



Published in final edited form as:

Schizophr Res. 2018 February ; 192: 357–363. doi:10.1016/j.schres.2017.05.032.

Depression and clinical high-risk states: Baseline presentation of depressed vs. non-depressed participants in the NAPLS-2 cohort

Emily R. Kline^{a,*}, Larry J. Seidman^{a,b}, Barbara A. Cornblatt^c, Kristen A. Woodberry^a, Caitlin Bryant^a, Carrie E. Bearden^d, Kristin S. Cadenhead^e, Tyrone D. Cannon^f, Daniel H. Mathalon^g, Thomas H. McGlashan^h, Diana O. Perkinsⁱ, Ming T. Tsuang^e, Elaine F. Walker^j, Scott W. Woods^h, and Jean Addington^k

^aDepartment of Psychiatry, Harvard Medical School at Beth, Israel Deaconess Medical Center, Boston, MA, United States

^bDepartment of Psychiatry, Harvard Medical School at Massachusetts General Hospital, Boston, MA, United States

^cDepartment of Psychiatry, Zucker Hillside Hospital, Long Island, NY, United States

^dDepartments of Psychiatry and Biobehavioral Sciences and Psychology, UCLA, Los Angeles, CA, United States

^eDepartment of Psychiatry, UCSD, San Diego, CA, United States

^fDepartment of Psychology, Yale University, New Haven, CT, United States

^gDepartment of Psychiatry, UCSF and SFVA Medical Center, San Francisco, CA, United States

^hDepartment of Psychiatry, Yale University, New Haven, CT, United States

ⁱDepartment of Psychiatry, University of North Carolina, Chapel Hill, NC, United States

^jDepartments of Psychology and Psychiatry, Emory University, Atlanta, GA, United States

^kDepartment of Psychiatry, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

Abstract

Depressed mood appears to be highly prevalent in clinical high risk (CHR) samples. However, many prior CHR studies utilize modest size samples and do not report on the specific impact of depression on CHR symptoms. The aim of the current paper is to investigate the prevalence of

*Corresponding author at: Massachusetts Mental Health Center, Commonwealth Research Center, Room 618, 75 Fenwood Road, Boston, MA 02115, United States. ekline@bidmc.harvard.edu (E.R. Kline).

Contributors

Drs. Addington, Cadenhead, Cannon, Cornblatt, McGlashan, Perkins, Seidman, Tsuang, Walker, Woods, Bearden, and Mathalon, were responsible for the design of the study and for the supervision of all aspects of data collection. Dr. Woodberry and Ms. Bryant contributed to data collection at the Beth Israel Deaconess Medical Center (BIDMC) site, and helped contribute to the manuscript presentation. Dr. Kline conceptualized the analyses, drafted the manuscript, created the figure and tables, and was responsible for data analysis. All authors contributed to and approved the final manuscript.

Conflict of interest statement

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

depressive disorders and the impact of lifetime depression on baseline clinical presentation and longitudinal outcomes in a large cohort of individuals meeting CHR criteria in the second phase of the North American Prodrome Longitudinal Study (NAPLS-2). Depression was assessed both categorically (via DSM-IV-TR diagnoses) and symptomatically (using a clinician-rated scale of depressive symptoms) within a sample of 764 individuals at CHR and 279 controls. Current and lifetime depressive disorders were highly prevalent (60%) in this sample. Depression diagnoses were associated with more pronounced negative and general symptoms; individuals with remitted depression had significantly less severe negative, disorganized, and general symptoms and better social and role functioning relative to those with current depression. Current mood disturbance, as measured by scores on a clinician-rated symptom scale, contributed beyond the impact of positive and negative symptoms to impairments in social functioning. Both symptomatic and diagnostic baseline depression was significantly associated with decreased likelihood of remission from CHR status; however depression did not differentially distinguish persistent CHR status from transition to psychosis at follow-up. These findings suggest that depressed mood may function as a marker of poor prognosis in CHR, yet effective treatment of depression within this population can yield improvements in symptoms and functioning.

Keywords

Mood; Prodrome; Psychosis; Remission; Schizophrenia

1. Introduction

Interest in early detection and prevention of schizophrenia and other psychotic disorders has focused attention on teenagers and young adults who may be at risk of developing a psychotic illness. Identifying predictors and mechanisms of transition to psychosis among individuals deemed to be at clinical high risk (CHR) for psychosis is necessary for the development of effective early interventions. Identification and intervention early in the course of psychosis appears to maximize treatment effectiveness and quality of life (Marshall et al., 2005; Woodberry et al., 2016b).

Although criteria for CHR states focus mainly on attenuated psychotic symptoms, depressed mood appears to be highly prevalent in CHR samples. One meta-analysis found that 41% of CHR individuals meet DSM-IV criteria for a depressive disorder (Fusar-Poli et al., 2014). In the first phase of the North American Prodrome Longitudinal Study (NAPLS-1) sample of 377 CHR participants, 55% met DSM-IV criteria for a non-bipolar mood disorder (Woods et al., 2009). The prevalence of depressive symptoms such as dysphoric mood and suicidal ideation in CHR cohorts is likely far higher than the prevalence of diagnosed depressive disorders (Hui et al., 2013). Dysphoric mood appears to contribute uniquely to impairments in social and role functioning (Fulford et al., 2013), and has been associated with poor prognosis (though not necessarily increased conversion to psychosis) within CHR cohorts (Falkenberg et al., 2015; Lim et al., 2015; Schlosser et al., 2012). Thus depression appears to constitute a central clinical feature and risk factor within this already vulnerable population.

The high prevalence of depressed mood within CHR cohorts complicates the conceptualization of CHR youth as primarily ‘prodromal’ to non-affective psychotic disorders. One theory is that depression is a common but ultimately transient feature of the early course of schizophrenia (Häfner et al., 2005). In a review of 23 studies involving 2182 participants at risk for psychosis, only 11% of those who transitioned to psychosis received an outcome diagnosis of affective psychosis (i.e. depression [5%] or bipolar disorder [6%] with psychotic features), and an additional 8% developed schizoaffective disorder (Fusar-Poli et al., 2013). This low proportion of affective disorder outcomes among converters could suggest that although depression is common during a prodromal phase of illness, mood dysfunction remains secondary to emerging psychosis for those at highest risk for conversion.

A different hypothesis holds that the prevalence of depression is high in CHR samples because of the inclusion of individuals with primarily affective disorders who experience waxing and waning subthreshold psychotic symptoms over the course of mood episodes (Sullivan et al., 2014; Wigman et al., 2012); attenuated psychotic symptoms among such individuals may never progress to frank psychosis. Additionally, psychosis occurring in the context of anxiety and depressive disorders may be more common than previously thought (Koyanagi et al., 2016; Wigman et al., 2012). A third potential explanation for the high prevalence of depression in CHR samples is that depressive appraisals of positive symptoms, reduced functioning due to negative symptoms, and/or stigma related to emerging mental illness could trigger depression for individuals experiencing subthreshold psychosis (Krabbendam et al., 2005). In this scenario, depressive mood that *follows* the onset of attenuated psychotic symptoms further increases the risk of poor outcome through the interactive effects of thought disorder and affect dysregulation; this “negative appraisal” model also aligns with the common clinical observation of depression among patients dealing with shame and loss following a first psychotic episode (Uptegrove et al., 2014). A related conceptualization of the role of depression in psychosis is that depressive symptoms (e.g., dysphoric mood, low self-worth, negative evaluations) exacerbate existing psychotic disorders by worsening distress, pre-occupation, and conviction related to delusional experiences (Smith et al., 2006; Vorontsova et al., 2013); this may be mechanistically related to abnormalities in limbic-prefrontal activity and connectivity observed in schizophrenia spectrum disorders (Phillips and Seidman, 2008). Finally, given evidence for shared genetic etiology (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), simultaneous emergence of depressive and psychotic symptoms during adolescence may represent a phenotype that is poorly captured by our current nosologic system (Murray and Jones, 2012; Smoller, 2013). In this model, depressed mood may be an intrinsic feature of psychosis even among individuals with “non-affective” or “primary” psychotic disorders (Stochl et al., 2015). The CHR construct likely reflects a heterogeneous population that includes individuals at-risk for worsening psychosis, patients already manifesting the full expression of an affective illness, as well as persons with both symptomatic manifestations.

Despite the body of recent literature describing the prevalence of depression in CHR population, the specific influence of depression on CHR symptom presentation, and the role of depression as a prognostic marker within CHR, is poorly understood. Many prior CHR studies utilize small or modest size samples and do not report on the specific associations

between depression and attenuated psychosis symptoms. The aim of the current paper is to investigate the prevalence of depressive disorders and the impact of depression on baseline clinical presentation and CHR-status outcomes in the largest cohort of individuals meeting criteria for a CHR syndrome studied to date (NAPLS-2). We also wish to examine whether the impact of depression on symptoms and functioning is better explained by an altered mood “state” vs. a persistent subgroup “trait” model. Informed by models emphasizing shared etiology of mood and psychotic disorders as well as models positing an interactive effect in which psychotic and mood symptoms are seen as mutually exacerbating, we hypothesize that depression is highly prevalent in this CHR sample relative to the control sample, and that CHR participants with a depressive disorder will experience more severe positive and negative symptoms than CHR participants with no depression. An additional exploratory aim is to examine whether the presence of baseline depression may heighten risk for conversion to psychosis over time.

2. Methods

2.1. Sample

The NAPLS-2 sample comprises 764 help-seeking teens and young adults ages 12–35, and 279 controls. Participants were recruited across the eight sites between January 2009 and March 2013. Referrals to the study were made by health care providers, community mental health practitioners, schools, and self/family inquiries. Inclusion/exclusion criteria for the CHR group were: participants met criteria of a prodromal syndrome (COPS) per the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan et al., 2010), or were under age 19 and met criteria for schizotypal personality disorder (SPD). Participants could not meet criteria for a current or lifetime Axis I psychotic disorder (including affective psychoses). Other exclusion criteria were estimated IQ \leq 70, a central nervous system disorder, or substance dependence in the past 6 months. CHR participants could be included if they met DSM-IV criteria for any other non-psychotic disorder, as long as the disorder did not clearly account for the individual’s prodromal symptoms. Control subjects could not meet criteria for any prodromal syndrome, any current or past psychotic disorder, or a Cluster A personality disorder. They could not have a family history (in first-degree relatives) of any psychotic disorder or any other disorder involving psychotic symptoms.

2.2. Baseline clinical measures

2.2.1. Structured Clinical Interview for Psychosis-Risk Syndromes (SIPS)—

The SIPS is a semi-structured interview targeting interviewees’ experiences of attenuated symptoms and other indicators of psychosis risk (McGlashan et al., 2010; Miller et al., 1999). The SIPS contains probes and rating conventions for 19 symptom constructs, referred to as the Scale of Psychosis-Risk Symptoms or “SOPS.” Items sum to four symptom subscales (positive, negative, disorganized, and general). Each item is rated by the interviewing clinician on a Likert-style scale ranging from zero to six. Reliability was assessed annually based on a video-taped interview. Intraclass correlations, over 4 years, for the total SOPS scores ranged from 0.82 to 0.93 (Addington et al., 2015). The SIPS was administered at baseline and at six, twelve, eighteen, and twenty-four months after study entry.

At follow-up assessments, conversion to psychosis was defined by SIPS presence of psychosis (POPS) criteria (McGlashan et al., 2010). Remission from CHR was defined by failure to meet any of the SIPS psychosis risk syndrome criteria. At follow-up assessments, individuals with “persistent CHR” were those who did not convert to psychosis or remit but continued to experience positive symptoms at a SIPS level of 3–5 even if their symptoms showed no increase in the past year (see Addington et al., 2015).

2.2.2. Structured Clinical Interview for the DSM-IV (SCID-IV)—The structured clinical interview for DSM-IV (SCID) (First, 1995) was used to assess current and lifetime depression as well as other Axis 1 disorders.

2.2.3. Calgary Depression Scale for Schizophrenia (CDSS)—The CDSS (Addington et al., 2007) was used to measure current depressive symptom severity over the past two weeks and has been validated in CHR individuals (Addington et al., 2014).

2.3. Global functioning social and role scales

The social and role functioning scales are clinician-scored scales ranging from 1 to 10. Developmentally appropriate, detailed descriptions are provided to illustrate the range of functioning captured by each point on the scale, with lower scores indicating more impairment (Cornblatt et al., 2007a).

2.4. Demographic and medication logs

The following information was collected through demographic and medication forms: participants’ age, sex, ethnic background, and current and past use of psychotropic medication.

2.5. Analyses

NAPLS-2 baseline assessments were obtained for 1043 participants. Twenty-three participants (20 CHR, 3 controls) had missing SCID diagnoses and were excluded from the current study, leaving a sample of 744 CHR and 276 control participants. Of the remaining 744 CHR participants, 59 (7.9%) had a missing social or role functioning rating; 4 (0.5%) had one or more missing symptom severity ratings on the SIPS; and 24 (3.2%) were missing CDSS scores. Due to the overall low proportion of missing data, individuals with a missing data point were dropped per analysis but retained within the sample; mean substitutions or other imputation methods were not used.

Chi-square tests were performed to compare the prevalence of depression in CHR vs. control groups and to test for significant differences in demographic and medication profiles among participants with and without depression. Multivariate ANOVA controlling for age and gender with Bonferroni correction was used to compare group means on quantitative variables including SOPS ratings and functioning scales. Linear regressions with simultaneous independent variable entry were used to examine the impact of positive, negative, and depressive symptom ratings on current social and role functioning. To avoid construct overlap between independent and dependent variables in the regression, items

reflecting social (N1) and occupational (N6) functioning were removed from negative symptom totals (Meyer et al., 2014).

A one-way ANOVA with Bonferroni corrections was conducted to test for differences in baseline CDSS scores among participants with remitted vs. persistent vs. conversion outcomes. Chi-square tests were used to examine the relative likelihood of the three categorical outcomes among participants with and without a current or past diagnosis of depression at baseline.

3. Results

CHR participants' mean age was 18.5 years (19.8 for controls), with 11.3 years of education (12.7 for controls). Fifty-seven percent of those at CHR and 50% of controls were male. Thirty-seven percent of CHR and 40% of controls identified as non-white, and 19% of CHR and 18% of controls were Hispanic/Latino. The vast majority (95% of each group) were never married. The majority reported that they resided with family (76% of CHR, 63% of controls). Addington et al. (2015) present complete NAPLS-2 demographic information (one control participant was subsequently dropped from the original sample due to a previously unknown family history of psychosis).

Sixty percent of CHR subjects and 7% of controls had a lifetime (current OR past) diagnosis of a unipolar depressive disorder ($\chi^2 [1,1020] = 223.19, p < 0.001$); 42% of CHR and 4% of controls met DSM-IV criteria for current depression at the time of their baseline assessment ($\chi^2 [1,1020] = 157.37, p < 0.001$). An additional 56 participants met DSM-IV criteria for a bipolar mood disorder; these individuals were not included in the "depressed" subgroup (Fig. 1). Major depressive disorder (MDD) was the most common diagnosis, accounting for 77% of lifetime depressive disorder diagnoses within the CHR group (Fig. 1). Among the 444 CHR participants with a lifetime diagnosis of a depressive disorder, 314 met criteria for a current diagnosis of depression, with the other 130 cases meeting criteria for remitted depressive episodes.

CHR participants with a lifetime diagnosis of unipolar depression (MDD, dysthymic disorder, or depression NOS) were somewhat older (18.9 vs. 18.0; $t [df = 742] = -2.77, p = 0.006$) relative to those with no lifetime depression diagnosis. Women in the cohort had a higher lifetime prevalence of depression than men (64% vs. 56%; $\chi^2 [1744] = 4.62, p = 0.032$). There was no significant difference in the lifetime prevalence of depression among white vs. non-white participants (60% vs. 60%), Asian vs. non-Asian participations (57% vs. 60%), or Hispanic vs. non-Hispanic participants (64% vs. 59%). Black participants had significantly lower lifetime prevalence of depression than non-black participants (50% vs. 62%; $\chi^2 [1743] = 5.33, p = 0.021$). Participants who identified more than one ethnicity had higher lifetime prevalence of depression (70%) than those who identified a single ethnic category (58%) ($\chi^2 [1743] = 4.54, p = 0.033$).

Individuals with a current or past depressive disorder presented at baseline with greater exposure across multiple categories of psychiatric medications relative to non-depressed individuals in the CHR cohort. Specifically, those with depression were significantly more

likely to have taken antidepressants or any type of psychotropic medication, and less likely to have taken mood stabilizers, relative to those without depression (Table 1).

Relative to never-depressed CHR subjects, those with current or past depression presented with significantly more severe negative and general symptoms, and greater impairments in social functioning, but no significant differences in positive or disorganized symptoms or role functioning (Table 2). Relative to those with current depression at the time of assessment, those with remitted depression had less severe negative, general, and disorganized symptoms, as well as better role and social functioning. Using the continuous data (i.e., CDSS), there was a moderate positive correlation of $r = 0.35$ ($p < 0.001$) of depression with SIPS negative symptom total scores. Remitted vs. currently depressed subjects did not differ with regard to positive symptom presentation (Table 2).

Within the full CHR sample, participants' continuously-rated depressive symptoms contributed uniquely to social functioning impairments beyond the impact of positive and negative psychosis-related symptoms (Table 3). This was also true when the impact of depression, positive, and negative symptoms was examined only among those with a current or past depression diagnosis (Table 3).

Follow-up SIPS diagnoses were available for 559 (73%) of CHR participants (a detailed description of longitudinal outcomes has been reported in a prior publication (Addington et al., 2015)). An ANOVA analyzing mean differences in CDSS scores between the three outcome groups (remitted, persistent or converted) was significant ($F [2549] = 4.77$, $p = 0.009$).¹ Comparisons revealed that CHR-remitted subjects had significantly lower baseline CDSS scores relative to those with persistent CHR. Further, participants with a lifetime diagnosis (past or present) of depression tended to be less likely to achieve CHR remission than those with no history of depression ($\chi^2 [1558] = 3.76$, $p = 0.052$); however, depression diagnoses were not significantly associated with increased risk for conversion ($\chi^2 [1558] = 0.01$, $p = 0.926$). Antidepressant medication exposure at baseline did not predict CHR-status outcomes (i.e., remission/persistence/conversion) among the CHR subgroup with a current or past depression diagnosis ($\chi^2 [2334] = 0.473$, $p = 0.789$). The prevalence of lifetime substance use disorders did not differ significantly between CHR participants with and without a depressive disorder (22% vs. 18%; $\chi^2 [1744] = 1.20$, $p = 0.272$).

4. Discussion

In the largest and most detailed study of CHR prodromal cases to date, we demonstrated that unipolar depressive disorders were highly prevalent among participants in the NAPLS-2 baseline cohort. Three hundred and sixteen (42%) met DSM-IV criteria for a current depressive disorder, and an additional 133 (18%) met criteria for past depression currently in remission. Most of these participants met criteria for Major Depressive Disorder as opposed to dysthymia or depression "NOS," indicating a high frequency of serious mood disturbance. Relative to never-depressed subjects, CHR participants with current or past depression

¹This analysis was also conducted controlling for age, sex, and multi-ethnic identity; in the corrected model, differences in CDSS scores among the outcome groups remained significant.

presented with more prior exposure to psychotropic medications (in particular, antidepressants), which could reflect a greater tendency toward seeking mental health treatment (for any reason) among CHR individuals suffering from dysphoric mood (Falkenberg et al., 2015). NAPLS participants with depression were also previously shown to have higher rates of prior psychosocial treatment in addition to pharmacologic treatment, and generally sought treatment prior to the observed onset of their psychosis-risk symptoms (Woodberry et al., 2016a).

The lower prevalence of depression among Black participants is consistent with national data reflecting somewhat lower lifetime prevalence of major depression within Black Caribbean (12.9%) and African American (10.4%) populations relative to whites (17.9%) in the United States general population (Williams et al., 2007). The higher prevalence of depression among multi-ethnic and female participants also reflects national trends (Fisher et al., 2014; Kessler et al., 2005).

With regard to attenuated psychotic symptoms, participants with current or past depression presented with significantly worse negative and general symptoms than those without depression. Further, these symptoms as well as disorganized symptoms also varied significantly between individuals with a current vs. remitted depressive episode. This finding potentially supports a ‘state’ interpretation, i.e. that current mood state accounts for considerable variation in an individual’s CHR symptom profile. Positive symptoms, however, were unassociated with either ‘state’ or ‘trait’ mood differences. One clinical implication of this finding may be that treatments targeting depression in CHR patients are likely to alleviate general, disorganized, and negative – but not necessarily positive – symptoms.

Within the NAPLS-2 sample, both depression and negative symptoms impacted functioning. The negative correlates of mood disturbance – both within the entire CHR sample, and within the ever-depressed subsample – were more pronounced for social than for role functioning. Individuals with remitted depression were comparable in role functioning to their never-depressed peers. Although depression did contribute uniquely to impairments in social functioning, it was not as strong a predictor of functioning as negative symptoms. The critical impact of negative symptoms on social and occupational functioning is well documented within both clinical high-risk samples (Corcoran et al., 2011; Meyer et al., 2014; Schlosser et al., 2015) and established psychosis (Albert et al., 2011; Gee et al., 2016; Milev et al., 2005; Stouten et al., 2015). Research on treatment effects in first episode psychosis, however, indicates that effective treatment of depression within this population may be a key mediator of changes in social and role functioning (Minor et al., 2015). Studies of treatment of depression in CHR samples are naturalistic and not controlled trials (Cornblatt et al., 2007b), suggesting a need for new trials of depression treatment within this population. It is possible that the additional treatment received by those with a history of depression may have been protective against conversion in some cases; more research is needed to systematically explore depression-targeted treatments for the prevention of psychosis progression in CHR populations.

The current study replicated prior findings that comorbid depression (dimensional or diagnostic) is not associated with increased risk of conversion to psychosis (Lim et al., 2015; Rutigliano et al., 2016). However, by examining likelihood of remission as well as conversion, this study offers a novel finding as well: that the relative absence of depression did predict *remission* of attenuated psychotic symptoms on follow-up. In other words, participants without a diagnostic history of depression and low baseline depression symptoms were more likely to experience a resolution of their CHR syndrome compared to more depressed participants. This finding replicates the earlier observation of Schlosser et al. (2012) and lends support to models that emphasize shared genetic risk and simultaneous emergence of co-occurring disorders (Stochl et al., 2015) as well as models that regard depression as an additional risk factor for psychosis (Wigman et al., 2012). These data do not support the conceptualization of depression as primarily a reaction to psychosis, as even a diagnosis of MDD in remission was associated at a trend level with lower likelihood of future CHR remission.

It is difficult to compare the prevalence and impact of depression within CHR vs. established psychosis samples because existing categorization strategies for disorders involving psychotic symptoms typically seek to characterize mental disorders as ‘primarily’ affective vs. psychotic in nature. The temporal relationship of affective and psychotic symptoms was not assessed in this cohort and may still be evolving even during a first episode of psychosis. Thus, the prognostic meaning of depression within first-episode psychosis remains unclear. Although some studies report that the presence of depression in non-affective first episode psychosis is associated with worse functioning and more difficulty in recovery (Chang et al., 2015), affective psychoses are generally thought to be more responsive to treatment and less chronically impairing than nonaffective psychotic disorders (Tohen et al., 2000). Further complicating this picture is the issue of diagnostic instability early in the course of psychotic illness. One prospective study found that only 47% of DSM-IV diagnoses of major depression with psychotic features remained consistent after 10 years; many of these cases had ‘migrated’ into a schizophrenia diagnosis over time (Heslin et al., 2015), thus potentially lending support to the theory that depression with psychotic features may in fact represent prodromal schizophrenia. In sum, the extremely high prevalence of depression in both the current CHR sample and the broader first episode psychosis literature raises questions about the appropriateness of the terminology “non-affective psychosis” to describe a condition in which affect disturbance is such a common associated feature.

4.1. Limitations and directions for future research

The current study is limited to a cross-sectional, baseline clinical snapshot and cannot offer insight into the trajectories of mood disturbance over time in individuals at risk for psychosis. Retrospective diagnoses of remitted depression were obtained using a SCID at the time of baseline assessment, so the accuracy of these diagnoses may be less than optimal. Similarly, the lack of information about the temporal onset of psychotic and depressive symptoms, as well as the timing of medication exposure relative to symptom onset, are limitations. This study is also somewhat limited by the fact that participants in NAPLS represent for the most part a help-seeking group, which likely differs both clinically and demographically from the total population of individuals prodromal to schizophrenia

and other psychoses in the community (Woodberry et al., 2016a). Finally, NAPLS-2 used the SIPS to define CHR status, and thus the sample may not align with high-risk samples identified using alternative psychosis-risk criteria. Future research is needed to examine the impact of depression on selection and effectiveness of treatment for individuals at CHR for psychosis.

5. Conclusions

The current study adds to the existing literature by examining the concurrent impact and prognostic meaning of depression within a large cohort of newly diagnosed CHR participants. This work complements recent research establishing individualized risk prediction from clinical and neuropsychological factors that can easily be assessed in individuals meeting SIPS criteria for high risk states (see Cannon et al., 2016; Carrión et al., 2016). Within this cohort, a diagnosis of depression was associated with more pronounced negative and general symptoms, indicating exacerbations in sleep and mood problems, poor stress tolerance, and decreased hygiene. Current (symptomatic, rather than diagnostic) depressed mood contributed beyond the impact of positive and negative symptoms to impairments in social functioning. Individuals with remitted depression had significantly less severe negative and general symptoms, and better social and role functioning, relative to those with current depression. A diagnosis of current or past depression was also associated with greater prior exposure to antidepressant and antipsychotic medications, a possibly proxy for past treatment seeking. Those with less depression at baseline were more likely to achieve CHR remission over time. These findings suggest that absence of depression in CHR serves as a marker of good prognosis, and that treatment for depression in CHR states may be helpful for reducing disability and improving social functioning.

Acknowledgments

Robert Heinessen, PhD, of the National Institute of Mental Health, provided study support. We would like to acknowledge Victoria Choate Hasler, Michelle Friedman-Yakoobian, Anthony Giuliano, Andrea Gnono-Granato, Matcheri S. Keshavan, Robert W. McCarley, Raquelle Mesholam-Gately, Jayne-Marie Nova, Corin Pilo-Comtois, Janine Rodenhiser-Hill, Rachael Serur, Lynda Tucker, and Joanne Wojcik for their valued assistance with the study at the Beth Israel Deaconess Medical Center site. We are grateful to the many staff at the eight participating sites and the participants who contributed to this study.

Role of the funding source

This study was supported by the National Institute of Mental Health (NIMH) grants U01 MH081928, and the Commonwealth of Massachusetts SCDMH82101008006 to Dr. Seidman; grant U01 MH081984 to Dr. Addington; grants R01 MH60720, U01 MH082022 and K24 MH76191 to Dr. Cadenhead; grant U01 MH081902 to Dr. Cannon; P50 MH066286 (Prodromal Core) to Dr. Bearden; U01 MH081857 grant to Dr. Cornblatt; grant U01 MH082004 to Dr. Perkins; grant U01 MH081988 to Dr. Walker; grant U01 MH082022 to Dr. Woods; Clinical Translational Science Award (UL1RR025758) and General Clinical Research Center Grant (M01RR01032) from the National Center for Research Resources to Harvard University and Beth Israel Deaconess Medical Center, the National Center for Research Resources (P41RR14075), and Shared Instrumentation Grants (1S10RR023401, 1S10RR019307, 1S10RR023043). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. The NIMH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

- Addington D, Addington J, Maticka-Tyndale E, 2007 Assessing depression in schizophrenia: the Calgary Depression Scale. *Br. J. Psychiatry* 163 (S22), 39–44.
- Addington J, Liu L, Buchy L, Cadenhead KS, Cannon TD, Cornblatt BA, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Bearden CE, Mathalon DH, McGlashan TH, 2015 North American Prodrome Longitudinal Study (NAPLS 2): the prodromal symptoms. *J. Nerv. Ment. Dis.* 203 (5), 328–335. [PubMed: 25919383]
- Addington J, Shah H, Liu L, Addington D, 2014 Reliability and validity of the Calgary Depression Scale for Schizophrenia (CDSS) in youth at clinical high risk for psychosis. *Schizophr. Res* 153 (1), 64–67. [PubMed: 24439270]
- Albert N, Bertelsen M, Thorup A, Petersen L, Jeppesen P, Le Quack P, Krarup G, Jørgensen P, Nordentoft M, 2011 Predictors of recovery from psychosis: analyses of clinical and social factors associated with recovery among patients with first-episode psychosis after 5 years. *Schizophr. Bull.* 125 (2), 257–266.
- Cannon TD, Yu C, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, ... Perkins DO, 2016 An individualized risk calculator for research in prodromal psychosis. *Am. J. Psychiatry* 173 (10), 980–988. [PubMed: 27363508]
- Carrión RE, Cornblatt BA, Burton CZ, Tso IF, Auther AM, Adelsheim S, ... Taylor SF, 2016 Personalized prediction of psychosis: external validation of the NAPLS-2 psychosis risk calculator with the EDIPPP project. *Am. J. Psychiatry* 173 (10), 989–996. [PubMed: 27363511]
- Chang WC, Cheung R, Hui CLM, Lin J, Chan SK, Lee EH, Chen EY, 2015 Rate and risk factors of depressive symptoms in Chinese patients presenting with first-episode non-affective psychosis in Hong Kong. *Schizophr. Res.* 168 (1), 99–105. [PubMed: 26235752]
- Corcoran CM, Kimhy D, Parrilla-Escobar MA, Cressman VL, Stanford AD, Thompson J, David SB, Crumley A, Schobel S, Moore H, Malaspina D, 2011 The relationship of social function to depressive and negative symptoms in individuals at clinical high risk for psychosis. *Psychol. Med.* 41 (2), 251–261. [PubMed: 20444306]
- Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, Cannon TD, 2007a Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophr. Bull.* 33 (3), 688–702. [PubMed: 17440198]
- Cornblatt BA, Lencz T, Smith CW, Olsen R, Auther AM, Nakayama E, Tai JY, Shah MR, Foley CA, Kane JM, Correll CU, 2007b Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. *J. Clin. Psychiatry* 68 (4), 546–557. [PubMed: 17474810]
- Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013 Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* 45 (9), 984–994. [PubMed: 23933821]
- Falkenberg I, Valmaggia L, Byrnes M, Frascarelli M, Jones C, Rocchetti M, Straube B, Badger S, McGuire P, Fusar-Poli P, 2015 Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? *Psychiatry Res.* 228 (3), 808–815. [PubMed: 26071897]
- Fisher S, Reynolds JL, Hsu WW, Barnes J, Tyler K, 2014 Examining multiracial youth in context: ethnic identity development and mental health outcomes. *J. Youth Adolesc.* 43 (10), 1688–1699. [PubMed: 25100614]
- First MB, 1995 Structured Clinical Interview for the DSM (SCID). John Wiley & Sons, Inc., New Jersey.
- Fulford D, Niendam TA, Floyd EG, Carter CS, Mathalon DH, Vinogradov S, Stuart BK, Loewy RL, 2013 Symptom dimensions and functional impairment in early psychosis: more to the story than just negative symptoms. *Schizophr. Res.* 147 (1), 125–131. [PubMed: 23587696]
- Fusar-Poli P, Bechdolf A, Taylor MJ, Bonoldi I, Carpenter WT, Yung AR, McGuire P, 2013 At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. *Schizophr. Bull.* 39 (4), 923–932. [PubMed: 22589370]

- Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK, 2014 Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophr. Bull.* 40 (1), 120–131. [PubMed: 23180756]
- Gee B, Hodgekins J, Fowler D, Marshall M, Everard L, Lester H, Jones PB, Amons T, Singh PS, Sharma V, Freemantle N, Birchwood M, 2016 The course of negative symptoms in first episode psychosis and the relationship with social recovery. *Schizophr. Res.* 174 (1–3), 165–171. [PubMed: 27131912]
- Häfner H, Maurer K, Trendler G, an der Heiden W, Schmidt M, Könnicke R, 2005 Schizophrenia and depression: challenging the paradigm of two separate diseases—a controlled study of schizophrenia, depression and healthy controls. *Schizophr. Res.* 77 (1), 11–24. [PubMed: 16005381]
- Heslin M, Lomas B, Lappin JM, Donoghue K, Reininghaus U, Onyejiaka A, Croudace T, Jones PB, Murray RM, Fearon P, Dazzan P, Morgan C, Doody GA, 2015 Diagnostic change 10 years after a first episode of psychosis. *Psychol. Med.* 45 (13), 2757–2769. [PubMed: 25936425]
- Hui C, Morcillo C, Russo DA, Stochl J, Shelley GF, Painter M, Jones PB, Perez J, 2013 Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. *Schizophr. Res.* 148 (1), 175–180. [PubMed: 23773297]
- Kessler RC, Chiu WT, Demler O, Walters EE, 2005 Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *JAMA Psychiat.* 62 (6), 617–627.
- Koyanagi A, Sitckley A, Haro JM, 2016 Subclinical psychosis and pain in an English national sample: the role of common mental disorders. *Schizophr. Res.* 175 (1–3), 209–215. [PubMed: 27156241]
- Krabbendam L, Myin-Germeys I, Hanssen M, de Graaf R, Vollebergh W, Bak M, van Os J, 2005 Development of depressed mood predicts onset of psychotic disorder in individuals who report hallucinatory experiences. *Br. J. Clin. Psychol.* 44 (1), 113–125. [PubMed: 15826348]
- Lim J, Rekhi G, Rapisarda A, Lam M, Kraus M, Keefe RS, Lee J, 2015 Impact of psychiatric comorbidity in individuals at Ultra High Risk of psychosis — findings from the Longitudinal Youth at Risk Study (LYRIKS). *Schizophr. Res.* 164 (1–3), 8–14. [PubMed: 25818728]
- Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T, 2005 Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *JAMA Psychiat.* 62 (9), 975–983.
- McGlashan T, Walsh B, Woods S, 2010 *The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-Up*. Oxford University Press, New York.
- Meyer EC, Carrión RE, Cornblatt BA, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, Perkind DO, Tsuang MT, Walker EF, Woods SW, Heinssen R, Seidman LJ, NAPLS group. 2014 The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the North American Prodrome Longitudinal Study. *Schizophr. Bull.* 40(6) 1452–1461. [PubMed: 24550526]
- Milev P, Ho BC, Arndt S, Andreasen NC, 2005 Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am. J. Psychiatry* 162 (3), 495–506. [PubMed: 15741466]
- Miller TJ, McGlashan TH, Woods SW, Stein K, Driesen N, Corcoran CM, Hoffman R, Davidson L, 1999 Symptom assessment in schizophrenic prodromal states. *Psychiatry Q.* 70 (4), 273–287.
- Minor KS, Friedman-Yakoobian M, Leung YJ, Meyer EC, Zimet SV, Caplan B, Monteleone T, Bryant C, Guyer M, Keshavan MS, Seidman LJ, 2015 The impact of premorbid adjustment, neurocognition, and depression on social and role functioning in patients in an early psychosis treatment program. *Aust. N. Z. J. Psychiatry* 49 (5), 444–452. [PubMed: 25586755]
- Murray GK, Jones PB, 2012 Psychotic symptoms in young people without psychotic illness: mechanisms and meaning. *Br. J. Psychiatry* 201 (1), 4–6. [PubMed: 22753849]
- Phillips LK, Seidman LJ, 2008 Emotion processing in persons at risk for schizophrenia. *Schizophr. Bull.* 34 (5), 888–903. [PubMed: 18644853]
- Rutigliano G, Valmaggia L, Landi P, Frascarelli M, Cappucciati M, Sear V, Rocchetti M, De Micheli A, Jones C, Palombini E, McGuire P, Fusar-Poli P, 2016 Persistence or recurrence of non-

- psychotic comorbid mental disorders associated with 6-year poor functional outcomes in patients at ultra high risk for psychosis. *J. Affect. Disord* 203, 101–110. [PubMed: 27285723]
- Schlosser DA, Campellone TR, Biagianni B, Delucchi KL, Gard DE, Fulford D, Stuart BK, Fisher M, Loewy RL, Vinogradov S, 2015 Modeling the role of negative symptoms in determining social functioning in individuals at clinical high risk of psychosis. *Schizophr. Res* 169 (1), 204–208. [PubMed: 26530628]
- Schlosser DA, Jacobson S, Chen Q, Sugar CA, Niendam TA, Li G, Bearden CE, Cannon TD, 2012 Recovery from an at-risk state: clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. *Schizophr. Bull* 38 (6), 1225–1233. [PubMed: 21825282]
- Smith B, Fowler D, Freeman D, Bebbington P, Bashforth H, Garety P, ... Kuipers E, 2006 Emotion and psychosis: links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations. *Schizophr. Res* 86 (1), 181–188. [PubMed: 16857346]
- Smoller JW, 2013 Disorders and borders: psychiatric genetics and nosology. *Am. J. Med. Genet* 162 (7), 559–578.
- Stochl J, Khandaker GM, Lewis G, Perez J, Goodyer IM, Zammit S, Sullivan S, Croudace TJ, Jones PB, 2015 Mood, anxiety and psychotic phenomena measure a common psychopathological factor. *Psychol. Med* 45 (7), 1483–1493. [PubMed: 25394403]
- Stouten LH, Veling W, Laan W, van der Helm M, van der Gaag M, 2015 Psychosocial functioning in first-episode psychosis and associations with neurocognition, social cognition, psychotic and affective symptoms. *Early Interv. Psychiatry* 10.1111/eip.12210.
- Sullivan SA, Wiles N, Kounali D, Lewis G, Heron J, Cannon M, Mahedy L, Jones PB, Stochl J, Zammit S, 2014 Longitudinal associations between adolescent psychotic experiences and depressive symptoms. *PLoS One* 9 (8), e105758. [PubMed: 25162230]
- Tohen M, Strakowski SM, Zarate C, Hennen J, Stoli AL, Suppes T, Faedda GL, Cohen BM, Gebre-Medhin P, Baldessarini RJ, 2000 The McLean–Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. *Biol. Psychiatry* 48 (6), 467–476. [PubMed: 11018220]
- Uptegrove R, Ross K, Brunet K, McCollum R, Jones L, 2014 Depression in first episode psychosis: the role of subordination and shame. *Psychiatry Res* 217 (3), 177–184. [PubMed: 24726817]
- Vorontsova N, Garety P, Freeman D, 2013 Cognitive factors maintaining persecutory delusions in psychosis: the contribution of depression. *J. Abnorm. Psychol* 122 (4), 1121–1131. [PubMed: 24364615]
- Wigman JT, van Nierop M, Vollebergh WA, Lieb R, Beesdo-Baum K, Wittchen HU, van Os J, 2012 Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity—implications for diagnosis and ultra-high risk research. *Schizophr. Bull* 38 (2), 247–257. [PubMed: 22258882]
- Williams DR, Gonzalez HM, Neighbors H, Nesse R, Abelson JM, Sweetman J, Jackson JS, 2007 Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and non-Hispanic whites: results from the National Survey of American Life. *JAMA Psychiat*. 64 (3), 305–315.
- Woodberry KA, Seidman LJ, Bryant C, Addington J, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt TD, McGlashan TH, Mathalon DH, Perkins DO, Tsuang MT, Walker EF, Woods SW, 2016a Treatment precedes positive symptoms in North American adolescent and young adult clinical high risk cohort. *J. Clin. Child Adolesc. Psychol* 10.1080/15373316.2016.1212361.
- Woodberry KA, Shapiro DI, Bryant C, Seidman LJ, 2016b Progress and future directions in research on the psychosis prodrome: a review for clinicians. *Harv. Rev. Psychiatry* 24 (2), 87–103. [PubMed: 26954594]
- Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinsen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH, 2009 Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophr. Bull* 35 (5), 894–908. [PubMed: 19386578]

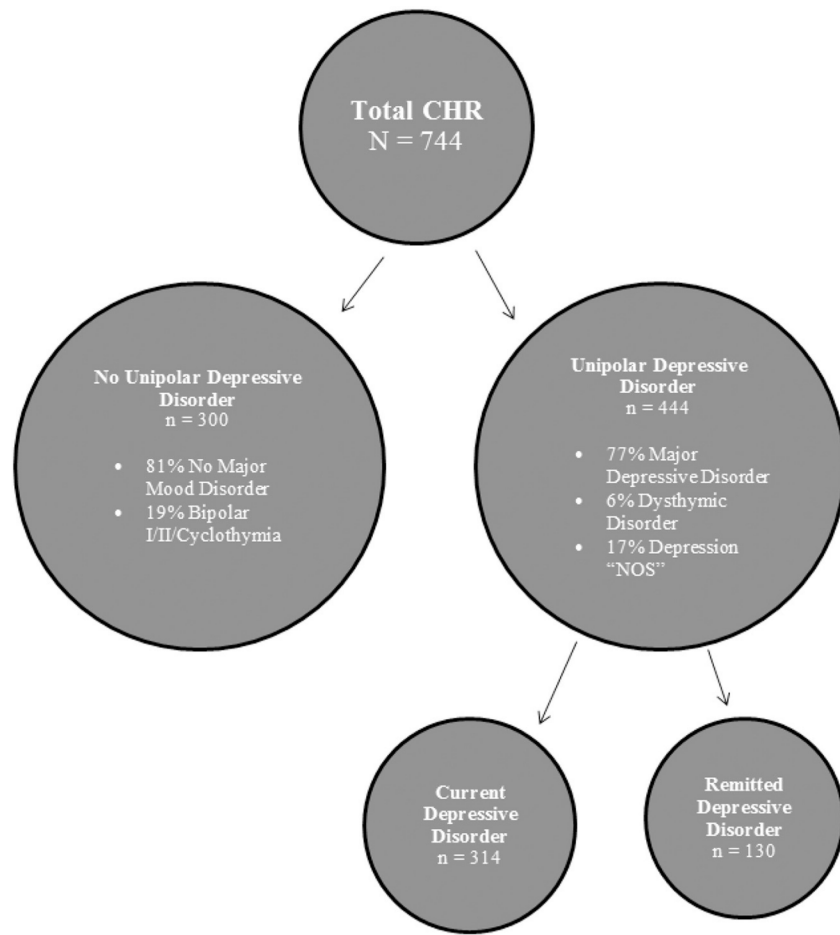


Fig. 1.
Depressive disorders in NAPLS-2.

Table 1

Lifetime medication exposure among CHR participants with and without depression.

	Lifetime depression ^a (<i>n</i> = 444)	No lifetime depression (<i>n</i> = 300)
Antipsychotics (%)	28	22
Antidepressants (%)	50 ^b	29
Mood stabilizers (%)	7	11 ^b
Stimulants (%)	20	25
Benzodiazepines (%)	11	12
Any medication (%)	63 ^b	54

^aIncludes participants with current or past depressive episode, per SCID criteria.

^bChi-square test indicates significant difference ($p < 0.05$).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Symptoms and functional impairments in CHR participants with and without depression.

	ANOVA Result			
	Never depressed	Ever depressed ^a	ANOVA Result	
	(N = 300)	(N = 444)	F	p
	Mean (SD)	Mean (SD)		Effect size d
Positive symptoms	11.97 (3.65)	11.79 (3.97)	0.96	0.33 0.06
Negative symptoms ^b	5.88 (4.06)	7.25 (3.97)	23.74	<0.01 0.36
Disorganized symptoms	5.08 (3.14)	5.22 (3.16)	0.34	0.56 <0.01
General symptoms	7.89 (4.02)	10.00 (4.23)	40.78	<0.01 0.47
Global functioning: social	6.59 (1.65)	6.08 (1.53)	16.18	<0.01 0.31
Global functioning: role	6.17 (2.06)	5.96 (2.25)	2.56	0.11 0.13

	ANOVA Result			
	Remitted depression	Current depression	ANOVA Result	
	(N = 130)	(N = 314)	F	p
	Mean (SD)	Mean (SD)	F	Effect size d
Positive symptoms	11.82 (4.12)	11.78 (3.92)	<0.01	0.99 <0.01
Negative symptoms ^b	6.08 (3.60)	7.72 (4.02)	14.76	<0.01 0.37
Disorganized symptoms	4.68 (2.86)	5.43 (3.25)	5.27	0.02 0.22
General symptoms	8.03 (4.04)	10.79 (4.04)	45.44	<0.01 0.65
Global functioning: social	6.36 (1.49)	5.96 (1.54)	5.74	0.01 0.24
Global functioning: role	6.37 (2.14)	5.80 (2.28)	5.11	0.01 0.22

SOPS items (Positive, Negative, Disorganized, General) scored 0–6; higher scores represent more severe symptoms.

Global Functioning scales scored 1–10; higher scores represent better functioning.

^aIncludes participants with current or past depressive episode, per SCID criteria^bDoes not include N1 or N6 so as to avoid overlap with GF-S/R constructs.

Table 3

Regression analyses predicting social and role functioning.

Entire CHR sample (N = 744)						
	GF-social			GF-role		
	<u>R = 0.37, F = 35.27, p < 0.001</u>			<u>R = 0.31, F = 23.71, p < 0.001</u>		
	β	t	p	β	t	p
Constant	N/A	35.32	<0.001	N/A	24.92	<0.001
P-total	0.06	1.50	0.133	0.03	0.82	0.414
N-total ^a	-0.30	-7.79	<0.001	-0.32	-8.15	<0.001
CDSS total	-0.16	-4.17	<0.001	0.01	0.32	0.747

CHR participants with lifetime (current or past) depression only (N = 444)						
	GF-social			GF-role		
	<u>R = 0.33, F = 16.14, p < 0.001</u>			<u>R = 0.28, F = 11.42, p < 0.001</u>		
	β	t	p	β	t	p
Constant	N/A	26.37	<0.001	N/A	18.06	<0.001
P-total	0.10	2.03	0.043	0.06	1.19	0.236
N-total ^a	-0.29	-5.66	<0.001	-0.28	-5.47	<0.001
CDSS total	-0.10	-2.03	0.043	-0.01	-0.28	0.783

^aDoes not include N1 or N6.