JAMA Psychiatry | Original Investigation

Clinical Stage Transitions in Persons Aged 12 to 25 Years Presenting to Early Intervention Mental Health Services With Anxiety, Mood, and Psychotic Disorders

Frank Iorfino, PhD; Elizabeth M. Scott, MD, FRANZCP; Joanne S. Carpenter, PhD; Shane P. Cross, PhD; Daniel F. Hermens, PhD; Madhura Killedar, PhD; Alissa Nichles, PGDipAppPsy; Natalia Zmicerevska, MCouns; Django White, BLaS (Stats); Adam J. Guastella, PhD; Jan Scott, PhD, FRCPsych; Patrick D. McGorry, MD, PhD, FRCP, FRANZCP; Ian B. Hickie, MD, FRANZCP, FASSA, FAHMS

IMPORTANCE The large contribution of psychiatric disorders to premature death and persistent disability among young people means that earlier identification and enhanced long-term care for those who are most at risk of developing life-threatening or chronic disorders is critical. Clinical staging as an adjunct to diagnosis to address emerging psychiatric disorders has been proposed for young people presenting for care; however, the longer-term utility of this system has not been established.

OBJECTIVES To determine the rates of transition from earlier to later stages of anxiety, mood, psychotic, or comorbid disorders and to identify the demographic and clinical characteristics that are associated with the time course of these transitions.

DESIGN, SETTING, AND PARTICIPANTS A longitudinal, observational study of 2254 persons aged 12 to 25 years who obtained mental health care at 2 early intervention mental health services in Sydney, Australia, and were recruited to a research register between June 18, 2008, and July 24, 2018 (the Brain and Mind Centre Optymise Cohort).

MAIN OUTCOMES AND MEASURES The primary outcome of this study was transition from earlier to later clinical stages. A multistate Markov model was used to examine demographic (ie, age, sex, engagement in education, employment, or both) and clinical (ie, social and occupational function, clinical presentation, personal history of mental illness, physical health comorbidities, treatment use, self-harm, suicidal thoughts and behaviors) factors associated with these transitions.

RESULTS Of the 2254 individuals included in the study, mean (SD) age at baseline was 18.18 (3.33) years and 1330 (59.0%) were female. Data on race/ethnicity were not available. Median (interquartile range) follow-up was 14 (5-33) months. Of 685 participants at stage 1a (nonspecific symptoms), 253 (36.9%) transitioned to stage 1b (attenuated syndromes). Transition was associated with lower social functioning (hazard ratio [HR], 0.77; 95% CI, 0.66-0.90), engagement with education, employment, or both (HR, 0.47; 95% CI, 0.25-0.91), manic-like experiences (HR, 2.12; 95% CI, 1.19-3.78), psychotic-like experiences (HR, 2.13; 95% CI, 1.38-3.28), self-harm (HR, 1.42; 95% CI, 1.01-1.99), and older age (HR, 1.27; 95% CI, 1.11-1.45). Of 1370 stage 1b participants, 176 (12.8%) transitioned to stage 2 (full-threshold) disorders. Transition was associated with psychotic-like experiences (HR, 2.31; 95% CI, 1.65-3.23), circadian disturbance (HR, 1.66; 95% CI, 1.17-2.35), psychiatric medication (HR, 1.43; 95% CI, 1.03-1.99), childhood psychiatric disorder (HR, 1.62; 95% CI, 1.03-2.54), and older age (HR, 1.24; 95% CI, 1.05-1.45).

CONCLUSIONS AND RELEVANCE Differential rates of progression from earlier to later stages of anxiety, mood, psychotic, or comorbid disorders were observed in young persons who presented for care at various stages. Understanding the rate and factors associated with transition assists planning of stage-specific clinical interventions and secondary prevention trials.

Editorial page 1121

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 1216

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Frank Iorfino, PhD, Youth Mental Health Team, Brain and Mind Centre, University of Sydney, 94 Mallet St Camperdown, Sydney, New South Wales, Australia 2050 (frank.iorfino@sydney.edu.au).

JAMA Psychiatry. 2019;76(11):1167-1175. doi:10.1001/jamapsychiatry.2019.2360
Published online August 28, 2019.

The large contribution of psychiatric disorders to premature death and disability is associated with their early age of onset, prevalence, chronicity, and comorbidity.[1,2] Although 75% of major psychiatric disorders begin before the age of 25 years,[3,4] current adult-based thresholds for diagnosis often map weakly onto earlier and nonspecific patterns of illness in young people.[5-8] Common symptoms of psychiatric disorders (eg, depressed mood, sleep disturbance, motor activation) that may seem diagnostically specific are shared across diagnoses, are common among patients with subthreshold and full-threshold disorders, and have variable patterns of association, differentiation, or severity across the illness course.[9-13] In addition, syndromes such as anxiety and neurodevelopmental disorders that are evident before age 12 years often precede the later development of a broad range of syndromes in the same individuals.[14] Consequently, the challenge is to derive classification systems that are consistent with the neurobiological development of young people and patterns of disease development, and that are clinically useful.

A response to this challenge has been to apply clinical staging as an adjunct to formal diagnosis.[15-19] Clinical staging recognizes that the boundaries between common psychiatric disorders are often unclear and that an approach that accounts for their comorbidity is needed.[20,21] In other medical specialties (eg, oncology), it is commonly accepted that it is not ideal to choose treatments or plan health care for persons who are likely to experience illness progression or recurrence based solely on a cross-sectional diagnosis.[22] Young people experiencing mental ill health vary along a continuum by factors including severity, duration of symptoms, and illness course (eg, first episode vs recurrent illness). Such factors are associated with different patterns of response to psychological or pharmacological interventions,[23-27] and different individuals may benefit from variable types of secondary prevention strategies.[28-32] Consequently, we have proposed a framework for clinical staging among young people presenting with anxiety, mood, or psychotic syndromes.[15]

This framework proposes that earlier stages are clinically heterogeneous and more likely to be characterized by lower rates of impairment and different rates of progression to more discrete, persistent, or recurrent disorders. When applied to young people who present for care, the first distinction is between those in early subthreshold phases (stage 1a [nonspecific symptoms] or 1b [attenuated syndromes]) and those who have reached full threshold for major, discrete, and persistent or recurrent disorders (stage 2) (**Figure 1**). Within stage 1 (subthreshold), we differentiate 2 levels: stage 1b, which we describe as *attenuated syndromes* and stage 1a, *nonspecific* anxiety and depressive symptom clusters. Individuals assigned to stage 1b often have the symptoms, duration, and impairment to meet *DSM-5* criteria[33] or *International Classification of Diseases, Tenth Revision, Clinical Modification* criteria[34] for specific anxiety or mood disorders; however, compared with stage 2 disorders, these are typically less severe, brief, or not persistent or recurrent. Individuals assigned to stage 1a typically have fewer symptoms and impairment and a shorter duration of illness and, as such, usually do not meet *DSM-5* criteria[33] or *International Classification of Diseases, Tenth Revision, Clinical Modification* criteria.[34]

Key Points

Question What demographic and clinical factors are associated with transition from early (subthreshold) to full-threshold major persistent or recurrent psychiatric disorders?

Findings This longitudinal cohort study of persons aged 12 to 25 years who presented to early intervention services found significant and ongoing risk of transition to major anxiety, mood, psychotic, or comorbid disorders. Poorer social function, psychotic-like experiences, manic-like experiences, and circadian disturbance were associated with illness progression.

Meaning A clinical staging model for specific youth services may support the efficient allocation of appropriate care to young people and support the evidence-based planning of relevant early intervention and secondary prevention strategies.

Previous longitudinal studies indicate that within 12 months approximately 15% to 20% of patients with disorders rated as stage 1b progress to a later stage and many of these clinical transitions occur within the first 3 months of mental health care.[35] The differentiation of these stages is supported by other independent neuropsychological, neurobiological, and circadian markers identified among young people with emerging anxiety, mood, or psychotic syndromes.[36-43]

This study describes the characteristics of a cohort of young people presenting with a broad range of anxiety, mood, or psychotic syndromes and examines the rates of transition from stage 1a to 1b, and from stage 1b to 2, and the demographic and clinical characteristics associated with the time course of these transitions.

Methods

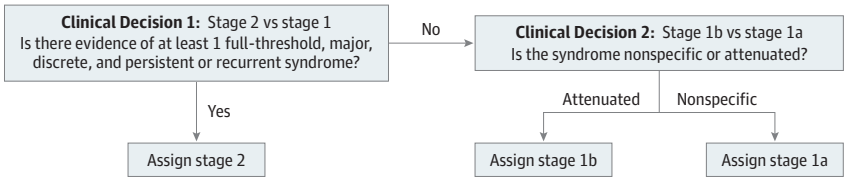
This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The study was approved by the University of Sydney Human Research Ethics Committee and participants, their guardians, or both gave written informed consent for the use of routinely collected clinical data for research purposes.

Participants

Participants were drawn from a cohort of 6743 individuals aged 12 to 30 years who presented to the Brain and Mind Centre's youth mental health clinics in Sydney, Australia, and recruited to a research register between June 18, 2008, and July 24, 2018. These clinics include primary care services (ie, headspace, a "1-stop-shop" for young people who need help with mental health, physical health [including sexual health], alcohol and other drugs or work and study support[44-46]) as well as more specialized mental health services. Young people were self-referred, referred via a family member or friend, or the community (eg, general practitioner).[46] All participants received clinician-based case management and psychological, social, medical, or a combination of interventions as part of standard care.

Figure 1. Two-Step Decision-Making Process Used to Assign Those Presenting to Care to the Appropriate Stage

A Process



B Guidelines

Clinical decision-making principle: Assign highest achieved in lifetime, and when in doubt, rate down and reassess in 4 to 6 wk.

Clinical Decision 1: Stage 2 vs stage 1	**Clinical Decision 2:** Stage 1b vs stage 1a	
Stage 2: Full-threshold, major, discrete, and persistent or recurrent	Stage 1b: Attenuated syndrome	Stage 1a: Nonspecific symptoms
Functioning Episode of illness is clearly having an ongoing and major impact on social, educational, or occupational functioning + **Mania** Clear manic syndromes (not just symptoms) for more than 4 d during a specific illness event; hypomanic symptoms or brief hypomanic syndromes alone do not constitute a discrete disorder **Psychosis** Clear psychotic syndrome for more than a week **Depression** Features indicative of more severe syndromes including psychomotor retardation, marked agitation, impaired cognitive function, severe circadian dysfunction, psychotic features, brief hypomanic periods, severe neurovegetative changes, pathological guilt, or severe suicidality **Anxiety** Features indicative of more severe syndromes, such as significant or persistent avoidant behaviors, and moderate to severe depressive syndromes, typically associated with marked agitation, fixed irrational beliefs, overvalued ideas, or attenuated psychotic symptoms or substantial and persistent substance misuse **Comorbidity** Significant and clear symptoms (depressive, manic, or psychotic) within the context of a more severe persistent syndrome. The significant comorbidity may include alcohol or substance misuse, abnormal eating behavior, or other relevant psychological syndromes	**Functioning** Episode of illness is having a moderate to severe impact on social, educational, or occupational function + **Depression** Depressive syndromes of moderate severity without specific features indicative of a stage 2 syndrome **Anxiety** Specific and more severe symptoms of anxiety, such as the development of avoidant behavior **At-risk mental states** Hypomanic symptoms less than 4 d; and/or attenuated or brief psychotic symptoms **Comorbidity** Syndromes that are somewhat mixed in terms of their symptomatology or complicated by alcohol or substance misuse	**Functioning** Episode of illness is having a mild to moderate impact on social, educational, or occupational function + **Depression** Mild to moderate levels of depressive ideation without specific features indicative of a more disabling syndrome **Anxiety** Mild to moderate levels of arousal without significant or persistent avoidant behaviors

A, Process used to assign clinical stage. B, Guidelines used to make these decisions.

Eligibility Criteria

As of December 18, 2018, phase 1 of data entry was completed, and so data were available for 2767 participants, with 78 excluded owing to insufficient data. The inclusion criteria for this study were age 12 to 25 years at baseline and at least 1 month of follow-up.

Data Collection

Data were extracted from clinical files and code inputs according to a standardized form at predetermined time points.[47] The first available clinical assessment at the mental health service is taken as the baseline time point for each participant, and the date of this assessment is used to determine each of the follow-up time points. If there is no clinical information available for a time point (ie, the participant did not attend the service during that time), that entry is left missing. All clinical notes from the preceding time points, up to and including the current time point are used to inform and complete the current entry.

Assessments

The proforma was used to record specific illness course characteristics. More detailed descriptions about the proforma, including the interrater reliability are reported in the supplement and cohort article.[48] The measures used here include (eAppendix in the Supplement); demographic features, social and occupational functioning (including the Social and Occupational Functioning Assessment Scale [SOFAS],[49] a clinician-rated measure that assesses functioning on a 0 to 100 scale, with lower scores suggesting functional impairment. The instructions emphasize that the rater should avoid confounding the rating with clinical symptoms,[47-49] and Not in Education, Employment or Training [NEET] status as a measure of participation and engagement with education or work), psychiatric disorder diagnoses, clinical stage, at-risk mental states, self-harm, suicidal thoughts and behaviors, physical health comorbidities, personal mental illness history, and treatment use.

Statistical Analyses

Analyses were performed using R statistical software (R Foundation).[50] Differences in demographic and clinical characteristics between groups defined by clinical stage at baseline were assessed using 1-way analysis of variance for continuous variables and χ^2 tests for categorical variables. Pairwise comparisons were carried out for stage 1a vs stage 1b and stage 1b vs stage 2; owing to the number of univariate analyses conducted, an α correction using the Bonferroni method was made. For these analysis, statistical significance was set at 2-sided $P < .001$.

A multistate Markov model (*msm* package version 1.6.6; R Foundation)[51] was fitted to determine which demographic and clinical characteristics at baseline were associated with time course of transitions. This analysis modeled 2 transitions: stage 1a to stage 1b and stage 1b to stage 2. The progressive Markov model only allows forward transitions without skipping. The risk of transition for each individual in the cohort is quantified by that individual's unique transition intensity, which depends on personal demographic features and baseline clinical characteristics; these dependencies form the main parameters of the model. The *msm* package fits the model to longitudinal panel-observed data, whereby individuals are followed up and classified intermittently, but the exact time of transition to the later stage (eg, stage 1a to stage 1b) is not known. Therefore, these data are assumed to be interval censored, whereby the exact time of transition is only known to lie within an interval (ie, 2 observational time points). Hazard ratios (HRs) and 95% CIs were estimated to determine the change in probability of transitions for each variable at baseline relative to a reference value or absence of that characteristic. Survival probability plots were generated to model the empirical and fitted time-to-transition for transitions using the *msm* package, which is suited to plotting interval-censored data.

Differences in follow-up time between those who transitioned to stage 2 vs those who did not were assessed using the nonparametric Kruskal-Wallis test. χ^2 Analyses were undertaken to determine differences in the overall rate of transition from stage 1a and stage 1b at baseline to stage 2 at last follow-up.

Results

Sample Characteristics

The cohort comprised 2254 individuals; 1330 (59.0%) were female with a mean (SD) age of 18.18 (3.33) at baseline and a median (interquartile range [IQR]) follow-up of 14 (5-33) months. Data on race/ethnicity were unavailable. Pairwise comparisons of characteristics according to clinical stage at baseline are in **Table 1**. Participants who were classified as being at the earlier stages were younger ($F_{2,2251} = 88.91$; $P < .001$) and more likely to present with less functional impairment, as determined by both lower NEET rates ($\chi^2_2 = 86.67$; $P < .001$) and higher SOFAS ($F_{2,2231} = 169.17$; $P < .001$).

The pattern of differences between all 3 groups in terms of at-risk mental states, treatment use, and suicidality was positive. Specifically, more-advanced clinical stages were associated with higher rates of manic-like experiences ($\chi^2_2 = 162.32$; $P < .001$); psychotic-like experiences ($\chi^2_2 = 245.54$; $P < .001$), circadian (or sleep-wake) disturbance ($\chi^2_2 = 85.81$; $P < .001$), hospitalization ($\chi^2_2 = 566.16$; $P < .001$), and psychiatric medication (χ^2_2) = 455.06; $P < .001$). There were no differences between participants with stage 1b and stage 2 disorder at baseline in terms of self-harm ($\chi^2_1 = 2.79$; $P = .08$) and suicidal ideation ($\chi^2_1 = 0.15$; $P = .88$); however, participants with stage 2 disorder at baseline were more likely to have a previous suicide attempt ($\chi^2_1 = 24.06$; $P < .001$). Compared with stage 1a, participants with stage 1b disorder at baseline reported higher rates of self-harm ($\chi^2_1 = 135.45$; $P < .001$), suicidal ideation ($\chi^2_1 = 108.27$; $P < .001$), and suicide attempts ($\chi^2_1 = 90.77$; $P < .001$).

Multi-State Model of Clinical Stage Transitions

For the 685 participants initially classified at stage 1a, 253 (36.9%) progressed to stage 1b (**Figure 2**). Notably, 110 (46.8%) of these transitions occurred within 6 months and 153 (65.1%) within 12 months of baseline. The model identified 6 factors associated with transition from stage 1a to 1b (**Table 2**): older age (HR, 1.27; 95% CI, 1.11-1.45), lower social functioning (HR, 0.77; 95% CI, 0.66-0.90), engagement in education, employment, or training (HR, 0.47; 95% CI, 0.25-0.91), manic-like experiences (HR, 2.12; 95% CI, 1.19-3.78), psychotic-like experiences (HR, 2.13; 95% CI, 1.38-3.28), and self-harm (HR, 1.42; 95% CI, 1.01-1.99). Childhood attention-deficit/hyperactivity disorder was associated with a lower risk of transition (HR, 0.43; 95% CI, 0.24-0.78).

For the 1370 participants initially classified at stage 1b, 176 (12.8%) progressed to stage 2 (Figure 2). Eighty of the 176 (45.4%) of these transitions occurred within 12 months of baseline. The multi-state Markov model identified 5 factors associated with transition from stage 1b to stage 2 (Table 2): older age (HR, 1.24; 95% CI, 1.05-1.45), psychotic-like experiences (HR, 2.31; 95% CI, 1.65-3.23), circadian disturbance (HR, 1.66; 95% CI, 1.17-2.35), previous use of psychiatric medication (HR, 1.43; 95% CI, 1.03-1.99), and a history of childhood psychiatric disorders (HR, 1.62; 95% CI, 1.03-2.54).

Transition to Stage 2 and Associated Follow-up Time

Of the 685 individuals who presented as stage 1a, 18 (2.6%) transitioned to stage 2, compared with 176 of 1370 individuals (12.8%) who presented as stage 1b ($\chi^2_1 = 55.78$; $P < .001$) (Figure 2; **Table 3**). Those stage 1a participants who did transition to stage 2 were followed up for a median (IQR) of 51 (42) months, compared with 11 (20) months for those who had not transitioned to stage 2 ($\chi^2_1 = 26.32$; $P < .001$). Similarly, those who were stage 1b at baseline and transitioned to stage 2 were followed up for a median of 37 (41) months, compared with 13 (23) months for those who did not transition ($\chi^2_1 = 129.51$; $P < .001$). Among the 194 who transitioned to stage 2, 47 (24.2%) primarily had a psychotic-type syndrome, 86 (44.3%) had a bipolar syndrome, and 61 (31.4%) had a major anxiety or depressive syndrome.

Discussion

This study reports the longer-term rates of progression from early to later clinical stages and the demographic and clinical factors associated with transitions for a large clinical cohort engaged in active psychological, social, medical, or a combi-

Table 1. Baseline Demographic and Clinical Characteristics of 2254 Participants in Longitudinal Youth Cohort by Clinical Stage

Characteristic	No. (%)					
					Comparison[a]	
	Stage 1a	Stage 1b	Stage 2	*P* Value[a]	1a vs 1b	1b vs 2
Stage at baseline	685 (30.4)	1370 (60.8)	199 (8.8)	NA	NA	NA
Age, mean (SD), y	17.02 (3.24)	18.47 (3.25)	20.18 (2.79)	<.001	<.001	<.001
Female	393(57.4)	835 (60.9)	106 (53.3)			
NEET	46 (6.7)	240 (17.5)	64 (32.2)	<.001	<.001	<.001
Social and occupational function						
SOFAS score, mean (SD)[b]	66.93 (8.07)	60.87 (8.41)	56.38 (10.11)	<.001	<.001	<.001
Clinical presentation						
Manic-like experiences	21 (3.1)	216 (15.8)	74 (37.2)	<.001	<.001	<.001
Psychotic-like experiences	43 (6.3)	268 (19.6)	110 (55.3)	<.001	<.001	<.001
Circadian disturbance	46 (6.7)	229 (16.7)	64 (32.2)	<.001	<.001	<.001
Neurodevelopmental—ASD	23 (3.4)	66 (4.8)	7 (3.5)			
Neurodevelopmental—ADHD	61 (8.9)	119 (8.7)	10 (5.0)			
Neurodevelopmental—other	23 (3.4)	28 (2.0)	1 (0.5)			
Substance-related or addictive disorder	20 (2.9)	137 (10.0)	33 (16.6)	<.001	<.001	
Personal history of mental illness						
Any childhood disorder	70 (10.2)	213 (15.5)	24 (12.1)			
Any family history	268 (39.1)	691 (50.4)	99 (49.7)	<.001	<.001	
Physical health comorbidities						
Any major physical illness	108 (15.8)	240 (17.5)	49 (24.6)			
Treatment utilization						
Any hospitalization	5 (0.7)	163 (11.9)	130 (65.3)	<.001	<.001	<.001
Any psychiatric medication	116 (16.9)	763 (55.7)	184 (92.5)	<.001	<.001	<.001
Self-harm and suicidal thoughts and behaviors						
Self-harm	150 (21.9)	665 (48.5)	84 (42.2)	<.001	<.001	
Suicidal ideation	199 (29.1)	730 (53.3)	109 (54.8)	<.001	<.001	
Suicide attempt	17 (2.5)	234 (17.1)	63 (31.6)	<.001	<.001	<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; NA, not applicable; NEET, not in education, employment or training; SOFAS, Social and Occupational Functional Assessment Scale.

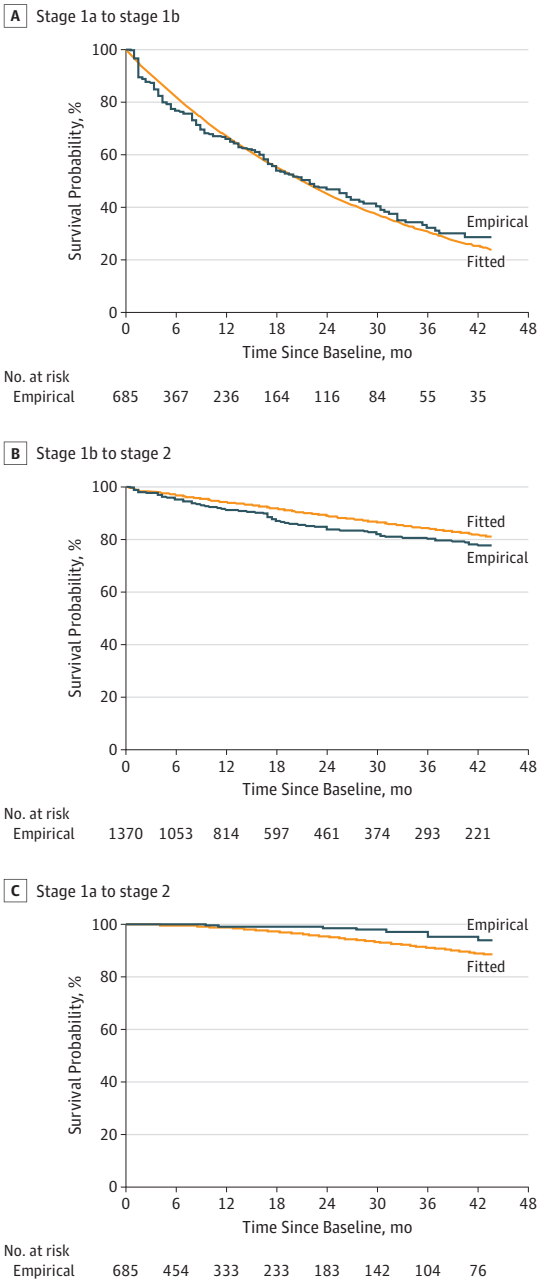
[a] $P < .001$ is the adjusted α level for statistical significance.

[b] Missing data for SOFAS score were as follows; stage 1a (1 participant), stage 1b (16 participants), and stage 2 (3 participants). The SOFAS score is a clinician-rated measure that assesses functioning on a 0 to 100 scale, with lower scores suggesting functional impairment. The instructions emphasize that the rater should avoid confounding the rating with clinical symptoms.[49]

nation of interventions as part of standard care. First, this study demonstrates that young people who present at stage 1a are at low risk of early progression to full-threshold disorders; however, a significant subgroup characterized by more complex clinical presentations such as manic-like experiences and psychotic-like experiences are at increased risk of early transition to stage 1b syndromes. Whether this group is also at increased risk of longer-term transition to stage 2 full-threshold disorders is not yet known. Second, a substantial subgroup of stage 1b participants are at risk of early progression to full-threshold, persistent, or recurrent disorders. Psychotic-like experiences and circadian disturbances have some capacity to predict these transitions. Finally, within the transdiagnostic model proposed, the differentiation of stage 1a from stage 1b disorders is justified by the differential rates of progression to stage 2 disorders.

Consistent with previous reports,[52] 176 of 1370 (12.8%) of participants with stage 1b syndromes at baseline progressed to a more severe stage, with at least 45% of those transitions occurring in the first 12 months after presentation to care. Furthermore, although 34.3% of those at stage 1a progressed to stage 1b, 2.6% progressed to stage 2. The differential rates of progression to stage 2 support the assumptions about longitudinal trajectories that underpin the clinical staging model, namely, that young people at stage 1b at baseline have a higher early risk of developing a major discrete, persisting, or recurrent disorder than young people at stage 1a. Transition to stage 2 disorder does not simply equate with movement from a single subthreshold anxiety, mood, or psychotic-like syndrome to a first episode of mania or single major depressive, bipolar, or psychotic disorder (as described by *DSM-5* criteria[33] or *International Classification of Diseases, Tenth Revision, Clinical Modification* criteria[34]). In this model,[52] transition is associated with progression to a more crystallized and enduring syndrome that has distinct features (eg, severely depressed mood associated with psychomotor agitation or retardation) or the development of additional features (eg, psychotic symptoms). The present findings support the health services utility of this model for guiding resource allocation with regard to treatment intensity and strategies toward patients with a greater risk of transition, and avoiding the limitations of premature or arbitrary subclassifications, particularly for young people whose clinical presentations are often mixed or associated with substantial comorbidity.[53]

Figure 2. Kaplan-Meier Curves of Time to Transition



A, Survival probability plots of the empirical and fitted time to transition for stage 1a to stage 1b. B, Survival probability plots of the empirical and fitted time to transition for stage 1b to stage 2. C, Survival probability plots of the empirical and fitted time to transition for stage 1a to stage 2.

Table 2. Hazard Ratios Associated With the Change in Probability of Clinical Stage Transitions

Characteristic	HR (95% CI)	
	Stage 1a to Stage 1b	Stage 1b to Stage 2
Demographic features		
Age[a]	1.27 (1.11-1.45)[b]	1.24 (1.05-1.45)[b]
Male sex	1.12 (0.85-1.48)	0.83 (0.59-1.17)
NEET status	0.47 (0.25-0.91)[b]	0.93 (0.61-1.43)
Social and occupational function		
SOFAS score[c]	0.77 (0.66-0.90)[b]	0.87 (0.73-1.03)
Clinical presentation		
Manic-like experiences	2.12 (1.19-3.78)[b]	0.94 (0.63-1.39)
Psychotic-like experiences	2.13 (1.38-3.28)[b]	2.31 (1.65-3.23)[b]
Circadian disturbance	1.58 (1.00-2.50)	1.66 (1.17-2.35)[b]
Neurodevelopmental—ASD	0.46 (0.16-1.34)	0.79 (0.39-1.60)
Neurodevelopmental—ADHD	0.43 (0.24-0.78)[b]	0.48 (0.23-1.00)
Neurodevelopmental—other	1.45 (0.69-3.03)	0.59 (0.21-1.63)
Substance-related or addictive disorder	1.03 (0.44-2.41)	0.86 (0.48-1.53)
Personal history of mental illness		
Any childhood disorder	0.69 (0.39-1.22)	1.62 (1.03-2.54)[b]
Any family history	0.89 (0.68-1.17)	1.03 (0.76-1.38)
Physical health comorbidities		
Any major physical illness	0.94 (0.65-1.36)	1.29 (0.91-1.82)
Treatment use		
Any hospitalization	1.39 (0.41-4.64)	1.31 (0.83-2.08)
Any psychiatric medication	1.37 (0.94-2.00)	1.43 (1.03-1.99)[b]
Self-harm and suicidal thoughts and behaviors		
Self-harm	1.42 (1.01-1.99)[b]	1.10 (0.79-1.54)
Suicide ideation	1.08 (0.79-1.47)	0.79 (0.56-1.10)
Suicide attempt	1.05 (0.41-2.68)	1.03 (0.65-1.62)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; HR, hazard ratio; NEET, not in education, employment or training; SOFAS, Social and Occupational Function Scale.

[a] For age, the hazard ratios were calculated for an increase by 3.27 years (SD of the distribution of ages).

[b] Significant factor.

[c] For SOFAS scores, HRs were calculated for an increase in 8.78 points (SD of distribution of SOFAS). The SOFAS score is a clinician-rated measure that assesses functioning on a 0 to 100 scale, with lower scores suggesting functional impairment. The instructions emphasize that the rater should avoid confounding the rating with clinical symptoms.[49]

An important clinical consideration is whether we can go beyond broad clinical stage and identify individuals who are at greatest risk of progression to full-threshold, more severe, or persistent forms of illness. Herein, we extend earlier illness progression work carried out among ultrahigh-risk groups[54] by evaluating these transitions among a transdiagnostic sample of young people. For individuals initially classified as having stage 1b syndromes, psychotic-like experiences and circadian disturbance were associated with transition and demonstrate the heterogeneity of clinical characteristics associated with major anxiety, mood, or psychotic disorders. There is ongoing debate as to whether psychotic-like experiences are principally a marker of illness severity or comorbidity, rather than having any specific capacity to predict later psychotic disorders.[55-58] Circadian disturbance is increasingly recognized as a major characteristic of more severe mood disorders, including bipolar disorder, psychotic depression, and atypical depression in younger cohorts.[59-61] Such characteristics may reflect the possible pathophysiological mechanisms (eg, circadian, hypothalamic-pituitary-adrenal axis dysfunction) that differentiate the earliest subthreshold stages from full-threshold syndromes, which is consistent with differential changes in neuropsychological function, structural

brain change, and circadian disruption observed previously.[37-43] Importantly, neither suicidal ideation nor previous suicide attempt discriminated between these 2 groups, indicating that the course of suicidality may run somewhat independent of illness progression or specific diagnosis.

With regard to the characteristics of those in stage 1a who transitioned to stage 1b, a broader range of impairment (lower social and occupational functioning at baseline) and clinical (psychotic-like experiences, manic-like experiences, and self-harm) features were associated with transition. Presumably, this reflects the greater underlying heterogeneity of illness trajectories in this subgroup with a mixture of features that is consistent with emerging psychopathology.[52,62] Specifically, despite the absence of substantial severity, specificity, or impairment, these features may indicate a higher degree of complexity, characterized by the presence of major risk factors or underlying pathophysiology. It does suggest that intervention and secondary prevention strategies for this group may need to focus more selectively on those individuals who present with 1 or more of these clinical characteristics.

There were also several clear differences in demographic, clinical, and functional characteristics of participants with early subthreshold (stages 1a or 1b) and later full-threshold (stage 2 or above) disorders at entry to care. The differences in age are notable, with 8.8% of the sample presenting with a discrete disorder (stage 2) and being approximately 3 years older than those presenting at stage 1a. If we are to increase the chance of making clinical contact with young people before they reach stage 2 or higher, we must continue to enhance strategies that attract younger persons to clinical care, potentially at earlier phases of illness.

Limitations

This cohort is a selected subset of a larger cohort of young people presenting for care (2254 of a cohort of 6743 [33%]). Given that phase 1 data entry focused on individuals who had also participated in other more detailed neurobiological research studies, this sample may not be representative of all treatment-seeking young people in this region, and this subgroup may be biased toward inclusion of those who already have stage 1b attenuated syndromes, more severe depressive syndromes, more comorbidity and clinical complexity, alcohol or substance misuse, and suicidality. Furthermore, the subgroup used here varied in duration of follow-up, which means that those engaged for longer periods of time tended to be more likely to transition.

Table 3. Clinical Stage at Time Last Seen Compared With Clinical Stage at Baseline

Entry to Care (Baseline)	Time Last Seen, No. (%)			
	Stage 1a	Stage 1b	Stage 2	Total
Stage 1a	432 (61)	235 (34)	18 (3)	685 (100)
Stage 1b	0	1194 (87)	176 (13)	1370 (100)
Stage 2	0	0	199 (100)	199 (100)
Total	432 (19)	1429 (63)	393 (17)	2254 (100)

Consequently, the rates of progression over time and the factors associated with progression may differ if follow-up was more consistent across this sample or among less-severely unwell cohorts including participants with early-phase but less-complex disorders. Yet, given the long periods of untreated illness in the community, the degree of progression among this cohort may actually be in line with comparable cohorts in cities throughout the United States or Europe where early intervention campaigns and services for youth mental health, such as headspace in Australia, are not widespread.

Another limitation is that the data are extracted from clinical records, rather than via prospective structured assessments. However, the data collection is structured, conducted by trained staff, completed independently of treating clinicians, and has acceptable interrater reliability. A final limitation, the use of a prespecified list of factors that did not include other potentially relevant factors such as temperament or other social factors, means that there may be other relevant factors that were not considered by the current analyses but may be important.

Conclusions

These findings, when considered alongside the concurrent neurobiological data we have presented previously,[37-43] provide the basis for the implementation of the clinical staging model in daily practice with young people; the design of specific youth clinical service models to support the efficient allocation of appropriate care[63-65]; and the evidence-based planning of stage-based early intervention and secondary prevention studies. In association with those clinical studies, there is a need to investigate other potentially differentiating neurobiological, psychosocial, or pathophysiological markers within those young people who present for care at early stages of illness.

ARTICLE INFORMATION

Accepted for Publication: June 3, 2019.

Published Online: August 28, 2019. doi:10.1001/jamapsychiatry.2019.2360

Author Affiliations: Youth Mental Health Team, Brain and Mind Centre, University of Sydney, New South Wales, Australia (Iorfino, E. M. Scott, Carpenter, Cross, Hermens, Nichles, Zmicerevska, White, Guastella, Hickie); The University of Notre Dame, St Vincent's and Mater Clinical School, Sydney, New South Wales, Australia (E. M. Scott); Sunshine Coast Mind and Neuroscience Thompson Institute, University of the Sunshine Coast, Birtinya, Queensland, Australia (Hermens); Sydney Informatics Hub, University of Sydney, New South Wales, Australia (Killedar); Academic Psychiatry, Institute of Neuroscience, Newcastle University, United Kingdom (J. Scott); Orygen, National Centre of Excellence in Youth Mental Health, Melbourne, Australia (McGorry); Centre for Youth Mental Health, University of Melbourne, Victoria, Australia (McGorry).

Author Contributions: Drs Hickie and Iorfino had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs E. M. Scott and Iorfino are joint first authors.

Concept and design: Iorfino, E. M. Scott, Carpenter, Cross, Hermens, J. Scott, McGorry, Hickie.
Acquisition, analysis, or interpretation of data: Iorfino, Carpenter, Cross, Hermens, Killedar, Nichles, Zmicerevska, White, Guastella, J. Scott, Hickie.
Drafting of the manuscript: Iorfino, Hermens, Killedar, J. Scott.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Iorfino, Killedar, J. Scott.
Obtained funding: Hickie.

Administrative, technical, or material support: E. M. Scott, Carpenter, Zmicerevska, White, Guastella, Hickie.
Supervision: E. M. Scott, Cross, Hermens, Guastella, J. Scott, Hickie.

Conflict of Interest Disclosures: Dr E. M. Scott is medical director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst; discipline leader of Adult Mental Health, School of Medicine, University of Notre Dame; Research Affiliate, The University of Sydney; and Consultant Psychiatrist. She has received honoraria from Laboratoires Servier and Eli Lilly and Company for presenting educational seminars related to the clinical management of depressive disorders and has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the national coordinator of an antidepressant trial sponsored by Laboratoires Servier. Dr J. Scott is a visiting professor at Diderot University, the Norwegian University of Science and Technology, Swinburne University of Technology, and The University of Sydney and a Science Without Borders fellow (Brazil). She has received grant funding from the UK Medical Research Council and from the UK Research for Patient Benefit program. Dr Hickie was an inaugural Commissioner on Australia's National Mental Health Commission (2012-18). He is the co-director, Health and Policy at the Brain and Mind Centre (BMC), University of Sydney. The BMC operates an early-intervention youth service at Camperdown under contract to headspace, National Youth Mental Health Foundation Ltd. Dr Hickie has previously led community-based and pharmaceutical industry–supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He was a member of the Medical Advisory Panel for Medibank Private until October 2017, a board member of Psychosis Australia Trust, and a member of Veterans Mental Health Clinical Reference group. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PricewaterhouseCoopers ([PwC] Australia; 45% equity) to deliver the $30 million Australian Government-funded Project Synergy (2017-2020; a 3-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies. No other conflicts were reported.

Funding/Support: This work was partially supported by grants from the National Health & Medical Research Council Centre of Research Excellence grant 1061043, and Australia Fellowship 511921 (both, Dr Hickie).

Role of the Funder/Sponsor: The funders had no input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We would like to thank all the young people who have participated in this study and all the staff in the Youth Mental Health Team at the Brain and Mind Centre, past and present, who have contributed to this work.

REFERENCES

1. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747-1757. doi:10.1016/S0140-6736(06)68770-9

2. Gustavsson A, Svensson M, Jacobi F, et al; CDBE2010Study Group. Cost of disorders of the brain in Europe 2010 [published correction appears in *Eur Neuropsychopharmacol*. 2012;22(3):237-238]. *Eur Neuropsychopharmacol*. 2011;21(10):718-779. doi:10.1016/j.euroneuro.2011.08.008

3. Jones PB. Adult mental health disorders and their age at onset. *Br J Psychiatry Suppl*. 2013;54(s54):s5-s10. doi:10.1192/bjp.bp.112.119164

4. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry*. 2005;62(7):768]. *Arch Gen Psychiatry*. 2005;62(6):593-602. doi:10.1001/archpsyc.62.6.593

5. McGorry PD. Risk syndromes, clinical staging and DSM V: new diagnostic infrastructure for early intervention in psychiatry. *Schizophr Res*. 2010;120(1-3):49-53. doi:10.1016/j.schres.2010.03.016

6. McGorry PD, Yung AR, Bechdolf A, Amminger P. Back to the future: predicting and reshaping the course of psychotic disorder. *Arch Gen Psychiatry*. 2008;65(1):25-27. doi:10.1001/archgenpsychiatry.2007.9

7. McGorry PD. Issues for DSM-V: clinical staging: a heuristic pathway to valid nosology and safer, more effective treatment in psychiatry. *Am J Psychiatry*. 2007;164(6):859-860. doi:10.1176/ajp.2007.164.6.859

8. Hickie IB, Scott EM, Hermens DF, et al. Applying a clinical staging framework in young people who present with admixtures of anxious, depressive or psychotic symptoms. *Early Interv Psychiatry*. In press.

9. Merikangas KR, Cui L, Kattan G, Carlson GA, Youngstrom EA, Angst J. Mania with and without depression in a community sample of US adolescents. *Arch Gen Psychiatry*. 2012;69(9):943-951. doi:10.1001/archgenpsychiatry.2012.38

10. Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980-989. doi:10.1016/j.jaac.2010.05.017

11. Merikangas KR, Herrell R, Swendsen J, Rössler W, Ajdacic-Gross V, Angst J. Specificity of bipolar spectrum conditions in the comorbidity of mood and substance use disorders: results from the Zurich cohort study. *Arch Gen Psychiatry*. 2008;65(1):47-52. doi:10.1001/archgenpsychiatry.2007.18

12. Kelleher I, Keeley H, Corcoran P, et al. Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *Br J Psychiatry*. 2012;201(1):26-32. doi:10.1192/bjp.bp.111.101543

13. Murray GK, Jones PB. Psychotic symptoms in young people without psychotic illness: mechanisms and meaning. *Br J Psychiatry*. 2012;201(1):4-6. doi:10.1192/bjp.bp.111.107789

14. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry*. 2003;60(7):709-717. doi:10.1001/archpsyc.60.7.709

15. Hickie IB, Scott EM, Hermens DF, et al. Applying clinical staging to young people who present for mental health care. *Early Interv Psychiatry*. 2013;7(1):31-43. doi:10.1111/j.1751-7893.2012.00366.x

16. Fava GA, Kellner R. Staging: a neglected dimension in psychiatric classification. *Acta Psychiatr Scand*. 1993;87(4):225-230. doi:10.1111/j.1600-0447.1993.tb03362.x

17. McGorry PD, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging of psychiatric disorders: a heuristic framework for choosing earlier, safer and more effective interventions. *Aust N Z J Psychiatry*. 2006;40(8):616-622. doi:10.1080/j.1440-1614.2006.01860.x

18. Scott J, Leboyer M, Hickie I, et al. Clinical staging in psychiatry: a cross-cutting model of diagnosis with heuristic and practical value. *Br J Psychiatry*. 2013;202(4):243-245. doi:10.1192/bjp.bp.112.110858

19. Kapczinski F, Magalhães PV, Balanzá-Martinez V, et al. Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. *Acta Psychiatr Scand*. 2014;130(5):354-363. doi:10.1111/acps.12305

20. McGorry P, Nelson B. Why we need a transdiagnostic staging approach to emerging psychopathology, early diagnosis, and treatment. *JAMA Psychiatry*. 2016;73(3):191-192. doi:10.1001/jamapsychiatry.2015.2868

21. Plana-Ripoll O, Pedersen CB, Holtz Y, et al. Exploring comorbidity within mental disorders among a Danish national population [published online January 16, 2019]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2018.3658

22. Scott J, Henry C. Clinical staging models: from general medicine to mental disorders. *BJPsych Adv*. 2017;23(5):292-299. doi:10.1192/apt.bp.116.016436

23. Scott J. Bipolar disorder: from early identification to personalized treatment. *Early Interv Psychiatry*. 2011;5(2):89-90. doi:10.1111/j.1751-7893.2011.00274.x

24. McGorry PD, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust*. 2007;187(7)(suppl):S40-S42.

25. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry*. 2006;188(4):313-320. doi:10.1192/bjp.188.4.313

26. Amminger GP, Schäfer MR, Schlögelhofer M, Klier CM, McGorry PD. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. *Nat Commun*. 2015;6:7934. doi:10.1038/ncomms8934

27. Liu P, Parker AG, Hetrick SE, Callahan P, de Silva S, Purcell R. An evidence map of interventions across premorbid, ultra-high risk and first episode phases of psychosis. *Schizophr Res*. 2010;123(1):37-44. doi:10.1016/j.schres.2010.05.004

28. Fowler D, Hodgekins J, French P, et al. Social recovery therapy in combination with early intervention services for enhancement of social recovery in patients with first-episode psychosis (SUPEREDEN3): a single-blind, randomised

controlled trial. *Lancet Psychiatry*. 2018;5(1):41-50. doi:10.1016/S2215-0366(17)30476-5

29. Fowler D, Hodgekins J, Painter M, et al. Cognitive behaviour therapy for improving social recovery in psychosis: a report from the ISREP MRC Trial Platform Study (Improving Social Recovery in Early Psychosis). *Psychol Med*. 2009;39(10):1627-1636. doi:10.1017/S0033291709005467

30. Bond GR, Drake RE, Campbell K. Effectiveness of individual placement and support supported employment for young adults. *Early Interv Psychiatry*. 2016;10(4):300-307. doi:10.1111/eip.12175

31. Bond GR, Drake RE, Luciano A. Employment and educational outcomes in early intervention programmes for early psychosis: a systematic review. *Epidemiol Psychiatr Sci*. 2015;24(5):446-457. doi:10.1017/S2045796014000419

32. Killackey E, Allott K, Woodhead G, Connor S, Dragon S, Ring J. Individual placement and support, supported education in young people with mental illness: an exploratory feasibility study. *Early Interv Psychiatry*. 2017;11(6):526-531. doi:10.1111/eip.12344

33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

34. National Center for Health Statistics. *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)*. http://www.cdc.gov/nchs/icd/icd10cm.htm. Published 2012. Accessed August 15, 2019.

35. Cross SPM, Scott J, Hickie IB. Predicting early transition from sub-syndromal presentations to major mental disorders. *BJPsych Open*. 2017;3(5):223-227. doi:10.1192/bjpo.bp.117.004721

36. Hickie I, Carpenter J, Iorfino F, Scott E, Cross SPM, Hermens D. The utility of clinical staging in youth mental health settings: neurobiological and longitudinal data from Sydney-based studies of transdiagnostic cohorts. Cambridge University Press.; In press.

37. Hermens DF, Naismith SL, Lagopoulos J, et al. Neuropsychological profile according to the clinical stage of young persons presenting for mental health care. *BMC Psychol*. 2013;1(1):8-8. doi:10.1186/2050-7283-1-8

38. Lagopoulos J, Hermens DF, Hatton SN, et al. Microstructural white matter changes are correlated with the stage of psychiatric illness. *Transl Psychiatry*. 2013;3(4):e248. doi:10.1038/tp.2013.25

39. Lagopoulos J, Hermens DF, Naismith SL, Scott EM, Hickie IB. Frontal lobe changes occur early in the course of affective disorders in young people. *BMC Psychiatry*. 2012;12(1):4. doi:10.1186/1471-244X-12-4

40. Scott EM, Robillard R, Hermens DF, et al. Dysregulated sleep-wake cycles in young people are associated with emerging stages of major mental disorders. *Early Interv Psychiatry*. 2016;10(1):63-70. doi:10.1111/eip.12143

41. Naismith SL, Hermens DF, Ip TKC, et al. Circadian profiles in young people during the early stages of affective disorder. *Transl Psychiatry*. 2012;2:e123. doi:10.1038/tp.2012.47

42. Eggins PS, Hatton SN, Hermens DF, Hickie IB, Lagopoulos J. Subcortical volumetric differences between clinical stages of young people with affective and psychotic disorders. *Psychiatry Res Neuroimaging*. 2018;271:8-16. doi:10.1016/j.pscychresns.2017.11.015

43. Tickell AM, Lee RS, Hickie IB, Hermens DF. The course of neuropsychological functioning in young people with attenuated vs discrete mental disorders. *Early Interv Psychiatry*. 2019;13(3):425-433. doi:10.1111/eip.12499

44. McGorry PD, Tanti C, Stokes R, et al. headspace: Australia's National Youth Mental Health Foundation—where young minds come first. *Med J Aust*. 2007;187(7)(suppl):S68-S70.

45. McGorry P, Bates T, Birchwood M. Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. *Br J Psychiatry Suppl*. 2013;54:s30-s35. doi:10.1192/bjp.bp.112.119214

46. Scott EM, Hermens DF, Glozier N, Naismith SL, Guastella AJ, Hickie IB. Targeted primary care-based mental health services for young Australians. *Med J Aust*. 2012;196(2):136-140. doi:10.5694/mja11.10481

47. Iorfino F, Hermens DF, Cross SP, et al. Delineating the trajectories of social and occupational functioning of young people attending early intervention mental health services in Australia: a longitudinal study. *BMJ Open*. 2018;8(3):e020678. doi:10.1136/bmjopen-2017-020678

48. Carpenter J, Iorfino F, Cross SPM, et al. Protocol for the Brain and Mind Centre Optymise Cohort: tracking multi-dimensional outcomes in young people presenting for mental health care. *BMC Psychiatry*. Under review.

49. Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. *Am J Psychiatry*. 1992;149(9):1148-1156. doi:10.1176/ajp.149.9.1148

50. R: A language and environment for statistical computing. https://www.gbif.org/en/tool/81287/r-a-language-and-environment-for-statistical-computing. Accessed July 26, 2019.

51. Jackson CH. Multi-state models for panel data: the msm package for R. *J Stat Softw*. 2011;38(8):1-29. doi:10.18637/jss.v038.i08

52. Hickie IB, Hermens DF, Naismith SL, et al. Evaluating differential developmental trajectories to adolescent-onset mood and psychotic disorders. *BMC Psychiatry*. 2013;13(1):303. doi:10.1186/1471-244X-13-303

53. Cross SP, Hermens DF, Hickie IB. Treatment patterns and short-term outcomes in an early intervention youth mental health service. *Early Interv Psychiatry*. 2016;10(1):88-97. doi:10.1111/eip.12191

54. McGorry PD, Nelson B, Markulev C, et al. Effect of ω-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders: the NEURAPRO randomized clinical trial. *JAMA Psychiatry*. 2017;74(1):19-27. doi:10.1001/jamapsychiatry.2016.2902

55. Wigman JT, van Nierop M, Vollebergh WA, et al. Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity—implications for diagnosis and ultra-high risk research. *Schizophr Bull*. 2012;38(2):247-257. doi:10.1093/schbul/sbr196

56. Owen MJ, Craddock N. Diagnosis of functional psychoses: time to face the future. *Lancet*. 2009;373(9659):190-191. doi:10.1016/S0140-6736(09)60053-2

57. McGrath JJ, Saha S, Al-Hamzawi A, et al. The bidirectional associations between psychotic experiences and DSM-IV mental disorders. *Am J Psychiatry*. 2016;173(10):997-1006. doi:10.1176/appi.ajp.2016.15101293

58. Saha S, Scott JG, Varghese D, McGrath JJ. The association between general psychological distress and delusional-like experiences: a large population-based study. *Schizophr Res*. 2011;127(1-3):246-251. doi:10.1016/j.schres.2010.12.012

59. Hickie IB. Evidence for separate inheritance of mania and depression challenges current concepts of bipolar mood disorder. *Mol Psychiatry*. 2014;19(2):153-155. doi:10.1038/mp.2013.173

60. Merikangas KR, Swendsen J, Hickie IB, et al. Real-time mobile monitoring of the dynamic associations among motor activity, energy, mood, and sleep in adults with bipolar disorder [published December 12, 2018]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2018.3546

61. Scott J, Murray G, Henry C, et al. Activation in bipolar disorders: a systematic review. *JAMA Psychiatry*. 2017;74(2):189-196. doi:10.1001/jamapsychiatry.2016.3459

62. van Os J. The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. *Am J Psychiatry*. 2013;170(7):695-698.

63. Cross S, Hermens D, Hickie I. Clinical staging in an early intervention youth mental health service: patient characteristics, treatment patterns and clinical outcomes [abstract 106]. *Early Interv Psychiatry*. 2014;8(special issue)(suppl 1):90.

64. Cross SP, Hermens DF, Scott J, Salvador-Carulla L, Hickie IB. Differential impact of current diagnosis and clinical stage on attendance at a youth mental health service. *Early Interv Psychiatry*. 2017;11(3):255-262. doi:10.1111/eip.12319

65. Cross SPM, Hermens DF, Scott EM, Ottavio A, McGorry PD, Hickie IB. A clinical staging model for early intervention youth mental health services. *Psychiatr Serv*. 2014;65(7):939-943. doi:10.1176/appi.ps.201300221