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Characterizing psychosis risk traits in Africa: A longitudinal study of Kenyan adolescents

Daniel Mamah [a,*], Abednego Musau [c], Victoria N. Mutiso [c], Akinkunle Owoso [a], Arbi Ben Abdallah [b], Linda B. Cottler [d], Catherine W. Striley [d], Elaine F. Walker [e], David M. Ndetei [c,f]

[a] Department of Psychiatry, Washington University Medical School, St. Louis, MO, United States
[b] Department of Anesthesiology, Washington University Medical School, St. Louis, MO, United States
[c] Africa Mental Health Foundation, Nairobi, Kenya
[d] Department of Epidemiology, University of Florida, Gainesville, United States
[e] Department of Psychology, Emory University, Atlanta, United States
[f] Department of Psychiatry, University of Nairobi, Kenya

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ABSTRACT

The schizophrenia prodrome has not been extensively studied in Africa. Identification of prodromal behavioral symptoms holds promise for early intervention and prevention of disorder onset. Our goal was to investigate schizophrenia risk traits in Kenyan adolescents and identify predictors of psychosis progression.

135 high-risk (HR) and 142 low-risk (LR) adolescents were identified from among secondary school students in Machakos, Kenya, using the structured interview of psychosis-risk syndromes (SIPS) and the Washington early recognition center affectivity and psychosis (WERCAP) screen. Clinical characteristics were compared across groups, and participants followed longitudinally over 0-, 4-, 7-, 14- and 20-months. Potential predictors of psychosis conversion and severity change were studied using multiple regression analyses.

More psychiatric comorbidities and increased psychosocial stress were observed in HR compared to LR participants. HR participants also had worse attention and better abstraction. The psychosis conversion rate was 3.8%, with only disorganized communication severity at baseline predicting conversion ($p = 0.007$). Decreasing psychotic symptom severity over the study period was observed in both HR and LR participants. ADHD, bipolar disorder, and major depression diagnoses, as well as poor occupational functioning and avolition were factors relating to lesser improvement in psychosis severity.

Our results indicate that psychopathology and disability occur at relatively high rates in Kenyan HR adolescents. Few psychosis conversions may reflect an inadequate time to conversion, warranting longer follow-up studies to clarify risk predictors. Identifying disorganized communication and other risk factors could be useful for developing preventive strategies for HR youth in Kenya.

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1. Introduction

The onset of schizophrenia typically occurs during late adolescence or early adulthood (Jablensky et al., 1992; Kirkbride et al., 2006), a critical period of development during which young people are usually going through school and are becoming independent from their parents. Understanding how psychosis presents across cultures is crucial to both elucidating etiological process and improving treatment. However, there is relatively little information about psychotic disorders in the developing world (Saxena et al., 2006), and in particular, few epidemiologic studies of psychosis development in Africa (Guinness, 1992; Saha et al., 2005). The need for more studies is underscored by existing data, which suggests that there are differences in the presentation and course of psychotic disorders in Africa compared to developed countries (German, 1972; Guinness, 1992). For example, delusional content often reflects the prevalent cultural beliefs, with themes of witchcraft or ancestral worship more commonly experienced in Africa (Hurst, 1975). Also, existing studies suggest that while the prevalence of schizophrenia is comparable across the world, the course and outcome is often more severe in the developed world than in developing countries (Hopper and Wanderling, 2000; Kulhara, 1994; Sartorius et al., 1986).

In recent years, there has been a growing recognition of the need to develop pre-emptive strategies for schizophrenia that derail progression toward independence and productivity. In sub-Saharan Africa, where financial and health care resources for managing psychotic disorders are extremely limited, the role of early intervention strategies prior

* Corresponding author at: Department of Psychiatry, Washington University Medical School, 660 S. Euclid, Saint Louis, MO 63110, United States.
E-mail address: mamahd@psychiatry.wustl.edu (D. Mamah).

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to disorder onset is particularly relevant (Ndetei, 2008). Clinical high risk (CHR) criteria for developing psychotic disorder, comprised primarily of attenuated psychotic symptoms, aim to identify the prodromal stage of schizophrenia (Cannon et al., 2008). Studies indicate that 16% to 54% of youth who meet current clinical risk criteria develop a major psychotic disorder within 1–2.5 years (Cannon et al., 2008; Ruhrmann et al., 2010; Schultze-Lutter et al., 2015; Yung et al., 2008). Major global research efforts involving CHR include the North American Prodrome Longitudinal Study (NAPLS), the European Prediction of Psychosis Study (EPOS), and the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne Australia. The NAPLS study, which comprises of the largest database on prospectively followed prodromal cases worldwide previously found five features that contributed uniquely to the prediction of psychosis: familial risk with functional decline, unusual thought content, paranoia, low social functioning, and substance abuse (Cannon et al., 2008). These predictors had a substantial, but not complete, overlap with predictors found in related studies (Addington et al., 2015; Thompson et al., 2011). Based on identified predictors from existing studies, an individualized risk calculator for psychosis conversion has also been proposed (Schultze-Lutter et al., 2015).

To our knowledge, our group was the first to investigate the CHR state in Africa and we have maintained an active research program characterizing psychosis-risk traits in Kenyan youths. Our previous investigations using various psychosis-risk screening instruments showed relatively high rates of psychotic experiences in Kenyan children (Mamah et al., 2013a), adolescents (Mamah et al., 2013a) and young adults (Mamah et al., 2012; Ndetei et al., 2012) in school and community settings. These findings may have overestimated psychotic experience prevalence rates, as these were higher than those observed in some studies done in developed countries (e.g. (Gale et al., 2011; Kelleher et al., 2012; Mojtabai, 2006)). Large variations in prevalence rates have been reported globally (Nuevo et al., 2012), which suggests that assessment tools may not always be cross-culturally applicable. Results of our previous studies as well as information gathered from focus groups (Mamah et al., 2013b) contributed to our development of culturally-sensitive research tools to better characterize the CHR state in Kenya. The current study is the most extensive investigation of psychosis-risk individuals in Africa, incorporating multiple behavioral assessments in an adolescent population and including longitudinal investigations of at-risk individuals for the first time in the continent.

2. Methods

2.1. Recruitment

The study was approved by the ethical review board of the Kenya Medical Research Institute and the Institutional Review Board of Washington University in St. Louis. Participants were students from 22 secondary schools in *Machakos* county, Kenya, a largely rural area near Nairobi. Participants were selected from among 2800 students in the 10th–12th grades of study, aged 14–20 years, who completed the Washington Early Recognition Center Affectivity and Psychosis (WERCAP) Screen (Mamah et al., 2014). The selection process is summarized in Fig. 1. As a preliminary selection process, screened subjects were divided into those at preliminary high-risk (HR) and those at preliminary low-risk (LR) based on WERCAP psychosis-risk scores (i.e. ≥30 and <30 respectively) (Mamah et al., 2014). Based on preliminarily assigned risk status, 330 individuals were enrolled in the study. Determination of final risk status was done as described below. Written consent was provided by a parent or guardian or by the student if aged 18 or older.

2.2. Inclusion and exclusion criteria

Participants were excluded from the HR or LR groups if they met criteria for current or lifetime Axis I psychotic disorder. Participants in the HR groups met diagnostic criteria for a prodromal syndrome using the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2010) or the WERCAP Screen criteria (Mamah et al., 2014). The decision to use both structured and self-report measures to estimate risk state capitalizes on the strengths of each assessment format in obtaining behavioral data. Structured assessments alone can be influenced by perceived stigma and rater characteristics, while self-report questionnaires may not be adequately understood by the respondent (Mamah et al., 2014).

2.3. Clinical assessments and core evaluations

Psychosis-risk symptoms were assessed using the positive symptom subscale of the SIPS and the WERCAP Screen. The SIPS is a structured interview that includes five positive symptom subscales: P1-unusual thought content/delusional ideas, P2-suspiciousness/persecutory ideas, P3-grandiose ideas, P4-perceptual abnormalities, and P5-disorganization communication. Positive symptoms are rated from 0 (absent) to 6 (severe/psychotic). In addition to the positive symptom subscale, the SIPS contains three additional subscales that were also assessed: negative, disorganization and general symptoms. The WERCAP Screen estimates the severity of psychotic symptoms and "affectivity", a measure of mood dysregulation (Mamah et al., 2014). Psychiatric diagnoses were assessed using the computerized Diagnostic Interview Schedule version IV (c-DIS-IV) (Robins et al., 1981) using laptop computers. Cognitive functioning was assessed using 11 test modules (Continuous Performance Task – Number Letter; Short Letter N-Back Test – 2 Back; Word Memory Test for Children; Facial Memory Test; Visual Object Learning Test – Short; Logical Reasoning Test For Children – Short; Motor Praxis Test; Matrix Analysis Test; List Learning Test; Emotion Recognition Test for Children – 40 Faces; and Measured Emotion Differentiation Test) from the University of Pennsylvania Computerized Neurocognitive Battery (CNB) (Gur et al., 2010). Quantitative measures of psychosocial stress was assessed using the WERC Stress Screen (Mamah et al., 2014). The Dyskinesia Identification System: Condensed User Scale (DISCUS) (Kalachnik and Sprague, 1993) was used to rate items relating to dyskinesia in six upper body regions. Head size was estimated by measuring the circumference of the head with a cloth tape measure wrapped around the glabella and the opisthocranion.

2.4. Timeline and schedule of assessments

Participants were evaluated between January 2014 and December 2015. The assessment schedule was baseline, 4-, 7-, 14- and 20-months, as depicted in Fig. 1. All assessments took place on site in the respective secondary schools, in confidential spaces within various school meeting rooms and classrooms.

2.5. Assessing psychosis conversion and progression

Clinical outcome at specific follow-up assessments was evaluated using results from the c-DIS-IV and the SIPS. Transition to psychosis was determined by the presence of a new psychotic diagnosis on the c-DIS-IV, and/or by meeting psychosis criteria on the SIPS(McGlashan et al., 2010), i.e. that at least one of the five SIPS positive symptoms reached a psychotic level of intensity for a frequency of ≥1 h per day for 4 days per week during the past month or that symptoms seriously impacted functioning.

2.6. Statistical analysis

All statistical analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC). Chi-square and two-sided Wilcoxon-Mann-Whitney tests were used to compare groups on clinical and demographic variables, considering that many variables did not meet criteria for normality. Cognitive domains were derived similarly as previously described

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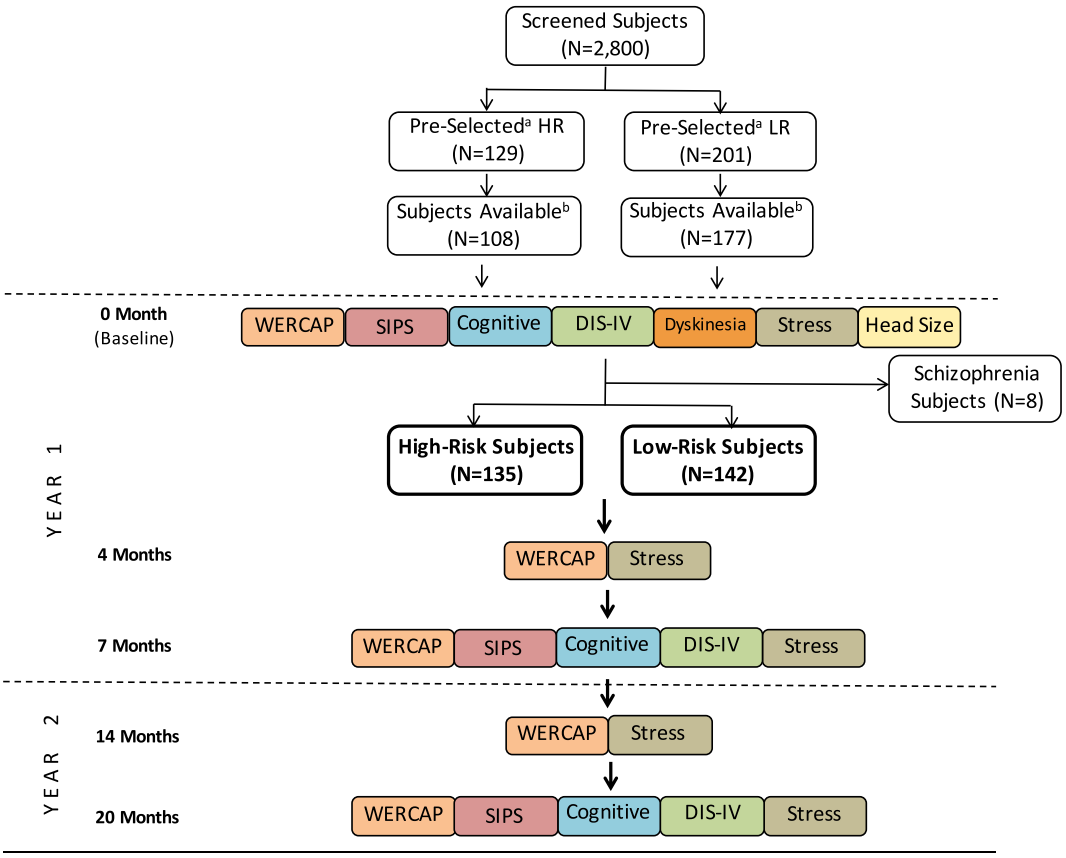

Fig. 1. Flowchart depicting selection process and assessment schedule. [a]Pre-selection was done using cutoff scores on the WERCAP Screen, deriving 129 high-risk (scores > 30) and 201 low-risk (scores < 30) participants. Final designation of high-risk status was based on meeting criteria on the WERCAP Screen or SIPS, and exclusion of psychotic subjects. [b]"Subject available" refers to those that were available during the baseline assessment period.

(Mamah et al., 2014). Changes in psychosis severity were examined using scores on the psychotic section of the WERCAP Screen, estimated over the prior 3-months, and the slopes were compared across groups using the Student's *t*-test. Stepwise logistic and linear regression were used to investigate baseline predictors of psychosis conversion or psychosis severity progression respectively.

3. Results

3.1. Sample characteristics

Demographic data are presented in Table 1. Among HR participants, 119 (i.e. 88.2%) completed at least one follow-up evaluation. 132 (i.e. 93.0%) of the LR participants completed at least one follow-up evaluation. Overall retention rates at 4-, 7-, 12- and 20-months were 79.3%, 77.8%, 53.3% and 49.6% for HR: and 82.4%, 83.8%, 58.5% and 54.2% for LR.

3.2. Clinical characteristics

Table 1 summarizes clinical trait differences across groups. Of the HR sample, 64 (47.4%) met psychosis-risk criteria on the SIPS, and 105 (78.9%) met risk criteria on the WERCAP. Overall, 34.1% of HR and 11.3% of LR participants had at least one psychiatric comorbidity. Among the cognitive measures studied, the score on attention was higher in LR compared to HR participants ($Z = -2.2$; $p = 0.027$), however HR participants scored better on abstraction ($Z = 2.4$; $p = 0.017$). Total stress severity was significantly higher in HR than in LR participants ($Z = 5.2$; $p < 0.0001$). Mean severities of individual psychosocial stressors across groups are shown in Fig. 2. Multiple stressors were found significantly higher in HR compared to LR participants, particularly those involving family relationships, death, school and finances.

3.3. Risk traits associated with baseline schizophrenia diagnosis

All variables were investigated as potentially associated with a SZ diagnosis at baseline in relation to HR participants. A stepwise logistic regression resulted in only impaired personal hygiene severity being selected in the final model. The results indicated that baseline SZ was associated with more impaired personal hygiene at baseline than HR individuals (estimated OR = 7.4; 95% CI = 1.1, 49.9; B = 2.0, $p < 0.0001$). A comparison of clinical profiles in SZ vs. HR participants are also shown in Table 1.

3.4. Psychosis conversion and prediction

At 7-months, five of 131 HR cases (i.e. who had completed c-DIS-IV or SIPS data) converted to psychosis (3.8%) based on the SIPS, and there were no further conversion at the 20-month timepoint. None of the cases met diagnostic criteria for schizophrenia using the c-DIS-IV. In contrast, there were no LR participants that converted to psychosis.

A comparison of demographic and clinical profiles in converters vs. nonconverters are shown in Table 2. Considering the small number of converters, we conducted a backward logistic regression including in the model only the two variables that showed the most significant differences in univariate analysis (i.e. disorganized communication and expression of emotions & self, $p < 0.01$). This analysis showed a significant association of conversion only with disorganized communication (est. OR = 2.43; 95% CI = 1.28, 4.63; B = 0.89, $p = 0.007$). Results were identical when logistic regression was conducted using forward selection to test the stability of the model. Logistic regression was also conducted using all seven variables that showed significant ($p < 0.05$) univariate effects. Disorganized communication similarly emerged as

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Table 1
Baseline demographic and clinical characteristics across participant groups.

Characteristic	LR (n = 142)	HR (n = 135)	SZ (n = 8)	p (LR vs. HR)	p (HR vs. SZ)
Age (SD)	17.1 (1.3)	17.4 (1.3)	17.1 (1.1)	0.12	0.64
Gender (%)				0.64	0.01*
Female	84 (59.2)	83 (61.5)	1 (14.3)		
Male	58 (40.8)	52 (38.5)	6 (85.7)		
Baseline education (%)				0.98	0.36
Grade 10	49 (36.0)	48 (38.1)	2 (28.6)		
Grade 11	59 (43.4)	48 (38.1)	2 (28.6)		
Grade 12	28 (20.6)	30 (23.8)	3 (42.9)		
[a]**Highest maternal education (SD)**	9.6 (2.8)	9.8 (3.0)	9.9 (2.3)	0.35	0.95
[a]**Highest paternal education (SD)**	9.8 (3.9)	9.8 (3.7)	9.8 (3.0)	0.81	0.23
WERCAP					
Psychosis (chronic)	15.9 (11.2)	34.1 (10.7)	28.9 (10.6)	<0.0001**	0.07
Psychosis (3-month)	7.9 (9.8)	18.7 (14.5)	24.3 (9.6)	<0.0001**	0.15
Affectivity (Chronic)	12.5 (7.8)	21.9 (9.6)	18.5 (9.1)	<0.0001**	0.34
Affectivity (3-month)	8.2 (7.5)	15.9 (10.6)	21.6 (4.1)	<0.0001**	0.04*
SIPS positive symptoms					
Unusual thought	0.35 (0.6)	1.37 (1.3)	2.25 (1.8)	<0.0001**	0.14
Persecutory	0.27 (0.6)	1.23 (1.3)	1.88 (1.4)	<0.0001**	0.15
Grandiosity	0.55 (0.8)	1.26 (1.2)	1.75 (1.7)	<0.0001**	0.44
Hallucinations	0.25 (0.6)	1.37 (1.5)	2.63 (1.5)	<0.0001**	0.03*
Disorg. communication	0.06 (0.3)	0.53 (1.0)	1.50 (1.6)	<0.0001**	0.02*
SIPS negative symptoms					
Social anhedonia	0.30 (0.6)	1.01 (1.6)	1.88 (2.3)	<0.0001**	0.33
Avolition	0.14 (0.6)	0.29 (0.8)	1.63 (1.8)	0.03*	0.006*
Emotion expression	0.04 (0.2)	0.22 (0.7)	1.25 (1.6)	0.006*	0.001**
Emotion/self-experience	0.03 (0.2)	0.23 (0.8)	1.38 (2.0)	0.005*	0.002**
Difficulty understanding	0.96 (1.3)	1.17 (1.3)	1.50 (1.4)	0.07	0.47
Occupational functioning	0.24 (0.7)	0.51 (1.0)	0.50 (0.5)	0.0048**	0.35
SIPS disorganization symptoms					
Odd behavior appearance	0.03 (0.2)	0.20 (0.6)	0.88 (1.5)	0.0006**	0.05
Bizarre thinking	0.01 (0.1)	0.22 (0.7)	0.50 (0.8)	0.0002**	0.047*
Trouble focus attention	0.25 (0.5)	0.78 (1.1)	2.00 (1.8)	<0.0001**	0.03*
Personal hygiene	0.05 (0.2)	0.06 (0.3)	0.88 (1.8)	0.86	0.01*
SIPS general symptoms					
Sleep disturbance	0.07 (0.0)	0.40 (0.9)	0.63 (1.1)	0.0004**	0.29
Dysphoric mood	0.32 (0.8)	1.24 (0.2)	2.25 (1.8)	<0.0001**	0.07
Motor disturbances	0.01 (0.1)	0.18 (0.6)	0	0.002**	0.34
Stress tolerance	0.06 (0.3)	0.30 (0.7)	1.50 (1.7)	<0.0001**	0.0006**
Diagnostic comorbidity					
Panic attack	3 (2.2)	9 (7.0)	2 (25.0)	0.06	0.07
Agoraphobia	2 (1.5)	14 (10.9)	3 (37.5)	0.001**	0.03*
Specific phobia	5 (3.7)	10 (7.8)	1 (12.5)	0.15	0.63
Social phobia	2 (1.5)	8 (6.2)	2 (25.0)	0.04*	0.047*
Generalized anxiety	0	4 (3.1)	0	0.04*	0.61
PTSD	1 (0.7)	11 (8.5)	0	0.002**	0.39
Depression	4 (2.9)	12 (9.3)	2 (25.0)	0.03*	0.15
Bipolar disorder	0	9 (8.3)	0	0.002**	0.43
Obsessive compulsive	0	3 (3.3)	1 (12.5)	0.07	0.10
Eating disorder	1 (0.7)	3 (2.3)	0	0.29	0.66
ADHD	1 (0.7)	4 (3.1)	1 (12.5)	0.15	0.17
ODD	4 (2.9)	22 (17.1)	4 (50.0)	0.0001**	0.02*
ASPD/conduct	5 (3.7)	16 (12.4)	3 (37.5)	0.008*	0.046*
Tobacco	2 (1.5)	1 (0.8)	0	0.60	0.80
Alcohol	1 (0.7)	7 (5.4)	2 (25.0)	0.03*	0.03*
Drugs	2 (1.5)	3 (2.3)	1 (12.5)	0.60	0.10
Pathological gambling	0	8 (6.2)	1 (12.5)	0.003*	0.49
Cognitive functioning (z-score)					
Abstraction	−0.15 (0.9)	0.17 (1.1)	−0.07 (1.2)	0.02*	0.57
Attention	0.14 (0.9)	−0.13 (1.0)	0.04 (1.5)	0.03*	0.29
Working memory	0.04 (1.0)	−0.06 (1.0)	0.16 (0.7)	0.42	0.86
Verbal memory	0.06 (1.0)	−0.06 (1.0)	−0.12 (0.9)	0.36	0.71
Visual memory	0.02 (1.0)	−0.01 (1.0)	−0.10 (1.5)	0.86	0.57
Language & reasoning	0.01 (0.9)	−0.00 (1.1)	0.07 (1.6)	0.98	0.98
Sensorimotor	−0.16 (1.1)	0.14 (0.9)	0.41 (1.6)	0.07	0.34
Emotional cognition	−0.11 (0.9)	0.10 (0.8)	0.08 (0.9)	0.11	0.97
Stress	21.93 (21.2)	38.12 (29.6)	43.38 (26.0)	<0.0001**	0.42

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Table 1 (*continued*)

Characteristic	LR (n = 142)	HR (n = 135)	SZ (n = 8)	p (LR vs. HR)	p (HR vs. SZ)
Dyskinesia	3.17 (2.8)	3.58 (3.1)	4.25 (3.8)	0.35	0.68
Head circumference	55.3 (1.8)	55.7 (1.9)	55.6 (1.8)	0.07	0.87

Values are given as means (SD) or number per group (%). Results derived from results of two-sided Wilcoxon-Mann-Whitney tests or Chi-Square analyses.
[a] Education indicated as years of schooling.
** $p < 0.005$.
* $p < 0.05$.

the only significant predictor, using either forward and backward selection.

3.5. Psychotic symptom severity progression and prediction

In both HR and LR groups, mean psychotic symptoms improved over the 20-month study period (Fig. 3). The mean (SD) psychotic symptom slope was −0.022 (0.06) in HR and −0.013 (0.02) in LR, without significant differences ($F = 2.3$; $p = 0.13$). A post-hoc investigation of the relationship of the psychotic symptom slope in HR subjects showed a direct correlation with the affective symptom slope ($R = 0.82$; $p < 0.0001$) and with the stress slope ($R = 0.76$; $p < 0.0001$). A similar relationship was also seen in LR subjects for both the affective ($R = 0.31$; $p = 0.0008$) and stress ($R = 0.56$; $p < 0.0001$) slopes.

A stepwise multiple regression identified a subset of 11 explanatory variables as being important in predicting the slope of psychosis severity change, and these accounted for 74.4% of the variance. The majority of the variance (24.7%) of the psychotic symptom slope was associated with an ADHD diagnosis ($B = 0.16$; $p < 0.0001$). A minor positive association with the psychosis symptom slope was also seen with a diagnosis of major depression ($B = 0.05$) and bipolar disorder ($B = 0.11$), occupational functioning ($B = 0.01$), and avolition ($B = 0.02$). Minor negative associations were found with a diagnosis of an eating disorder ($B = -0.09$), generalized anxiety disorder ($B = -0.06$), and alcohol use disorder ($B = -0.01$). Results of the stepwise procedure are summarized in Table 3.

4. Discussion

Our current study is the most elaborate investigation of the psychosis-risk state in an African population. We found that there were three times as many HR as LR adolescents with at least one psychiatric comorbidity, and the rate of almost every disorder was higher in the HR group. The association of psychiatric disorders with psychotic-like experiences have been reported in other global populations (Lim et al., 2015). Additionally, the majority of HR offspring of those with schizophrenia often have one or more lifetime diagnoses of major psychiatric disorders (Keshavan et al., 2008). It was notable that among the comorbidities found in our HR adolescents, the externalizing disorders, ODD and conduct disorder, had the highest prevalence. Similar reports have been previously reported in other psychosis-risk populations (Keshavan et al., 2008). Analyzing data from the NIMH Catchment Area Project, a childhood conduct disorder history was also found to be at increased prevalence in adults with schizophrenia and other major psychiatric disorders (Robins and Price, 1991).

The schizophrenia prodrome is often associated with increasing psychosocial stress preceding disorder onset. Our studies found that psychosocial stressors are reported at greater severity in HR compared

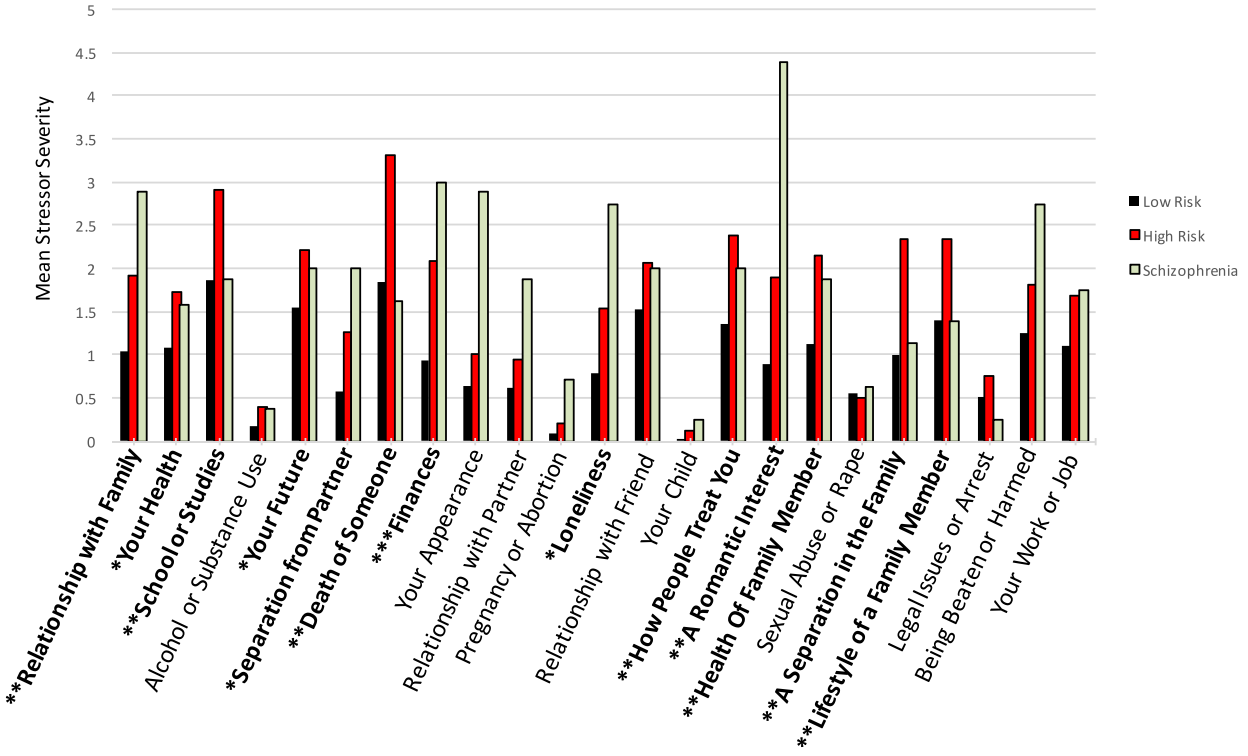

Fig. 2. Psychosocial stress scores across groups. The figure shows group mean scores of each stress item obtained from the WERC Stress Screen. Asterisks indicate statistically significant differences, derived from Students' *t*-tests of high-risk and low-risk participants only.

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Table 2
Baseline characteristics of HR converters and HR nonconverters.

Characteristic	HR converters (n = 5)	HR nonconverters (n = 95)	Z/χ^2	p
Age (SD)	17.6 (2.1)	17.5 (1.2)	−0.29	0.77
Gender (%)			3.86	0.05
Female	1 (20.0)	60 (63.8)		
Male	4 (80.0)	34 (36.2)		
WERCAP				
Psychosis (chronic)	30.2 (4.1)	34.6 (9.6)	−1.45	0.15
Psychosis (3-month)	33.2 (18.3)	17.4 (14.9)	2.01	0.04*
Affectivity (chronic)	20.0 (12.3)	21.4 (8.6)	−0.14	0.89
Affectivity (3-month)	26.4 (11.4)	15.2 (11.3)	2.11	0.04*
SIPS positive symptoms				
Unusual thought	2.00 (1.6)	1.33 (1.3)	1.04	0.30
Persecutory	1.20 (1.3)	1.25 (1.3)	−0.04	0.97
Grandiosity	1.40 (1.3)	1.25 (1.2)	0.22	0.82
Hallucinations	2.60 (1.5)	1.25 (1.5)	1.73	0.08
Disorg. communication	1.80 (1.6)	0.36 (0.8)	2.49	0.01*
SIPS negative symptoms				
Social anhedonia	2.80 (2.6)	0.89 (1.5)	1.66	0.10
Avolition	0.80 (1.1)	0.22 (0.7)	1.72	0.09
Emotion expression	0.40 (0.9)	0.22 (0.7)	0.50	0.61
Emotion/self experience	1.00 (1.7)	0.18 (0.73)	2.45	0.01*
Difficulty understanding	0.80 (0.4)	1.19 (1.3)	−0.29	0.77
Occupational functioning	0	0.52 (1.0)	−1.33	0.18
SIPS disorganization symptoms				
Odd behavior appearance	0.20 (0.4)	0.20 (0.6)	0.33	0.74
Bizarre thinking	0.20 (0.4)	0.27 (0.8)	0.32	0.75
Trouble focus attention	0.20 (0.4)	0.85 (1.2)	−1.20	0.23
Personal hygiene	0	0.05 (0.3)	−0.37	0.71
SIPS general symptoms				
Sleep disturbance	2.00 (1.6)	1.33 (1.3)	1.28	0.20
Dysphoric mood	1.20 (1.3)	1.11 (1.7)	0.61	0.54
Motor disturbances	0.40 (0.5)	0.11 (0.4)	2.34	0.02*
Stress tolerance	0.60 (0.9)	0.32 (0.7)	0.93	0.35
Diagnostic comorbidity				
Panic attack	0	7 (7.6)	0.41	0.52
Agoraphobia	1 (20.0)	10 (10.9)	0.39	0.53
Specific phobia	1 (20.0)	3 (3.3)	3.36	0.07
Social phobia	0	5 (5.4)	0.29	0.59
Generalized anxiety	0	3 (3.3)	0.17	0.68
PTSD	0	10 (10.9)	0.61	0.44
Depression	0	8 (8.7)	0.47	0.49
Bipolar disorder	0	6 (7.6)	0.25	0.62
Obsessive compulsive	0	3 (3.3)	0.17	0.68
Eating disorder	1 (20.0)	2 (2.2)	5.03	0.02*
ADHD	1 (20.0)	2 (2.2)	5.03	0.02*
ODD	0	19 (20.1)	1.28	0.26
ASPD/conduct	1 (20.0)	11 (12.0)	0.28	0.59
Tobacco	0	1 (1.1)	0.05	0.81
Alcohol	0	6 (6.5)	0.35	0.56
Drugs	0	2 (2.2)	0.11	0.74
Pathological gambling	1 (20.0)	3 (3.3)	3.36	0.07
Cognitive functioning (z-score)				
Abstraction	0.29 (1.3)	0.24 (1.1)	0.08	0.93
Attention	−0.69 (1.2)	−0.01 (1.0)	−1.47	0.14
Working memory	0.11 (1.2)	−0.01 (1.0)	0.61	0.54
Verbal memory	−0.59 (1.4)	−0.07 (1.0)	−0.96	0.34
Visual memory	−0.71 (1.0)	−0.02 (1.0)	−1.39	0.16
Language & reasoning	−0.08 (1.2)	0.07 (1.1)	−0.37	0.71
Sensorimotor	−0.14 (1.2)	0.15 (0.8)	−0.44	0.66
Emotional cognition	−0.03 (1.0)	0.12 (0.8)	−0.72	0.47
Stress	49.4 (53.7)	37.5 (29.4)	0.19	0.85
Dyskinesia	3.20 (3.0)	3.60 (3.3)	−0.26	0.79
Head circumference	55.90 (1.3)	55.62 (2.0)	0.30	0.76

Values are given as means (SD) or number per group (%). Results derived from results of two-sided Wilcoxon-Mann-Whitney tests or Chi-Square analyses.
* $p < 0.05$.

to LR adolescents. It is however unclear from our findings if group differences resulted from an increased stress burden in HR adolescents, or rather from an increased perception of stress severity. Increased stress reported across multiple items in most HR participants supports the latter concept. Psychosis liability and pre-existing psychotic experiences have been previously associated with heightened sensitivity to environmental social stress (Veling et al., 2016). In the NAPLS study, higher baseline cortisol levels were also seen in those who transitioned to psychosis compared to remitters and healthy controls (Walker et al., 2013). Underlying increased stress sensitivity appears to be a hypothalamic-pituitary-axis (HPA) dysfunction, as elevated resting cortisol levels are often found in psychosis-risk subjects (Aiello et al., 2012; Carol and Mittal, 2015). Increased sensitivity to stress is known to play an important role in the transitioning to first episode psychosis (Aiello et al., 2012), thus markers of stress sensitivity such as cortisol levels and behavioral measures like those used in our current study, may be promising in illness prediction.

In our study, HR participants showed a unique pattern of cognitive functioning compared to LR individuals, with worse performance in attention and higher functioning in abstraction. This may represent a unique cognitive profile associated with subthreshold psychotic experiences in Kenya. Cognitive deficits are often reported in those at high risk for psychosis, although generalization of findings is difficult owing to the diversity of cognitive assessments methods used (de Paula et al., 2015). In the NAPLS study, tests of processing speed and verbal learning and memory were most significant in discriminating HR from controls, however cognitive functioning was not found to contribute uniquely to prediction of psychosis conversion (Seidman et al., 2010). In general, improved cognitive performance in psychotic disorders has not been described, although improved task performance as a result of aberrant brain connectivity has been reported (Barch et al., 2012; Dima et al., 2009).

Our longitudinal observations showed that 3.8% of HR subjects converted to psychosis while none of the LR participants did. These conversion rates are substantially less than those observed in other global populations, with previously reported rates of 16–54% after 1–2.5 years (Cannon et al., 2008; Ruhrmann et al., 2010; Yung et al., 2008). A few factors may account for this discrepancy across studies. Firstly, the secondary school students investigated may not have been a cohort in whom significant deterioration would be present at high rates. The majority of patients with schizophrenia transition post-adolescence, with a peak age of schizophrenia onset in the early to mid 20's for males and in the late 20's for females (APA, 2013). Thus, it would be likely that most psychosis conversions would occur subsequent to our study time frame (Schultze-Lutter et al., 2015). Prodromal studies done in other countries where higher conversion rates have been reported generally include older populations. For example in the first NAPLS study (Cannon et al., 2008), the mean age of HR participants was about a year older than our Kenyan cohort, while other studies had two years or higher mean ages than in our study (Addington et al., 2015; Yung et al., 2004). Longer follow-up periods in the future, ideally spanning the second decade of life, would therefore be important to more accurately capture conversion rates. Secondly, the outcome of those with significant psychotic experiences in Kenya may be intrinsically more favorable than those in some other populations, in line with disparities in some disorder outcomes globally. The course of schizophrenia, for example, has been reported to be less severe in Africa and other developing countries compared to industrialized countries (Hopper and Wanderling, 2000; Sartorius et al., 1986). Thus it is plausible that psychotic symptoms would tend to also progress more favorably in these developing countries. Lastly, there was a substantial drop out by study completion, which could have led to the more severely affected HR cases being disproportionately lost, leading to an underestimation of conversion rates. These drop out rates however were comparable to those reported in the largest North American prodromal study to date (Addington et al., 2015), although earlier studies have found

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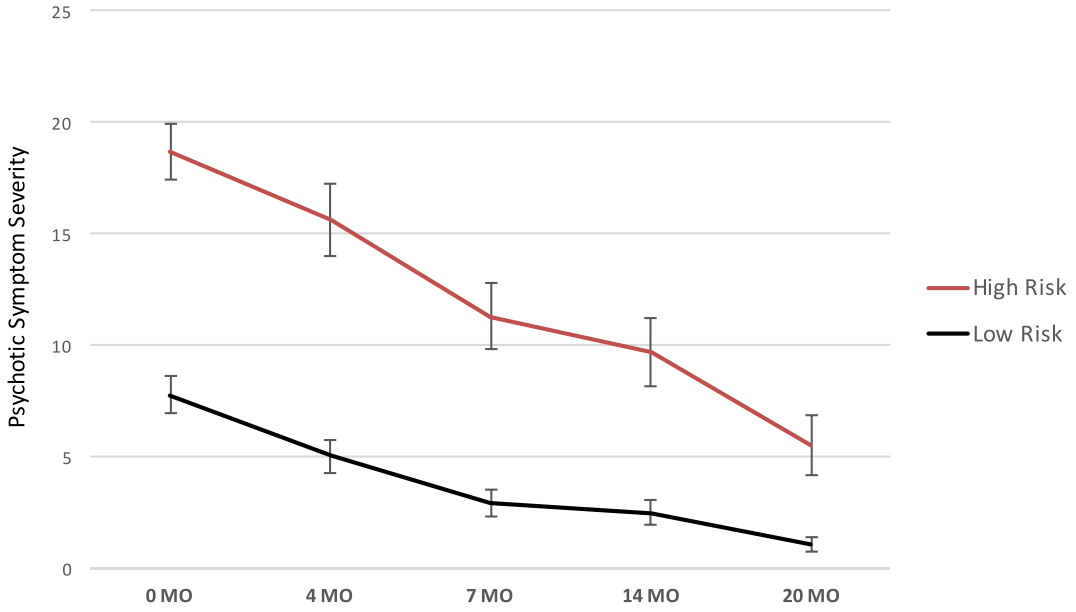

Fig. 3. Progression of psychotic symptom severity in high-risk and low-risk participants. Psychotic symptom severity was assessed using the psychotic section of the WERCAP Screen, specified to reflect symptoms experienced over the preceding 3 months.

lower drop out rates (Cannon et al., 2008). Increased hospitalization, missed school days, or apprehension associated with research participation could have selectively affected converted cases, and resulted in an underestimation of our conversion rates. However, most of the drop-outs by the final time point were related to school graduation in the older students, and there was no increased psychopathology in those lost to follow-up.

Results from a logistic regression identified only disorganized communication as associated with psychosis conversion. Interestingly, disorganized communication at baseline has also been found by other groups to predict psychosis onset in HR individuals (Bearden et al., 2011; DeVylder et al., 2014). Similar to the study by DeVylder et al. (2014), conducted in North America, other than disorganized communication, we found no other positive or negative symptoms predictive of psychosis onset. Clinically, disorganized speech is generally considered to be reflective of an underlying thought disorder, and can involve a variety of manifestations including derailment, poverty of speech, tangentiality, perseveration, neologism or thought blocking. Previous studies have found that unlike some other behavioral symptoms, clinically relevant thought disorder present at ascertainment tended to persist and eventually lead to psychosis onset (DeVylder et al., 2014). These data support the concept of disorganized communication as a potential endophenotype or stable trait marker for schizophrenia risk, consistent with the finding that disorganized communication aggregates in family members of individuals with schizophrenia (Levy et al., 2010) and predicts psychosis onset also in genetic HR individuals (Ott et al., 2002). While disorganized speech and thought disorder may be a useful marker for psychosis development risk, it is important to note that thought disorder is not unique to psychotic disorders, and may also be a symptom of other conditions, including mania. Although we did not identify other behavioral features predicting psychosis risk, future longer duration studies may reveal additional predictive risk traits. Some of these may involve traits found to be more severe in the small number of schizophrenia patients in our study, compared to our HR participants. Most notable among these were negative symptoms, impaired personal hygiene and impaired stress tolerance. Disorganized communication, accompanied by negative symptoms and impaired personal hygiene could therefore potentially be behavioral features that may warrant closer monitoring in Kenyan adolescent populations.

Unlike results from Northern American (Addington et al., 2015; Cannon et al., 2008) or Australian (Thompson et al., 2011; Yung et al., 2004) studies, we did not find other traits such as unusual thought content, paranoia, low social functioning, substance abuse or familial risk with functional decline, as predictors of psychosis conversion. This may partly have been due to the younger cohort in our studies and inadequate time to conversion, as described above. Substance use was also very rare among our HR cohorts, thus would be unlikely to show up as a predictor. Familial risk was not applicable to our study as none of our participants reported a family history of psychotic disorders. In Kenya, as in many other developing countries, psychiatric disorders are diagnosed at relatively low rates and for many youths, there is an unfamiliarity with diagnostic entities (Mamah et al., 2013b). This underscores the need for increased mental health education in Africa, particularly in rural communities.

A unique approach to risk analysis in our studies involved the investigation of changes in psychotic symptom severity. This approach acknowledges that clinical outcomes not meeting a diagnostic threshold for a psychotic disorder like schizophrenia, may also be significantly disabling. Results of our cross-sectional studies, showing increased comorbidity, stress, negative symptoms, disorganization and general symptoms in HR individuals, further confirms that overall disability and functioning is associated with high psychotic symptomatology despite an absence of a psychotic disorder diagnosis. Statistically, investigating a range of psychotic severity outcomes would also have more power to identify risk factors in regression analysis. Our findings showed decreased psychotic symptom severity over the course of the

Table 3
Variables identified by stepwise logistic regression analysis as predicting psychosis severity progression.

Independent variables	R^2	Coefficient	Std error	F value	p value
ADHD	0.247	0.159	0.003	20.32	<0.0001
Bipolar I disorder	0.091	0.105	0.002	8.33	0.0054
Occupational functioning	0.067	0.010	0.004	6.69	0.012
pWERCAP (3-month)	0.092	−0.001	0.000	10.72	0.002
Emotion differentiation	0.037	−0.013	0.005	4.56	0.037
Major depression	0.033	0.049	0.002	4.29	0.043
Eating disorder	0.039	−0.092	0.003	5.46	0.023
Avolition	0.033	0.023	0.007	4.96	0.03
Alcohol use disorder	0.041	−0.009	0.003	6.76	0.012
Odd behavior/appearance	0.042	−0.029	0.010	7.83	0.007
Generalized anxiety disorder	0.026	−0.059	0.003	5.21	0.027

Total variance (R^2) = 74.4%. Model $F(11,63) = 13.75$; $p < 0.0001$; Intercept = −0.0026.

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study period in HR participants, as well as in LR participants. Improving psychotic symptomatology in longitudinal studies has been reported by other groups, and it has been speculated that this may represent the natural course of psychotic symptomatology in HR individuals (Addington et al., 2015; Lee et al., 2014). In our study, there were no known unique external events, which may have contributed to symptom improvement. It is plausible that participant interactions with the research team members during the course of the study may have inadvertently led to a "therapeutic" symptom reduction. Some evidence to this presumption is the observation of gradually decreasing stress levels alongside psychotic symptom improvement. Participants, who previously had little or no exposure to mental health care, may have directly benefited by talking about their symptoms and receiving psychoeducation, support and/or information about treatment options during the course of the study. While the majority of our HR participants showed improvement in psychotic symptom severity, a multiple regression analysis showed that some factors were associated with less improvement, including a baseline diagnosis of ADHD, bipolar disorder and major depression. Pre-illness, non-specific affective symptomatology has been suggested as useful in the prediction of schizophrenia and related psychotic disorders (Owens and Johnstone, 2006), and relatively high rates of ADHD have been reported in familial psychosis-risk populations, suggesting that a liability of this disorder might be mediated by genetic factors that might overlap with the susceptibility to schizophrenia (Keshavan et al., 2008). Interestingly, having a baseline diagnosis of an eating disorder, generalized anxiety disorder and alcohol use disorder were associated with greater psychosis improvement, which indicates that the presence of these disorders may be markers of underlying pathology that is unrelated to an impending psychotic disorder development. Poor occupational functioning and avolition were also among the factors associated with less psychosis severity improvement, implying that impaired functioning at baseline may also help predict clinical outcomes in HR individuals.

As our study only had a limited number of psychotic conversions, a larger cohort of Kenyan adolescents would be required to validate our risk prediction results. More importantly, future studies would benefit by investigating HR populations for longer time periods to identify other potential markers of risk as conversion continues to occur at older ages. Assessments could be conducted in tertiary institutions or community settings during early adulthood, when the first episode of a psychotic disorder usually occurs. Incorporation of biological measures as potential risk markers such as DNA or neuroimaging data, may also be helpful for identifying those at the greatest risk for psychosis. Such studies would require significant investment in mental health research in Africa, but would likely yield substantial benefits in the prevention of debilitating psychotic disorders such as schizophrenia.

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Contributor

Daniel Mamah wrote the first draft of the manuscript. Musau, Mutiso and Ndetei coordinated research on-site in Kenya and project planning. Cottler, Striley and Walker were involved in project planning and assessment training. Ben Abdallah oversaw statistical analyses. Owoso was involved in statistical analysis and project planning.

Conflict of interest

Dr. Mamah has received grants from the NIMH, NARSAD, the McDonnell Center for Systems Neuroscience, the Taylor Family Institute and Eli Lilly.

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