taxonomy of Psychopathology (HiTOP), which classifies psychopathology dimensions at multiple hierarchical levels (Kotov et al., 2017; Kotov et al., 2018; Conway et al., 2021); and the related general psychopathology ('p' factor) approach (Caspi et al., 2014), which suggests that a single dimension of psychopathology may underlie all mental disorders. However, the longitudinal, stage-based nature of the clinical staging model makes it particularly suitable as a guiding model for constructing transdiagnostic risk identification approaches (Eaton et al., 2023) and for applying clinically (McGorry & Hickie, 2019).

In order to identify young people at transdiagnostic risk, a set of clinical criteria are required. We have previously introduced these clinical criteria, referred to as the Clinical High At Risk Mental State (CHARMS) criteria (Hartmann et al., 2019; Hartmann et al., 2020; Hartmann et al., 2021). They include, but go beyond the established UHR for psychosis criteria and attempt to operationalise Stage 1b of the clinical staging model (attenuated symptoms across syndromes). The current paper reports on a cohort study that aimed to validate these criteria for identifying young people at transdiagnostic risk for Stage 2 psychosis, bipolar disorder, major depressive disorder, and borderline personality disorder. These 'outcome' disorders were chosen as previous research has identified a clear prodromal period for these disorders whereby subthreshold symptoms often precede onset of a first episode (Hartmann et al., 2019; Duffy et al., 2016). Researcher expertise was also a consideration in choosing these specific outcome disorders. Outcomes of individuals meeting CHARMS criteria (Stage 1b, 'at-risk individuals' referred as 'CHARMS+') were compared with clinical control individuals falling below the CHARMS cut-off points (Stage 1a, referred as 'CHARMS-'). We hypothesised that the at-risk group (i.e., CHARMS+) would show

higher transition rates to Stage 2 disorder and more severe psychopathology at follow-up compared to the control group (i.e., CHARMS-). The study also aimed to identify clinical predictors of progression to Stage 2 disorders in the CHARMS+ group.

2. METHODS

2.1 Participants

Participants were recruited from Orygen Specialist Program or one of two headspace clinical centres in Melbourne, Australia. The Orygen Specialist Program is a specialist mental health program for youth in Western Metropolitan Melbourne. Headspace centres are part of a national network of primary care youth mental health centres. Participants were help-seeking and received treatment as usual at these clinics. The inclusion criteria were: (1) capacity to give informed consent; (2) help-seeking; (3) aged 12-25 years (at entry in the study); (4) ability to speak adequate English (for the purpose of assessment). The exclusion criteria were: (1) a documented intellectual disability or (2) Stage 2 disorder, i.e. exceeding the CHARMS threshold for any of first episode psychosis (FEP), first episode mania (FEM), severe major depressive disorder (MDD), or borderline personality disorder (BPD). Assessment points were at baseline, 6- and 12-month follow-up. Further detail on the study protocol and design are available in Hartmann et al. (2019). The study adhered to the Declaration of Helsinki, was performed according to ICH-Good Clinical Practice (GCP), and was approved by the Melbourne Health Human Research Ethics Committee (#HREC/15/MH/276). The current paper is reported according to Strengthening the Reporting of Observational studies in Epidemiology (STROBE) criteria (Cuschieri 2019).

2.2 Design and Procedure

The CHARMS study was a longitudinal, prospective cohort study. The CHARMS criteria were assessed at the initial screening visit. If the young person met the CHARMS

criteria, they were included in the CHARMS+ group (i.e., clinical high risk). If their symptoms fell below the CHARMS criteria threshold, they were included in the control group (CHARMS-). If their symptoms exceeded the CHARMS threshold (i.e., Stage 2 disorder), they were excluded from the study. Further detail on the CHARMS criteria and threshold definitions can be found in Supplementary Table 1 and 2. A range of interviewer-rater and self-report measures were completed at baseline and readministered at 6- and 12-months follow-up (Hartmann et al., 2019). Throughout 2020 and 2021, 20 follow-up assessments (6- and 12- months follow-ups) were conducted via telehealth due to COVID-19 pandemic restrictions (8 participants completed their 6-month follow-up over telehealth and 12 participants completed their 12-month follow-up over telehealth).

2.3 Measures

2.3.1 Clinical interview measures:

Comprehensive Assessment of At-Risk Mental States (CAARMS). The CAARMS is a semi-structured interview developed to identify help-seeking individuals who are at UHR of psychosis (Yung et al., 2005). The CAARMS includes 7 domains. Each domain in the CAARMS receives a severity rating score (0-6), a frequency score (0-6) and pattern of symptoms with substance use/stress score (0-2). The CAARMS is widely used by researchers to identify individuals at high risk of psychotic disorders. The CAARMS severity score is defined as the summed score of the product of global rating scale and frequency of the 4 positive symptoms in CAARMS, as per previous research (Morrison et al., 2012). The CAARMS was used to identify individuals at-risk to transition to psychosis.

Quick Inventory of Depressive Symptomatology-Clinician rated (QIDS-C) (Rush et al., 2003). The QIDS-C is an interviewer-rated 16-item questionnaire that assesses the severity of depressive symptoms over the previous week. All QIDS items are weighted on a 4-point Likert scale from 0 to 3 with a higher score reflecting greater symptom severity. The

QIDS-C shows high internal consistency (α = .86) (Rush et al., 2003). The QIDS-C has good psychometric properties and is widely used to screen depression (Yeung et al., 2012). The QIDS was used to identify individuals at-risk of transitioning to severe depression. A score of 11-15 was considered 'at-risk' for MDD and a score of ≥ 16 was considered Stage 2 (severe MDD).

Social and Occupational Functioning Scale (SOFAS) (Goldman et al., 1992). The SOFAS is an observer-rated scale that assesses social and occupational functioning on a 0-100 scale, with higher scores indicating better functioning.

Structured Clinical Interview for DSM-5 (SCID-5) and the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD). SCID-5 and SCID-5-PD are semi-structured interviews that determine diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association 2015). Only the BPD and schizotypal personality disorder (SPD) modules of the SCID-5-PD were used in the current study. Each DSM-5 criterion is rated 0 (not present), 1 (subthreshold), 2 (present) (Shankman et al., 2018).

Young Mania Rating Scale (YMRS) (Young et al., 1978). The YMRS contains 11 interviewer-rated items that assess the severity of manic symptoms over the previous 48 hours. Four of the items are rated on a 0-8 scale, with the remaining 5 items rated on a 0-4 scale. A score of ≤ 12 indicates non-clinically significant symptoms. The YMRS shows good internal consistency (α =.88) and is considered the 'gold standard' of mania rating scales (Lam et al., 2006).

Global Functioning Scale: Social (GFS) (Cornblatt et al., 2007) ***and Global Functioning Scale: Role (GFR)*** (Cornblatt et al., 2007). GFS and GFR are complementary scales derived from the Global Assessment of Functioning (GAF). The GFS assess quality and quantity of peer relationships, level of peer conflict, age-appropriate intimate

relationships and functioning with family members. The GFR assesses age-appropriate performance in school and work duties. Both scales are rated using a 1 (extreme dysfunction) to 10 (superior functioning) scale.

2.3.2 Self-report measures:

Personality Inventory for DSM-5 Brief version (PID-5-BF) (Krueger et al., 2012). The PID-5-BF assesses maladaptive personality traits. The 25-item version aims to screen for personality pathology. The PID-5-BF measures 5 maladaptive traits, using 5 items for each trait. Each item is on a 4-point Likert scale ranging from 0-3. The overall score ranges from 0-75, with higher scores indicating greater personality dysfunction. The PID-5-BF is a reliable screening tool, with adequate internal consistency (Anderson et al., 2018).

Davos Assessment of Cognitive Biases Scale (DACOBS) (van der Gaag et al., 2013). The DACOBS measures 4 cognitive biases specific to positive symptoms of psychosis, 2 cognitive limitations and avoidance behaviour. It has 42 items scored on a 7-point Likert scale with a 2-week time frame, with higher score indicating greater cognitive biases/cognitive limitations/avoidance behaviour. The DACOBS has demonstrated good reliability (Cronbach'α = .90; reliability =.86) (van der Gaag et al., 2013).

Depression Anxiety Stress Scale-21 (DASS-21) (Lovibond & Lovibond 1995). The DASS-21 is a short version of the 42-item DASS. It is a dimensional self-report scale designed to assess negative emotional states of depression, anxiety, and stress over the past week. Responses are rated on a 4-point Likert scale (0-3). The scores from the 3 sub-scales are multiplied by two to enable comparison with the DASS-42, with a total score ranging from 0 to 42. The DASS-21 has strong psychometric properties, including internal consistency (α = .87) and validity (r=.76) (Weiss et al., 2015).

Bipolar Spectrum Diagnostic Scale (BSDS) (Ghaemi et al., 2005). The BSDS is a narrative-based scale that assesses the entire bipolar spectrum, including sub-threshold manic

states. The BSDS is composed of two parts. Part one is a paragraph containing 19 positively valanced sentences describing symptoms of bipolar disorder. Each sentence is followed by a space for individuals to checkmark if that sentence applies to them or not. Each checkmark corresponds to 1 point (19 points maximum). The second part is one simple multiple-choice question asking participants to rate how well a story presented in the scale described them overall. The total score ranges from 0-25, with a higher score indicating a strong probability of screening positive for bipolar disorders. The BSDS has been demonstrated to be an efficient self-rating scale with good sensitivity (α =.75 for bipolar type I and α =.79 for bipolar type II) and a high specificity of 0.85, making it useful in determining sub-threshold states of bipolar disorder.

2.4 Data analysis

Descriptive statistics compared CHARMS+ and CHARMS- groups on demographic and clinical characteristics (Table 1). The threshold for α was set at 0.05. At baseline, 122 participants completed the measures. One participant's CHARMS group status could not be determined due to missing data and was therefore removed from all analysis (n=121). 100 participants completed the 6- and 12-month follow-up. The analyses were conducted using survival analysis and mixed effect modelling. All cases (n=121) were included in analysis except in the linear mixed-effects (LME) analysis on the DASS-21 and PID5. For these two measures, several cases (3 and 4 respectively) had missing data on all time points and were not included. The R statistical system was used for the analysis (Team, R. C., 2013). In particular, the following R packages were used: 'survival' for the Kaplan-Meier and Cox regression analysis, 'glmnet' for LASSO and 'nlme' for the LME analysis.

Transition to a Stage 2 exit syndrome within the study follow-up timeframe was analysed using survival analysis. The Kaplan-Meier method was used to estimate the transition rates and the log-rank test was used to compare the CHARMS+ and CHARMS-

groups on transition rates, where transition means transition to a full-threshold disorder: FEP, FEM, MDD, and BPD (i.e., Stage 2 disorder). To compare the CHARMS+ and CHARMS- groups on symptomatology at 6 and 12 months, linear mixed-effects (LME) modelling was used at both time points. The Least Absolute Shrinkage and Selection Operator (LASSO) and Cox regression were used to examine the significance of clinical predictors of transition in the CHARMS+ group, where predictors mean clinical variables that predict progression to full-threshold disorder (Stage 2).

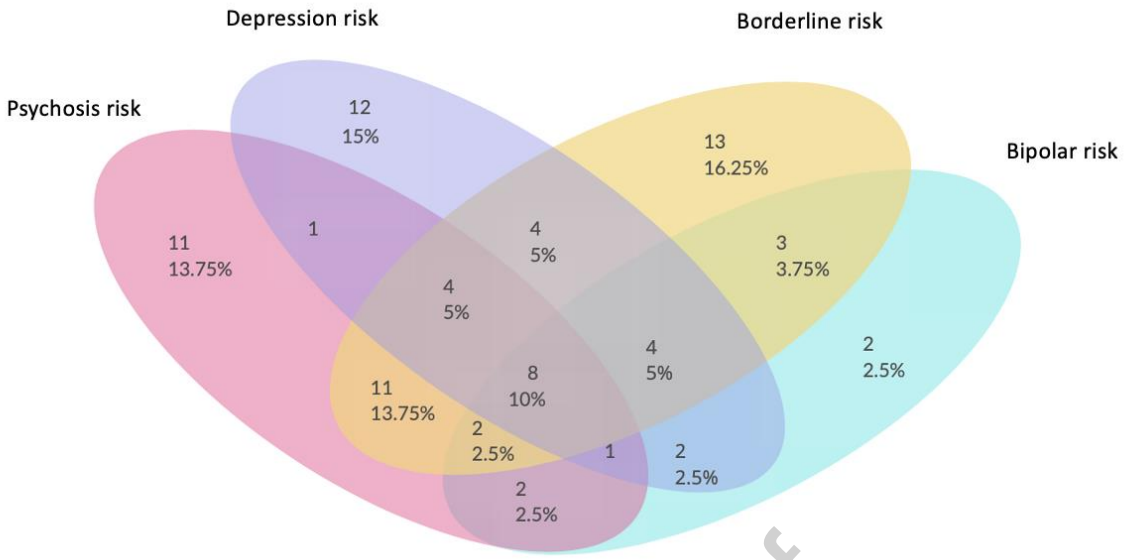
3. RESULTS

3.1 Participants

The study included 121 participants at baseline (74 females; 47 males) aged between 13-25 years (*M*=19.2 years, *SD*=2.9). 108 (89.3% participants) were recruited from headspace primary care clinics and 13 (10.7%) were recruited from Orygen Specialist Program. 80 (66.1%) were included in the CHARMS+ group. 41 (33.9%) were included in the CHARMS- group. 21 participants (17.4%; 14 from the CHARMS+ group, 7 from the CHARMS- group) were lost to follow-up.

Figure 1 shows the overlap of the four CHARMS+ at-risk subgroups at baseline. 38 (47.5%) individuals met criteria for being at-risk for only one disorder. 42 (52.5%) participants met criteria for being at-risk for more than one disorder: 23 (28.75%) for two disorders, 11 (13.75%) for three disorders, and 8 (10%) for four disorders.

Figure 1. Venn Diagram showing the overlap of the four CHARMS+ at-risk subgroups at baseline (*n=80*).



3.2 Treatment

A higher proportion of CHARMS+ participants than CHARMS- participants received pharmaceutical and psychosocial treatments over the follow-up period (see Supplementary Tables 1 and 2). However, these differences were not statistically significant.

3.3 Transition rates

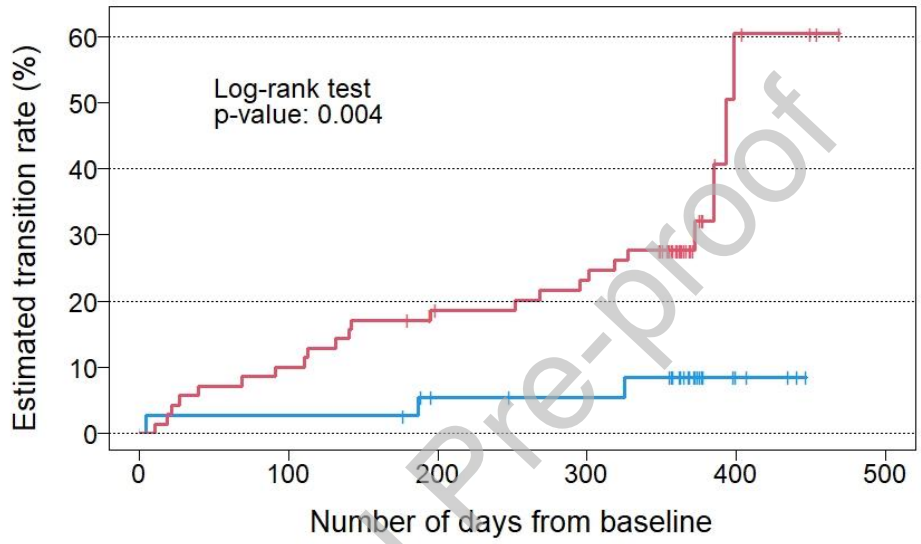
A transition was defined as meeting threshold for a Stage 2 disorder for MDD, FEP, FEM, or BPD by 6- or 12-month follow-up. Further details on meeting criteria for a Stage 2 disorder for FEP, FEM, MDD, BPD can be found in Supplementary Tables 3 and 4.

In total, there were 26 transitions to at least one Stage 2 syndrome over the 12-month follow-up period. Twenty-three of these transitioned cases (i.e., 89%) were from the CHARMS+ group. All transitions apart from one case (who transitioned to FEM) were initially to severe MDD. Three of the cases who initially transitioned to severe MDD developed a second Stage 2 disorder (FEP = two, BPD = one) by time of 12-month follow-up. These three cases were CHARMS+ cases.

Figure 2 shows the Kaplan-Meier curves for the transition rates of the two groups. The CHARMS+ group showed a significantly higher curve than the CHARMS- group. The

CHARMS+ group had a 17% transition rate at 6 months follow-up and a 27.6% transition rate at 12 months follow-up compared to 2.7% and 8.5% at 6- and 12-month follow-up respectively for the CHARMS- group. Further details on the Kaplan-Meier transition rates and the associated 95% CIs for the CHARMS+ and CHARMS- groups can be found in Supplementary Table 5.

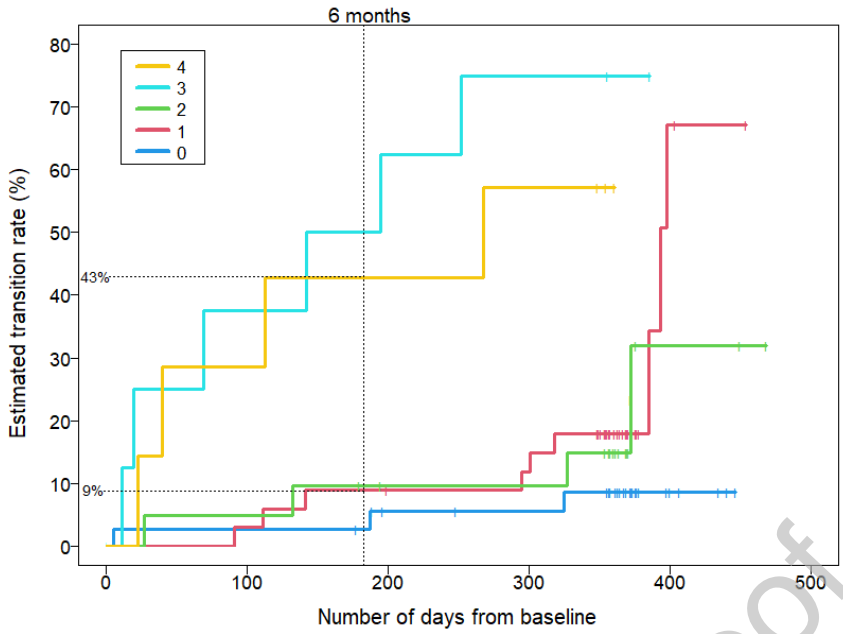
Figure 2. Kaplan-Meier transition rates.



Note: Blue: CHARMS-, red: CHARMS+. ('|' indicates censoring times.)

Figure 3 shows the survival curves of transition rate at different time points by number of CHARMS+ at-risk subgroups met at entry, as estimated by the Kaplan-Meier method. Meeting criteria for three or more at-risk subgroups was associated with a significantly higher transition risk than meeting one at-risk subgroup: meeting one at-risk subgroup = 24% transition rate; meeting two at-risk subgroups = 17% transition rate (p=0.648); meeting three at-risk subgroups = 55% transition rate (p=0.001); meeting four at-risk subgroups = 50% transition rate (p=0.026) (see Figure 3). Further details on the Kaplan-Meier transition rates and the associated 95% CIs for months 6 and 12 for the different CHARMS+ at-risk groups can be found in Supplementary Table 6.

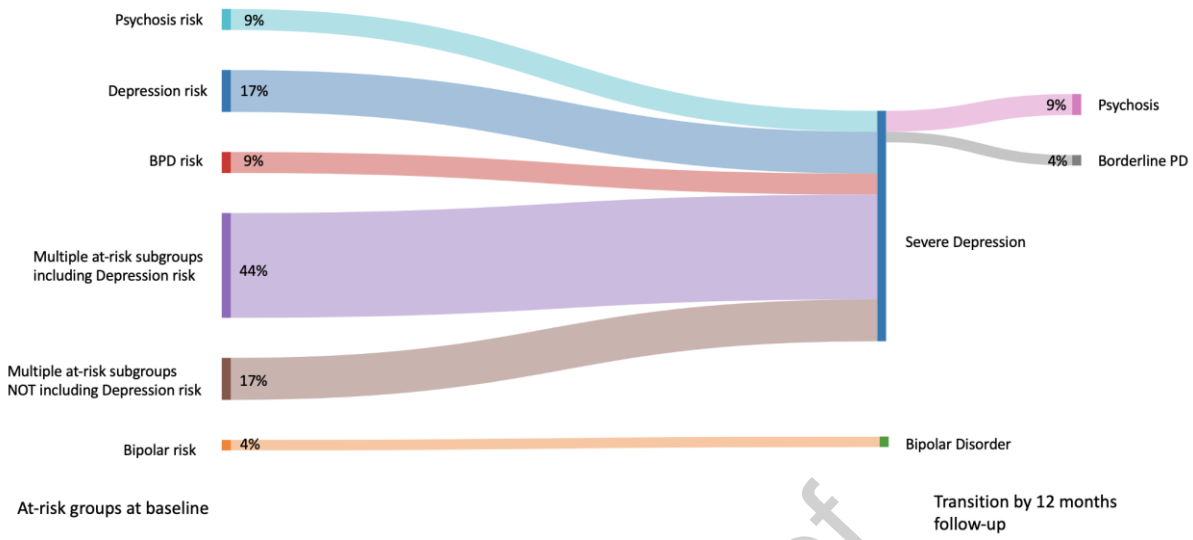
Figure 3: Kaplan-Meier transition rates by number of at-risk groups.



Note: red: meeting criteria for 1 at-risk subgroup; green: meeting criteria for 2 at-risk subgroups; aqua: meeting criteria for 3 at-risk subgroups; yellow: meeting criteria for 4 at-risk subgroups; blue: CHARMS-group.

Figure 4 shows the trajectory of the transitioned cases (*n*=23) in the CHARMS+ subgroups. The figure shows that there were 2 (9%) at-risk for psychosis cases who transitioned to MDD; 1 (4%) case was at-risk for bipolar disorder and transitioned to bipolar disorder; 4 (17%) individuals were at-risk for MDD and transitioned to MDD, and 2 (9%) were at-risk for BPD and transitioned to MDD. 10 (44%) individuals met criteria for multiple at-risk subgroups, which included being at-risk for depression and all transitioned to severe depression. 4 (17%) individuals met criteria for multiple at-risk subgroups (not including at-risk for depression) and all transitioned to severe depression. Additionally, from the cases who initially transitioned to severe depression, two (9%) subsequently transitioned to psychosis and one (4%) transitioned to BPD. Further details on clinical trajectories of Stage 1b and Stage 1a cases over a 12-month period can be found in Supplementary Figure 1.

Figure 4 Sankey Diagram showing homotypic and heterotypic clinical trajectory from baseline to 12-month follow-up in the CHARMS+ group.



Note: % indicate the trajectory of the transitioned cases per at-risk subgroup.

3.4 Severity of psychiatric symptoms

Table 1 shows symptom and functioning ratings at 6- and 12-month follow-up points. The CHARMS+ had more severe ratings than the CHARMS- group on all measures apart from the YMRS at 12-month follow-up points.

Table 1. Estimated means for the 2 CHARMS groups based on LME modelling.

			Baseline			6 months				12 months			
				95% CI values			95% CI values				95% CI values		
		n	Mean	Lower	Upper	Mean	Lower	Upper	P-value*	Mean	Lower	Upper	P-value*
DASS21 Total	C-	40	15.1	11.3	18.8	12.5	9.4	15.5	<0.001	9.8	6.3	13.3	<0.001
	C+	78	27.1	24.4	29.8	23.5	21.3	25.7		19.9	17.4	22.4	
BPD Total	C-	41	0.05	0.00	0.16	0.04	0.00	0.12	<0.001	0.03	0.00	0.14	<0.001
	C+	80	1.42	1.14	1.73	0.97	0.77	1.19		0.60	0.40	0.84	
CAARMS Severity	C-	41	7.0	2.6	11.5	5.7	1.9	9.6	<0.001	4.5	0.0	8.9	0.007
	C+	80	22.0	18.8	25.2	17.0	14.2	19.7		12.0	8.8	15.2	
GF Role	C-	41	7.5	7.1	7.9	7.5	7.1	7.9	0.001	7.5	7.1	8.0	0.004
	C+	80	6.8	6.5	7.1	6.7	6.5	7.0		6.7	6.4	7.0	
GF Social	C-	41	7.1	6.8	7.5	7.2	6.9	7.5	0.003	7.3	6.9	7.7	0.002
	C+	80	6.6	6.4	6.9	6.6	6.3	6.8		6.5	6.2	6.8	
QIDS Total	C-	41	4.6	3.4	5.8	4.3	3.3	5.3	<0.001	4.0	2.7	5.2	0.026
	C+	80	8.2	7.4	9.1	7.0	6.3	7.7		5.7	4.8	6.6	
SOFAS	C-	41	69.4	65.3	73.4	71.4	67.7	75.1	<0.001	73.4	69.1	77.6	<0.001
	C+	80	61.4	58.5	64.3	62.4	59.7	65.0		63.3	60.3	66.4	
YMRS Total	C-	41	1.0	0.3	1.7	0.9	0.4	1.3	0.002	0.8	0.3	1.3	0.342
	C+	80	2.4	1.9	3.0	1.7	1.4	2.1		1.1	0.7	1.4	

Note. DASS-21: Depression Anxiety Stress Scale-21; BPD: Borderline Personality Disorder (module from the SCID); CAARMS: Comprehensive Assessment of At-Risk Mental States; GFS: Global Functioning Social; GFR: Global Functioning Role; QIDS-C: Quick Inventory of Depressive Symptomatology-Clinician rated; SOFAS: Social and Occupational Functioning Scale; YMRS: Young Mania Rating Scale; C-: CHARMS-; C+: CHARMS+; ***** = statistically significant $p < 0.05$.

3.5 Predictors of transition in CHARMS+ individuals

When applying LASSO to examine the combination of baseline variables that would best predict transition to Stage 2 disorder in the CHARMS+ group, only the QIDS total score was selected. QIDS total remained a significant predictor after adjusting for each of the other variables but none of the other variables were significant predictors after adjusting for QIDS total. Further details on the predictive significance of QIDS total after adjusting for each of the other variables and the predictive significance of each variable after adjusting for QIDS total can be found in Supplementary Table 7. Further details on the predictive significance of each baseline clinical variable when considered individually using Cox regression can be found in Supplementary Table 8. In addition to this, as an exploratory analysis, we also examined the significance of site as a predictor of transition. We found that inclusion of site did not change the LASSO results. Also, site was not significant as a predictor by itself ($p=0.256$) and after adjusting for QIDS total ($p=0.367$).

4. DISCUSSION

This study aimed to prospectively validate the CHARMS criteria for identifying young people at risk of imminent progression to a severe mental disorder. The results showed that the CHARMS+ group showed a significantly higher transition rate and more severe symptomatology at follow-up compared to the CHARMS- group. They also had higher treatment needs, as reflected in the higher rates of pharmaceutical and psychosocial treatment compared to the CHARMS- group (although the difference was not statistically significant). Most transitions were initially to severe MDD. Severity of depressive symptoms at baseline were found to be the main predictor of transition by 12-month follow-up. The results also showed that having a greater array of symptomatology (i.e., meeting criteria for three or more 'at-risk' subgroups) was associated with significantly increased risk of progression to Stage 2

disorder (>50% transition rates). A high proportion (61%) of individuals who transitioned to a Stage 2 disorder met criteria for multiple at-risk groups at baseline. This indicates that symptom 'extension' (i.e., more complex illness presentations such as presence of comorbidities (Shah, Scott et al. 2020)) may be an important indicator of risk. The high proportion of participants who met multiple at-risk groups (24% of CHARMS+ participants met risk criteria for 3 or 4 disorders) is consistent with the high comorbidity rates and diffuse symptom presentations in psychiatry, particularly in youth (Fornaro, et al., 2016; Keck et al., 2003; Wilson et al., 2020).

This is one of the first studies to adopt a risk identification approach to prospectively identify a subgroup of young people at transdiagnostic risk of full-threshold (Stage 2) disorders. The results provide partial support for the CHARMS approach to transdiagnostic risk identification. By 12-month follow-up, a significantly higher rate of transition was observed in the CHARMS+ group (28%), which is substantially higher than 12-month psychosis transition rates reported in recent UHR studies (de Pablo et al., 2021). A recent meta-analysis indicated that UHR psychosis transition rates were 15% by 12-month follow-up and increased to 25% by 3 years follow-up (de Pablo et al., 2021). To the best of our knowledge, only one prior study has adopted a similar risk identification approach, the PROCAN study (Addington et al., 2021). The PROCAN study also used the clinical staging model to identify individuals at-risk of disorder progression and had a 6- and 12-month follow-up. The authors found that 7.5% of participants at Stage 1a transitioned to Stage 1b or a Stage 2 disorder at 12-month follow-up (Addington et al., 2021). This is similar to the current study which found a 5% transition rate from Stage 1a (CHARMS-) to Stage 1b (CHARMS+) at 12-month follow-up. The PROCAN study reported that 9.5% of participants at Stage 1b transitioned to a serious mental disorder (Stage 2) within 12-months. While the stage 1a outcomes are similar to the outcomes of the 1a cases (CHARMS-) in the current

study, the PROCAN 1b transition rate was substantially lower than that observed in the current study (9.5% vs 28%). This difference could be due to differences in sample ascertainment and therefore pre-screening risk enrichment between the two studies. CHARMS recruited all of its participants via clinical services, while PROCAN recruited 69% of its sample from community respondents to study advertisements. Additionally, another study that looked at predictors of transition also found that individuals at stage 1b were more likely to transition to a stage 2 disorder than to stage 1a individuals (Iorfino et al., 2019). This highlights the importance of using the clinical staging model which posits that more intensive clinical care is warranted for those who present with attenuated symptoms (stage 1b) compared to milder symptoms (stage 1a) as there is a greater likelihood of this group transitioning to a stage 2 disorder (Iorfino et a., 2019).

While the current results provide some initial validation of the CHARMS criteria, it is noteworthy that the main outcome was severe depression. Although the sample met at-risk criteria for a range of conditions at baseline (33% met criteria for FEP, FEM, and BPD only) at baseline, most (96%) of the transitions to Stage 2 disorder were to severe depression. These results suggest a transition pattern consistent with both a heterotypic development of disorder (i.e., symptomatology evolving into a different type over time) and homotypic development (i.e., symptomatology remaining the same type over time). This highlights the fluidity and complexity of clinical trajectory. A longer window of observation (follow-up period) is required to properly observe disorder evolution. In the psychosis risk area, long term follow-up studies indicate that many transitions to severe mental disorder occur after the first year of presentation to services (Nelson et al., 2013). In fact, depression is often present in the early stages of other psychiatric disorders such as psychosis (Upthegrove, 2009) and bipolar disorder (Perich et al., 2015). Therefore, the current cohort may show a higher transition rate and more varied illness course when followed over a longer time period. Also,

broadening Stage 2 clinical outcomes beyond the current primary outcomes of interest may be required to capture a wider range of disorders (e.g., obsessive-compulsive disorder, severe substance use, severe anxiety, etc). Some of these outcomes were captured in the current study and will be reported in a subsequent paper. Additionally, disorders such as OCD and anxiety disorders have been suggested to be common amongst children and young people and may therefore precede the onset of other psychiatric disorders (Mohatt et al., 2014; Geller et al., 2021). It is possible that the upper age range of 25 in this study may have contributed to the low transition rate to psychosis, as the onset age range for psychosis extends beyond the age of 25 (Solmi et al., 2022).

The results thus far suggest that revisions of the CHARMS criteria may need to be considered for more accurate assessment of homotypic and heterotypic symptom trajectories. The high transition rate to severe depression may partly reflect the higher prevalence of major depression compared to other disorders. It is also possible that the cut-off score for Stage 2 depression may have been set too low in this study (QIDS≥16), inflating this outcome. The transition rates to FEP, BPD, and FEM were lower than expected. Individuals who met one of the at-risk subgroups but who presented with severe depression (i.e., already at Stage 2 on the basis of depression score) were excluded from the study due to being over CHARMS criteria threshold. Previous studies have indicated that individuals with subthreshold psychotic and bipolar symptoms often show comorbid depressive symptoms (Kato 2007; Wilson et al., 2020), and these depressive symptoms are often more severe than for individuals with depression alone (Häfner & Maurer 2013). This would be consistent with the notion that an individual might first develop severe depression and another condition subsequently (i.e., heterotypic development of illness). Thus, a higher depression cut-off score, such as QIDS≥21, may be more appropriate for determination of Stage 2 depression and may reduce exclusion of cases who may be at risk of other Stage 2 disorders. It is

important to note that some of the follow-ups were conducted during the Covid-19 pandemic which may have possibly also contributed to increased rates of depression in our findings (Santomauro et al., 2021; Daly & Robinson, 2022).

Secondly, the duration of symptoms required to be categorised as a transition to full-threshold BPD may need to be increased (currently set at 6 months) to better capture the persistence of symptomatology associated with personality disorder. Third, using a more general measure of psychopathology such as the Symptom Checklist-90-Revised (Derogatis & Savitz, 1999) or the Brief Psychiatric Rating Scale (Overall & Gorham, 1962) alongside a revised version of the CHARMS criteria may be indicated. Using a more general measure of psychopathology akin to the 'P' factor approach and moving towards a continuum-based risk identification approach may better capture the broad array and fluidity of psychopathology in youth (i.e., as opposed to using disorder specific at-risk sub-groups). While in research studies using a continuum of illness according to symptom severity has become more widely adopted (Verdoux & van Os, 2002; Schomerus et al., 2016), it remains a challenge in clinical practice as clinical decisions still rely on illness thresholds for decision making (Pickles & Angold, 2003; Widiger & Samuel, 2005).

The findings from our study have potential implications for future clinical care. The CHARMS approach offers an alternative whereby clinicians might be able to utilise the CHARMS criteria as a tool to identify a subgroup of individuals with attenuated symptoms who might be at greater risk than other Stage 1 help-seeking individuals for transitioning to a full-threshold disorder. There is an indication in the current data that onset of serious depression may be a 'gateway' for transitioning to serious psychopathology more broadly (given the transitions to other disorders after Stage 2 depression onset), a possibility that needs to be tested with another wave of longitudinal follow-up in order to ascertain whether severe depression might further enrich for risk of a severe mental disorder

transdiagnostically. Additionally, individuals with more severe symptoms and a greater array of symptoms (i.e., meeting criteria for multiple at-risk subgroups) might also be at greater risk of progressing to more severe mental disorder. Broadening the entry criteria as well as having a longer period of follow up will increase our understanding of shared risk factors across disorders. This may also reveal more transitions to other Stage 2 syndromes and may shed further light on symptom trajectory. Further exploration, refinement and validation of the criteria may introduce a new sampling frame for research into transdiagnostic mechanisms and early treatments, both psychosocial and pharmacological. The use of pharmacological treatment and its impact on transitions will also need to be addressed in future follow-ups to account for potential masking of the onset of a serious mental disorder. Further work is therefore needed before being able to evaluate implications for clinical care.

Despite the above limitations, the CHARMS criteria show potential for identifying young people at risk of serious mental disorder. Future work is required to determine the issue of specific vs transdiagnostic risk. Further follow-up is also required to determine whether the CHARMS criteria can be used to identify young people at transdiagnostic risk (as opposed to identifying depression progression risk alone). The results support the need to match clinical care to stage of disorder, given Stage 1b cases (CHARMS+) had a substantially higher risk of disorder progression and more severe symptoms at follow-up than Stage 1a (CHARMS-) cases. More intensive and sustained care may be indicated for this group.

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Authors statement

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