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An Epidemiological Study on Risk Factors for the Development of Serious Mental Illness In At-Risk Youth

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An Epidemiological Study on Risk Factors for the Development of Serious Mental Illness In At-Risk Youth

by

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Abstract

Usually, mental illnesses begin in adolescence and early adulthood, and for many, persist over time. Consequently, mental illnesses lead to significant personal and societal burden. In response, there has been increasing effort in early intervention strategies that may help with delaying or stopping the progression of a mental illness to a more serious state. Aside from finding early intervention strategies best suited for young people, it is imperative to understand the psychosocial, biological and environmental factors that may lead to the development of a mental illness. Research on these early factors in youth mental illness development is limited. The aim of this study was to determine which clinical factors might be related to the development of a serious mental illness (SMI) in at-risk youth. A total of 162 participants aged 12-26 years and at various stages of risk for SMI were included in the study. Out of these participants, 31 developed a SMI. Comparisons were made on a range of baseline clinical and functional measures between two groups; those that made a transition to a SMI (n=31) and those that did not (n=131). A cox regression analysis was used to assess the relationship between measures and SMI development. Female sex, attenuated psychotic symptoms as assessed with the Scale of Psychosis-risk Symptoms (SOPS), and higher ratings on the K-10 Distress Scale were found to be significantly related to later transition to a SMI. Female participants were 2.77 times more likely to transition to SMI compared to the males. There was a 14% increased risk of transition with each one-point increase in the SOPS, and a 7% increase with a one-point increase in the K-10 scale. Results from this longitudinal study may help improve understanding of illness trajectory and aid with early detection in mental illnesses.

Preface

The current thesis represents the original and independent work by the author Sara Jalali. The experiments reported and discussed across chapters 2 and 4 were covered by Ethic Certificate number REB14-1710 and was approved by the University of Calgary Conjoint Health Research Ethics Board on 12/01/2015.

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AUS/DUS	Alcohol and Drug Use Scales
BCSS	Brief Core Schema Scales
BDI	Beck Depression Inventory
BPD	Bipolar Disorder
CDSS	Calgary Depression Scale for Schizophrenia
CHR	Clinical High Risk
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
FACE-IV	The Family Adaptability and Cohesion Scale IV
FIGS	Family Interview for Genetic Studies
GAD-7	Generalized Anxiety Disorder 7-item
GAF	Global Assessment of Functioning
GF:R	Global Functioning: Role Scale
GF:S	Global Functioning: Social Scale
HC	Healthy Control
K10	K10-Distress Scale
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MDD	Major Depressive Disorder
PAS	Premorbid Adjustment Scale
PROCAN	The Adolescent Mental Health: Canadian Psychiatric Risk and Outcome Study

PSQI	Pittsburgh Sleep Quality Index
QIDS SR-16	Quick Inventory of Depressive Symptomatology
RRS	Ruminative Responses Subscales
SAS	Social Anxiety Scale
SCID-5	Structured Clinical Interview for DSM-5
SHAPS	Snaith Hamilton Pleasure Scale
SIAS	Social Interaction Anxiety Scale
SIPS	Scale of Psychosis-risk Syndromes
SMI	Serious Mental Illness
SOPS	Scale of Psychosis-Risk Symptoms
YMRS	Young Mania Rating Scale

Chapter 1: Introduction to Risk of Developing a Serious Mental Illness in Youth

1.1 Introduction

There has been tremendous growth in the field of youth mental health in recent years. The Global Burden of Disease Study of 2010 demonstrated that mental disorders are a leading cause of years lived with disability and are one of the most prominent health concerns contributing to global burden (Whiteford et al., 2013). Lifetime prevalence of experiencing a mental disorder varies by country, but has been observed at approximately 47% for the US population (Kessler et al., 2007). Compounding this issue further is that most mental disorders start before the age of 25 during adolescence (Jones, 2013). Furthermore, 75% of those experiencing a mental disorder go on to a more chronic and persistent state (De Girolamo et al., 2012). A serious mental illness commonly refers to a diagnosis of schizophrenia spectrum disorders, bipolar disorder, or recurrent major depressive disorder. Many individuals with a serious mental illness (SMI) have difficulties maintaining normal function and experience a significant decline in their overall quality of life compared to those without a mental illness (Evans et al., 2007). This highlights the importance of early identification and prevention of the development of SMI in youth.

There are limited ways of identifying individuals at risk for developing a SMI. It has been shown that early manifestations of a mental disorder may appear much before it reaches criteria for a diagnosable condition (Van Os et al., 2009) and that the subsyndromal symptoms can still be disabling for individuals (Purcell et al., 2015). Therefore, even without a diagnosed condition, people can suffer from symptoms associated with a mental illness, suggesting a continuum of illness and illness progression as opposed to the current categorical model. One suggested solution has been to do more screening to find more cases within the population. However, some argue that increased screening and outreach will not necessarily lead to a better understanding of

the number of people at risk or affected by a disorder because of the potential of receiving false negatives and positives (Fusar-Poli et al., 2016). Consequently, those at risk for SMI who go without intervention will likely experience the continuum of illness and disease progression. Given the debilitating nature of many mental illnesses, finding effective methods of detection and prevention can prove beneficial for those at risk.

1.2 Early identification of youth at risk of serious mental illness

Early identification research in the field of youth mental health has aided in the development of a transdiagnostic clinical staging model (Hickie et al., 2013; McGorry et al., 2007). In this model, disorders are defined according to multiple stages, each stage increasing in severity and intensity of symptoms experienced and level of intervention required (McGorry et al., 2007). The clinical staging model has been used in research studies looking at those at risk for psychosis, bipolar disorder, and depression (Addington et al., 2019; Hartmann et al., 2019). Although there are still debates around whether this staging model is disorder specific or can be transdiagnostic (Hartmann et al., 2019) clinical staging has demonstrated clinical utility. A systematic review of clinical staging has revealed that clinical staging is valuable since it can help differentiate important prognostic and therapeutic differences between patients that may have the same disorder but be at different stages (Cosci & Fava, 2012).

In the clinical staging model, disorders are defined according to multiple stages (McGorry et al., 2006). Stage 0 is the pre-symptomatic at-risk stage. This would include asymptomatic young people with family predispositions for a SMI. Stage 1 is separated into two substages and includes non-specific symptoms associated with the early phases of a mental illness. Stage 1a represents those with undifferentiated general symptoms that are mild to moderate. Stage 1b

includes those with more moderate to severe attenuated symptoms who may also present with moderate functional impairment. Individuals at this stage are often described as being clinical high risk for a serious mental disorder (e.g., clinical high risk for psychosis). Stage 2 describes the first episode of a psychotic or severe mood disorder. Stage 3 is separated into three substages. Stage 3a is the stage of incomplete remission, Stage 3b consists of recurrence of disorder or relapse, and Stage 3c includes multiple relapses and worsening clinical symptoms. The last stage is Stage 4 which describes a severe and persistent illness that is unremitting.

The staging model has been used in three large research studies looking at individuals at risk for developing SMI. These studies demonstrate how the use of clinical staging model can help identify people at risk for SMIs and provide a more dimensional approach to interventions in mental health. The first is the Clinical High at Risk Mental State (CHARMS) study of the Orygen group in Melbourne which uses the principles of clinical staging and attempts to broaden the identification of risk (Hartmann et al., 2021; Hartmann et al., 2019). They have placed individuals meeting stage 1a into the CHARMS- group (control group) and those meeting stage 1b into the CHARMS+ group. Their 12-month follow-up assessed the transition rate to Stage 2 for both groups and found a 34% transition rate for the CHARMS+ group, as opposed to the 3% for the control group (Hartmann et al., 2021). The second study was done by a group in Sydney, Australia (Iorfino et al., 2019). The focus of this study was to report on the transition rates and demographic and clinical characteristics of transitions for participants assigned to three clinical stages (stage 1a, 1b, and 2). It was found that 2.6% of stage 1a participants transitioned to stage 1b and 12.8% of stage 1b participants transitioned to stage 2. They concluded that this lower transition rate suggested an increased risk of the development of full-threshold disorder for those in stage 1b compared to 1a. The third study is The Adolescent Mental Health: Canadian

Psychiatric Risk and Outcome (PROCAN) study which is the focus of this thesis and will be addressed in Chapters 2 and 3.

Although clinical staging has gained traction, there are notable criticisms that should be mentioned. One of the primary concerns in clinical staging is whether to favour a staging model that is disorder specific or a transdiagnostic model that encompasses many disorders (McGorry et al., 2007). The concern is that a transdiagnostic approach would 'lump' all disorders together and lose the specificity offered by a disorder specific model (Hartmann, Nelson, Ratheesh, et al., 2019). This issue of 'splitting vs lumping' highlights a prevalent concern in psychiatric criteria for diagnoses, and that is that many disorders share similar antecedents, but some have notable differences with disorder specific symptoms (Hartmann, Nelson, Ratheesh, et al., 2019). A transdiagnostic model, as currently described now, would be poorer at detecting risk for the development of a particular disorder based on certain disorder-specific symptoms. Another concern has been that there is not adequate research on the pluripotency of the expression of early clinical symptoms (Duffy & Malhi, 2017). However, a review on clinical staging implemented in psychosis, bipolar disorder and depression has shown that there are in fact overlapping and non-specific antecedents in the three disorders which helps emphasize the importance of a transdiagnostic model for at-risk mental states (Hartmann, Nelson, Ratheesh, et al., 2019).

Chapter 2: The Adolescent Mental Health: Canadian Psychiatric Risk and Outcome (PROCAN) Study

2.1 Background

PROCAN was a 1-year longitudinal study, funded by Brain Canada with J Addington as the principal investigator. In this study, a cohort of youth at various stages of risk for developing SMI were assessed using the clinical staging model described previously. The study aimed to address three key areas in youth mental health: clinical outcome, brain changes and prediction of SMI (Addington et al., 2018). The previously published key objectives of the PROCAN study were:

1) Clinical
    (i) Improve ability to identify youth at risk of SMI by determining clinical, social, and cognitive factors associated with level of risk.
    (ii) Better understand factors that predict key outcomes, such as advancing disability, secondary substance misuse, non-participation in education and employment, and new self-harm.
2) Imaging
    (i) Identify structural and functional correlates of a predisposition to develop a SMI.
    (ii) Understand how progression through the clinical stages of illness is associated with progressive brain changes.
3) Prediction Models
    (i) Develop models that predict transition to illness.
    (ii) Determine whether incorporating imaging data with clinical data improves the predictive value of the model.

2.2 Method of the PROCAN Study

PROCAN was initially a 1-year longitudinal study. Participants were assessed at baseline on all measures, followed by short clinical assessments at 6 and 12 months. If participants made a transition to a SMI at any point in the study, clinical assessments were repeated (see Table 2.1 for schedule of events). Additional funding was acquired to complete additional assessments and first to follow the Calgary sample at 18 and 24 months and secondly to follow at 30, 36, 42 and 48 months.

Table 2.1. Schedule of Events

Assessment	BL	6M	12M	18M	24M	30M	36M	42M	48M	Transition
Demographics	✓									
SCID-5	✓		✓			✓	✓	✓	✓	✓
Scale of Psychosis-Risk Symptoms (SOPS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Family History (FIGS)	✓									
Global Assessment of Functioning (GAF)	✓	✓	✓	✓	✓					✓

Schizotypal Personality Disorder Criteria	✓	✓	✓							✓
Stage of Risk	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Client Interview:										
Premorbid Adjustment Scale	✓									
Documentation of Trauma	✓									
Young Mania Scale	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Calgary Depression Scale for Schizophrenia	✓	✓	✓	✓	✓					✓
Alcohol/Drug Use Scale (AUS/DUS)	✓	✓	✓							✓
Client Self Reports:										
Generalized Anxiety Disorder 7-item (GAD-7)	✓	✓								
Quick Inventory of Depressive	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Symptomatology (QIDS-SR)										
Social Interaction Anxiety Scale (SIAS)	✓	✓	✓	✓	✓					✓
Social Anxiety Scale (SAS)	✓	✓	✓	✓	✓					✓
K10-Distress Scale	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Beck Depression Scale	✓	✓	✓	✓	✓					✓
Brief Core Schema Scales	✓	✓	✓							✓
Ruminative Responses Subscale	✓	✓	✓							✓
Snaith-Hamilton Pleasure Scale (SHAPS)	✓		✓							
Life Events	✓		✓							✓
Daily Stress Inventory	✓	✓	✓							✓

Sleep Measure (PSQI-NH)	✓		✓							✓
Ongoing Treatment Log:										
Medication Log	✓	✓	✓		✓	✓	✓	✓	✓	✓
Psychosocial Log	✓	✓	✓			✓	✓	✓	✓	✓
Resource Utilization Log	✓	✓	✓			✓	✓	✓	✓	✓
Functioning:										
Global Functioning: Social Scale (GF:S)	✓	✓	✓		✓	✓	✓	✓	✓	✓
Global Functioning: Role Scale (GF:R)	✓	✓	✓		✓	✓	✓	✓	✓	✓
Neurocognition:										
Wide Range Achievement Test (WRAT)	✓									
Wechsler Abbreviated	✓									

Scale of Intelligence (WASI-2)										
MATRICS Cognitive Battery	✓		✓							✓

Note. BL: Baseline, M: Months

2.2.1 Participants

The PROCAN study recruited a total of 243 adolescents and young adults (age 12-25), with 201 from the University of Calgary site and 42 from the Sunnybrook Health Sciences Centre in Toronto. Data has already been collected for these participants at baseline, 6-, and 12-months for both sites, and 18-, 24-, 32-, 36-, 42- , and 48-months for the Calgary site. Of the 243 participants, 42 were healthy controls (HC), 41 were in stage 0, 52 were in stage 1a, and 108 in stage 1b. Details of how many participants were assessed at each site and in each stage is presented in Table 2.2.

Table 2.2. Detailed Number of Participants from Each Site

	BL	**6M**	**12M**	**18M**	**24M**	**30M**	**36M**	**42M**	**48M**
HCs									
C	27	25	22	4	3	5	11	10	12
T	15	12	11	0	0	0	0	0	0
Total	**42**	**37**	**33**	**4**	**3**	**5**	**11**	**10**	**12**
Stage 0									
C	28	27	24	18	19	3	10	12	15

T	13	11	10	0	0	0	0	0	0
Total	**41**	**38**	**34**	**18**	**19**	**3**	**10**	**12**	**15**
Stage 1a									
C	44	39	35	30	26	2	11	21	25
T	9	7	6	0	0	0	0	0	0
Total	**53**	**46**	**41**	**30**	**26**	**2**	**11**	**21**	**25**
Stage 1b									
C	102	82	67	51	46	2	15	29	42
T	5	4	3	0	0	0	0	0	0
Total	**107**	**86**	**70**	**51**	**46**	**2**	**15**	**29**	**42**
TOTAL	**243**	**207**	**178**	**103**	**94**	**12**	**47**	**72**	**94**

Note. BL: Baseline, M: Months, C: Calgary Site, T: Toronto Site.

2.2.2 Measures

The following measures were used to determine the clinical stage for each participant: The Structured Clinical Interview for DSM-5 (First, 2013), the Structured Interview for Psychosis-risk Syndromes (McGlashan et al., 2010), the Quick Inventory of Depressive Symptomatology (Rush et al., 2003) and the K10-Distress scale (Kessler et al., 2002). The Structured Clinical Interview for DSM-5 (SCID-5) was used to assess the presence of Axis 1 disorders. The Scale of Psychosis-risk Syndromes (SIPS) was used to determine if participants met criteria for psychosis risk and the Scale of Psychosis-Risk Symptoms (SOPS) which is part of the (SIPS) was used to assess the severity of attenuated psychotic symptoms. The SOPS

subscales assess positive and negative symptoms, disorganization, and general symptoms. The positive symptoms rated are: P1) Unusual Thought Content/Delusional Ideas, P2) Suspiciousness/Persecutory Ideas, P3) Grandiose Ideas, P4) Perceptual Abnormalities/Hallucinations, and P5) Disorganized Communication. The ratings on the positive items are used to define the presence of psychotic symptoms and psychosis-risk syndromes. The severity of each of these symptoms is rated from 0-6, and a rating between 3 to 5 is associated with psychosis-risk syndromes and a rating of 6 is associated with current psychosis. The Quick Inventory of Depressive Symptomatology (QIDS) is a self-report scale that assesses level of depression. This 16-item scale assesses nine symptom criteria domains over the past 7 days. The symptom domains include: 1) Sleep disturbances, 2) Sad mood, 3) Decrease/increase in appetite/weight, 4) Concentration, 5) Self-criticism, 6) Suicidal ideation, 7) Interest, 8) Energy/fatigue, and 9) Psychomotor agitation/retardation. The total score range is 0-27 and a higher score is associated with increased severity in depression. The K10-Distress scale determines the level of distress by rating 10 questions about anxiety and depressive symptoms experienced over the last 30 days. The rating on this scale ranges from 1 (None of the time) to 5 (All of the time), for a total score range of 10-50. A higher score on this scale is associated with greater level of distress.

Mood was assessed with the Young Mania Rating Scale (Young et al., 1978), the Quick Inventory of Depressive Symptomatology (QIDS SR-16), the Calgary Depression Scale for Schizophrenia (Addington et al., 1993), and the Beck Depression Inventory (Beck et al., 1987). The Young Mania Scale is an 11-item scale used to assess manic symptoms. The Calgary Depression Scale for Schizophrenia is a specific scale used to assess depressive symptoms in people with schizophrenia. And, the Beck Depression Inventory is a measure that assesses

attitudes and symptoms of depression. A higher score on any of these measures is associated with more severe symptoms of their respective disorder. Anxiety was assessed using the Social Interaction Anxiety Scale (Mattick & Clarke, 1998) and the Social Anxiety Scale (Zung, 1971). The Social Interaction Anxiety Scale is a 20-item scale that includes self-statements of reactions to social interactions and relationships, and the Social Anxiety Scale is a 20-item scale includes self-statements of physical reactions of anxiety. Both scales have a range of 20-80 with a higher score indicating increased severity of anxiety symptoms. Additional clinical measures included the Ruminative Responses Subscale (Wilkinson & Goodyer, 2008) the Snaith Hamilton Pleasure scale (Snaith et al., 1995), and the Brief Core Schema Scales (Addington & Tran, 2009).. The Ruminative Responses Subscale is a 22-item scale rated from 1 (Almost Never) to 4 (Almost Always) and a higher score on this scale is reflective of greater rumination tendency. The Snaith Hamilton Pleasure Scale is a 14-item scale that assesses anhedonia. The scale is split into four categories of pleasure: 1) Interests/pastimes, 2) Social interactions, 3) Sensory experiences, 3) Food/drink. The Brief Core Schema Scales assesses beliefs of self and others. Functioning was measured using the Global Functioning: Social (GF:S) and Role (GF:R) scales (Cornblatt et al., 2007). A higher score on the GF:S and GF:R is associated with greater level of social and role functioning, respectively. Cognition was assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB).

2.2.3 Procedures

Initially in the PROCAN study assessments were planned for baseline, 6- and 12-months. This was later extended at the Calgary site to completing assessments at 18- and 24-months. The

third phase of this project at the Calgary site through additional funding was to complete brief clinical follow-up assessments at 30-, 36-, 42-, and 48 months.

All clinical raters completed a rigorous protocol training under the supervision of Dr. Addington (Addington et al., 2012). Clinical raters interviewed each participant and wrote comprehensive vignettes assessing stage of risk. Under the supervision of Dr. Addington, these vignettes were reviewed in weekly teleconference calls to come to a consensus decision on the assignment of stage of risk. Changes to stage of risk at 6- and 12-month follow ups was also confirmed using a consensus decision-making process.

Participants involved in the PROCAN study have previously signed informed consent, and consent was obtained from parents/legal guardians for those who were minors.

2.3 Review of previously published PROCAN papers

The PROCAN study consisted of the four groups as described above. There were 42 healthy controls, 41 in stage 0, 52 in stage 1a and 108 in stage 1b. Healthy controls were asymptomatic and had no family history of any serious mental illness. Stage 0 were asymptomatic but did have a family history of serious mental illness. Stage 1a participants did not meet any diagnoses but presented with mild symptoms of anxiety and/or depression and tended to be distressed. For stage 1b participants, 83 met criteria for psychosis risk, 1 presented with subthreshold symptoms of mania, 11 met criteria for moderate depression, 2 for self-harm, and 11 for anxiety syndromes (Addington et al., 2019). See Supplementary Table 1 for the details of the criteria for each group. Cross sectional and longitudinal findings from a variety of measures in the PROCAN study have previously been published. In these papers participants in the symptomatic groups (i.e., stages 1a and 1b) were generally younger, had less education, were more likely to be living at home, and

more likely to be unemployed, compared to the asymptomatic group (i.e., healthy controls and stage 0).

The first paper published was a clinical paper to validate placement of the participants into the different groups (Addington et al., 2019). Placement was based on the Structured Clinical Interview for DSM-5 (SCID-5), Structured Interview for Psychosis-risk Syndromes (SIPS), Scale of Psychosis-risk Symptoms (SOPS), and the Quick Inventory of Depressive Symptomatology (QIDS). Using additional clinical measures, it was observed that the groups did differ in depression, anxiety, self-evaluation, and attenuated psychotic symptoms demonstrating that placement into the different stages was a good fit for participants. Overall, stage 1b participants had more severe ratings on all clinical measures, except suicide attempts and substance use. Likewise, stage 1a participants had more severe ratings compared to the Healthy Control's and stage 0 participants. The results from the additional clinical measures validated placement of the individuals into their respective groups.

Other clinical issues that were examined in additional papers included sleep, substance use, trauma and personality. Stage 1a and 1b participants had notable sleep disturbances and significantly differed from the HCs in sleep quality, sleep latency, use of sleep medications and generally experienced more daytime dysfunction (Stowkowy, Brummitt, et al., 2020). With respect to substances, the most commonly used were alcohol (43.6%), cannabis (14.4%), and tobacco (12.4%) (Farris et al., 2021). However, severity and frequency of use did not differ between groups. The paper on trauma and bullying revealed that there were high frequencies of trauma in all stages, with approximately 50% of individuals in each of the at-risk groups reporting some experience of trauma (Stowkowy, Goldstein, et al., 2020). Those in stage 1a and 1b reported greater trauma and bullying compared to HCs, and those in stage 1b reported more

physical abuse (Stowkowy, Goldstein, et al., 2020). Finally, in terms of personality, differences were observed between the groups with the symptomatic group having low ratings on extraversion and conscientiousness (Santesteban-Echarri et al., 2021). More specifically, within the symptomatic group stage 1a participants scored higher on openness and stage 1b participants scored higher on neuroticism (Santesteban-Echarri et al., 2021).

Baseline functioning was examined in two papers, reporting that the symptomatic group (1a and 1b) was found to have poorer social and role functioning and lower IQ scores than the non-symptomatic group (HC and Stage 0) (Romanowska et al., 2018; Romanowska et al., 2020).

Treatment history was reported in a baseline (Farris et al., 2019) and then in a longitudinal paper (Farris et al., 2021). Three types of treatment were examined; psychotropic medications, psychosocial therapy, and hospital visits related to mental health. At baseline, none of the HCs were receiving medication, while 32.7% of stage 1a and 34.3% of stage 1b were on medication (Farris et al., 2019). Type of medication (antidepressants, mood stabilizers, anxiolytics, antipsychotics, simulants, and non-stimulants) was also examined. Use of antidepressants was most common in stage 1a and 1b participants, followed by stimulants. In all groups, mood stabilizers were the least commonly reported medication. A significant portion of stage 1b participants (49.1%) and 26.9% of stage 1a participants were receiving psychosocial therapy. Lastly, stage 1b had the highest frequency of lifetime treatment and psychiatric hospital visits. Longitudinally, the proportion of participants receiving medications was stable across follow-ups, with current medication use for stage 1a changing from 32.7% at baseline to 40.5% at 24-months, and stage 1b participants changing from 34.3% to 46.4% (Farris et al., 2021).

A one-year clinical follow-up was published to assess any transitions or changes within the stages of risk. It was observed that by 12-months, approximately 7% of participants in each

group moved to a more advanced clinical stage of risk (Addington, Liu, et al., 2021). Fifty percent of participants in stage 1a and 36% of stage 1b remained symptomatic and had not improved after 12-months (Addington, Liu, et al., 2021). Although, it is possible that the number of dropouts may have impacted these numbers and their significance.

Finally, since this was a young sample who predominantly lived at home, family functioning and communication and satisfaction were assessed at the different stages. Although, stage 1b participants were found to have significant differences for all the Family Adaptability and Cohesion Evaluation Scales (FACE-IV scales) compared to those in Stage 0 and HCs, these results were not clinically significant (Santesteban-Echarri et al., 2018). However, there was one exception, HCs and Stage 0 participants reported being moderately satisfied with their family life, whereas participants in stages 1a and 1b reported lower satisfaction.

In summary to date 18 papers from the PROCAN study have been published. Their results have shown that stage 1a and 1b participants scored poorer than HCs and stage 0 participants in clinical measures on depression, anxiety, self-evaluation, attenuated psychotic symptoms, had experienced more trauma and sleep disturbances, had poorer social and role functioning, and had more treatment and medication use. Family functioning differed between the stages as well, however, it was not clinically significant. Future work for this project will be to determine factors that may be associated with a later transition to a SMI.

Chapter 3: Factors Associated with Transition to Serious Mental Illness

3.1 Preface

Research presented as part of this chapter is currently under review as; Sara Jalali, Lu Liu, JianLi Wang, Sidney H. Kennedy, Glenda MacQueen, Catherine Lebel, Benjamin l. Goldstein, Signe Bray, & Jean Addington (Under Review). *Factors Associated with Transition to Serious Mental Illness.* Early Intervention in Psychiatry

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Factors Associated with Transition to Serious Mental Illness

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Abstract

Objective: There is increasing interest in early intervention and detection strategies for youth at-risk of developing a serious mental illness (SMI). Little is known about early factors that may be related to the later development of a SMI, thus, the aim of this study was to determine what clinical factors might relate to the development of a SMI in youth determined to be at risk.

Method: The sample consisted of 162 youth aged 12-26 years at different stages of risk. Thirty-one participants developed a SMI during the study. Those who made a transition were compared on a range of baseline clinical and functional measures with those who did not make the transition. A Cox regression model was used to assess the association between measures and later development of a SMI.

Results: Female sex, attenuated psychotic symptoms as assessed with the Scale of Psychosis-risk Symptoms (SOPS) and ratings on the K-10 Distress Scale, were found to be significantly associated with the later transition to mental illness. Females were 2.77 times more likely to transition compared to males. For the SOPS and K-10 scales, there is a 14% increase in the transition rate relative to a one scale increase in SOPS, and a 7% increase in the transition rate relative to a one scale increase in the K-10.

Conclusions: Results from these longitudinal data provide further insight into the specific clinical measures that may be pertinent in early detection of mental illnesses.

Keywords: youth mental health, transition to serious mental illness, clinical staging

3.2 Introduction

Mental disorders typically begin in adolescence and can cause significant personal and global burden (Kessler et al., 2007) and are the leading cause of disability in adolescents and young adults (Erskine et al., 2015). Given the possible long-term adverse consequences of mental illness, early identification of those at-risk of developing a mental disorder is warranted with the goal of preventing more serious mental illnesses (SMI). A transdiagnostic clinical staging model has been developed that describes disorders according to multiple stages, that increase in severity and intensity (McGorry et al., 2007). These stages range from stage 0 to stage 4, with substages for stages 1 and 3. For at-risk the relevant stages are stage 0, the pre-symptomatic stage and stage 1which is divided into two substages: stage 1a those with mild to moderate symptoms but no clear diagnosis and stage 1b those with an attenuated syndrome. The later stages are relevant for those with diagnosed disorders with stage 2 describing those experiencing a full threshold disorder, stage 3 ranges from incomplete remission to multiple relapses and worsening of symptoms and stage 4 describes a severe, persistent, and unremitting illness.

To date, several studies have used clinical staging models to better understand the illness trajectory of at-risk populations. The Clinical High At-Risk Mental State (CHARMS) study in Australia used clinical staging principles to better understand transition to a SMI in individuals at-risk for developing psychosis, severe depression, mania, or borderline personality disorder. Their preliminary findings suggest a transition rate of 3% for those in stage 1a and 34% for those in stage 1b (Hartmann et al., 2021; Hartmann, Nelson, Spooner, et al., 2019). A second Australian study (Iorfino et al., 2019) focused on transition rates from stage 1a to stage 1b, and from stage 1b to stage 2. This group observed a transition rate of 2.6% for stage 1a participants

moving to stage 1b and 12.8% for stage 1b participants transition to a SMI. Of those who transitioned, 24.2% developed a psychotic disorder, 44.3% developed bipolar disorder, and 31.4% developed an anxiety or depressive disorder. Thirdly, the Adolescent Mental Health: Canadian Psychiatric Risk and Outcome (PROCAN) is a longitudinal study conducted in Calgary and Toronto on at-risk youth (Addington et al., 2018).

In the PROCAN study, a wide range of measures were used to assess symptoms, and functioning. Assessments were conducted at baseline, with follow-ups at 6-months, 12-months and for a subsample up to 48 months. The sample consisted of four groups: healthy controls, stage 0, stage 1a and stage 1b with Stage 0 consisting of non-symptomatic participants with a family history of mental illness; stage 1a consisting of participants with mild symptoms of anxiety or depression, and stage 1b consisting of participants with attenuated syndromes.

Allocation of participants to the different stages was based on three measures the Structured Clinical Interview for DSM-5 (SCID), the Structured Interview for Psychosis-risk Syndromes (SIPS) and the Quick Inventory of Depressive Symptomatology (QIDS). Assessments with additional measures of depression, anxiety, self-evaluation, and level of functioning validated the placement into these different stages (Addington et al., 2019). Participants in stages 1a and 1b typically had more severe symptoms and poorer functioning than the healthy controls and non-symptomatic participants, and on several measures 1b participants presented with more severe symptoms than 1a (Addington et al., 2019). Other clinical phenomena were examined: the symptomatic groups (1a & 1b) were found to have significantly more sleep disturbances and poorer sleep quality compared to the non-symptomatic group (Stowkowy, Brummitt, et al., 2020); personality differences were observed with the symptomatic group scoring lower on extraversion and conscientiousness, and stage 1b scoring higher on

neuroticism (Santesteban-Echarri et al., 2021); and reports of trauma were high in all groups relative to healthy controls, but significantly more so in the symptomatic groups (Stowkowy, Goldstein, et al., 2020). In addition, although functioning was not used to differentiate the groups, the symptomatic group had poorer social and role functioning as well as lower IQ scores compared to the non-symptomatic group (Romanowska et al., 2018; Romanowska et al., 2020). However, no differences amongst the groups were observed with respect to substance use (Farris et al., 2021) or family functioning (Santesteban-Echarri et al., 2018).

The overall aim of the PROCAN study was to determine clinical factors associated with the transition to a SMI. Thus, the aim of this paper is to examine a range of the baseline clinical measures to determine what factors might be associated with the development of a SMI over a four-year period.

3.3 Methods

3.3.1 Participants

A total of 201 individuals at-risk for SMI aged 12 to 25 years were recruited for the PROCAN study in Toronto and Calgary. Since participants (n=27) from the Toronto site ended their participation after one year and made up only 13% of the total sample, this paper will only focus on the at-risk youth recruited from the Calgary site. Recruitment was through referrals by mental health professionals, counselling services, schools, advertisements, and from self-referrals. Participants were assessed for study eligibility through a telephone screening. Those who met inclusion criteria were evaluated by clinical raters who had completed rigorous protocol training under the supervision of Dr. J Addington. Clinical raters wrote comprehensive vignettes assessing the stage of risk of each participant. These vignettes were reviewed by all raters and JA

to make a consensus decision on the stage of risk of the participant. More details on recruitment and methodology have been reported elsewhere (Addington et al., 2018; Addington et al., 2019).

Participants (n=174) fell into 3 groups: Stage 0 (n=28), Stage 1a (n=44), and Stage 1b (n=102). Supplementary Table 1 presents a detailed outline of the stages and their criteria. Twelve participants dropped out after baseline and had no follow-up: thus 162 have at least one follow-up assessment and will be the sample addressed in the analyses. Of those, 31 made a transition to serious mental illness within the four years of the study. Of the 131 non-transitioning participants with at least one follow-up only 69 participants completed a final assessment between 42 and 48 months.

3.3.2 Procedures

Informed consent was obtained from all participants and parental informed consent was obtained for those under the age of 18. The University of Calgary Conjoint Health Research Ethics Board provided ethical approval of the study.

PROCAN was funded by Brain Canada as a 1-year longitudinal study. Participants were assessed at baseline on all measures, followed by short clinical assessments at 6 and 12 months. The Calgary sample was followed for an additional year to two years and subsequently additional funding was acquired to follow the Calgary sample for two more years to complete brief clinical assessments, at 30, 36, 42 and 48 months after baseline to determine if the participant had made a transition to a SMI. If there was a suspected transition to a SMI, the consensus decision making process was used to confirm the transition.

3.3.3 Measures

To determine participant stage at baseline the following measures were used: The Structured Clinical Interview for DSM-5 (First, 2014), the Scale of Psychosis-risk Syndromes (McGlashan et al., 2010), the Quick Inventory of Depressive Symptomatology (Rush et al., 2003) and the K10 distress scale (Kessler et al., 2002). The SCID-5 was used to assess the presence of Axis 1 disorders (First, 2013).

The following measures were used at baseline to assess clinical features that may be related to later transition to a SMI. Mood was assessed with the Calgary Depression Scale for Schizophrenia (Addington et al., 1993), and the Young Mania Rating Scale (Young et al., 1978). Anxiety was assessed using the Social Anxiety Scale (Zung, 1971). Functioning was assessed using the Global Functioning: Social (GF:S) scale (Cornblatt et al., 2007) and the Global Assessment of Functioning (GAF). Other measures included the K10 distress scale (Kessler et al., 2002), family history of SMI from the Family Interview for Genetic Studies (Maxwell, 1992) and endorsement of bullying and trauma (Janssen et al., 2004). Psychosis-risk positive and negative symptoms were assessed using the Scale of Psychosis-Risk Symptoms (McGlashan et al., 2010).

3.3.4 Statistical Analyses

Statistical analyses were performed with SPSS 28 and STATA 17. T-tests were performed for continuous socio-demographic variables, and chi-squared test for categorical variables, to compare transition and non-transition groups Cox regression analysis to examine which factors impact transition to SMI. Univariate Cox proportional hazard regression analyses were performed to decide which predictors to include in the cox model. Predictors were considered for the model if $p<0.25$ in the univariate analyses. Backward variable selection was

performed for the final Cox regression model. Interactions between predictors were also assessed. The interactions with $p<0.05$ were included in the model. The models with and without the interactions were compared to see which model better fit the data. Lastly, the Schoenfeld and scaled Schoenfeld residuals were used to test the proportionality assumption.

3.4 Results

3.4.1 Demographics

There were 162 participants, with 131 participants in the non-transition group and 31 participants in the transition group. The majority were white, single, lived at home, enrolled as students, and not employed. There were five males and 26 females in the transition group and 62 males and 69 females in the non-transition group. The mean age in the transition group was 17 years and 17.18 in the non-transition group. The only significant difference between groups was sex, with significantly more females than males in the transition group (see table 3.1).

Table 3.1. Demographics of transition and non-transition groups

	Non-Transition (n=131) M (SD)	**Transition (n=31) M (SD)**	**t**	**p-values**
Years of education	10.03 (3.53)	10.9 (2.04)	-1.820	0.073
Age	17.18 (3.56)	17 (2.79)	0.310	0.757
	N (%)	**N (%)**	**$\chi 2$**	**p-values**
Sex				
Male	62 (47.3)	5 (16.1)[a]	10.061	0.002
Female	69 (52.7)	26 (83.9)[a]		

Racial Background				
Asian	15 (11.4)	3 (9.7)	-	1.000
First Nations	1 (0.8)	0 (0)		
Black	4 (3.1)	1 (3.2)		
Central/South American	5 (3.8)	1 (3.2)		
White	88 (67.2)	22 (71.0)		
Mixed Race	18 (13.7)	4 (13.0)		
Marital Status				
Single, never married	125 (95.4)	31 (100)	-	1.000
Other	6 (4.6)	0 (0)		
Current living arrangement				
Living with family	104 (81.3)	29 (93.5)	-	0.909
Living with spouse/partner	7 (5.5)	1 (3.2)		
Living on own	6 (4.7)	0 (0)		
Other	11 (8.6)	1 (3.2)		
Current student				
Yes	107 (82.3)	29 (93.5)	-	0.492
No	23 (17.7)	2 (6.5)		
Current employment				
Employed	51 (39.2)	9 (29.0)	-	0.551
Not employed	79 (60.8)	22 (71.0)		

Note. [a] Post-hoc Bonferroni correction (alpha level set at 0.05); Significantly differs from non-transition group. Fisher's exact test was used for variables with less than 5 counts in a cell.

3.4.2 Transitions to SMI

Of the 31 participants who transitioned to a SMI, 27 made a transition to major depressive disorder (MDD), three to bipolar disorder (BPD) and one to psychosis. Details of transition diagnoses are presented in Table 3.2. The mean number of days from baseline to time of transition was 767 days, SD=435 and range was 133-1460 days. Ten participants transitioned in year 1, five in year 2, eight in year 3 and eight in year 4.

Table 3.2. Details of Transitions

Stage of Risk	**# of transitions**	**Diagnostic Outcome (number with that diagnosis)**
Stage 0	1	**MDD severe**
Stage 1a	5	**MDD severe (3), MDD recurrent (2)**
Stage 1b		
CHR	10	Psychosis (1), bipolar (1), MDD recurrent (7), MDD severe (1)
CHR + mood	6	MDD recurrent (5), MDD severe (1)
CHR + mania	3	Bipolar, psychotic features (1), bipolar (1), MDD recurrent (1)
Mood	5	MDD severe (1), MDD recurrent (4)
Anxiety	1	MDD recurrent
Total for Stage 1b	25	

Note. CHR: Clinical High Risk and MDD: Major Depressive Disorder.

3.4.3 Comparison of baseline measures

Participants who dropped out after baseline did not differ on baseline measures from those who did not drop out except for ratings on the GAF where the dropouts had significantly lower ratings. See Supplementary Material Table 2. For those who dropped out after at least one follow-up there were no differences between those groups and those who remained for 42-48 months. See Supplementary Material Table 3.

Differences between the transition and the non-transition groups are presented in Table 3.3. The transition and non-transition groups differed on all variables apart from negative symptoms, social functioning, family history and past bullying and trauma.

Table 3.3. Clinical differences between those who transitioned and those who did not

	Non-transition (n = 131)	**Transition (n = 31)**		
Measure	**M (SD)**	**M (SD)**	**t**	**P-value**
SOPS				
SOPS Positive	4.28 (3.49)	6.97 (4.64)	-3.60	<0.001
SOPS Negative	2.66 (2.50)	3.32 (2.48)	-1.34	0.184
Young Mania Scale	2.34 (2.22)	4.42 (3.68)	-3.03	0.005
CDSS	3.16 (3.37)	5.45 (4.57)	-3.16	0.002
SAS	33.68 (11.34)	43.97 (11.57)	-4.52	<0.001

K10-Distress Scale	21.65 (8.61)	29.42 (7.25)	-4.64	<0.001
GAF	64.65 (13.58)	55.19 (14.30)	3.45	<0.001
GF:S	7.26 (1.30)	7.16 (1.32)	0.38	0.706
	N (%)	**N (%)**	**$\chi 2$**	**P-value**
SOR				
Stage 0	26 (19.8)	1 (3.2)	-	0.010
Stage 1a	36 (27.5)	5 (16.1)		
Stage 1b	69 (52.7)	25 (80.6) [a]		
FIGS				
Family history of SMI	23 (62.2)	8 (72.7)	0.414	0.520
Trauma				
Reported past bullying	88 (67.2)	20 (64.5)	0.08	0.778
Reported past trauma	58 (44.3)	19 (61.3)	2.91	0.088

Note. CDSS: Calgary Depression Scale for Schizophrenia, FIGS: Family Interview for Genetic Studies, GAF: Global Assessment of Functioning, GF:S: Global Functioning: Social, SAS: Social Anxiety Scale, SOPS: Scale of Psychosis-risk Symptoms, and SOR: Stage of Risk. Fisher's exact test was used for variables with less than 5 counts in a cell.

3.4.4 Model building

Cox regression analysis was performed on the clinical measures from the 162 participants to test the association between time to transition and predictor variables. Cox regression is a method used to investigate the effect of several variables upon the time it takes for a specific event to occur. The test yields hazard ratios that reflect the relative risk of the event occurring in the given time. In this model, the hazard is the development of a SMI and the hazard ratio reflects the likelihood of developing a SMI. Univariate Cox proportional hazard regressions were performed on all variables before proceeding to model building (see Supplementary Table 4).

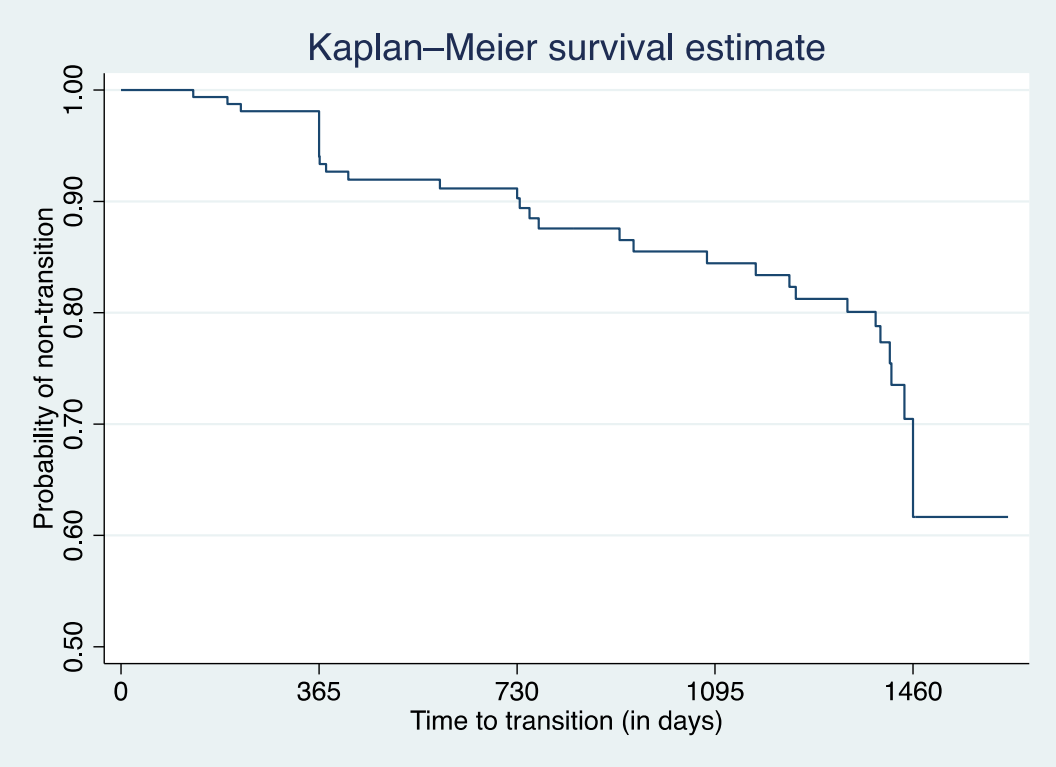
The Kaplan-Meier survival estimate of the probability of non-transition is presented in Figure 3.1. In a backward selection fashion, the least significant variables were removed from the full model until the final model was obtained, X^2 (3, N=162) =32.13, p<0.0001 (see Table 3.4). The final model included the SOPS positive, the K10-Distress Scale and sex.

Table 3.4. Cox Proportional Hazards Estimates of the Determinants of SMI by Baseline Measures

Variable	**Hazard ratio**	**Z**	**P-value**	**HR 95% confidence interval**	
SOPS Positive	1.14	2.94	0.003	1.04	1.24
K10	1.07	3.34	0.001	1.03	1.12
Sex	2.77	2.05	0.040	1.05	7.36

Note. SOPS: Scale of Psychosis-risk Symptoms, K-10: K-10 Distress Scale.

Figure 3.1. Kaplan-Meier Curve



Note. Each time interval reflects a year after. Last data point for time to transition is 1635 days.

SOPS positive. There were significant differences between the mean scores of the non-transition group (M=4.28, SD=3.49) and the transition group (M=6.97, SD=4.64). In the model, a higher SOPS positive symptom rating reflected an increased risk of SMI (HR=1.14, Z=2.94, P=O.003, 95% CI [1.04-1.24]).

K10-Distress Scale. The transition group had significantly poorer scores (M=29.42, SD=7.25), compared to the non-transition group (M=21.65, SD=8.61). The model indicated an increased risk of developing SMI with higher K10 ratings (HR=1.07, Z=3.34, P=0.001, 95% CI [1.03-1.12]).

Sex. There were 62 male (47.3%) and 69 female (52.7%) participants in the non-transition group, and 5 males (16.1%) and 26 females (83.9%) participants in the transition group. The model indicated that females had a greater risk of developing a SMI compared to males (HR=2.77, Z=2.05, P=0.04, 95% CI [1.05-7.36]). All details in Supplementary Table 4.

All possible interactions between variables were considered and none were significant. Therefore, no interaction terms are included in the final model. Proportionality assumption was tested using the Schoenfeld and scaled Schoenfeld residuals. The overall test and individual variables were non-significant, suggesting no violation of the proportionality assumption.

3.4.5 Testing the model in a second smaller sample

Since in our sample of 162 it is unclear if participants who did not complete the final assessments might have made a transition to a SMI, a second smaller sample was examined which included the 31 transitions and the 69 participants who completed a final assessment at 48-months. In this sample there were significantly more females in the transition group.

As in the larger sample Cox regression analysis was performed on the clinical measures from the 100 (31+69) participants. Univariate Cox proportional hazard regressions were performed on all variables before proceeding to model building. Univariate Cox proportional hazard regression results showed that the same variables as in the larger sample except for trauma were to be included in the full model in a stepwise fashion until the final model was obtained, X^2 (2, N = 99) = 23.71, p = 0.0000. The final model included the SOPS positive and K10 Distress Scale with sex approaching significance. For SOPS positive in this smaller sample, there were significant differences between the mean scores of the non-transition group (M=3.93, SD=3.66) and the transition group (M=6.97, SD=4.64). Once again, the model suggested an increased risk with higher SOPS ratings (HR=1.13, 95% CI [1.03-1.23]). For the K10-Distress Scale the transition group had significantly higher scores on this scale (M=29.42, SD=7.25), compared to the non-transition group (M=21.79, SD=8.29). The model once again indicated an

increased risk of developing SMI with higher K10 ratings (HR=1.08, 95% CI [1.04-1.13]). These results are presented in Supplementary Tables 5-8.

3.5 Discussion

In this paper, clinical measures and demographic factors that might be associated with the later development of a SMI in youth were examined. The factors under consideration included anxiety, depression, attenuated psychotic symptoms, negative symptoms, mania, social functioning, trauma, and family history, as well as demographic factors including sex and age.

Baseline comparisons between those who made a transition and those who did not, revealed that the transition group had more severe ratings on SOPS attenuated positive scale, the Young Mania Scale, the CDSS, the SAS, and the K10-Distress Scale and had poorer ratings on the global functioning scale. Those that transitioned to SMI tended to be female, and at a higher stage of risk (1b). Furthermore, there were significantly more females in the transition group which will be addressed below. The increased likelihood of developing a SMI with increasing stage of risk is to be expected and has been demonstrated elsewhere (Iorfino et al., 2019).

In terms of transitions, from our total study sample 31 made a transition to a SMI. Thus a 17.8% transition rate overall, with 3.5% of stage 0, 11% of stage 1a, and 24.5% of stage 1b and making a transition. These rates are slightly higher than the 12.8% for stage 1b and 2.6% for stage 1a reported in a previous study (Iorfino et al., 2019). Although both this and the Iorfino study attempted to follow participants for up to 42 months, 45% of the transitions in the Iorfino study occurred within the first year whereas in PROCAN only 35% occurred in the first year (Addington et al., 2019).

In the final model of potential predictors of developing a SMI, more severe ratings on the SOPS-positive, and K-10 distress scales plus being female were most significant. A one-point increase in the score on the SOPS-positive scale was associated with a 14% increase in risk of developing a SMI. The significance of positive symptoms may seem surprising since the majority of participants transitioned to a depressive disorder, and not psychosis. However, 60% of stage 1b participants who made the transition and 50% of all who made the transition to a SMI were stage 1b participants who met criteria for CHR. There are several possibilities for attenuated psychotic symptoms being a possible predictor. First, it is well established that approximately 50% of CHR participants have a high rate of comorbid depression at baseline (Fusar-Poli et al., 2014) and for some CHR youth more serious depression or recurrent depression can develop over the course of two years following baseline (Addington, Farris, et al., 2021). Secondly, in CHR studies typically it is less than 20% who go on to develop a psychotic illness and it may be that some CHR individuals, although presenting with attenuated psychotic symptoms, are more at risk of developing a mood versus a psychotic disorder. Thirdly, it has been suggested that prior to developing a SMI such as bipolar disorder or a schizophrenia spectrum disorder an individual may first develop an MDD (Wilson et al., 2020), implying that attenuated psychotic symptoms are indicative of a more serious mental illness. Finally, similar to our findings, the Iorfino study found that psychotic-like experiences were a risk factor for the development of a SMI and not just a psychotic disorder (Iorfino et al., 2019).

The K-10 Distress scale was a significant variable in the model suggesting that each one-point increase in K-10 scores is associated with a 7% increased risk of developing a SMI. The K-10 was used in a large Australian epidemiological study of over 10,000 respondents. For those who scored in the non-transitioning group range, approximately 10% developed an affective

disorder whereas of those who rated similarly to the transition group approximately 28% developed a mood disorder (Andrews & Slade, 2001).

Finally, being female was associated with almost three times greater risk of developing a serious mental illness. Although sex was not significant in the second model, it is likely that the smaller sample size affected the power, and therefore the importance of sex in influencing SMI development is worthy of consideration. Several studies have shown that females have a higher prevalence of depressive disorders compared to males (Merikangas et al., 2010; Shorey et al., 2022) and that this sex difference emerges during adolescence and persists through early adulthood (Altemus et al., 2014).

Numerous studies have investigated sex differences in the prevalence of depression. The transition from adolescence to early adulthood is a stressful period that predisposes some to developing mood and anxiety disorders. Some studies suggest that females experience more interpersonal stressors and this sex difference in stress exposure mediates the increased prevalence of depression in adolescence (Hankin et al., 2007; Hankin et al., 2015). Sex differences in severity of depressive symptoms have also been attributed to cognitive factors such as a higher ruminative response style and negative cognitive styles that could lead to greater reporting of depressive symptoms among females (Hankin, 2009). Furthermore, it has been shown that better mental health literacy in young women leads to more accurate recognition of depressive symptoms (Coles et al., 2016). Neurobiological underpinnings, such as puberty related changes in the estrogen levels and associated changes in the HPA axis, have also been suggested (Albert, 2015).

One of the strengths of this study is the use of a clinical staging model which allowed consideration of the different stages of risk relative to transition. Secondly, longitudinal youth

studies examining transition to a SMI are rare, and in this study, follow-up assessments occurred every 6 months with many participants being followed up to 48 months. Finally, unlike earlier studies conducted in Australia, this is a Canadian study and may have relevance for Canadian youth.

However, there are several limitations. First, for a study that is examining transition to a SMI the sample is small. Although higher rates of transition to a SMI would be expected compared to transition rates to a psychotic illness, several CHR studies have samples in excess of 600 participants. Secondly, although we report on follow-up to 48 months, this was not planned in the initial proposal, and these were added on as more funding became available. This meant that not only were there a substantial number of dropouts over the course of four years, but there were also participants who had completed the original study and could not be found for these later follow-ups. Longer term follow-ups need to be included as part of the initial design. Thirdly, without access to these dropouts it is unclear how many of our 131 non-transitioning participants might have made a transition. Although in our smaller sample, that consisted of those who did not transition by the 48-month assessment, we found similar associations between variables and risk of SMI. Fourthly, unlike the Iorfino and CHARMS studies only a small proportion of our sample came directly from clinical services, the majority were recruited by advertising to the public and community clinics which might have resulted in a diluted risk group. Finally, although transition to a severe MDD was the most common diagnosis even in CHR participants it is possible that some of these transitions may still go on to develop a psychotic disorder. Unfortunately, once a participant made a transition to an SMI their study participation ended. Thus, we are unable to comment on potentially complex trajectories of SMI from a risk stage.

In conclusion, this longitudinal study was designed to examine clinical associations with the later development of SMI. Young participants were followed for up to 48 months with 31% developing a serious mental illness. The majority of the transitions came from group 1b, attenuated syndromes and the most common transition diagnosis was recurrent or serious MDD. Clinical implications are that it is valuable to consider risk factors for the later development of a SMI and to address these concerns and that a transdiagnostic staging model where non-specific subthreshold symptoms precede stages of threshold-level illnesses may be important. Finally, there is need for much larger scale longitudinal studies to (1) validate and expand on these results, (2) to have more precise risk criteria, and (3) to monitor different illness and remission trajectories.

Data Access

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest Disclosure

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Chapter 4: Conclusions

Mental illness is one of the most prevalent health conditions for adolescents and young adults (Whiteford, et al., 2013). Considering the long-term consequences on the individual and those around them, it is important to find efficient prevention strategies that delay or stop the development of SMI's. The PROCAN study was a longitudinal research project that allocated individuals to different stages of risk according to the clinical staging model and measured their clinical and psychosocial factors for a period of four years. Several papers have previously been published from this comprehensive study describing the clinical and demographic differences between participants at the different stages. The key component of this thesis was a specific study aimed at identifying the factors that may influence the development of an SMI in this population. Two samples' sizes were created from the data; sample one consisting of participants that completed at least one follow-up, and sample two consisting of participants that completed at least the 42- or 48-month follow-up. The results suggested that more severe ratings on the SOPS-Positive symptom scale, and K-10 distress scale, as well as being female were significant factors associated with the subsequent development of an SMI. In the smaller sample, results suggested that only higher ratings on the SOPS-Positive symptom scale and K-10 distress scale were significantly associated with a later transition to an SMI. An analysis of the outcomes of transition showed that most participants, the majority being female, developed a recurrent major depressive disorder, while only a few developed bipolar disorder and psychosis.

This study has several strengths that were mentioned in the previous chapter. Notably, the use of the clinical staging model for the allocation of participants to the different risk stages. This model is considered to be more appropriate than current diagnostic approaches as it represents the progressive and dynamic nature of mental illness, including both the undifferentiated early-

stage symptoms and the more specific late-stage symptoms of illness (McGorry et al., 2007). Results from this study further validated the need for such a model as most participants that presented at CHR went on to develop a major depressive disorder, representing the heterogeneity of mental illness. However, one participant did develop psychosis, reflecting the pluripotential nature of early symptoms, and consequently the importance of a transdiagnostic clinical staging model. Therefore, in the issue of 'splitting vs lumping' mentioned in Chapter 1, our results suggest that even disorder specific clinical presentations (i.e., a higher SOPS positive scale score) may not yield the anticipated results (i.e., individual developing a psychotic disorder). Therefore, a 'lumping' of symptoms in the earlier stages is more representative of the trajectory of mental illness and therefore more appropriate in the clinical setting.

There are further criticisms to the clinical staging model not previously mentioned. One of the main criticisms of the staging model is that it still relies on the DSM-5 diagnostic criteria for describing transition to a mental illness (Dalgleish et al., 2020). Therefore, even though participants are placed in different risk stages, the criteria for transition are still described by the existing criteria in the DSM-5. However, some argue that considering that there are no other valid alternatives that can be directly implemented in the clinical setting, the staging model in early intervention research is currently the most appropriate approach (Hartmann et al., 2021). Furthermore, the staging model does allow for both homotypic and heterotypic descriptions of the progression of illnesses which ultimately improves the prediction potential for the course of illness in the clinical setting (Scott et al., 2013). Another limitation of the clinical staging approach is that it may only be appropriate for disorders that can progress if left untreated or for which the pathophysiology is known. Since the key outcome of the clinical staging model is the prevention of the progression of a mental illness to a more severe stage, it may not be a useful

model for all mental disorders, especially those that are less severe or for which the underlying pathology is less understood (Scott, & Henry, 2017). Research in less commonly observed and understood mental illnesses is needed to deduce the clinical staging model's potential as a framework for understanding all mental health conditions.

There are several limitations to this particular study as well, specifically in terms of sample size and transitions, which may have contributed to selection bias. Firstly, the number of participants that transitioned are few, and the sample size as a whole is modest considering the interest in observing transition rates and better understanding the clinical factors associated with transition. However, part of this discrepancy in sample size can be attributed to the recruitment methods used for this study. In CHR studies mentioned previously (Hartmann et al., 2019; Iorfino et al., 2019), participants were predominantly recruited from clinics, where they were receiving help for their mental health concerns. In PROCAN, participants were recruited from clinics, schools, and general advertising on and off campus. However, another reason for this discrepancy is the attrition rate. The PROCAN study was initially not planned to have follow-ups for 48 months. This change in the duration of the study impacted attrition rates as there were many participants that completed the original study who were not available for later follow-ups. There are many reasons for why a participant may have dropped out such as no longer being interested in the study, becoming symptomatic and experiencing distress, seeking treatment, or no longer experiencing symptoms, to name a few. However, to address concerns of attrition bias, comparisons were made between those that dropped out and those that did not, and it was found that the GAF scores of those that dropped out right after baseline were higher than the rest of the samples. Furthermore, because there were many participants that did not stay for the full length of the study, there exists a possibility that the transition rate for our sample is not representative

of the actual transition rate had all participants stayed for the full study. Lastly, we did not follow participants after they transitioned. Therefore, we are unclear of their potentially complex mental health trajectories from the different risk stages. Further longitudinal studies with follow-ups after transition are needed to fully capture the dynamic progression of these illnesses and the factors that may have influenced the trajectory of the illness.

The results from this study helped improve our understanding of the clinical and demographic factors that lead to the development of an SMI. Findings from this study have shown the need for more longitudinal research observing transition rates in youth at-risk for SMI, in particular, observing youth after transition to better understand illness and potential remission trajectories. However, there is still limited research on the specific interventions and targeted treatments for each stage of the model. Stage-specific prevention and intervention strategies has been defined for first-episode psychosis (Fusar-Poli et al., 2017), but these are yet to be defined for other mental illnesses. To better understand the interventions required, there needs to be a more thorough understanding of the social, biological, and environmental factors that may positively or negatively influence movement across the stages. Future research can focus on both risk factors and protective factors at each stage and their influence on transition times and outcomes. For a better understanding of the protective factors associated with non-transition, future studies can focus more on individuals that stay in a persistent subthreshold symptomatic state to understand what factors are stopping the further development of an illness. Having a clearer understanding of the risk and protective factors at play, will better define the stage-specific interventions required both for specifically and more broadly for all mental illnesses. And ultimately, a clinical model that considers the relationship between all factors and

the pathogenesis of a mental illness may help alter or create new intervention strategies, as well as validate or redefine current clinical diagnostic criteria for mental illness.

In conclusion, this study elucidated some clinical and demographic factors that increase the risk of developing serious mental illness. Moreover, the findings in this project provided more evidence for the value of clinical staging models in mental health research and care. In addition, the SOPS Positive scale results reflected the heterotypic progression of mental illness in some individuals and the importance of a broader view of mental illnesses rather than the current diagnostic silos. Our findings also reflect the importance of larger-scale longitudinal studies to help with expanding the literature and better illustrating illness and remission trajectories. Having a better understanding of risk stages and illness trajectories may allow for more efficient intervention and targeted treatment plans, and in return, reduce the incidence and prevalence of psychiatric disorders.

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Appendix A: Supplementary material

Supplementary Table 1. Detailed Criteria for the Clinical Staging Framework

Stage	Definition	Clinical Features
0	**ASYMPTOMATIC INDIVIDUALS** Subjects at increased risk of psychotic or severe mood disorder. No anxiety, depressive or psychotic symptoms currently. Stage 0 is not assigned to cases with symptoms presenting for assessment in healthcare settings.	Not help seeking – typically recruited from the population based on the presence of recognized risk factor to psychiatric illness. Typically, at-risk populations specifically recruited for research based on one or more of the following: 1. First-degree relatives of probands 2. Family history of mental illness in multiple relatives other than first-degree (this includes participants' reports of mental illness in family members) 3. Preterm delivery or low birthweight 4. Childhood physical or sexual abuse 5. Presence of a major developmental disorder
1a	**HELP-SEEKING INDIVIDUALS WITH SYMPTOMS** Non-specific symptoms of anxiety or depression	Typically help-seeking individuals with non-specific anxiety or depressive symptoms. For anxiety – mild to moderate levels of arousal without significant or persistent avoidant behaviours.

	*Symptoms may include subjective or objective evidence of mild neuropsychological deficits. *Evidence of only recent or mild impacts of illness on social, educational or occupational function.	For depression – mild to moderate levels of depressive ideation without specific features indicative of a more disabling disorder. May include those with earlier childhood-onset symptoms who have re-presented or worsened during the adolescent period. May include those with earlier onset neurodevelopmental or attentional disorders who now present with anxiety or depressive symptoms in the adolescent years. Typically, adolescent or early adult populations assessed in primary care or educational settings or identified by screening within relevant primary care, employment or educational settings of relevant populations.
1b	**ATTENUATED SYNDROMES** Specific symptoms of brief psychotic phenomena, brief hypomania, moderate depression, severe anxiety or presence of self-harm. *May include subjective or objective evidence of at least	Development of more specific anxiety, depressive or mixed symptoms of at least moderate severity. Symptoms at this stage should be persisting and clearly having a significant impact on major aspects of psychosocial function. Comorbidity of anxiety, depressive, attenuated psychotic symptoms and substance misuse are common at this stage.

	moderate neuropsychological change or moderate to severe impact of illness on social, education or employment functioning.	Treatment may have already commenced and/or the person may have been referred for further specialized assessment. Some degree of treatment with an antidepressant, antipsychotic or mood-stabilizing agent is common for Individuals in this stage, particularly where there has been limited access to specialized psychological therapies. **Clinical Stage 1b criteria:** **3.1 Criteria of Prodromal Syndromes (COPS) criteria including longstanding symptoms** NB. Symptoms can have been present in last year vs. begun or worsened in the past year. **3.2 Subthreshold manic symptoms** (A) period of abnormally and persistently elevated, expansive or irritable mood as well as at least 2 of the following (B) criteria (3 in the case of irritable mood) present at least 4 hours per day in each of at least 2 consecutive days in the last 6 months: • Inflated self-esteem or grandiosity

		• Decreased need for sleep (e.g. feels rested after only three hours sleep) • Much more talkative than usual or pressure to keep talking • Flight of ideas or subjective experience that thoughts are racing • Distractibility • Increased goal directed activity (either socially, at work, or sexually) or psychomotor agitation • Excessive involvement in pleasurable activities with a high risk for painful consequences. Duration can be 3 or less days if there is (C) unequivocal change in functioning that is uncharacteristic of the person, and (D) change in functioning is observed by others. Duration can be up to 6 days if only C or D is met **<u>Exclusion.</u>** One week or longer of full threshold manic symptoms. **3.3. Moderate MDD** Current mild depressive episode (MDE) according to DSM-V

		Current MDE of moderate severity (i.e. 11-15 on the QIDS) **<u>NB.</u>** The following are exclusion criteria: Current severe and persistent depression present for ≥ 6 weeks, more days than not as diagnosed on the SCID **OR** Up to 2 past episodes of greater severity than the current episode as determined on the SCID and/or QIDS **3.4 Anxiety syndromes** Characterized by more severe symptoms and development of specific avoidant behaviours **3.5 Self-harm** The presence of regular, deliberate self-harm without overt suicidal intent may occur in this stage. This includes impulsive low lethality overdose occurring in context of psychosocial stressor and in the absence of severe depression.

Note. Participants that met criteria for stages 0 to 1b were allowed to participate in the PROCAN study. These criteria are a part of the published criteria by Hickie et al., but for the purpose of

this study, we have only included definitions for the relevant stages.

Supplementary Table 2. Comparison of participants that dropped out at baseline.

	Baseline Dropouts (N=12)	**Non-dropouts (N=131)**		
	N (%)	**N (%)**	X^2	**P-value**
Sex				
Male	8 (66.7)	62 (47.3)	1.645	0.200
Female	4 (33.3)	69 (52.7)		
Stage of Risk				
Stage 0	1 (8.3)	26 (19.8)	1.197	0.550
Stage 1a	3 (25.0)	36 (27.5)		
Stage 1b	8 (66.7)	69 (52.7)		
	M (SD)	**M (SD)**	**t**	**P-value**
Age	19.33 (4.27)	17.18 (3.56)	1.967	0.051
SOPS Positive	4.75 (4.25)	4.28 (3.49)	0.436	0.664
QIDS	11.40 (4.12)	8.60 (5.52)	1.562	0.121
CDSS	4.00 (2.95)	3.16 (3.37)	0.833	0.406
SAS	31.42 (6.64)	33.68 (11.34)	-0.681	0.497
K10	23.91 (6.91)	21.65 (8.61)	0.845	0.399
GAF	54.58 (15.44)	64.65 (13.58)	-2.430	0.016
GF:S	6.83 (0.72)	7.26 (1.30)	-1.804	0.088

Note. SOPS: Scale of Psychosis-risk Symptoms, QIDS: Quick Inventory of Depressive Symptomatology, CDSS: Calgary Depression Scale for Schizophrenia, SAS: Social Anxiety

Scale, K-10: K-10 Distress Scale, GAF: Global Assessment of Functioning, GF:S: Global Functioning: Social.

Supplementary Table 3. Comparison of participants that dropped out at different times in the study.

	Group 1 (N = 35)	**Group 2 (N = 27)**	**Group 3 (N = 69)**		
	N (%)	**N (%)**		X^2	**P-value**
Sex					
Male	19 (54.3)	16 (59.3)	27 (39.1)	4.082	0.130
Female	16 (45.7)	11 (40.7)	42 (60.9)		
Stage of Risk					
Stage 0	4 (11.4)	7 (25.9)	15 (21.7)	6.050	0.195
Stage 1a	9 (25.7)	4 (14.8)	23 (33.3)		
Stage 1b	22 (62.9)	16 (59.3)	31 (44.9)		
	M (SD)	**M (SD)**	**M (SD)**	**F**	**P-value**
Age	16.60 (3.43)	17.15 (3.69)	17.49 (3.60)	0.727	0.485
SOPS Positive	4.91 (3.16)	4.37 (3.48)	3.93 (3.66)	0.937	0.394
QIDS	8.42 (5.05)	7.58 (5.48)	9.05 (5.61)	0.631	0.534
CDSS	3.24 (3.54)	2.93 (3.27)	3.22 (3.36)	0.082	0.921
SAS	34.03 (11.41)	31.56 (9.57)	34.35 (11.98)	0.606	0.547
K10	23.03 (9.45)	19.52 (8.14)	21.79 (8.29)	1.292	0.278
GAF	60.37 (13.72)	67.48 (14.86)	65.71 (12.66)	2.597	0.078
GF:S	6.89 (1.35)	7.63 (1.39)	7.30 (1.20)	2.654	0.074

Note. Group 1 consists of those who dropped out at 6-, 12-, or 18-months. Group 2 consists of those who dropped out at 24-, 30- or 36-months. Group 3 consists of those who completed assessments at 42- and/or 48-months. SOPS: Scale of Psychosis-risk Symptoms, QIDS: Quick Inventory of Depressive Symptomatology, CDSS: Calgary Depression Scale for Schizophrenia, SAS: Social Anxiety Scale, K-10: K-10 Distress Scale, GAF: Global Assessment of Functioning, GF:S: Global Functioning: Social.

Supplementary Table 4. Univariate Analyses

Variable	Hazard ratio	z	P-value	95% confidence interval	
SOPS Positive	1.16	3.63	0.000	1.07	1.25
SOPS Negative	1.07	1.08	0.280	0.94	1.22
Young Mania Scale	1.18	3.72	0.000	1.08	1.29
CDSS	1.16	3.38	0.001	1.06	1.26
SAS	1.06	4.30	0.000	1.03	1.08
K-10	1.09	4.54	0.000	1.05	1.13
GAF	0.95	-3.72	0.000	0.93	0.98
GF:S	0.92	-0.57	0.569	0.71	1.21
Sex	3.69	2.67	0.008	1.42	9.65
Stage of Risk	2.99	3.03	0.002	1.47	6.07
FIGS	1.54	0.64	0.524	0.41	5.81
Reported past bullying	0.82	-0.51	0.608	0.39	1.72
Reported past trauma	1.60	1.26	0.207	0.77	3.30

Note. CDSS: Calgary Depression Scale for Schizophrenia, FIGS: Family Interview for Genetic Studies, GAF: Global Assessment of Functioning, GF:S: Global Functioning: Social, K-10: K-10 Distress Scale, SAS: Social Anxiety Scale, and SOPS: Scale of Psychosis-risk Symptoms.

Supplementary Table 5. Demographics of transition and non-transition groups in smaller sample

Demographics	**Non-Transition (n=69) M (SD)**	**Transition (n=31) M (SD)**	**Test Statistic t**	**p-value**
Years of education	10.03 (3.46)	10.9 (2.04)	-1.569	0.120
Age	17.49 (3.60)	17 (2.79)	0.744	0.459
	N (%)	**N (%)**	**$\chi 2$**	**p-value**
Sex				
Male	27 (39.1)	5 (16.1)[a]	5.201	0.023
Female	42 (60.9)	26 (83.9)[a]		
Racial Background				
Asian	10 (14.5)	3 (9.7)	-	1.000
Black	3 (4.3)	1 (3.2)		
Central/South American	4 (5.8)	1 (3.2)		
White	44 (63.8)	22 (71.0)		
Mixed Race	8 (11.6)	4 (13.0)		
Marital Status				
Single, never married	64 (92.8)	31 (100)	-	0.592
Other	5 (5.2)	0 (0)		
Current living arrangement				
Living with family	55 (83.3)	29 (93.5)	-	0.788

Living with spouse/partner	4 (6.1)	1 (3.2)		
Living on own	2 (3.0)	0 (0)		
Other	5 (7.5)	1 (3.2)		
Current student				
Yes	55 (80.9)	29 (93.5)	-	0.522
No	13 (19.1)	2 (6.5)		
Current employment				
Employed	30 (43.5)	9 (29.0)	2.870	0.412
Not employed	39 (56.5)	22 (71.0)		

Note. [a] Significantly differs from non-transition group.

Supplementary Table 6. Differences in continuous clinical measures between those who transitioned and those who did not in the smaller sample.

	Non-transition (n = 69)	**Transition (n = 31)**		
Measure	**M (SD)**	**M (SD)**	**T-test statistic**	**P-value**
SOPS				
SOPS Positive	3.93 (3.66)	6.97 (4.64)	-3.53	<0.001
SOPS Negative	2.84 (2.29)	3.32 (2.48)	-0.95	0.346
Young Mania Scale	2.45 (2.19)	4.42 (3.68)	-2.77	0.008
CDSS	3.22 (3.36)	5.45 (4.57)	-2.74	0.007
SAS	34.35 (11.98)	43.97 (11.57)	-3.75	<0.001
K10-Distress Scale	21.79 (8.29)	29.42 (7.25)	-4.41	<0.001
GAF	65.71 (12.66)	55.19 (14.30)	3.69	<0.001
GF:S	7.30 (1.20)	7.16 (1.32)	0.53	0.595
			Chi-square test	**P-value**
Sex				
Male	27 (39.1)	5 (16.1) [a]	5.20	0.023
Female	42 (60.9)	26 (83.9) [a]		

SOR				
Stage 0	15 (21.7)	1 (3.2)	-	0.002
Stage 1a	23 (33.3)	5 (16.1)		
Stage 1b	31 (44.9) [a]	25 (80.6) [a]		
FIGS				
Reported family history of SMI	7 (63.6)	8 (72.7)	0.21	0.647
Trauma				
Reported past bullying	48 (69.6)	20 (64.5)	0.51	0.617
Reported past trauma	31 (44.9)	19 (61.3)	2.29	0.130

Note. SOPS: Scale of Psychosis-risk Symptoms, CDSS: Calgary Depression Scale for Schizophrenia, SAS: Social Anxiety Scale, GAF: Global Assessment of Functioning, GF:S: Global Functioning: Social. SOR: Stage of Risk and FIGS: Family Interview for Genetic Studies.

[a] Post-hoc Bonferroni correction (alpha level set at 0.05); Significantly differs from non-transition group.

Supplementary Table 7. Univariate Analyses for smaller sample

Variable	Hazard ratio	z	P-value	95% confidence interval	
SOPS Positive	1.14	3.44	0.001	1.06	1.23
SOPS Negative	1.07	0.87	0.383	0.92	1.23
Young Mania Scale	1.16	3.27	0.001	1.06	1.27
CDSS	1.14	3.10	0.002	1.05	1.24
SAS	1.05	3.85	0.000	1.02	1.08
K-10	1.08	4.18	0.000	1.04	1.13
GAF	0.96	-3.62	0.000	0.93	0.98
GF:S	0.93	-0.53	0.598	0.71	1.22
Sex	3.21	2.38	0.017	1.23	8.41
Stage of Risk	3.05	3.06	0.002	1.49	6.23
FIGS	1.41	0.51	0.612	0.37	5.33
Reported past bullying	0.78	-0.68	0.499	0.37	1.62
Reported past trauma	1.51	1.11	0.266	0.73	3.11

Note. SOPS: Scale of Psychosis-risk Symptoms, CDSS: Calgary Depression Scale for Schizophrenia, SAS: Social Anxiety Scale, K-10: K-10 Distress Scale, GAF: Global Assessment of Functioning, GF:S: Global Functioning: Social, FIGS: Family Interview for Genetic Studies.

Supplementary Table 8. Cox Proportional Hazards Estimates of the Determinants of SMI by Baseline Measures for smaller sample

Variable	**Hazard ratio**	**Z**	**P-value**	**HR 95% confidence interval**	
SOPS Positive	1.12	2.71	0.007	1.03	1.23
K10	1.08	3.62	0.000	1.04	1.13
Sex	2.33	1.68	0.094	0.87	6.24

Note. SOPS: Scale of Psychosis-risk Symptoms, K-10: K-10 Distress Scale.