

Shift in sex and age of individuals at a clinical high risk (CHR) for psychosis: relation to differences in recruitment methods and effect on sample characteristics

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Historically, large samples of individuals at clinical high risk (CHR) for psychosis have mirrored overt psychotic disorders in both sex (predominantly male) and age representation (adolescent to early adulthood onset). We report on a recent CHR sample suggesting a shift in these distributions and explore contributing factors and clinical implications. We hypothesized that demographic differences would be related to recruitment sources and that age, sex, and recruitment sources would be related to baseline clinical profiles. Baseline data were included from the recent computerized assessment of psychosis risk (CAPR) study and the second and third waves of the North American Prodrome Longitudinal Study (NAPLS-2 and 3). Hierarchical regression was used to examine differences in sex, age, and recruitment sources between samples and relationships with clinical characteristics. Univariate analyses revealed a significant shift to female predominance, older age, and a change in recruitment source from NAPLS to CAPR. Multivariate analyses indicated that between-study differences in sex and age were conditional on recruitment source, with the apparent study effect driven by differences in the non-self-referred groups. More than 60% of participants recruited through internet self-referrals were female across samples. Clinical heterogeneity was partly related to age, sex, and recruitment source differences. Internet-based self-referrals were older and showed less severe negative symptoms, disorganization, and general symptoms and higher role functioning than non-self-referred participants. Findings highlight the importance of recruitment sources for CHR sample characteristics. Recruitment source effects, including those from internet sources, should be investigated in other CHR samples.

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INTRODUCTION

Historically, many large observational samples of individuals at clinical high risk for psychosis (CHR)^{1–3} have been male-predominant^{3–18}, while few have had a female preponderance^{19,20}. This finding is consistent with incidence rates of psychotic disorders^{21–27}, with international findings approximating rates 1.44 times higher for men compared with women²⁷. Similar to sex differences, age distribution in CHR samples has typically aligned with first-episode psychosis epidemiology, showing peak onset during adolescence and early adulthood^{4–6,9–11,14,17,28}. However, experience in the current study suggests a shift both in sex at birth representation and in age distribution, prompting an exploration into the underlying factors driving these demographic changes and their potential implications on clinical profiles.

Potentially related to demographic shifts, various recruitment and referral methods have been employed in CHR research^{29–35}, including outreach and educational campaigns, screening in the general population and within healthcare settings, traditional research advertisements (e.g., flyers), and, more recently, online and social-media-based advertisements (e.g., Facebook, Instagram). These recruitment strategies yield both self-referrals and referrals from others (e.g., community members, healthcare providers, school professionals). As recruitment approaches diversify, it is increasingly important to distinguish between broader categories such as self-referral and more specific mechanisms like internet-based recruitment. These may capture overlapping but distinct populations, each with different implications for outreach, engagement, and clinical presentation.

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Emerging evidence suggests that recruitment and referral sources are associated with differing participant profiles. Investigations have suggested that differential pretest risks for psychosis (i.e., one's risk of developing psychosis before they receive a specialized evaluation) are associated with specific recruitment methods^{36,37}. For example, more selective or sequential outreach strategies (e.g., provider referral and clinical screening) might identify individuals with higher pretest risk for psychosis but may underrepresent females and older individuals.

Notably, sex has also been linked to risk of psychosis onset, with studies showing that a lower proportion of females in CHR samples is associated with increased conversion risk. Those studies have reported that, with recruitment strategies that stringently filter individuals from the general population, the pretest risk for psychosis is enhanced, and there is a propensity to identify fewer females as being at CHR³. Meta-analytic findings further support that a lower proportion of females in CHR samples is related to increased risk of psychosis onset^{38,39}, underscoring the importance of considering sex differences in CHR research and sample recruitment.

However, it is possible that these various recruitment methods are complementary, allowing for more inclusive identification of youth at CHR who would not have otherwise been recognized through traditional strategies. Although recruitment strategies that promote greater inclusion of the general population, such as self-referrals, broad intensive community outreach, and population-based screening, have been associated with lower conversion risk³⁶, it is possible that they enhance the likelihood of identifying individuals at CHR with different risk factors or trajectories of symptoms^{23,36,40,41}. Additionally, as internet-based outreach continues to expand, it remains unclear how this shift in referral source may alter the demographic and clinical profile of CHR samples. Understanding how recruitment methods shape who is identified, and when, is critical for evaluating generalizability, representativeness, and equity in early detection efforts.

The present study compared recruitment strategies and demographic and clinical characteristics between a recent CHR sample (Computerized Assessment of Psychosis Risk, CAPR)⁴² and two waves of the North American Prodrome Longitudinal Study (NAPLS-2 and 3)^{4,14}. The current study aimed to (1) examine differences in sex and age across CHR samples; (2) evaluate whether these differences varied by recruitment source; and (3) assess whether sex, age, and recruitment source predicted variation in clinical profiles. We hypothesized that (1) differences in sex and age between samples would be statistically significant, (2) demographic differences (sex and age) would be related to differences in recruitment sources, and (3) age, sex, and recruitment sources would be related to differences in baseline clinical profiles of individuals at CHR.

METHODS

Participants

Baseline data were included from three sources: the Computerized Assessment of Psychosis Risk (CAPR)⁴² and the second and third waves of the North American Prodrome Longitudinal Study (NAPLS-2 and NAPLS-3)^{4,14}. NAPLS-2 baseline data was collected 2009–2013, NAPLS-3 2015–2018, and CAPR 2020–2024. A list of the sites included in these multisite observational studies is included in Supplementary Table S1. All participants provided written informed consent for the respective studies, and all study procedures were approved by the Northwestern University IRB (STU00211351) and acknowledged by the IRBs of participating sites.

All participants met criteria for a CHR syndrome based on the Structured Interview for Psychosis-Risk Syndromes (SIPS). Specifically, they had no lifetime presence of psychotic symptoms (POPS

criteria), and they met criteria for one or more of the three SIPS CHR syndromes: Attenuated Psychotic Symptoms Syndrome (APSS), Brief Intermittent Psychosis Syndrome (BIPS), or Genetic Risk and Deterioration (GRD)^{4,14}. Other common inclusion criteria included: ages 12–30, English fluency, and sufficient cognitive capacity to consent and complete assessments. Individuals with current or past psychotic disorders, neurological disorders, or an IQ < 70 were excluded. NAPLS-3 included a CHR cohort enriched for psychosis risk who underwent intensive biomarker assessments, and a cohort of CHR patients included for clinical assessments who either did not meet the enrichment criteria or could not participate in biomarker assessment (also see Supplementary Methods)¹⁴. Since both NAPLS samples only enrolled individuals in CHR progression (i.e., onset or worsening in severity within the past 12 months)⁴³, only those in current progression of a SIPS CHR syndrome were selected from CAPR to allow for comparison with NAPLS. Information about participants from the CAPR CHR group that were not in current progression (i.e., CHR syndrome persistence) is provided in Supplementary Table S2. Additionally, the CAPR study was enrolling new participants at the time of analysis. Baseline data were included for all participants with complete demographic and baseline SIPS evaluation prior to February 2024. Data from participants between the ages of 12 and 30 were included in the present analyses, as there were differences in the included age ranges across the three studies (ages 12–35 in NAPLS-2, 12–30 in NAPLS-3, and 12–34 in CAPR).

Measures

In all three studies, participants were administered a variety of interviews, tasks, and self-report measures. Demographic data were collected using self-report measures and interviews. Sex refers to sex assigned at birth (male, female). Demographic characteristics examined were limited to sex and age, which have been identified as key sources of variability in CHR samples.

The Structured Interview for Psychosis-risk Syndromes (SIPS)^{44,45} was used to ascertain individuals at CHR in all three studies and to quantify the severity of symptoms. The SIPS is a widely used measure to detect the presence of the three psychosis-risk syndromes. Within the SIPS is the Scale of Psychosis-risk Symptoms (SOPS), which rates the severity of specific symptoms on a 7-point Likert scale, ranging from absent (0–2), moderate to severe but not psychotic (3–5), and severe and psychotic (6). Items on the SOPS correspond to one of four symptom domains, including positive, negative, disorganization, and general symptoms. The sum of scores of all items within a domain was then used to obtain the SOPS domain total scores.

The Global Functioning: Social (GF: Social) and Role (GF: Role) scales were used to evaluate participants' levels of functioning at the time of baseline assessment^{46,47}. These scales were designed to measure functioning and functional decline in youth at CHR and have been shown to have excellent accuracy and inter-rater reliability. The GF: Social scale assesses peer relationships, peer conflict, age-appropriate intimate relationships, and family involvement. The GF: Role scale assesses demands of the individual's current role (school or work), level of independence and supports provided, and overall performance in the role given supports. The scales were designed for a trained rater to use previously collected interview data to rate each participant from 1 to 10, with 1 = extreme dysfunction and 10 = superior functioning. Each scale results in three scores (lowest in the past month, highest in the past year, and lowest in the past year), and the lowest in the past month (i.e., "current score") was used for the present study.

Recruitment source information was collected through self-report in NAPLS-3 and CAPR. Recruitment source data were not collected in NAPLS-2 at the individual participant level. In NAPLS-3, recruitment information was collected by two variables: (1) referral source and (2) how the referral source heard about the

program. Participants told a research assistant how and where they heard about the study, and then the research assistant coded that information into predefined categories. In CAPR, recruitment source information was collected through a Qualtrics survey. When recruitment source data were missing, research coordinators at each site supplied information about recruitment sources that were collected as part of the individual site's internal tracking. Due to differences in source categories across studies, recruitment source data were re-coded into three groups based on our research questions: (1) self-referred, internet-based ("self-referred online"), (2) self-referred, not internet-based ("self-referred, not online"), and (3) not self-referred ("other-referred"). Although self-referral and internet-based recruitment are related constructs, not all self-referred individuals came through internet sources (e.g., subway ads, flyers, and pamphlets). We retained these distinctions to evaluate whether internet-based outreach, specifically, influenced sample characteristics. Data was coded independently by two raters, and any discrepancies were resolved through discussion. Definitions of each group and the resulting coding scheme for each study can be found in Supplementary Tables S3–S5.

Statistical analyses

IBM SPSS Version 29 was used for all statistical analyses. The first aim was to determine whether statistically significant differences in participant sex and age existed between the recent CAPR sample compared to the prior NAPLS-2 and NAPLS-3 samples. To address Aim 1, we compared participants from CAPR and NAPLS-3 on key demographic and clinical variables to evaluate shifts in sample composition. Chi-square and ANOVA were used to test for differences in participant sex and age between studies. Follow-up Bonferroni-adjusted z-tests were used to determine which samples differed significantly at the 0.05 level.

The second aim was to identify factors that may have contributed to differences in sample demographics. To examine Aim 2, we tested whether differences in referral source contributed to demographic (sex and age) variation across samples. Hierarchical regression models were used to examine demographic differences between samples and further to examine whether sample differences persisted after accounting for these covariates. Hierarchical binary logistic regression was used to examine whether the probability of participants being female varies as a function of study, age, and recruitment source. All categorical variables were dummy coded as 0.5 and –0.5. First, univariate models testing the independent contributions of each model were evaluated, and then the hierarchical model was run to examine the relative contribution of each variable, controlling for all others. Next, hierarchical linear regression was used to examine whether age varied as a function of study, sex, and recruitment source. In each of these models, interaction effects were first examined. Nonsignificant interactions were removed from the final models. In cases when interaction effects significantly improved the model, simple main effects of the predictors were calculated. As has been done previously⁴⁸, if simple main effects were in the same direction, the overall main effect was considered interpretable and was reported. When simple main effects were in opposite directions but were not statistically significant, the overall main effect was deemed interpretable and was reported. Conversely, when simple main effects were in opposite directions and one or both were statistically significant, the overall main effects were deemed non-interpretable, and the simple main effects were reported.

The third aim was to determine whether clinical profiles varied between samples, and whether differences in demographics and recruitment source accounted for the variance between samples. For Aim 3, we conducted regression analyses to evaluate how sex and age were associated with sample, referral source, and each

other. Hierarchical linear regression models were used to examine six different clinical variables: the four SOPS symptom domains (positive, negative, disorganized, and general) and two functioning scales (social and role). In each model, predictors were entered in three steps: (1) sample alone, (2) sample, age, and sex, (3) sample, age, sex, and recruitment source (dummy coded). A visual depiction of the basic model is displayed in Supplementary Methods.

RESULTS

Sample description

Table 1 shows participant demographic and clinical characteristics by study sample. Of the total 318 individuals enrolled in CAPR at the time of analysis, 154 (48%) met criteria for progression, and the final sample of individuals aged 12–30 was 146 (46%). The mean age in years of each sample was 18.32 (NAPLS-2), 18.19 (NAPLS-3), and 22.10 (CAPR). CAPR was 67.1% female, while NAPLS-2 was 42.9% and NAPLS-3 was 45.8% female. In CAPR, the majority of participants were self-referred via the internet, while in NAPLS-3, the majority were other-referred (Fig. 1). Significant differences among samples were present, including age, recruitment source, positive symptom severity, negative symptom severity, general symptom severity, disorganized symptom severity, social functioning, and role functioning.

A significant female preponderance was observed in the CAPR sample

The proportion of females in the three CHR samples differed significantly ($\chi^2(2) = 28.98, p < 0.001$). The proportion of females in CAPR differed significantly from each of the NAPLS samples, while the two NAPLS samples had a male predominance and were not significantly different from each other. The odds of being female in CAPR were 2.71 times higher than in NAPLS-2 (95% CI = 1.87, 3.95) and 2.42 times higher than in NAPLS-3 (95% CI = 1.66, 3.52). The female preponderance pattern in CAPR did not significantly differ across the six data collection sites, ranging from 53 to 80% female (Supplementary Table S6).

The CAPR sample was older than the NAPLS samples

Figure 2 shows the age distribution by sex in each dataset. The CAPR sample was significantly older than both the NAPLS-2 and NAPLS-3 samples, which was a medium-sized effect ($\eta^2 = 0.07$). No differences in age were present between NAPLS samples.

Predictors of participant sex in CHR samples

Table 2 details the results of the three univariate and final hierarchical binary logistic regression models predicting participant sex at birth. Univariate models indicated that a higher odds of female sex was separately associated with the CAPR sample and self-referred recruitment sources, whether internet-based or not, but not with age. In the second step, the model remained significant when sample and age were entered simultaneously as predictors, and the CAPR sample was still related to a higher odds of female enrollment.

In the final two steps of the hierarchical model, all interaction terms were initially included (sample by age, sample by recruitment source, recruitment source by age, and three-way interactions). The three-way interactions were not significant and were removed from the model. Examination of two-way interactions showed that the interaction terms for sample × age and recruitment source × age did not improve the model, and they were also removed. The final model was significant. Age was uniquely associated with the odds of female sex in the final model. As shown in Table 2, the main effect of age on sex (older age associated with a lower odds of female sex) was significant, an

Table 1. Baseline characteristics of CHR with progression by study sample.

Characteristic	Mean (SD) or <i>n</i> (% within study)			Statistic
	NAPLS-2 (<i>n</i> = 757)	NAPLS-3 (<i>n</i> = 710)	CAPR (<i>n</i> = 146)	
Age (years)	18.32 (4.03) ^a	18.19 (4.04) ^a	22.10 (3.84) ^b	$F(2,1610) = 60.84^{***}$
Sex (Female)	325 (42.9) ^a	325 (45.8) ^a	98 (67.1) ^b	$\chi^2(2) = 28.98^{***}$
Recruitment Source				
Self, internet		50 (7.2) ^a	65 (51.2) ^b	$\chi^2(2) = 188.21^{***}$
Self, not internet		76 (11.0) ^a	22 (17.3) ^b	
Other-referred		567 (81.8) ^a	40 (31.5) ^b	
SIPS Domains				
Positive	11.92 (3.80) ^a	12.93 (3.41) ^b	11.29 (3.77) ^a	$F(2,1609) = 20.62^{***}$
Negative	11.90 (6.05) ^a	12.09 (6.35) ^a	8.31 (5.20) ^b	$F(2,1571) = 24.05^{***}$
Disorganized	5.18 (3.16) ^a	5.20 (3.21) ^a	4.38 (2.88) ^b	$F(2,1572) = 4.33^*$
General	9.15 (4.28) ^a	9.42 (4.27) ^a	7.96 (4.19) ^b	$F(2,1570) = 7.07^{**}$
Functioning				
Social	6.19 (1.57) ^a	6.42 (1.52) ^b	7.31 (1.37) ^c	$F(2,1591) = 32.45^{***}$
Role	5.95 (2.14) ^a	6.22 (2.22) ^a	7.42 (1.86) ^b	$F(2,1584) = 27.97^{***}$

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Superscripts denote groups within the row that do (different superscripts) or do not (same superscript) differ significantly at the $p < 0.05$ level.

effect illustrated in Fig. 3A by the similar regression line slopes across all referral and study groups. The interactions between sample and recruitment sources significantly improved the model, indicating that the overall main effect of sample on sex, which had been statistically significant in the univariate analyses and all previous steps, was conditional upon recruitment source. Contingency tables examining simple main effects can be found in Supplementary Tables S7 and S8. Simple main effects analysis of the sample within recruitment source revealed that a higher proportion of females in CAPR vs NAPLS-3 was present only within the other-referred group, in which NAPLS-3 was 42.5% female and CAPR was 72.5% (Fig. 3B; $\chi^2(1) = 13.61$, $p < 0.001$). Simple main effects of recruitment source within sample revealed that within NAPLS-3, participants recruited from other-referred sources were less likely to be female compared to self-referrals (Fig. 3B; $\chi^2(2) = 15.77$, $p < 0.001$), including whether internet-based (Wald = 13.84, $p < 0.001$, OR = 3.36, 95% CI = 1.78, 6.37) or not-internet-based self-referrals (Wald = 15.59, $p < 0.001$, OR = 2.94, 95% CI = 1.72, 5.01). However, in the CAPR sample, the effects of recruitment source were not significant ($ps > 0.05$), where the proportions of females were greater than 50% for each of the three referral sources.

Predictors of participant age in CHR samples

Figure 4A shows the mean age in the CAPR and NAPLS-3 samples as a function of sex and referral source. Table 3 shows the results of the univariate and final hierarchical linear regression models predicting participant age. Univariate models indicated that older age was separately associated with the CAPR sample and self-referred recruitment sources, whether internet-based or not internet-based, but was not associated with sex. In the next step of the hierarchical model, the model remained significant when sample and sex were entered simultaneously as predictors, and older age was still associated with the CAPR sample and with sex.

In the final two steps of the hierarchical model, all interaction terms were initially included (sample by sex, sample by recruitment source, recruitment source by sex, and the three-way interactions). The three-way interactions were not significant and were therefore removed from the model. Examination of two-way

interactions showed that the sample by sex and recruitment source by sex interaction terms were non-significant, and they were also removed from the model. The final model was significant (Table 3). The interactions between sample and recruitment sources significantly improved the model, indicating that the overall main effect of study on age, which had been statistically significant in the univariate analyses and all previous steps, was conditional upon recruitment source. Simple main effects analysis of study within recruitment source revealed that the older age in CAPR vs NAPLS-3 was present within the other-referred group (mean difference = 4.56; $t(605) = 7.70$, $p < 0.001$) and this was a large effect size (Cohen's $d = 1.26$; illustrated in Fig. 4). This effect was also observed in the internet self-referrals (mean difference = 1.67; $t(113) = 2.22$, $p < 0.05$), though it was a small effect (Cohen's $d = 0.42$). As illustrated in Fig. 4B, NAPLS-3 participants recruited through self-referrals were older compared to other-referred sources, including whether internet-based (mean difference = 4.07; $t(615) = 7.63$, $p < 0.001$) or not internet-based (mean difference = 4.27; $t(641) = 9.64$, $p < 0.001$). In the CAPR sample, the relationships between recruitment source and age were non-significant ($ps > 0.05$). A small but significant independent main effect of sex (females younger across studies, Fig. 4A) became apparent that had been obscured in the univariate model.

Differences in clinical profiles based on sample, sex, age, and recruitment source

As shown in Table 1, clinical variables differed significantly between samples. Detailed results of each model predicting clinical variables are found for positive symptoms in Supplementary Table S9, for negative symptoms in Supplementary Table S10, for disorganization symptoms in Supplementary Table S11, for general symptoms in Supplementary Table S12, for social functioning in Supplementary Table S13, and for role functioning in Supplementary Table S14. All final models were significant. In the final models, older age was associated with higher negative and general symptom severities and lower social and role functioning. Female sex was only associated with higher general symptom severity. Self-referred internet-based sources were related to lower negative, disorganized, and general symptom

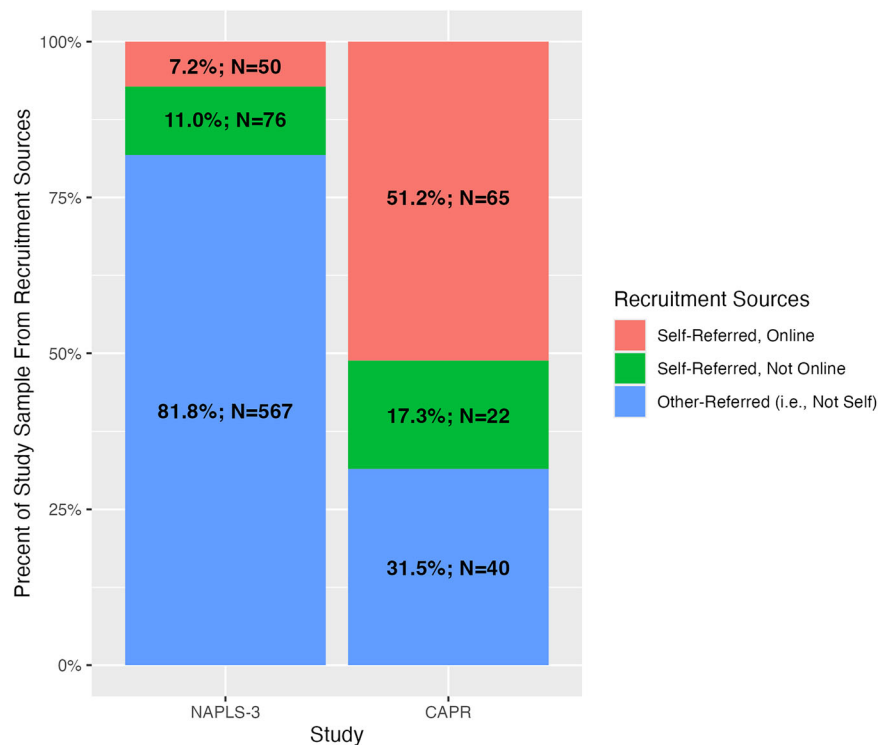


Fig. 1 Recruitment source within NAPLS-3 and CAPR datasets. The percent of cases coming from each recruitment source within each sample is plotted. Recruitment source data were not available from NAPLS-2.

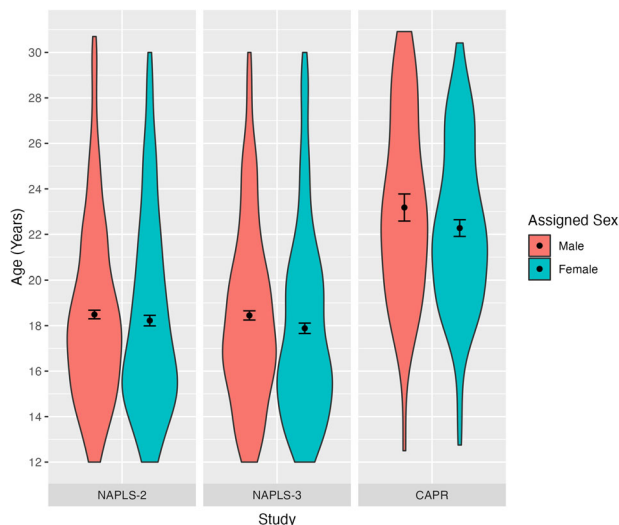


Fig. 2 Age distribution by sex within the NAPLS and CAPR datasets. Mean age is plotted for each sample. Error bars represent the standard error of the mean. Full age distribution is shown for descriptive purposes; analytic comparisons between CAPR and NAPLS-3 were restricted to participants ages 12–30 to ensure consistency.

severity and better role functioning compared to non-self-referred sources. Self-referred not-internet-based sources were related to lower positive and negative symptom severity and better role functioning compared to non-self-referred sources. Although significant sample differences were initially observed in all models, the variance accounted for by sample differences was partially or completely reduced in most models. Differences between samples in disorganized symptoms were no longer significant. In three of

the models (positive and negative symptoms and role functioning), the NAPLS-3 sample was associated with higher clinical severity compared to the CAPR sample, though with a slightly reduced regression coefficient after accounting for recruitment source differences.

DISCUSSION

The main findings of the present study are: (1) consistent with our first hypothesis, we observed significant demographic and clinical differences between CAPR and NAPLS-3 participants; the majority of participants were recruited via internet-based self-referred sources in CAPR and via non-self-referred sources in NAPLS-3 (Table 1 and Figs. 1), (2) consistent with our second hypothesis, differences in referral source accounted for several of the observed demographic differences between samples; differences in sex at birth representation and age distribution among these CHR studies were partly attributable to differences in recruitment sources, with the difference between studies in sex only observed in the other-referred group (Fig. 3) and the difference in age between studies predominantly observed in the other-referred group (Fig. 4); and (3) consistent with our third hypothesis, age, sex, and recruitment sources partly accounted for between-sample heterogeneity in clinical severity. Given the different study methods for capturing non-self-referral source types (Supplementary Tables S4 and S5), it was not possible to determine whether the mix of non-self-referral sources accounted for the shifts.

Referral source differences

There are several possible explanations for the greater proportion of individuals recruited through self-referrals in CAPR vs in NAPLS-3, including increased use of internet-based recruitment in recent years and online-only participation in CAPR permitting nationwide recruitment from online sources.

Table 2. Hierarchical binary logistic regression predicting the likelihood that a CHR participant is female using sample (CAPR vs NAPLS-3), age, and recruitment source as predictors ($N = 820$).

Model	Model			Variables					
	Step	df	χ^2	Predictor	Wald	β	SE (β)	Odds ratio	95% CI for OR
Univariate models	1	1	16.23***	Sample	15.52	0.80***	0.20	2.21	1.49, 3.28
	1	1	0.11	Age	0.11	>−0.01	0.02	1.00	0.96, 1.03
	1	2	20.03***	Recruitment Source					
				Self, internet	14.80	0.81***	0.21	2.25	1.49, 3.41
				Self, not internet	7.20	0.59**	0.22	1.81	1.17, 2.79
Hierarchical model	1	1	16.23***						
				Sample	15.52***	0.80	0.20	2.22	1.49, 3.28
	2	2	20.23***						
				Sample	19.14***	0.96	0.22	2.60	1.70, 4.00
				Age	3.96	−0.04	0.02	0.97	0.93, 1.00
	3	4	36.53***						
				Sample	9.08**	0.71	0.24	2.04	1.28, 3.24
				Age	10.78**	−0.07	0.02	0.94	0.90, 0.97
				Self, internet	9.96**	0.79	0.25	2.20	1.35, 3.59
				Self, not internet	10.14**	0.76	0.24	2.14	1.34, 3.42
	4	6	48.73***						
				Sample	0.01	−0.03	0.32	0.97	0.52, 1.80
				Age	14.14***	−0.08	0.02	0.93	0.89, 0.96
				Self, internet	2.80	0.46	0.28	1.59	0.92, 2.73
				Self, not internet	0.20	0.14	0.31	1.15	0.63, 2.11
				Sample $\times$ self-internet	7.45**	−1.49	0.55	0.23	0.08, 0.66
				Sample $\times$ self not internet	9.00**	−1.87	0.62	0.16	0.05, 0.52

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Overall model correctly classified 59% of cases.

Sample was coded −0.5 = NAPLS 3, 0.5 = CAPR; Reference group for recruitment source was other referrals.

Female preponderance and older age in CAPR sample

The female predominance in CAPR is consistent with prior research suggesting a higher representation of females in internet recruitment for mental health research^{49–52}. While many of these referrals came through internet-based strategies, it is important to note that not all self-referrals occurred via the internet. Both self-referral and internet-based outreach may capture help-seeking individuals in different stages or courses of illness and may disproportionately reach youth who are more engaged in online spaces. As such, we view these categories as overlapping but conceptually distinct, each warranting independent consideration in future CHR research.

Beyond sample differences in non-self-referral sources or perhaps accounting for them, it is possible that these sample differences are evidence of other evolving factors, such as cohort-based demographic shifts in the newest generation of youth or changes in a post-pandemic world⁵³. This possibility is consistent with a female predominance that is also being observed in another recent large observational study (Accelerating Medicines Partnership Schizophrenia AMP SCZ)⁵⁴. Additionally, an increase in females seeking mental healthcare has been noted post-pandemic^{55,56}. This is also consistent with the pattern of females being more likely than males to seek our health-related information online and to prefer telehealth options for care across many areas of medicine^{57–60}. Moreover, it is possible that these demographic differences reflect changes in the proportion of females who are under a disproportionate amount of stress or of a post-pandemic surge in mental health awareness and destigmatization of mental illness through young people using

social media platforms^{53,56,61,62}. Yet another possibility is that differences in referral source could reflect underlying differences in symptom presentation, such as males being more likely to exhibit externalizing symptoms, such as aggression or excitement^{63,64}, which may lead to higher rates of other referrals in the pre-pandemic NAPLS-3 sample compared to females. The sample differences in age seem to be driven by the older age of individuals being referred through other-referred sources, and the causes of this difference should be investigated in datasets with detailed and comparable data on other (not self-referred) sources. These findings may reflect differences in stage of illness, as conceptualized by clinical staging models of psychosis risk, with older age and provider referrals potentially indexing more progressed stages of symptom severity or functional decline. The sex and age effects were related: even though the CAPR sample was both more female and older in age than NAPLS-3, younger age and a higher likelihood of female sex were significantly associated in the final models (Tables 2 and 3). The same direction of the relation was observed in each sample (Fig. 3) and in every combination of sample and recruitment source (Fig. 4A).

Clinical profile differences by sample

The differences observed in clinical profiles between samples are also consistent with prior work comparing studies using the SIPS, which has demonstrated considerable heterogeneity in CHR clinical profiles⁶⁵. For example, the mean SIPS positive symptom score varied nearly threefold across 38 published samples⁶⁵. While variability in clinical profiles between any two samples is to be

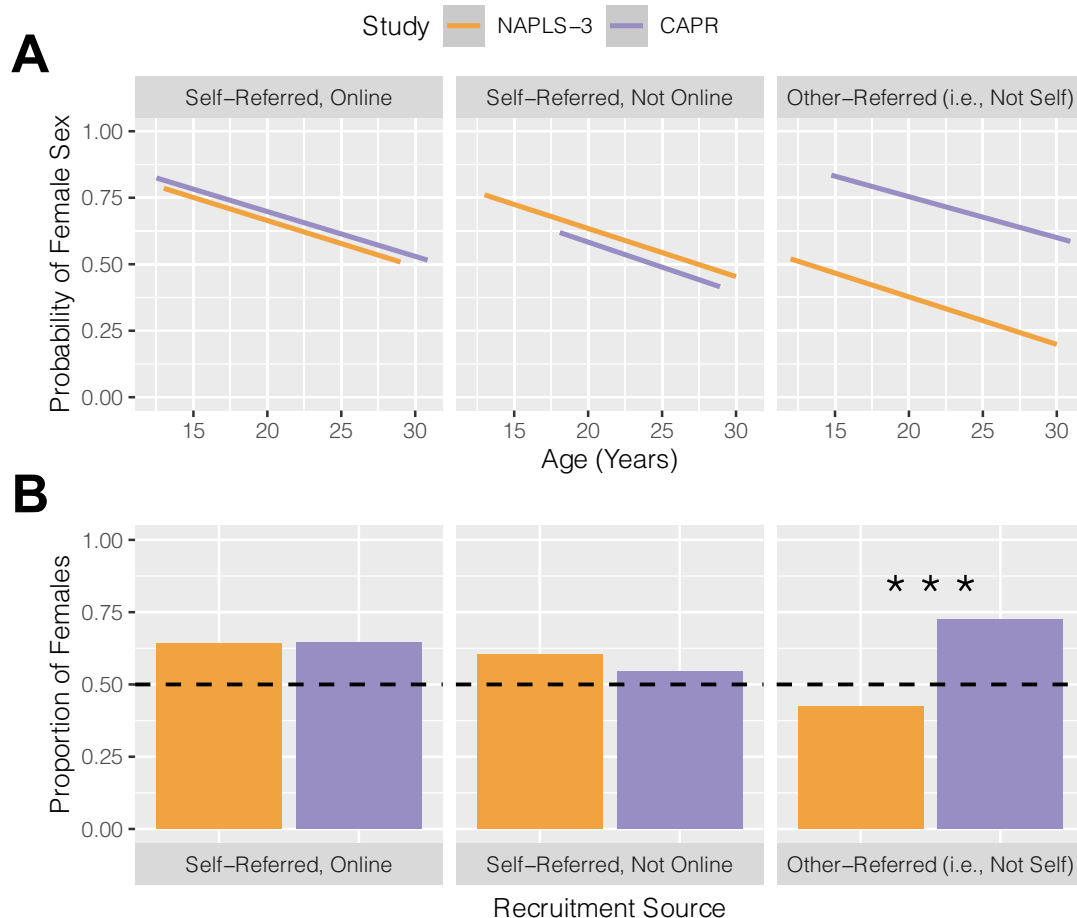


Fig. 3 Prediction of female sex in NAPLS-3 and CAPR. (***) $p < 0.001$) **A** Probabilities of female sex based on the logistic regression model as a function of actual age, recruitment source, and sample. Lines represent the relationship between age and probability of female sex adjusted for recruitment source and sample. Panel **A** displays findings for self-referred online sources (left), self-referred not-online sources (middle), and other-referred sources (right). The main effect of age on sex (older age associated with a lower odds of female sex) ($OR = 0.93$, 95% $CI = 0.89, 0.96$) was significant, an effect illustrated in **(A)** by the similar regression line slopes across all groups. The proportion of females differed across studies only in the other-referred groups, as shown by the separation between lines in the panel showing other-referred sources. **B** Proportion of females varied by recruitment source and sample. Simple main effects analysis of the sample within recruitment source revealed that a higher proportion of females in CAPR vs NAPLS-3 was present only within the other-referred group, in which NAPLS-3 was 42.5% female and CAPR was 72.5% (Fig. 3B; $\chi^2(1) = 13.61$, $p < 0.001$). Simple main effects of recruitment source within sample revealed that within NAPLS-3, participants recruited from other-referred sources were less likely to be female compared to self-referrals (Fig. 3B; $\chi^2(2) = 15.77$, $p < 0.001$), including whether internet-based (Wald = 13.84, $p < 0.001$, $OR = 3.36$, 95% $CI = 1.78, 6.37$) or not-internet-based self-referrals (Wald = 15.59, $p < 0.001$, $OR = 2.94$, 95% $CI = 1.72, 5.01$). However, in the CAPR sample, the effects of recruitment source were not significant ($ps > 0.05$), where the proportions of females were greater than 50% for each of the three referral sources.

expected in research, a clearer understanding of sources of sampling variability would inform study design and recruitment practices, ultimately improving detection of individuals at highest risk for developing psychosis. Our findings indicate that recruitment differences offer one source of variability, but do not fully account for between-sample differences. Further work comparing a wider breadth of samples, and direct comparisons of recruitment source types, along with other possible factors (e.g., study burden, study benefits, participant payment, and measurement reliability), is recommended.

Clinical profile differences by age and sex

Our results also demonstrated differences in clinical profiles related to the age and sex of CHR participants. Consistent with previous work^{66–69}, females had higher general symptoms and functioning compared to males. Contrary to prior work^{67,68}, we did not observe significantly higher negative symptoms in males. Also consistent with prior research, older age was associated with

higher symptom severity (general and negative) and lower social and role functioning^{70,71}. Overall, these findings underscore previously established demographic differences in clinical profiles and highlight the importance of accounting for demographic differences when examining CHR severity.

Clinical profile differences by recruitment source

Self-referred participants, particularly those coming through internet-based outreach, showed distinct demographic (Fig. 3, Fig. 4) and clinical characteristics (Supplementary Tables 9–14). These findings suggest that self-referral may increase access for older and female individuals at moderate clinical severity, which may be leveraged alongside provider-based outreach to broaden reach. The possible underrepresentation of young males in self-referrals and internet-recruited samples suggests a need for targeted outreach to this group if relying on internet-based recruitment. Inclusion of provider-based referral strategies, school-

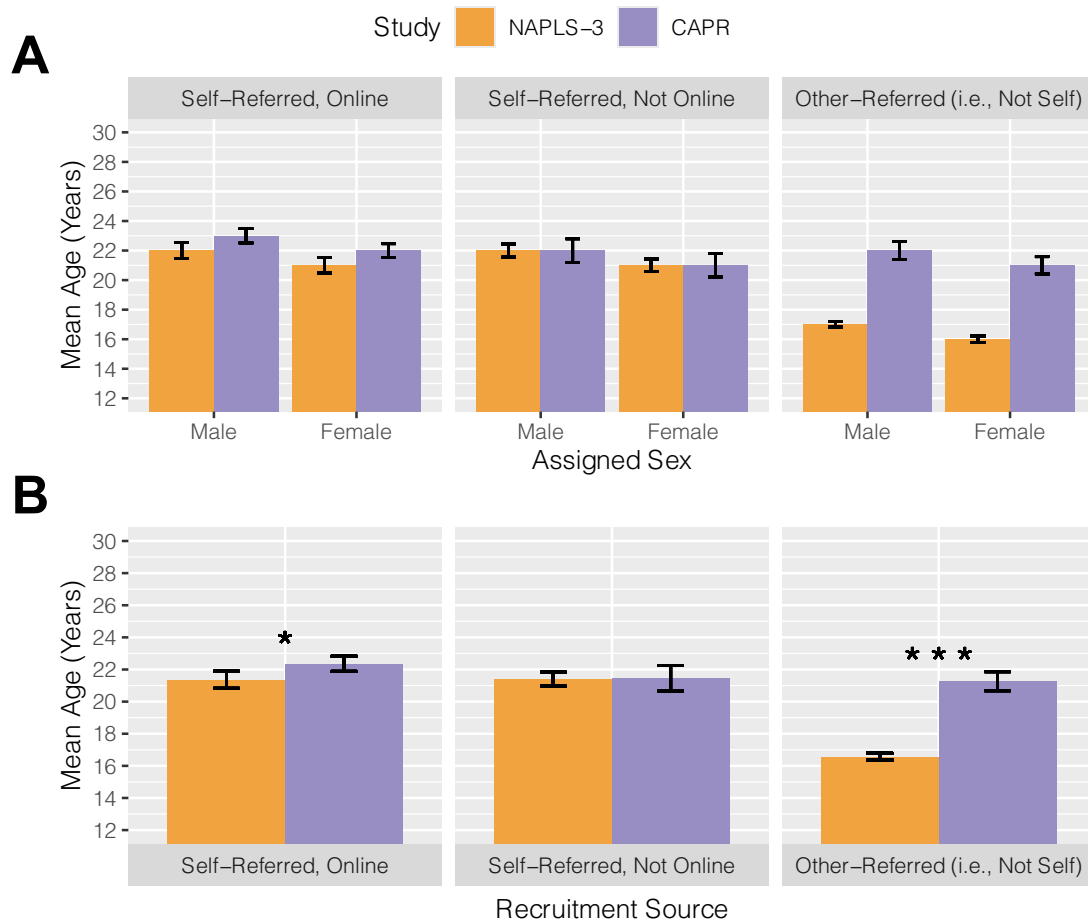


Fig. 4 Prediction of age in NAPLS-3 and CAPR. (* $p < 0.05$, *** $p < 0.001$) **A** Predicted age as a function of sex at birth, varied by sample and recruitment source. A small but significant independent main effect of sex (females younger across studies) was present. **B** Predicted age as a function of sample and recruitment source, controlling for sex at birth. Error bars represent $\pm$ standard error of the estimate (SEE). Simple main effects analysis of study within recruitment source revealed that the older age in CAPR vs NAPLS-3 was present within the other-referred group (mean difference = 4.56; $t(605) = 7.70$, $p < 0.001$) and this was a large effect size (Cohen's $d = 1.26$; illustrated in Fig. 4). This effect was also observed in the internet self-referrals (mean difference = 1.67; $t(113) = 2.22$, $p < 0.05$), though it was a small effect (Cohen's $d = 0.42$).

based screening, and additional strategies may help mitigate this imbalance and ensure that at-risk males are not overlooked.

While internet-based strategies for detection of CHR (“e-mental health”) show promise^{72–74}, we are unaware of studies that have directly examined potential implications of using such methods for CHR sample characteristics. In our study, more than 60% of participants recruited through internet-based self-referrals were female in both studies (Fig. 3). A similar female preponderance was observed in a study of voice hearers that relied on internet recruitment⁷⁵. Participants recruited through internet-based self-referrals were also significantly older (Fig. 4, Table 3) than those referred through more traditional recruitment sources. Our results also indicated that some aspects of clinical profiles were less severe when individuals at CHR were recruited through internet-based self-referrals (negative symptoms in Table S10, disorganization symptoms in Table S11, general symptoms in Table S12, and role functioning in Table S14). While some have suggested that internet-based recruitment may inadvertently attract samples less representative of historical clinical populations⁷⁶, an alternative plausible explanation is that these internet-based sources may enhance the detection of individuals at different stages of illness or with different trajectories over time. It is important to acknowledge that these recruitment methods can complement one another, combining to make for a more inclusive and effective overall strategy. New recruitment methods may help identify

youth at CHR who would not have been identified through traditional methods, such as youth in rural areas without readily accessible specialized clinics. Variance due to recruitment source has important implications for CHR research and suggests that future studies should carefully collect detailed information about recruitment sources⁷⁶.

Future directions

Future work should aim to better understand and refine internet-based recruitment strategies, especially given the potential advantages of such strategies proposed by some in the field (e.g., more efficient detection, cost-effective, and preferred by patients)^{72,73,76,77}. If the goal of a study is to recruit participants with higher severity of illness characteristics, one potential solution is to implement internet-based detection strategies in a consecutive screening model⁷⁸. For example, conducting online screening (e.g., through universal symptom-based screening or using a risk calculator to screen electronic health records) only after a person has entered secondary mental health services may offer an optimized detection strategy⁶². Preliminary reports suggest that this method could lead to retained severity characteristics, while also facilitating greater inclusion of female and older individuals⁷⁹. Additionally, attention could be paid to the language used in internet-based recruitment approaches,

Table 3. Hierarchical linear regression predicting CHR participant age using sample (CAPR vs NAPLS-3), sex at birth, and recruitment source as predictors ($N = 820$).

Model	Step	Model			Variables				
		df	F	R^2	Predictor	t	b	SE (b)	95% CI (b)
Univariate models	1	1	132.97***	0.14	Sample	11.53***	4.42	0.38	3.67, 5.18
	1	1	0.11	<0.01	Sex	-0.34	-0.10	0.29	-0.69, 0.49
	1	2	106.27***	0.21	Recruitment Source				
					Self, internet	12.15***	4.72	0.39	3.96, 5.48
					Self, not internet	9.78***	4.07	0.42	3.25, 4.88
Hierarchical model	1	1	132.97***	0.14					
					Sample	11.53***	4.42	0.38	3.67, 5.18
	2	2	68.72***	0.14					
					Sample	11.72***	4.53	0.39	3.77, 5.29
					Sex	2.00*	0.56	0.28	0.01, 1.11
	3	4	70.45***	0.26					
					Sample	6.91***	2.82	0.41	2.02, 3.62
					Sex	3.30**	0.87	0.26	0.35, 1.38
					Self, internet	8.11***	3.48	0.43	2.64, 4.32
					Self, not internet	9.15***	3.75	0.41	2.94, 4.55
	4	6	51.78***	0.28					
					Sample	1.80	1.01	0.56	-0.09, 2.11
					Sex	3.81***	0.99	0.26	0.48, 1.51
					Self, internet	5.92***	2.70	0.46	1.80, 3.59
					Self, not internet	4.11***	2.20	0.53	1.15, 3.25
					Sample $\times$ self-internet	-3.47***	-3.18	0.92	-4.97, -1.38
					Sample $\times$ self not internet	-4.22***	-4.52	1.07	-6.63, -2.42

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Overall model $R^2 = 0.29$.

Sample was coded $-0.5 = \text{NAPLS-3}$, $0.5 = \text{CAPR}$. Sex was coded $0.5 = \text{male}$, $-0.5 = \text{female}$.

Reference group for recruitment source was other referred.

attempting to optimize messaging to maximize sensitivity and specificity.

Limitations

Our findings should be considered in light of limitations. The NAPLS-3 sample was collected pre-pandemic, while the CAPR sample was collected during the pandemic, and we have no direct method of evaluating pandemic effects on our comparisons. Our findings need to be replicated in other large samples, with a more equivalent method of recording recruitment sources. Although we were able to categorize recruitment sources into meaningful categories based on our research questions, the methods for collecting recruitment source information differed substantially across our two studies. An additional limitation is that here we evaluate the effects of sex and age shifts only on baseline characteristics. The final CAPR longitudinal outcomes, when available, will offer a more complete picture of the effects of sample composition on sample characteristics.

Summary and conclusions

Our findings are aligned with previous literature showing that recruitment source has an important impact on CHR research^{36,37,73}, and underscore the need to consider recruitment source in analyses of demographic and clinical characteristics. We suggest that the CHR field would benefit from the development of methods to collect recruitment source information in a standardized format. A final limitation is that we compared two of many

possible samples in these analyses, and we do not expect that either one represents the ground truth. In this regard, it would be highly useful to conduct a large-scale epidemiology study of CHR in the United States.

In conclusion, our study showed evidence of variability in CHR sample demographics that was related to differing recruitment methods and referral sources. While internet-based detection methods are promising, individuals originating from these sources may tend to be more likely female and older and may have clinical profiles of more moderate severity. However, other hypotheses remain open at this time, including whether these findings are evidence of a cohort-based shift in demographics and whether internet-based methods enhance access to an otherwise invisible population in CHR research. Future research should collect detailed information about recruitment strategies and referral sources. Further examination of these hypotheses in studies that have used both internet-based and traditional recruitment methods is warranted.

DATA AVAILABILITY

Data for the ongoing Computerized Assessment for Psychosis Risk multi-site study is routinely uploaded to the National Institute of Mental Health Data Archive at <https://nda.nih.gov/>. The dataset with the sample and selected variables used in the present study analyses is available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Farina, Morgues-Codern, Saxena, and Mukhtar conducted statistical analyses and wrote the initial draft of the paper, with guidance from Woods. Stimler played a central role in data collection and coding. Gold, Mittal, Strauss, Corlett, Woods, and Ellman are Primary Investigators of the CAPR study. Walker, Schiffman, Powers, and Waltz are Co-Investigators, and Silverstein is a consultant. Kenney played a central role in preparing the CAPR study for remote administration. Addington, Bearden, Cadenhead, Cannon, Cornblatt, Keshavan, Mathalon, Perkins, Stone, Walker, Woods and Cannon were all investigators in the NAPLS study. All authors reviewed, edited and contributed critical feedback to the final paper.

COMPETING INTERESTS

Dr. Woods reports that he has received speaking fees from the American Psychiatric Association and from Medscape Features. He has been granted a US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists. He is a consultant to and is a partner and owns stock in NW PharmaTech. Philip Corlett is cofounder and board member and holds equity in Tetricus Labs, a Computational Psychiatry company. They did not fund this work. James Gold receives royalty payments from Vera Sci for the Brief Assessment of Cognition in Schizophrenia. The remaining authors declare no competing interests.

ADDITIONAL INFORMATION

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