Title

Sampling from different populations: Sociodemographic, clinical, and functional differences between samples of first episode psychosis individuals and clinical high-risk individuals who progressed to psychosis.

Authors

Hagler, Matthew
Ferrara, Maria
Yoviene Sykes, Laura
et al.

Publication Date

2023-05-01

DOI

10.1016/j.schres.2023.03.047

Peer reviewed

HHS Public Access

Author manuscript

Schizophr Res. Author manuscript; available in PMC 2024 May 01.

Published in final edited form as:

Schizophr Res. 2023 May ; 255: 239–245. doi:10.1016/j.schres.2023.03.047.

Sampling from different populations: Sociodemographic, clinical, and functional differences between samples of first episode psychosis individuals and clinical high-risk individuals who progressed to psychosis

Matthew A. Hagler[*,a,1], **Maria Ferrara**[a,b], **Laura A. Yoviene Sykes**[a], **Fangyong Li**[a], **Jean Addington**[c], **Carrie E. Bearden**[d], **Kristin S. Cadenhead**[e], **Tyrone D. Cannon**[f], **Barbara A. Cornblatt**[g], **Diana O. Perkins**[h], **Daniel H. Mathalon**[i], **Larry J. Seidman**[j], **Ming T. Tsuang**[e], **Elaine F. Walker**[k], **Albert R. Powers III**[a], **Adrienne R. Allen**[a], **Vinod H. Srihari**[a,2], **Scott W. Woods**[a,2]

[a]Department of Psychiatry, Yale University, New Haven, CT, United States of America

[b]Institute of Psychiatry, Department of Neurosciences and Rehabilitation, University of Ferrara, Ferrara, Italy

[c]Hotchkiss Brain Institute, Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

[d]Departments of Psychology and Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA, United States of America

[e]Department of Psychiatry, UCSD, San Diego, CA, United States of America

[f]Departments of Psychology and Psychiatry, Yale University, New Haven, CT, United States of America

[g]Department of Psychiatry, Zucker Hillside Hospital, Long Island, NY, United States of America

[h]Department of Psychiatry, University of North Carolina, Chapel Hill, NC, United States of America

[i]Department of Psychiatry, UCSF, San Francisco, CA, United States of America

[j]Department of Psychiatry, Harvard Medical School, Boston, MA, United States of America

[*]Corresponding Author, Matthew A. Hagler, Ph.D. Present/permanent address: Department of Psychology, Francis Marion University, 4822 E Palmetto St, Florence, SC 29506, USA, Matthew.Hagler@fmarion.edu.

[1]Present affiliation: Department of Psychology, Francis Marion University, Florence, SC, United States of America

[2]Joint last authors

Contributors

We have no contributors to acknowledge for this manuscript.

Conflicts of interest

We have no conflicts of interest to declare.

[k]Departments of Psychology and Psychiatry, Emory University, Atlanta, GA, United States of America

Abstract

Over the past two decades, research and clinical resources on clinical high risk (CHR) for psychosis have both expanded, with goals to better understanding risk and protective factors on the course of illness and inform early intervention efforts. However, some studies have highlighted potential sampling bias among CHR research studies, raising questions about generalizability of findings and inequitable access to early detection and intervention. The current study sought to explore these questions by comparing 94 participants in a CHR longitudinal monitoring study across North America (NAPLS-2) who converted to syndromal psychosis over the course of the study (CHR-CV) to 171 participants who presented for treatment at a localized first-episode psychosis service (FES) after converting. CHR-CV participants were significantly more likely to be White and have a college-educated parent, while FES participants were more likely to be Black and first- or second-generation immigrants. On average, CHR-CV participants were younger at onset of attenuated positive symptoms, had a longer period of attenuated symptoms prior to conversion, and were more likely to be treated with antipsychotics prior to conversion compared to those in FES programs. After controlling for time since conversion, CHR-CV participants had higher global functioning and were less likely to have experienced recent psychiatric hospitalization. Findings suggest that CHR research and FES clinics may be sampling from different populations, although conclusions are limited by inconsistent sampling frames and methods. Integrated early detection that targets defined geographic catchments may deliver more epidemiologically representative samples to both CHR research and FES.

Keywords

Clinical high risk; first episode; conversion; early detection; sampling bias

1. Introduction

Efforts to detect and treat psychosis-spectrum symptoms earlier in the course of illness have expanded significantly over the past two decades (Addington et al., 2008; Fusar-Poli et al., 2012; McGorry et al. 2007). Traditionally, the field defined the psychosis prodrome as a series of changes, potentially including onset of both nonpsychotic and subthreshold psychotic symptoms, preceding conversion to frank psychosis (Yung and McGorry, 1996). By definition, prodromes are identified retrospectively. More recently, researchers have defined syndromes of clinical high risk for psychosis (CHR), characterized by attenuated positive symptoms, functional declines, and/or genetic risk. Unlike prodromes, CHR syndromes can be identified before conversion and do not necessarily result in conversion (Addington et al., 2008; Tandon et al., 2012; Woods et al., 2001). A recent meta-analysis of 35 epidemiological studies estimated the prevalence of CHR to be 1.7% in general youth populations and 19.2% in clinical youth populations (Salazar de Pablo et al., 2021). A comprehensive review estimated that 10% of patients convert to frank psychosis within six months of CHR onset, 17% within one year, 20% within two years, and 22% within three years (Fusar-Poli et al., 2020). In contrast, an estimated 35% of CHR-presenting patients

experience full remission within two years (Simon et al., 2013). Among converters, most continue to meet diagnostic criteria for psychotic disorders one year later (Yoviene Sykes et al., 2020).

CHR researchers aim to pinpoint reliable predictors of conversion so that individuals at highest risk can be identified and treated (Cannon et al., 2016; Fusar-Poli et al., 2012). Yet, CHR research participants who convert to psychosis might not be representative of all individuals with first-episode psychosis (FEP) (van Os and Guloksuz, 2017). First, research participation itself may facilitate earlier access to treatment and improve prognosis. CHR studies provide participants and families with psychoeducation and referrals, often offering psychopharmacological and psychosocial treatment in affiliated clinics (Addington et al., 2008, 2007; Fusar-Poli et al., 2017; McGlashan et al., 2003; Riecher-Rössler et al., 2006). Second, despite extensive recruitment efforts, CHR studies likely access a small proportion of individuals with CHR who go onto experience frank psychosis (Addington et al., 2008; Ajnakina et al., 2017; Schultze-Lutter, et al., 2018; Valmaggia et al., 2015).

The empirical literature offers some evidence that systematic differences exist between FEP patients who do or do not receive CHR services prior to conversion. One study drew data from a FEP clinic in the UK, comparing FEP patients who had received specialized CHR services (n=14) to those who received no specialized services prior to conversion (n=324) (Ajnakina et al., 2017). Patients who had received prodromal services were more likely to be referred by general medical practitioners, less likely to be referred through acute/emergency services, less likely to be immigrants, and more likely to have insidious modes of onset. A second UK study compared patients who presented with psychosis-risk symptoms prior to conversion (n=42) to FEP patients who did not receive specialized services prior to conversion (n=147). FEP patients who had been prodromal help-seekers were more likely to be employed following conversion, had shorter durations of untreated psychosis (DUP), were less likely to be ethnic minorities, and were less likely to have experienced psychiatric hospitalization (Valmaggia et al., 2015).

These differences suggest that converters in CHR samples may represent a biased slice of FEP populations. CHR researchers have acknowledged that, based on epidemiological estimates, they have captured only a small portion of individuals with CHR, and that CHR individuals who do and do not come to clinical attention likely differ in sociodemographic and clinical profiles (Addington et al., 2008; Schultze-Lutter et al., 2018). Because of their focus on early-course, attenuated symptoms, CHR studies largely rely on self-referrals and referrals from non-emergency services like general medical practitioners and non-specialized mental health providers (Addington et al., 2008; Friedman-Yakoobian et al., 2018). Thus, individuals who are more help-seeking, educated, economically privileged, and/or who have greater access to preventive services may be more likely enroll in CHR research. In contrast, pre-psychotic individuals with social disadvantage may be less connected to preventive care, less help-seeking, and less likely to be referred for CHR research and services.

Another potential source of bias in CHR ascertainment efforts relates to mode of illness onset. Insidious onsets (i.e., longer prodromes) provide more time for CHR symptoms to be

detected. In contrast, rapid progression may preclude early risk identification, resulting in detection after conversion, often in acute care settings (Schultze-Lutter et al., 2015). Further, some studies have suggested that there may be a considerable proportion of FEP patients who never experienced identifiable CHR syndromes, though these individuals typically demonstrated other forms of psychopathology before converting (e.g., mood and substance use disorders; Guloksuz et al., 2020; Shah et al., 2017). These findings provide further evidence that CHR converters in research studies do not fully represent FES populations.

Few studies have directly compared CHR-presenting converters to patients who presented for specialized first-episode services (FES) following conversion. Existing studies are limited to small samples in the UK. The present study seeks to expand upon this research by examining larger samples of CHR- and FES-presenting participants in North America. These datasets included many of the same measures, facilitating direct comparisons of sociodemographic, clinical, and functional variables. We hypothesized that CHR-presenting converters (CHR-CV) would demonstrate social advantage compared to FES-presenting participants, indicated by several demographic factors (race/ethnicity, parental education, immigration, linguistic status). We also expected CHR-CV participants to have greater access to antipsychotic treatment prior to conversion, be higher functioning after conversion, and utilize acute psychiatric services at lower rates.

2. Method

2.1 Participants

The CHR-converter (CHR-CV) sample was drawn from the North American Prodrome Longitudinal Study (NAPLS-2), which recruited participants ages 12–35 who met criteria for CHR based on the Structured Interview of Psychosis-risk Syndromes (SIPS; n=743) or adolescent schizotypal personality disorder (SPD; n=21), across eight U.S. and Canadian sites between 2008 and 2013 (Addington et al., 2007). Each site developed extensive referral networks with regional healthcare providers, schools, and social services agencies, grown through community education efforts such as academic detailing, ground rounds, and psychoeducational presentations. Sites also publicly advertised on the internet and in public places. Approximately 39% of eligible NAPLS participants were primarily referred by self or family/friends, 17% by acute services, and 40% by non-acute agencies. Relative proportions of referral sources differed somewhat across NAPLS sites (see Addington et al., 2012). Individuals were ineligible for NAPLS if they met criteria for a DSM-IV Axis I psychotic disorder, had an IQ of less than 70, could not communicate in English, had any history of central nervous system disorders, met criteria for substance dependence in the past six months, and/or had psychotic symptoms secondary to substance use or medical conditions. Of 764 participants, 94 converted to psychosis during the 2.5-year study. All 94 converters experienced attenuated positive symptoms (APS) before converting. Among converters, 10% also met criteria for brief intermittent psychosis syndrome (BIPS), and 16% met for genetic risk and deterioration syndrome (GRD).

The sample presenting after conversion was drawn from a first-episode service (FES) within the Program for Specialized Treatment Early in Psychosis (STEP), which recruited individuals aged 16–35 who had experienced non-affective FEP within the previous three

years and resided in a 10-town catchment area within Greater New Haven, CT (Srihari et al., 2014). Individuals were ineligible if they experienced psychosis secondary to an affective, medical, or substance use disorders, were DDS-eligible (Department of Developmental Services), were legally mandated to treatment, could not communicate in English, and/or had unstable medical conditions. STEP engaged in an extensive catchment-wide campaign, targeting all potential stakeholders in patients' access to care through public education via social and mass media, professional outreach, and academic detailing (see Srihari et al., 2022). Participants were referred through the following agencies (non-mutually exclusive): hospitals/EDs (71%), police (8%), and non-acute agencies (33%). Only 2.5% of STEP patients were referred by family, friends, or self without agency involvement. Current analyses included all 171 FES patients who enrolled and completed baseline assessments between 2014 and 2019.

2.2 Measures

For the CHR-CV sample, most data for current analyses were collected as soon as possible after participants' conversion to psychosis, ascertained from participants, family members and/or providers. Some data (e.g., demographics, premorbid functioning) were taken from initial study visits (pre-conversion). For the FES sample, all data were derived from study admission assessments, which supplemented patient reports with collateral from family members and providers.

2.2.1 Demographics—Demographic data were collected for both samples. Dichotomous variables were created for ethnicity (Hispanic, non-Hispanic), the three largest racial categories (White, Black, Asian), immigration status (whether participants were first- or second-generation immigrants), and linguistic status (whether English was their first language). A dichotomous variable was created indicating whether each participant had at least one college-educated parent, used as a proxy indicator of socioeconomic status (SES).

2.2.2 Onset of APS, Conversion, and Antipsychotic Treatment—CHR-CV participants completed SIPS interviews at baseline and conversion visits. FES participants completed SIPS at study admission to date psychosis onset and duration. For both samples, dates of birth and SIPS data were used to calculate age at onset of attenuated positive symptoms (APS), age at conversion, days between APS onset and conversion (length of APS), and days from conversion until conversion visit (for CHR-CV) or admission visit (for FES) (Ferrara et al., 2021). Lifetime medication histories were collected from participants and collateral sources in both studies, used to determine whether participants had ever been treated with antipsychotic (AP) medication, age at first AP treatment, and whether they had received off-label AP treatment prior to conversion (but after onset of APS). As a measure of treatment delay, days from APS onset until AP treatment or enrollment in specialized services (whichever came first) was calculated.

2.2.3 Premorbid and Current Functioning—The Cannon-Spoor Premorbid Adjustment Scale (PAS) retrospectively assessed functioning across several domains (sociability, peer relationships, scholastic performance, adaptation to school, and socio-sexual relationships) during distinct developmental periods (Cannon-Spoor et al., 1982). For

current analyses, participants' scores during childhood (birth to 11) and early adolescence (12 to 15) were used. Per scoring guidelines, percentage scores combining domains were calculated for each period. Possible scores ranged from 0 to 1.00. Lower scores indicated *better* premorbid adjustment. Participants with FEP onset of 15 or younger were excluded from analyses using the early adolescence subscale (van Mastrigt and Addington, 2002).

The Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000) and Global Functioning: Social and Role scales (Cornblatt et al., 2007) assessed current functioning. Scores were taken from CHR-CV participants' conversion assessments and FES participants' admission assessments.

2.2.4 Acute Services Utilization—At study admission, FES participants completed the Service Utilization and Resources Form (SURF), reporting the number and length of psychiatric inpatient hospitalizations during the previous six months (Rosenheck and Lieberman, 2007; Srihari et al., 2014). CHR-CV participants provided lifetime histories, but data were restricted to the six months prior to conversion visit. A dichotomous variable was created indicating whether participants had any psychiatric hospitalization in the prior six months. A continuous variable was calculated for the total number of psychiatric hospitalization nights in the prior six months.

2.3 Statistical Analyses

Univariate group comparisons were conducted with independent *t*-tests for continuous variables and Fisher's exact tests for categorical variables, using an alpha level of .05 for statistical significance. Missing data were estimated using multiple imputation. To examine geographic differences between the multisite CHR-CV sample and the localized FES sample, descriptive statistics are presented for the small CHR-CV subsample (n=10) from the same geographic region as the FES sample. Inferential statistics were not conducted for this subsample due to its size.

Additionally, theory-driven, follow-up multivariate analyses (i.e., logistical regressions) were conducted among variables that differed significantly across groups and were expected to covary (e.g., race and parental education, days since conversion and current functioning). Pairs of variables and their interactional terms were entered as predictors of group membership.

3. Results

3.1 Demographics

CHR-CV participants' mean age at conversion visit was significantly lower than FES participants' mean age at study admission (See Table 1). A significantly higher proportion of FES participants were Black, and a significantly higher proportion of CHR-CV participants were White. A significantly higher proportion of FES participants were first- or second-generation immigrants. A significantly higher proportion of CHR-CV participants had a college-educated parent. Comparing FES and New Haven-area CHR-CV subsamples, age, race, and immigration differences were consistent with the FES vs. all-sites CHR-CV comparison. However, the New Haven CHR-CV subsample contained a smaller proportion

of individuals with college-educated parents compared to FES and all-sites CHR-CV samples.

3.2 Timeline of Onset and Treatment

CHR-CV participants were significantly younger at APS onset and conversion compared to FES participants (See Table 2). CHR-CV participants had significantly longer APS. A significantly higher proportion of FES participants had received AP treatment prior to their admission visit, but a significantly higher proportion of CHR-CV participants received AP treatment prior to conversion. A significantly shorter amount of time had elapsed from conversion to study visit among CHR-CV participants. Comparing FES and New Haven-area CHR-CV subsamples, differences across these variables were consistent with the FES vs. all-sites CHR-CV comparison.

3.3 Premorbid and Current Functioning

According to the PAS, CHR-CV participants had significantly worse premorbid adjustment during childhood and early adolescence compared to FES participants (See Table 3). However, at conversion, CHR-CV participants were rated significantly higher on the GAF and the Global Functioning: Social scale compared to FES participants. Comparing FES and New Haven-area CHR-CV subsamples, functional differences were somewhat inconsistent with the FES vs. all CHR-CV comparison. Specifically, New Haven CHR-CV participants had similar premorbid adjustment to the FES sample.

3.4 Acute Services Utilization

During the preceding six months, a significantly higher proportion of FES participants experienced psychiatric hospitalization, and FES participants spent significantly more nights in hospitalization, compared to CHR-CV participants (See Table 3). This difference was also apparent when comparing FES and New Haven-area CHR-CV subsamples.

3.5 Follow-up Multivariate Analyses

A series of logistical regressions examined covariation among theoretically linked variables that significantly differed between groups in univariate analyses (See Table 4). When entered as covariates with their interaction term, Black race predicted FES group membership, while having a college-educated parent predicted CHR-CV group membership. When entered as covariates with their interaction term, White race predicted CHR-CV group membership, while immigration status did not predict group membership. When entered as covariates with their interaction term, days since conversion predicted FES group membership, and GAF predicted CHR-CV group membership. When days since conversion and total nights in psychiatric hospitalization were entered as covariates with their interaction term, each independently predicted FES group membership. Similarly, when days since conversion and any psychiatric hospitalization were entered as covariates with their interaction term, each independently predicted FES group membership. When entered as covariates with their interaction term, GAF predicted CHR-CV group membership, while any hospitalization was not associated with group membership. Similarly, when entered as covariates with their interaction term, GAF predicted CHR-CV group membership, while total nights in

psychiatric hospitalization did not predict group membership. Finally, when length of APS and pre-conversion AP treatment were entered as covariates with their interaction term, each independently predicted CHR-CV group membership. No interactions were significant.

4. Discussion

This study compared sociodemographic, clinical, and functional differences among participants presenting with clinical high-risk symptoms before conversion to psychosis (CHR-CV) and those admitted to a first-episode service (FES) after conversion. Previous research on this topic had only been conducted among smaller samples in the UK. This study used larger, North American samples and examined a wider range of variables. Significant differences between CHR-CV and FES participants emerged. Specifically, CHR-CV participants were less likely to be Black, more likely to receive antipsychotic treatment prior to conversion, and younger at APS onset and at conversion. CHR-CV participants had longer prodromes, worse premorbid adjustment, better functioning after conversion, and were less likely to have recent psychiatric hospitalizations.

These findings raise the possibility that CHR-CV and FES studies are sampling from different populations, but they also must be interpreted with consideration of methodological differences across study samples. The CHR-CV study (NAPLS-2) recruited from eight sites based in Atlanta, GA, Boston, MA, Los Angeles, CA, San Diego, CA, Chapel Hill, NC, Queens, NY, New Haven, CT, and Calgary, Canada. All sites were combined to create a sufficiently large analytic sample. The FES sample (STEP) was drawn from one clinic with a defined geographic catchment area of approximately 400,000 residents (62% White, 22% Black, 4% Asian, 18% Hispanic, per U.S. 2010 Census), notable for a higher proportion of Black individuals and lower proportion of White individuals compared to the national population (72% White, 13% Black, 5% Asian, 16% Hispanic, per U.S. 2010 Census). Beyond demographic differences, NAPLS sites were located within unique communities with differing resources, referral networks, outreach norms, and pathways to care, evidenced by some differences in relative proportions of referral sources across NAPLS sites (see Addington et al., 2012). Further, STEP used an intensive, catchment-area recruitment method through extensive public education, professional outreach, and academic detailing (Srihari et al., 2022). Although NAPLS sites utilized similar strategies, they did not define catchment areas, and outreach efforts may not have been as consistent and comprehensive across their respective geographic regions. As a result, STEP may have been more successful at reaching marginalized and underserved groups.

Thus, differences between FES and CHR-CV samples could be attributable to the different stages of illness, inconsistent sampling methods, and/or sampling biases in both studies. However, some tentative interpretations can be made, based on magnitudes of difference and convergence with previous research. For example, the threefold difference in proportions of Black participants (45% of FES vs. 13% of CHR-CV), which remained significant after controlling for an SES proxy, is much larger than regional demographic differences, potentially indicating systematic sampling biases in CHR detection and treatment efforts. These results are consistent with previous findings that racial and ethnic minorities are less likely to receive specialized assessment and treatment prior to conversion (Valmaggia et

al., 2015). Due to social and economic disadvantage, Black individuals in North America are less likely to participate in preventive medical care (Arnett et al., 2016) and outpatient mental health services (Marrast et al., 2016), reducing likelihood that CHR will be identified and treated among Black youth.

Beyond demographics, differences emerged between the CHR-CV and FES groups regarding course of illness. In particular, the CHR-CV group, on average, had significantly earlier ages of APS onset and conversion. This may partly be attributed to the fact that NAPLS recruited participants as young as 12, while STEP had a minimum age of 16. Approximately 20% of the CHR-CV sample were under 16 at FES onset, although most of these "underage" converters were age 15 and would have aged into eligibility for the FES study. The difference in age at APS onset (average of 3.5 years) was large and not fully explained by sampling frames. One explanation is that attenuated symptoms may be more likely to be detected if they emerge at an earlier age, during which individuals have more supervision from families and schools (i.e., early to middle adolescence). Comparatively, symptoms manifesting later (i.e., late adolescence or young adulthood) may be more likely to go unnoticed until they worsen to the point of conversion. As a result, individuals with earlier onset APS might be more likely to be referred for early-course assessment and treatment. It is important to note that APS onset in both studies was estimated retrospectively using the SIPS, raising the possibility of recall bias.

Another notable finding regarding course of illness was that the CHR-CV sample, on average, experienced longer-lasting APS prior to conversion. This is consistent with previous research showing that CHR-presenting participants had more insidious modes of onset (Ajnakina et al., 2017). A lengthier prodrome likely provides more opportunity for detection prior to conversion. Although it is possible that the CHR-CV group had more treatment and protective factors to delay conversion, the difference in APS length remained significant when covaried with pre-conversion exposure to antipsychotics (AP).

This higher rate of pre-conversion AP treatment among CHR-CV may have resulted from study participation because all NAPLS sites were linked with specialty clinics. The efficacy of prescribing APs prior to conversion is widely debated. Meta-analyses suggest that AP-exposed CHR participants are *more* likely to convert to psychosis compared to AP-naïve CHR participants, presumably because AP prescription is a proxy indicator of symptomatic progression rather than having causal, iatrogenic effects (Raballo et al., 2021, 2020a, 2020b). Among CHR-converters, pre-conversion AP treatment is not associated with longer prodromes (Powers et al., 2020). Still, pre-conversion AP treatment might have functional, clinical, and neurobiological effects beyond prodrome length, and high proportions of CHR-CV participants treated with AP prior to conversion confounds efforts to generalize findings from CHR studies.

In addition to course of illness, CHR-CV and FES groups differed on some functional outcomes. After accounting for days since conversion, the CHR-CV group had higher GAF ratings and lower rates of psychiatric hospitalization, consistent with previous research showing better functioning and lower acute care utilization among FEP patients whose symptoms were detected prior to conversion (Ajnakina et al., 2017; Valmaggia et al.,

2015). These differences may be attributable to greater access to preventive care and other protective factors among CHR-presenting participants. Further, differences in hospitalization rates may reflect social marginalization of the FES group, considering previous research showing that psychotic patients from disadvantaged backgrounds are more likely to access care through negative pathways (Anderson et al., 2015; Archie et al., 2010; Pollard et al., 2020).

Interestingly, the CHR-CV group, on average, received worse retrospective ratings of premorbid adjustment during childhood and early adolescence, time periods that generally preceded APS onset and AP exposure. This may further support the notion that the CHR-CV group had earlier and more gradual modes of onset, showing general functional impairment earlier in development. However, differences in premorbid adjustment were not found when comparing the FES with CHR-CV participants from the same area, suggesting that geographic differences may have confounded this finding.

4.1 Limitations

There are several limitations of the current study. As discussed above, the FES sample was drawn from one metropolitan area (New Haven, CT) and recruited individuals ages 16 to 35. In contrast, the CHR-CV sample was drawn from sites across North America and recruited individuals ages 12 to 30. These differences in inclusion criteria and sampling frame likely contributed to differences between the samples. Although some multisite FES datasets are available (e.g., RAISE, EPINET), they do not contain SIPS data estimating CHR onset and duration, premorbid adjustment, and other variables of interest. Ultimately, it is impossible to draw definitive conclusions about differences between CHR-CV and full FES populations without more rigorous comparative data from the same geographic regions and sampling methods.

Second, the CHR-CV and FES samples, though larger than in previous studies, were modest and imbalanced, limiting statistical power and ability to examine larger multivariate models. Third, data capturing symptom onset were derived from retrospective SIPS interviews. The SIPS is a well-validated instrument (Woods et al., 2019) but is vulnerable to recall bias. The FES sample's SIPS data may have been more inaccurate because they had longer periods of untreated psychosis. Fourth, analyses only examined AP treatment and service utilization in the last six months. Lengthier histories would provide better understanding of differential access and pathways to care.

4.2 Future Directions

Due to sparse data availability and previous research, the current study is preliminary, meant to stimulate future investigations. Many limitations could be addressed with longitudinal, geographically defined, population-based studies that follow participants from childhood and track psychosis-spectrum symptoms, functioning, and treatment over time. Population-based sampling would mitigate sampling biases by enabling researchers to differentiate between healthy individuals, CHR-nonconverters, CHR-converters, and those who experience frank psychosis without identifiable CHR, all within the same geographic areas (Srihari and Kane, 2019). Further, prospective longitudinal methods reduce recall bias.

Although this will require expensive investments, gaining a better understanding of risk and protective factors, predictors, and courses of illness will improve treatment effectiveness, reducing personal and societal burdens of psychosis (Aceituno et al., 2019).

Acknowledgement

The co-authors would like to acknowledge Philip Markovich and Shadie Burke for their efforts in data collection for this manuscript.

Role of the Funding Source

This study was supported by the NIMH (U01MH081984 to JA; U01 MH081928; P50 MH080272; Commonwealth of Massachusetts SCDMH82101008006 to LJS; R01 MH60720, U01 MH082022, and K24 MH76191 to KSC; U01MH081902 to TDC; P50 MH066286 (Prodromal Core) to CEB; U01MH082004 to DOP; grant U01MH081988 to EFW; U01MH082022 to SWW; UO1 MH081857-05 to BAC; and R01 MH103831 to VHS.) The NIMH had no further role in study design; collection, analysis, and interpretation of data; writing of the report; and the decision to submit the paper for publication. This work was funded in part by the State of Connecticut, DMHAS, but this publication does not express the views of DMHAS or the State of Connecticut. The views and opinions expressed are those of the authors.

References

Aceituno D, Vera N, Prina AM, McCrone P, 2019. Cost-effectiveness of early intervention in psychosis: Systematic review. Br. J. Psychiatry 215, 388–394. 10.1192/bjp.2018.298 [PubMed: 30696495]

Addington J, Cadenhead KS, Cannon TD, Cornblatt B, McGlashan TH, Perkins DO, Seidman LJ, Tsuang M, Walker EF, Woods SW, Heinssen R, 2007. North American Prodrome Longitudinal Study: A collaborative multisite approach to prodromal schizophrenia research. Schizophr. Bull 33, 665–672. 10.1093/schbul/sbl075 [PubMed: 17255119]

Addington J, Cadenhead KS, Cornblatt BA, Mathalon DH, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Addington JA, Cannon TD, 2012. North American Prodrome Longitudinal Study (NAPLS 2): Overview and recruitment. Schizophr. Res 142, 77–82. 10.1016/j.schres.2012.09.012 [PubMed: 23043872]

Addington J, Epstein I, Reynolds A, Furimsky I, Rudy L, Mancini B, McMillan S, Kirsopp D, Zipursky RB, 2008. Early detection of psychosis: Finding those at clinical high risk. Early Interv. Psychiatry 2, 147–153. 10.1111/j.1751-7893.2008.00078.x [PubMed: 21352147]

Ajnakina O, Morgan C, Gayer-Anderson C, Oduola S, Bourque F, Bramley S, Williamson J, MacCabe JH, Dazzan P, Murray RM, David AS, 2017. Only a small proportion of patients with first episode psychosis come via prodromal services: A retrospective survey of a large UK mental health programme. BMC Psychiatry 17. 10.1186/s12888-017-1468-y

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders (4th ed., Text Revision). Author, Washington, D.C.

Anderson KK, Flora N, Ferrari M, Tuck A, Archie S, Kidd S, Tang T, Kirmayer LJ, McKenzie K, 2015. Pathways to first-episode care for psychosis in African-, Caribbean-, and European-origin groups in Ontario. Can. J. Psychiatry 60, 223–231. 10.1177/070674371506000504 [PubMed: 26174526]

Archie S, Akhtar-Danesh N, Norman R, Malla A, Roy P, Zipursky RB, 2010. Ethnic diversity and pathways to care for a first episode of psychosis in Ontario. Schizophr. Bull 36, 688–701. 10.1093/schbul/sbn137 [PubMed: 18987101]

Arnett MJ, Thorpe RJ, Gaskin DJ, Bowie JV, LaVeist TA, 2016. Race, medical mistrust, and segregation in primary care as usual source of care: Findings from the exploring Health Disparities in Integrated Communities Study. J. Urban Heal 93, 456–467. 10.1007/s11524-016-0054-9

Cannon-Spoor HE, Potkin SG, Wyatt RJ, 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr. Bull 8, 470–484. 10.1093/schbul/8.3.470 [PubMed: 7134891]

Cannon TD, Yu C, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, Heinssen R, Jeffries CD, Mathalon DH, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW,

Kattan MW, 2016. An individualized risk calculator for research in prodromal psychosis. Am. J. Psychiatry 173, 980–988. 10.1176/appi.ajp.2016.15070890 [PubMed: 27363508]

Cornblatt BA, Auther AM, Niendam T, Smith CW, Zinberg J, Bearden CE, Cannon TD, 2007. Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. Schizophr. Bull 33, 688–702. 10.1093/schbul/sbm029 [PubMed: 17440198]

Ferrara M, Guloksuz S, Mathis WS, Li F, Lin I-H, Syed S, Gallagher K, Shah J, Kline E, Tek C, Keshevan M, Srihari VH, 2021. First help-seeking attempt before and after psychosis onset: Measures of delay and aversive pathways to care. Soc. Psychiatry Psychiatr. Epidemiol. Epidemiol 10.1007/s00127-021-02090-0

Friedman-Yakoobian MS, West ML, Woodberry KA, O'Donovan KE, Zimmet SV, Gnong-Granato A, Giuliano AJ, Guyer ME, Rodenhiser-Hill J, Keshavan MS, Seidman LJ, 2018. Development of a Boston ttreatment program for youth at clinical high risk for psychosis: Center for Early Detection, Assessment, and Response to Risk (CEDAR). Harv. Rev. Psychiatry 26, 274–286. 10.1097/HRP.0000000000000181 [PubMed: 30188339]

Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire PK, 2012. Predicting psychosis: Meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry 69, 220. 10.1001/archgenpsychiatry.2011.1472 [PubMed: 22393215]

Fusar-Poli P, Rutigliano G, Stahl D, Davies C, De Micheli A, Ramella-Cravaro V, Bonoldi I, McGuire P, 2017. Long-term validity of the at risk mental state (ARMS) for predicting psychotic and non-psychotic mental disorders. Eur. Psychiatry 42, 49–54. 10.1016/j.eurpsy.2016.11.010 [PubMed: 28212505]

Fusar-Poli P, Salazar De Pablo G, Correll CU, Meyer-Lindenberg A, Millan MJ, Borgwardt S, Galderisi S, Bechdolf A, Pfennig A, Kessing LV, Van Amelsvoort T, Nieman DH, Domschke K, Krebs MO, Koutsouleris N, McGuire P, Do KQ, Arango C, 2020. Prevention of psychosis: Advances in detection, prognosis, and intervention. JAMA Psychiatry 77, 755–765. 10.1001/jamapsychiatry.2019.4779 [PubMed: 32159746]

Guloksuz S, Pries LK, ten Have M, de Graaf R, van Dorsselaer S, Klingenberg B, Bak M, Lin BD, van Eijk KR, Delespaul P, van Amelsvoort T, Luykx JJ, Rutten BPF, van Os J, 2020. Association of preceding psychosis risk states and non-psychotic mental disorders with incidence of clinical psychosis in the general population: A prospective study in the NEMESIS-2 cohort. World Psychiatry 19, 199–205. 10.1002/wps.20755 [PubMed: 32394548]

Marrast L, Himmelstien DU, Woodhandler S, 2016. Racial and ethnic disparities in mental health care for children and young adults: A national study. Int. J. Heal. Serv 46, 810–824. 10.1177/0020731416662736

McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller TJ, Woods SW, Hawkins KA, Hoffman R, Lindborg S, Tohen M, Breier A, 2003. The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis: I. Study rationale and design. Schizophr. Res 61, 7–18. 10.1016/S0920-9964(02)00439-5 [PubMed: 12648731]

McGorry PD, Killackey E, Yung AR, 2007. Early intervention in psychotic disorders: Detection and treatment of the first episode and the critical early stages. Med. J. Aust 187, 2–4.

Pollard JM, Ferrara M, Lin I-H, Kucukgoncu S, Wasser T, Li F, Srihari VH, 2020. Analysis of early intervention services on adult judicial outcomes. JAMA Psychiatry 77, 871–872. 10.1001/jamapsychiatry.2020.0448 [PubMed: 32320010]

Powers AR, Addington J, Perkins DO, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Mathalon DH, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH, Woods SW, 2020. Duration of the psychosis prodrome. Schizophr. Res 216, 443–449. 10.1016/j.schres.2019.10.051 [PubMed: 31806523]

Raballo A, Poletti M, Preti A, 2021. Antipsychotic treatment in clinical high risk for psychosis: Protective, iatrogenic or further risk flag? Aust. N. Z. J. Psychiatry 55, 442–444. 10.1177/0004867420984836 [PubMed: 33426910]

Raballo A, Poletti M, Preti A, 2020a. Attenuated psychosis syndrome or pharmacologically attenuated first-episode psychosis? An undesirably widespread confounder. JAMA Psychiatry 77, 1213–1214. 10.1177/0706743717719895 [PubMed: 32639551]

Raballo A, Poletti M, Preti A, 2020b. Meta-analyzing the prevalence and prognostic effect of antipsychotic exposure in clinical high-risk (CHR): When things are not what they seem. Psychol. Med 10.1017/S0033291720004237

Riecher-Rössler A, Gschwandtner U, Aston J, Borgwardt S, Drewe M, Fuhr P, Pflüger M, Radü W, Chindler C, Stieglitz R-D, 2006. The Basel Early-Detection-of-Psychosis (FEPSY)-Study: Design and preliminary results. Acta Psychiatr. Scand 115, 114–125.

Rosenheck RA, Lieberman JA, 2007. Cost-effectiveness measures, methods, and policy implications from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia. J. Clin. Psychiatry 68, 305. 10.4088/jcp.0207e05

Salazar de Pablo G, Woods SW, Drymonitou G, de Diego H, Fusar-Poli P, 2021. Prevalence of individuals at clinical high-risk of psychosis in the general population and clinical samples: Systematic review and meta-analysis. Brain Sci. 11, 1544. 10.3390/brainsci11111544 [PubMed: 34827543]

Schultze-Lutter F, Klosterkötter J, Gaebel W, Schmidt SJ, 2018. Psychosis-risk criteria in the general population: Frequent misinterpretations and current evidence. World Psychiatry 17, 107–108. 10.1002/wps.20498 [PubMed: 29352561]

Schultze-Lutter F, Rahman J, Ruhrmann S, Michel C, Schimmelmann BG, Maier W, Klosterkötter J, 2015. Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission psychosis patients. Soc. Psychiatry Psychiatr. Epidemiol 50, 1831–1841. 10.1007/s00127-015-1093-3 [PubMed: 26155901]

Shah JL, Crawford A, Mustafa SS, Iyer SN, Joober R, Malla AK, 2017. Is the clinical high-risk state a valid concept? Retrospective examination in a first-episode psychosis sample. Psychiatr. Serv 68, 1046–1052. 10.1176/appi.ps.201600304 [PubMed: 28617204]

Simon AE, Borgwardt S, Riecher-Rössler A, Velthorst E, de Haan L, Fusar-Poli P, 2013. Moving beyond transition outcomes: Meta-analysis of remission rates in individuals at high clinical risk for psychosis. Psychiatry Res. 209, 266–272. 10.1016/j.psychres.2013.03.004 [PubMed: 23871169]

Srihari VH, Ferrara M, Li F, Kline E, Gülöksüz S, Pollard JM, Cahill JD, Mathis WS, Yoviene Sykes LA, Walsh BC, McDermott G, Seidman LJ, Gueorguieva R, Woods SW, Tek C, Keshavan MS, 2022. Reducing the duration of untreated psychosis (DUP) in a US community: A quasi-experimental trial. Schizophr. Bull. Open 3, sgac020. 10.1093/schizbullopen/sgac020

Srihari VH, Kane JM, 2019. Early intervention services 2.0: Designing systems for the next generation of work. Biol. Psychiatry 88, 291–293. 10.1016/j.biopsych.2019.10.001

Srihari VH, Tek C, Pollard J, Zimmet S, Keat J, Cahill JD, Kucukgoncu S, Walsh BC, Li F, Gueorguieva R, Levine N, Mesholam-Gately RI, Friedman-Yakoobian M, Seidman LJ, Keshavan MS, McGlashan TH, Woods SW, 2014. Reducing the duration of untreated psychosis and its impact in the U.S.: The STEP-ED study. BMC Psychiatry 14, 1–14. 10.1186/s12888-014-0335-3

Tandon N, Shah J, Keshavan MS, Tandon R, 2012. Attenuated psychosis and the schizophrenia prodrome: Current status of risk identification and psychosis prevention. Neuropsychiatry (London). 2, 345–353. 10.2217/npy.12.36 [PubMed: 23125875]

Valmaggia LR, Byrne M, Day F, Broome MR, Johns L, Howes O, Power P, Badger S, Fusar-Poli P, McGuire PK, 2015. Duration of untreated psychosis and need for admission in patients who engage with mental health services in the prodromal phase. Br. J. Psychiatry 207, 130–134. 10.1192/bjp.bp.114.150623 [PubMed: 26045348]

van Mastrigt S, Addington J, 2002. Assessment of premorbid function in first-episode schizophrenia: Modifications to the Premorbid Adjustment Scale. J. Psychiatry Neurosci 27, 92–101. [PubMed: 11944510]

van Os J, Guloksuz S, 2017. A critique of the “ultra-high risk” and “transition” period. World Psychiatry 16, 200–206. 10.1002/wps.20423 [PubMed: 28498576]

Woods SW, Miller TJ, McGlashan TH, 2001. The “prodromal” patient: Both symptomatic and at-risk. CNS Spectr. 6, 223–232. 10.1017/S1092852900008609 [PubMed: 16951657]

Yoviene Sykes LA, Ferrara M, Addington J, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Perkins DO, Mathalon DH, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH, Woodberry KA, Powers AR, Ponce AN, Cahill JD, Pollard JM, Srihari VH, Woods SW, 2020. Predictive validity of

conversion from the clinical high risk syndrome to frank psychosis. Schizophr. Res 216, 184–191. 10.1016/j.schres.2019.12.002 [PubMed: 31864837]

Yung AR, McGorry PD, 1996. The prodromal phase of first-episode psychosis: Past and current conceptualizations. Schizophr. Bull 22, 353–370. [PubMed: 8782291]

Table 1.

Demographic differences among all clinical high-risk converters (CHR-CV, *n*=94), clinical high-risk converters from the greater New Haven area (NH, *n*=10), and those who initially presented for first-episode services after conversion (FES, *n*=171).

	Mean (Standard Error) or Percentage		
	FES	**CHR-CV (all)**	**CHR-CV (NH)**
Age (years) ***	22.0 (0.29)	19.0 (0.38)	17.3 (0.96)
Male	70.2%	62.7%	60.0%
Hispanic	19.3%	18.1%	30.0%
Black ***	45.0%	12.8%	20.0%
Asian	18.1%	9.6%	0.0%
White *	34.5%	55.3%	70.0%
1st or 2nd generation immigrant *	29.2%	18.1%	10.0%
English as first language	80.7%	86.2%	90.0%
At least one college-educated parent **	44.4%	63.8%	40.0%

Notes: Age was calculated at conversion visit for CHR-CV participants and at admission/baseline visit for FES participants. Fisher's exact tests or *t*-tests compared FES and all CHR-CV participants. Inferential statistics were not conducted for New Haven-only CHR-CV due to sample size, but data are presented descriptively.

* FES and CHR-CV (all) differed at $p < .05$, Fisher's exact test or *t*-test

** FES and CHR-CV (all) differed at $p < .01$, Fisher's exact test or *t*-test

*** FES and CHR-CV (all) differed at $p <. 001$, Fisher's exact test or *t*-test

Table 2.

Differences in symptom onset, timeline, and antipsychotic treatment among all clinical high-risk converters (CHR-CV, *n*=94), clinical high-risk converters from the greater New Haven area (NH, *n*=10), and those who initially presented for first-episode services after conversion (FES, *n*=171).

	Mean (Standard Error) or Percentage		
	FES	**CHR-CV (all)**	**CHR-CV (NH)**
Age at APS onset ***	19.62 (0.32)	16.20 (0.37)	14.9 (0.48)
Age at conversion ***	21.13 (0.29)	18.83 (0.38)	17.1 (0.89)
Ever treated with AP ***	97.1%	74.5%	90.0%
Treated with AP before conversion ***	2.9%	51.1%	40.0%
	Median (Interquartile Range)		
Length of APS (days) ***	290 (641)	719 (844)	570 (661)
Days since conversion ***	169 (418)	43 (91)	40.5 (101)
Days from APS onset to treatment	422 (689)	298 (795)	207 (869)

Notes: Days since conversion was calculated from date of conversion to date of conversion visit for CHR-CV participants and from conversion to admission/baseline visit for FES participants. Median and interquartile range are presented for skewed variables. Fisher's exact tests or *t*-tests compared FES and all CHR-CV participants. Inferential statistics were not conducted for New Haven-only CHR-CV due to sample size, but data are presented descriptively. AP=Antipsychotic medication; APS=Attenuated positive symptoms.

*** FES and CHR-CV (all) differed at $p < .001$, Fisher's exact test or *t*-test

Table 3.

Differences in symptom pre-morbid adjustment, current functioning, and acute services utilization in last six months among all clinical high-risk converters (CHR-CV, *n*=94), clinical high-risk converters from the greater New Haven area (NH, *n*=10), and those who initially presented for first-episode services after conversion (FES, *n*=171).

	Mean (Standard Error) or Percentage		
	FES	**CHR-CV (all)**	**CHR-CV (NH)**
Premorbid adjustment (childhood) *	0.19 (0.01)	0.24 (0.02)	0.12 (0.05)
Premorbid adjustment (early adolescence) **	0.24 (0.01)	0.30 (0.02)	0.22 (0.05)
Current GAF ***	31.3 (0.82)	39.1 (1.42)	35.9 (3.72)
Current role functioning	4.32 (0.16)	4.44 (0.28)	5.28 (0.82)
Current social functioning **	5.08 (0.11)	5.73 (.20)	6.31 (0.62)
Any psych. hospitalizations in last 6 mo. ***	73.7%	31.9%	20.0%
Psych. hospitalization nights in last 6 mo. ***	12.9 (1.37)	4.63 (1.30)	2.66 (4.25)

Notes: Current functioning was rated at conversion visit for CHR-CV participants and at admission/baseline visit for FES participants. Fisher's exact tests or *t*-tests compared FES and all CHR-CV participants. Inferential statistics were not conducted for New Haven-only CHR-CV due to sample size, but data are presented descriptively. GAF=Global Assessment of Functioning.

* FES and CHR-CV (all) differed at $p < .05$, *t-test*

** FES and CHR-CV (all) differed at $p < .01$, *t*-test

*** FES and CHR-CV (all) differed at $p <. 001$, Fisher's exact test or *t*-test

Table 4.

Logistic regessions predicting group membership (1=CHR-CV, 0=FES).

	OR	95% CI	*p*-value
White	1.89	0.84 – 4.27	.12
College-educated parent	1.76	0.84 – 3.66	.13
White × College-educated parent	1.24	0.42 – 3.65	.70
Black	0.21	0.08 – 0.55	.002
College-educated parent	1.93	1.05 – 3.54	.03
Black × College-educated parent	.78	0.21 – 3.21	.78
White	2.66	1.47 – 4.80	.001
1st or 2nd generation immigrant	0.93	0.43 – 2.00	.85
White × 1st or 2nd generation immigrant	0.30	0.07 – 1.42	.13
Days since conversion	0.99	0.98 – 1.00	.049
GAF	1.07	1.03 – 1.11	.001
Days since conversion × GAF	1.00	1.00 – 1.00	.58
Days since conversion	0.99	0.98 – 1.00	.10
Social functioning	1.26	0.98 – 1.63	.07
Days since conversion × Social functioning	1.00	0.99 – 1.00	.71
Days since conversion	0.99	0.98 – 0.99	<.001
Any psych. hospitalization	0.06	0.02 – 0.17	<.001
Days since conversion × Any psych. hospitalization	1.00	1.00 – 1.01	.31
Days since conversion	0.99	0.98 – 0.99	<.001
Total nights in psych. hospitalization	0.91	0.86 – 0.96	<.001
Days since conversion × Nights in psych. hospitalization	1.00	1.00 – 1.00	.35
GAF	1.06	1.02 – 1.11	.006
Any psych. hospitalization	0.48	0.06 – 3.89	.49
GAF × Any psych. hospitalization	0.98	0.92 – 1.03	.41
GAF	1.05	1.02 – 1.09	.02
Total nights in psych. hospitalization	0.98	0.88 – 1.09	.71
GAF × Nights in psych. hospitalization	1.00	1.00 – 1.00	.52
Length of APS	1.01	1.00 – 1.01	.02
AP treatment before conversion	47.9	9.41 – 244.4	<.001
Length of APS × AP treatment before conversion	1.00	1.00 – 1.00	.46

Logistic regressions predicting group membership (1=CHR-CV, 0=FES).

Note: OR=Odds Ratio; 95% CI=95% Confidence Interval; GAF=Global Assessment of Functioning; APS=Attenuate positive symptoms; AP=Antipsychotic medication.