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## Anxiety in Youth at Clinical High Risk for Psychosis

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### Abstract

**Aim**—High rates of anxiety have been observed in youth at clinical high risk (CHR) of developing psychosis. In CHR, anxiety often co-occurs with depression, and there is inconsistent evidence on anxiety in relation to transition to psychosis. The aim of this study was to examine (i) the prevalence of anxiety disorders in individuals at CHR, (ii) clinical differences between those with and without anxiety and (iii) the association of baseline anxiety with later transition to psychosis.

**Methods**—The sample consisted of 765 CHR individuals and 280 healthy controls. CHR status was determined with the Structured Interview of Prodromal Syndromes, mood and anxiety diagnoses with the Structured Clinical Interview for DSM-IV Disorders, and severity of anxiety with the Social Interaction Anxiety Scale and Self Rating Anxiety Scale.

**Results**—In the CHR sample, 51% met criteria for an anxiety disorder. CHR participants had significantly more anxiety diagnoses and severity than healthy controls. Anxiety was correlated to

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attenuated psychotic and negative symptoms in CHR and those with an anxiety disorder demonstrated more suspiciousness. CHR participants with OCD exhibited more severe symptomatology than those without OCD. An initial presentation of anxiety did not differ between those who did or did not transition to psychosis.

**Conclusions**—In this large sample of individuals at CHR, anxiety is common and associated with more severe attenuated psychotic symptoms. Treatment not only to prevent or delay transition to psychosis but also to address presenting concerns, such as anxiety, is warranted.

### Keywords

anxiety; clinical high risk; obsessive compulsive disorder; social phobia; suspiciousness

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### Introduction

There is currently a major focus on early identification and intervention for schizophrenia and other psychotic disorders, not only at the first episode but in what may be the pre psychotic phase of the illness. Criteria have been developed to identify those who are at clinical high risk (CHR) for psychosis based on the presence of attenuated psychotic symptoms, brief intermittent psychotic symptoms or genetic risk with a recent deterioration in functioning.<sup>1</sup> Comorbid diagnoses of anxiety are commonly observed in individuals with psychotic disorders.<sup>2–3</sup> In individuals with full blown psychosis, anxiety has been found to be related to positive symptom severity<sup>4</sup> and certain anxiety disorders may be specifically related to suspiciousness in schizophrenia.<sup>5</sup> Likewise, a significant proportion of CHR individuals present with DSM-IV diagnoses, the most common being anxiety and/or depression,<sup>6–9</sup> which are frequently endorsed as the first noticed symptoms that lead CHR individuals to seek treatment.<sup>10</sup> Anxiety may be particularly prominent in the CHR population, with reports that approximately 24–53% of people at CHR meet criteria for an anxiety disorder<sup>9,11–16</sup> and may be associated with severity of individual attenuated psychotic symptoms.<sup>16</sup> CHR individuals often report that their anxiety is at times more distressing than their sub threshold psychotic symptoms.<sup>16</sup>

Social phobia has been identified as one of the most common anxiety disorder diagnoses in CHR<sup>7–8,17</sup> with up to 42% of individuals meeting criteria for this disorder.<sup>18</sup> High rates of obsessive compulsive disorder (OCD) have also been reported in CHR samples<sup>19</sup> and in one study were identified as being more prevalent in those at CHR who transition to psychosis,<sup>20</sup> although not in another.<sup>19</sup> Several studies have compared those who transition to psychosis and those who do not on the presence of anxiety disorders and reported no difference.<sup>21–23</sup> One study found that those at CHR with an anxiety disorder were less likely to transition to psychosis.<sup>15</sup> Thus, although symptoms of anxiety appear to be a prominent concern for youth at CHR for psychosis, there seems to be little evidence that initially presenting with an anxiety disorder is associated with later transition to psychosis.<sup>16</sup>

Although the literature to date suggests that OCD and social phobia may be comorbid concerns in people at CHR of developing psychosis, less has been reported about the prevalence of other anxiety disorders (e.g., panic disorder, generalized anxiety disorder) in

the CHR population. Furthermore, anxiety is often reported as co-occurring with depression in CHR samples,<sup>6,16</sup> and is infrequently examined on its own.

The role of OCD in CHR may be particularly important to explore further, as OCD and obsessive-compulsive symptoms are frequently reported in schizophrenia<sup>24</sup> and are associated with a poorer prognosis, including more severe positive and negative symptoms,<sup>25</sup> earlier onset of illness,<sup>26</sup> increased hospitalizations, lower social and occupational functioning, and increased risk of suicidal ideation and attempts.<sup>27</sup> It is possible that those at CHR with obsessive-compulsive symptoms may have poorer outcome including higher levels of attenuated psychotic symptoms,<sup>19</sup> similar to what has been observed in schizophrenia.

Our aim in the current study is to first examine the prevalence of different anxiety disorders in a large sample of youth at CHR for psychosis in comparison to healthy controls; secondly to examine clinical correlates of anxiety and; thirdly to determine the impact of anxiety on transition to psychosis. Having a greater understanding of the role of anxiety will have implications for the treatment of those at CHR over and above interventions to prevent transition. Hypotheses are: 1) the prevalence of anxiety disorders and self-rated severity of anxiety in CHR is significantly higher than in a healthy control group; 2) high levels of anxiety will be significantly associated with increased severity of attenuated psychotic symptoms, particularly suspiciousness, in those at CHR; 3) CHR youth diagnosed with OCD display more severe overall symptomatology and; 4) anxiety will not be associated with later transition to psychosis.

## Methods

### Sample

All participants were recruited as part of the eight site (Emory University, Harvard University, University of Calgary, University of California, Los Angeles, University of California, San Diego, University of North Carolina, Yale University, and Zucker Hillside Hospital) NIMH funded North American Prodrome Longitudinal Study 2 (NAPLS 2) which was established to investigate predictors and mechanisms of conversion to psychosis. Participants were help seeking individuals who were referred from health care professionals, educators, community agencies and programs, or were self-referred. Potential participants were screened by experienced raters for eligibility and provided consent before beginning study measures. The NAPLS 2 sample consists of 765 CHR participants (436 male, 329 female) and 280 healthy controls (141 male, 139 female). Details on ascertainment, inclusion and exclusion criteria have been described in detail elsewhere.<sup>28</sup>

All CHR participants met the Criteria of Prodromal Syndromes (COPS) using the Structured Interview for Prodromal Syndromes (SIPS).<sup>29</sup> Both CHR and control participants were excluded if they met DSM-IV-TR criteria for any current or lifetime axis I psychotic disorder, had prior history of treatment with antipsychotic medication, demonstrated impaired intellectual functioning with a full scale IQ <70, had past or current history of a clinically significant central nervous system disorder, or met criteria for substance dependence within the last 6 months. Control participants were also excluded if they had a

first degree relative with a current or past psychotic disorder, or Cluster A personality disorder diagnosis based on the DSM-IV-TR.

## Measures

The Structured Interview for Prodromal Syndromes (SIPS) and the Scale for Assessment of Prodromal Symptoms (SOPS)<sup>29</sup> were used to determine criteria for a prodromal syndrome. The SOPS was also used to determine symptom severity of attenuated psychotic, negative, disorganized and general symptoms. The Structured Clinical Interview for DSM-IV (SCID)<sup>30</sup> was used to determine the presence of current mood and anxiety disorders.

Two scales were used to assess anxiety; the Social Interaction Anxiety Scale (SIAS),<sup>31</sup> a 20 item self-report questionnaire that rates experiences in social situations on a 5 point Likert scale from 0 (not at all characteristic of me) to 4 (extremely characteristic of me), and the Zung Self Rating Anxiety Scale (SAS)<sup>32</sup>, a self-report questionnaire with 20 items that assess general and somatic experiences of anxiety that are rated as being true of the participant on a 4 point Likert scale between 1 (none or little of the time) to 4 (most or all of the time).

## Procedures

Raters were experienced research clinicians who demonstrated adequate reliability on clinical measures at routine reliability checks. Gold standard post training agreement on determining the prodromal diagnoses was excellent ( $\kappa=0.90$ ). The study protocols and informed consents were reviewed and approved by Institutional Ethical Review Boards at all eight NAPLS sites. All participants provided informed consent or assent and parental or guardian consent was also obtained for participants under the age of 18.

After administering the SIPS, vignettes were developed for all CHR participants for the purpose of obtaining a consensus diagnosis. These vignettes contain the necessary information for another rater to review the vignette and be able to provide ratings. Vignettes were presented on a weekly call with all sites, chaired by JA. A consensus on diagnosis had to be reached before any CHR participant could be included in the study sample. Clinical assessments described in this study were collected at the baseline assessment. More specific details are described in the initial overview of the NAPLS project.<sup>28</sup>

## Statistical analysis

Chi-square tests were used to compare CHR and healthy control groups on diagnoses of current anxiety and depression, as well as to compare two year outcome groups and baseline anxiety disorders in those at CHR who transitioned versus did not transition to psychosis. Scores on the SOPS, SIAS and SAS were not normally distributed; therefore, nonparametric tests were used to analyze these data. Mann-Whitney U tests were used to compare SIAS and SAS scores between CHR and control groups and between those at CHR who did and did not transition to psychosis, and to examine differences in symptomatology between those at CHR with and without an OCD diagnosis. Spearman's rank order correlations were used to examine the relationships between anxiety measures and SOPS symptoms in CHR.

Since many CHR participants had diagnoses of anxiety and/or depression, participants were divided into four groups according to meeting DSM-IV criteria for an anxiety and/or depression diagnoses based on the SCID. These groups were created based only on the presence or absence of diagnosis of anxiety and depression. The groups were anxiety disorder no depression (ANX), depressive disorder no anxiety disorder (DEP), both anxiety and a depressive disorder (ANX+DEP), and no anxiety disorder and no depressive disorder (NO-DIAG). This allowed us to examine the severity of symptoms in people with an anxiety disorder in the absence of depressive disorders. Kruskal Wallis tests were used as an omnibus test to compare SOPS positive symptoms scores between groups defined by anxiety and/or depressive disorders. Mann-Whitney U tests were then used for post hoc analyses. A bonferroni correction was used to account for multiple comparisons.

## Results

### Demographics

The majority of CHR participants were single, Caucasian, living with their family, and enrolled as a student. Participants in the healthy control group were older and had a higher rate of employment than CHR participants. CHR participants were more likely to be living with family/spouse/partner or in a group home compared to controls whereas controls were more likely to be living on their own or with others outside of their family. See Table 1.

### Differences in anxiety between the CHR and healthy control groups

The CHR group presented with anxiety disorders significantly more often than the healthy control group, with the exception of agoraphobia. Results indicated that over half of the CHR sample met criteria for one or more anxiety disorder with social phobia being the most common. Individuals at CHR scored significantly higher on the SIAS and SAS relative to the healthy control group. See Table 2.

### Relationships between anxiety and symptoms in CHR

The two anxiety rating scales, SIAS and SAS, were significantly and positively correlated to symptoms on the SOPS. Increased attenuated psychotic symptom scores were associated with higher SIAS ( $r_s = 0.12, p < .01$ ) and SAS scores ( $r_s = 0.18, p < .001$ ), and more severe negative symptoms were associated with higher SIAS ( $r_s = 0.33, p < .001$ ) and SAS scores ( $r_s = 0.18, p < .001$ ).

### Diagnostic group differences on attenuated psychotic symptoms

There were 192 CHR participants (25.84%) in the ANX group, 140 (18.84%) in the DEP group, 186 (25.03%) in the ANX+DEP group, and 225 (30.28%) in the NO-DIAG group.

Groups significantly differed on the SOPS suspiciousness item, but not on any of the other four attenuated psychotic symptoms (unusual thought content, grandiosity, perceptual abnormalities, and disorganized communication). Follow up Mann-Whitney U tests indicated that the NO-DIAG group had significantly lower suspiciousness scores than the ANX ( $U = 16769.00, p < 0.001$ ), the DEP ( $U = 13229.00, p < 0.01$ ), and ANX+DEP groups ( $U = 15128.50, p < 0.001$ ). See Table 3.

### OCD and psychopathology in CHR

Compared to CHR individuals with no OCD diagnosis, CHR individuals with a diagnosis of OCD scored significantly higher on total attenuated psychotic symptoms ( $U= 14330.50, p < 0.05$ ), overall disorganization symptoms ( $U= 13737.50, p < 0.05$ ) and overall general symptoms ( $U= 12735.00, p < 0.01$ ). There was no significant difference in overall negative symptom scores ( $U= 15205.50, p= 0.14$ ).

### Anxiety and transition to psychosis

Two year outcome data was available for 321 CHR participants. Ninety-four had transitioned to psychosis. We compared those who made the transition to psychosis versus those who did not. There was no significant difference in the presence of anxiety disorders at baseline for those at CHR who transitioned to psychosis (50.5%) compared to those who did not transition (50.9%) ( $X^2= 0.01, p= 1.00$ ). There was also no difference between those at CHR who did and did not transition on SIAS ( $U= 25274.00, p= .72$ ) and SAS ( $U= 26032.50, p= .87$ ) scores at baseline. We found no significant difference in baseline OCD diagnoses between those at CHR who transitioned to psychosis (9.7%) versus those who did not (6.5%) ( $X^2= 1.32, p= .27$ ).

### Discussion

This multisite study examined anxiety in a large CHR sample. Our first hypothesis was confirmed in that the prevalence of anxiety disorders and self ratings of anxiety were significantly higher in those at CHR compared to healthy controls. Fifty one percent of CHR youth had a comorbid anxiety disorder and social phobia was the most prevalent anxiety diagnosis. These results are consistent with other findings that social phobia is typically one of the most prevalent anxiety diagnoses in CHR.<sup>7-8,15,17-18,33</sup>

As per our second hypothesis CHR participants who presented with increased levels of anxiety also presented with greater severity of attenuated psychotic and negative symptoms. CHR participants who had an anxiety disorder, depressive disorder or both anxiety and depression scored higher on suspiciousness than CHR participants without either diagnosis. This suggests that higher levels of suspiciousness is associated with both anxiety disorders as well as depressive disorders. It has been reported that individuals with schizophrenia and a comorbid anxiety disorder also evidence increased suspiciousness.<sup>5</sup> Furthermore, in people with first episode psychosis, social phobia has been found to be associated with the concern that others may intend to harm them.<sup>34</sup> Interestingly, this latter study found that a subthreshold versus a delusional level of suspicious ideation was associated with greater anxiety.

As per our third hypothesis, CHR youth with a comorbid OCD diagnosis demonstrated more severe attenuated psychotic symptoms and disorganized and general symptoms compared to CHR without this diagnosis. This fits with what has previously been reported with respect to individuals with schizophrenia and obsessive-compulsive symptoms.<sup>25</sup> However, this is in contrast to Niendam et al.<sup>19</sup> who failed to observe a difference in symptom severity between CHR participants with and without OCD.

There was no difference in baseline anxiety severity or prevalence of baseline anxiety disorders for those who made the transition to psychosis compared to those who did not. This large study thus supports findings from three previous works implying that anxiety does not predict transition to psychosis.<sup>21–23</sup> One study has even shown that CHR with an anxiety disorder were less likely to transition during an 18 month follow up;<sup>15</sup> however it should be noted that one study reported that a comorbid OCD diagnosis conferred greater risk of transition.<sup>20</sup> Although anxiety does not appear to be a marker for transition to psychosis, it is a prevalent concern and may contribute to the severity of attenuated psychotic and negative symptoms. Thus, assessment of anxiety should be an important consideration for all CHR individuals so that they can be connected to appropriate resources or adjunct therapies to address their presenting concerns.

Several possibilities have been proposed to explain the high prevalence of anxiety in CHR youth. First, it has been hypothesized that vulnerability to psychiatric symptoms may lie on a continuum where individuals who are vulnerable to either anxiety or depression are then more vulnerable to develop attenuated psychotic symptoms, and vice versa.<sup>35</sup> It has also been suggested that anxiety and attenuated psychotic symptoms may not represent two distinct disorders; rather, the two may represent a single disorder or condition with a diverse range of symptoms that reach a threshold level for multiple disorders or syndromes.<sup>16</sup> In the current study, social phobia was found to be the most common anxiety disorder in our CHR sample. It has been suggested that social phobia may be the initial concern that can trigger or maintain persecutory thinking, or that social phobia and suspiciousness develop together in early phases of psychosis and progress similarly, or that social phobia may develop in response to suspicious thoughts.<sup>34</sup>

Other CHR research has demonstrated an association between increased salivary cortisol, anxiety, and suspiciousness.<sup>36</sup> Additionally, those at CHR who transition to psychosis have been observed to have higher baseline cortisol levels than those at CHR who are later in remission from CHR criteria.<sup>37</sup> There may be implications for the presence of a heightened stress response for symptoms and outcomes of individuals at CHR.

The strengths of this study are that the sample is large, a range of anxiety disorders were examined as well as self-reported anxiety, comorbid depression was addressed, and differences in anxiety for those who transitioned to psychosis was examined. One limitation of the study is that information on the onset of anxiety was not collected and thus limits the ability to determine if anxiety preceded or followed the development of CHR criteria. Other limitations include not having data on medications and treatment in relation to anxiety between baseline and conversion, and not having data on the course of anxiety between baseline and transition. Furthermore, there may be other diagnoses present that may confound results, although we attempted to control for this by considering the presence of depressive disorders.

There are clinical implications of this study. Although anxiety may not play a role in later transition to psychosis, anxiety was common in this large sample of young people at CHR for psychosis, often co-occurring with more severe symptomatology. Thus, assessment of anxiety should be routine for all CHR individuals presenting for help. Treatment for these



CHR individuals is important not only to prevent or delay transition to psychosis but also to address presenting symptoms and concerns. It may be that the risk for schizophrenia or other psychotic disorders can be greatly improved by treating co-occurring anxiety disorders,<sup>38</sup> however, treatment options for CHR youth that consider the impact of treatment on anxiety is currently in the early phases of research.<sup>14,39–40</sup> Targeting anxiety would be a valuable treatment objective for this group, such as through cognitive behavioral therapy or family interventions and may be specifically advantageous in the context of suspiciousness.

Thus, in conclusion, data from this large sample study supports that initial presentation with an anxiety disorder and/or high levels of anxiety is not related to later transition to psychosis. However, it is related to higher levels of symptoms and as such those at CHR should routinely be assessed for anxiety and where necessary offered relevant treatment.

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**Table 1**

Demographic differences between Clinical High Risk and Healthy Controls

Demographics	CHR ( <i>n</i> =765)	Controls ( <i>n</i> =280)	Test Statistic
	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	<i>t</i>
Age in years	18.47 (4.24)	19.65 (4.67)	3.68 *
Sex	<i>N</i> (%)	<i>N</i> (%)	<i>X</i> <sup>2</sup>
Male	436 (56.99)	141 (50.36)	3.65
Female	329 (43.01)	139 (49.64)	
Race			
Caucasian	478 (62.48)	167 (59.64)	4.96
African-American	118 (15.42)	49 (17.50)	
Interracial	98 (12.81)	29 (10.36)	
Asian	55 (7.19)	30 (10.71)	
First Nations	13 (1.70)	4 (1.42)	
Native Hawaiian or Pacific Islander	3 (0.39)	1 (0.36)	
Single never married	721 (94.25)	266 (95.00)	0.01
Current living arrangement †			
Living with family/spouse/partner	613 (80.13)	195 (69.64)	22.43 *
Living on own in apartment/house	41 (5.36)	31 (11.07)	
Living in group home/shelter	23 (3.01)	4 (1.43)	
Living with others/other	83 (10.85)	50 (17.86)	
Currently employed	190 (24.84)	129 (46.07)	42.38 *
Currently enrolled as a student	626 (81.83)	227 (81.07)	0.28

\* *p* .01

† Data was missing for 5 CHR participants

**Table 2**

Prevalence of anxiety disorders and mean anxiety severity

<b>DSM-IV Anxiety diagnosis</b>	<b>CHR (n=743)</b>	<b>Controls (n=277)</b>	<b><math>\chi^2</math></b>
	<i>N</i> (%)	<i>N</i> (%)	
Any anxiety disorder <sup>†</sup>	378 (50.87)	10 (3.61)	191.25**
Social Phobia	107 (14.40)	1 (0.36)	42.01**
Anxiety disorder not otherwise specified	88 (11.84)	2 (0.72)	31.02**
Generalized anxiety disorder	86 (11.57)	2 (0.72)	30.15**
Specific phobia	75 (10.09)	4 (1.44)	21.13**
Obsessive-compulsive disorder	51 (6.86)	0 (0)	20.01**
Panic disorder without agoraphobia	45 (6.05)	2 (0.72)	13.06**
Panic disorder with agoraphobia	35 (4.71)	0 (0)	13.51**
Posttraumatic stress disorder	16 (2.15)	0 (0)	6.06*
Agoraphobia	7 (0.94)	0 (0)	2.69
<b>Anxiety measure</b>	<b>CHR</b>	<b>Controls</b>	<b><i>U</i></b>
	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	
SIAS <sup>‡</sup>	30.77 (17.41)	9.04 (8.72)	23036.50**
SAS <sup>§</sup>	37.89 (10.84)	22.99 (3.60)	11859.50**

\* *p* .01\*\* *p* .001

Note. SIAS, Social Interaction Anxiety Scale; SAS, Self-Rating Anxiety Scale; NOS, Not Otherwise Specified.

<sup>†</sup>Data was missing for 22 CHR and 3 control participants<sup>‡</sup>Data was missing for 77 CHR and 21 control participants<sup>§</sup>Data was missing for 73 CHR and 20 control participants

Table 3

Attenuated positive symptom scores for each CHR group

SOPS symptom	No anxiety or depression <i>M(SD)</i>	Anxiety only <i>M(SD)</i>	Depression only <i>M(SD)</i>	Anxiety and depression <i>M(SD)</i>	$\chi^2$
Unusual thought content	1.62 (1.82)	3.28 (1.42)	3.14 (1.47)	3.44 (1.24)	3.17
Suspiciousness	1.20 (1.54)	2.84 (1.51) <sup>a</sup>	2.72 (1.51) <sup>a</sup>	3.09 (1.32) <sup>a</sup>	28.60 <sup>**</sup>
Grandiose ideas	0.63 (1.12)	1.01 (1.33)	0.87 (1.27)	0.85 (1.19)	5.25
Perceptual abnormalities	1.61 (1.85)	2.85 (1.54)	2.92 (1.68)	3.01 (1.50)	2.82
Disorganized communication	0.91 (1.38)	1.77 (1.43)	1.55 (1.48)	1.64 (1.39)	3.84
Overall positive symptom score	5.97 (6.06)	11.73 (4.32)	11.19 (4.37)	12.03 (3.68)	3.86

<sup>\*\*</sup>  $p < .001$

<sup>a</sup> Significantly higher than “no anxiety or depression” group

Note. SOPS, Scale for Assessment of Prodromal Symptoms.