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REGULAR ARTICLE

Gray Matter Volume Abnormalities and the Association with the Trajectory of Symptoms and Functioning in Individuals at Clinical High Risk of Psychosis

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***Background*: Brain volume alterations in those at clinical high risk (CHR) of psychosis have been reported in many studies. However, the association between these alterations and the longitudinal trajectory of changes in symptoms and functioning remains unexplored.**

***Study Design:* T1-weighted magnetic resonance imaging (MRI) scans were acquired from 226 CHR and 65 healthy controls (HC) recruited from the EU-GEI high-risk study. Five a priori regions of interest were examined and segmented using FreeSurfer: total gray matter (GM) volume, anterior cingulate cortex (ACC), hippocampus, fusiform gyri, and insula. Brain volumes in the CHR and HC groups were compared at baseline. In the CHR group, linear mixed models were used to investigate the association between baseline brain volume and longitudinal changes in positive symptoms, negative symptoms, and functioning over a 2-year follow-up period. We also compared CHR participants who later transitioned to psychosis (CHR-T, $n = 48$) and those who did not (CHR-NT, $n = 178$) in terms of their trajectory of symptoms and functioning.**

***Study Results:* Compared with HC, CHR participants had lower total GM and fusiform volume at baseline. Lower total GM and hippocampus volume at baseline were associated with higher levels of positive symptoms at baseline and follow-up in CHR individuals, and lower baseline hippocampus volume also predicted future transition. CHR-T and CHR-NT individuals demonstrated distinct symptoms and functioning trajectories over time.**

***Conclusion:* Our findings suggest that CHR individuals show baseline differences in brain structure compared to**

HC, which may also predict changes in positive symptoms over the subsequent 2 years.

Key words: sMRI; psychosis; clinical high risk; gray matter volume.

Introduction

Approximately 20%-30% of individuals at clinical high risk (CHR) for psychosis transition to psychosis within 3 years after first clinical presentation, making this period a crucial phase for early detection and intervention.[1,2] Neuroimaging techniques, including structural magnetic resonance imaging (MRI), have been applied in previous studies aiming to identify biomarkers in CHR associated with future transition.[3] However, the clinical outcome of CHR is more complex than a dichotomous classification of transition/non-transition,[4] and few studies investigating how brain structure may be associated with other outcomes, such as role functioning and different types of symptoms.

Gray matter (GM) abnormalities in CHR at first presentation have been reported in by a number of studies.[5-7] The Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) consortium pooled a large sample of MRI scans from CHR individuals and used FreeSurfer to examine subcortical volumes and cortical thickness (CT). The study found that individuals with CHR exhibited widespread reductions in CT compared to healthy controls (HC), although these changes were small in magnitude.[5] Furthermore, the authors reported that lower fusiform, superior temporal, and paracentral CT were associated with transition to psychosis.[5]

While transition to psychosis is a critical clinical outcome, other changes in symptoms and functioning also strongly impact CHR individuals.[8] For example, Polari et al.[9] examined trajectories of symptoms in a large group of CHR individuals, and classified these as: transition, recovery, remission, recurrence, no remission or relapse; thus, transition was only one of the trajectories and occurred in a minority (16%) of the participants. Furthermore, while CHR transition criteria focus on positive symptoms, negative symptoms are common in CHR and are associated with poor outcomes and long-term disability.[10] Therefore, rather than simply studying biomarkers for predicting transition to psychosis, it is important to examine biomarkers linked to future trajectories of symptoms and functioning.

A small number of neuroimaging studies have identified markers associated with clinical outcomes other than transition; however, these studies measured clinical variables at a single follow-up point rather than determining how these clinical measures changed over time. Cropley et al.[11] found that among CHR individuals who did not transition to psychosis, those with persistent attenuated symptoms determined at follow-up showed reduced GM volume in small clusters in frontal and temporal regions. Additionally, lower GM volume at baseline was correlated with more positive, negative, and anxiety symptoms and worse functioning at follow-up. In a previous VBM study of the EU-GEI High Risk sample, poor functioning at the participants' last follow-up was associated with lower baseline striatum volume.[12] The anterior cingulate cortex (ACC), part of the limbic system, plays a key role in connecting subcortical regions (such as the hypothalamus and nucleus accumbens) and cortical regions (including insula and orbitofrontal cortex) and has been linked to negative symptoms in psychosis.[13,14] The insula together with ACC are important nodes of the salience network[15] where structural and functional abnormalities have been associated with both positive and negative symptoms.[16-18] However, the association between baseline brain structure and measures of trajectory of symptoms and functional changes recorded at multiple timepoints over time has not been studied. Including additional timepoints allows a better characterization of the trajectory of clinical measures and also improves statistical power.

The current study aimed to (1) investigate the association between baseline GM volume and the trajectories of positive, negative symptoms and functioning, as well as future transition to psychosis, (2) provide additional evidence for the regional brain volume differences at baseline between CHR individuals and HC from a prospectively collected international sample; finally, as transition status is the most common outcome in MRI studies rather than the trajectory of symptoms and functioning, we also wanted to (3) further explore the trajectory difference in positive, negative symptoms and functioning between individuals who later transition to psychosis (CHR-T) and those who do not (CHR-NT) in our sample regardless of MRI data.

Methods

Study Design and Participants

The "European Network of National Schizophrenia Networks studying Gene-Environment Interactions" (EU-GEI) high-risk study is a prospective longitudinal multicenter study of CHR individuals.[19] MRI scans of CHR individuals were prospectively obtained from 9 sites (London, Amsterdam, The Hague, Basel, Cologne, Melbourne, Vienna, Copenhagen, Paris), and HC were recruited from a subset of these sites (London, Amsterdam, The Hague, and Melbourne). Ethical approval for EU-GEI study was obtained from the local research ethics committee of each participating site, and participants gave written informed consent to take part in the study.

CHR participants were help-seeking individuals identified by each early detection center who met at least one of the CHR criteria assessed by Comprehensive Assessment of At-Risk Mental States (CAARMS[20]), namely:

Vulnerability Group, Attenuated Psychotic Symptoms, or Brief Limited Psychotic Symptoms. HC participants were recruited using GP lists, national postal address files, and website advertisements. Participants who met the following criteria were excluded: (1) past or present diagnosis of a psychotic disorder, determined by CAARMS and the Structured Clinical Interview for DSM-IV Disorders (SCID-IV); (2) past or present neurological disorder; (3) symptoms explained by substance abuse or dependency; (4) contraindication to an MRI scan or unwillingness to provide blood/saliva sample, or (5) estimated IQ < 60. HC participants were also excluded if they met CHR criteria.

In the present study, data were acquired from 226 CHR and 65 HC individuals included in the EU-GEI high-risk study, and 48 (21.2%) of the 226 CHR individuals transitioned to psychosis (CHR-T) during follow-up. Participants were invited for an interview and an MRI scan at baseline. At 12-month and 24-month follow-up after the initial assessment, the CAARMS interview was administered to determine whether the participant had transitioned to psychosis. Five sites (London, Amsterdam, The Hague, Paris, and São Paolo) also included an additional follow-up at 6 months. Where possible, sites extended follow-up for those who transitioned to psychosis for up to 2 years after transition. When follow-up interviews were not possible, clinical records were used to determine if CHR participants had transitioned to psychosis. 96% of CHR individuals completed their last follow-up assessments within 2.5 years, while a small number of CHR individuals had their last follow-up after 2.5 years.

Measurements and MRI Scans

The EU-GEI high-risk study collected multimodal data, including clinical, neuropsychological, MRI, and genetic data; hereafter, we describe the data included in the current study.

Baseline social demographic characteristics were collected according to the Medical Research Council sociodemographic schedule.[21] Positive symptoms were determined by the sum of the CAARMS positive subscale, which comprises a global rating from 0 to 6 points in 4 domains: unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganized speech. Negative symptoms were assessed using the sum of the Scale for the Assessment of Negative Symptoms (SANS[22]), which includes 25 items with each item marked on a 6-point scale. For 19 participants whom there was missing data for 1 or 2 items, these scores were imputed using the median of each relevant item. Participants who had missing data for more than 2 items were excluded from analyses using the SANS. Functioning was assessed by the Global Assessment of Functioning (GAF[23]) scale. The GAF score was split into symptoms and disability[24] and the latter was used in our study to represent the participants' capacity to carry out everyday activities.

All instruments were translated into the local language at each site and back-translated to ensure accuracy. Researchers responsible for interviewing participants were required to complete a short online training course for the CAARMS and GAF rating. Researchers were only permitted to interview patients after they had achieved an interrater reliability greater than 0.7.

Structural 3 T MRI scans were acquired using the Alzheimer's Disease Neuroimaging Initiative (ADNI-2) protocol (Table S1). The ADNI-2 protocol has been specifically designed for multicenter studies to reduce heterogeneity by keeping cerebral gray and white matter contrast consistent between centers, even with different scanner manufacturers.[25] The varying acquisition parameters for each site from the ADNI-2 protocol (Table S1) reflected the need for different parameters at each scanner to ensure harmonization across the different scanners. All structural images were processed using FreeSurfer v6.0.0 cross-sectional pipeline (https://freesurfer.net/). We have previously demonstrated excellent reliability of ADNI scans and the FreeSurfer pipeline.[26] Quality assessment was performed for all structural images using the ENIGMA Cortical QC Protocol (http://enigma.usc.edu), including checking internal cortical segmentation and externally checking anatomical boundaries. 7 participants were excluded due to organic brain abnormalities, artifacts, or poor scan quality (Figure S1). Regions of interest were carefully selected a priori based on meta-analytical evidence from psychosis, schizophrenia, and CHR MRI studies. A global measure of total GM volume was chosen as meta-analyses have shown widespread involvement of the cortex.[27-29] In addition, we chose 4 subregions which have consistently shown volume reductions with large effect sizes; the ACC,[27,29-31] fusiform gyrus,[32,33] insula[30,31] and hippocampus.[6,27,34]

Statistical Analysis

All statistical analyses were performed in STATA MP18 (StataCorp. 2023. *Stata Statistical Software: Multiple Core Release 18*. College Station, TX).

Baseline sociodemographic data between CHR and HC, and between individuals who transitioned (CHR-T) or did not transition (CHR-NT), were compared using chi-squared or Mann–Whitney U tests as appropriate.

Total and regional GM volumes (in milliliters) at baseline were compared between CHR and HC using multiple linear regression with GM volume as the dependent variable. The case–control analysis was limited to the four sites that recruited both CHR and HC groups. Models were fitted for each region of interest and statistically adjusted for age at baseline, scanner, total intracranial volume, ethnicity, and sex. The model was adjusted for scanner rather than site because the Amsterdam and The Hague sites both used the same scanner, and the scanner was changed during the study (see Table S1).

To investigate the impact of baseline brain volumes on the longitudinal trajectory over 4 timepoints (baseline, 6-month, 12-month, and 24-month) of positive symptoms, negative symptoms, and global functioning in CHR individuals, linear mixed models (LMM) were fitted for each region of interest. LMMs include both fixed and random effects, allowing repeated measures within participants to be modeled without requiring assessments to occur at identical intervals.[35] Fixed effects estimate the variables of interest, while random effects account for variability across different levels. In this analysis, symptoms and functioning served as dependent variables and brain volume, time (defined as years from the baseline assessment), and their interaction were included as the fixed effects of interest. The model was a 2-level hierarchical linear model with random intercepts at the participant level (to account for within-subject correlation across repeated measures) and the site level (to account for between-site variability). The default covariance structure for the STATA "mixed" command (independent structure) was applied. Additionally, all models were adjusted for age at baseline, sex, and ethnicity by including these as fixed effects of no interest. The interaction between time and baseline brain volume was initially included in the model and subsequently eliminated if the interaction effect was not significant.[36] Not all participants attended every follow-up assessment or scan, leading to missing data; however, LMM is able to incorporate missing data and include values that are recorded at different time points.

Logistic regression was applied to determine whether brain structure abnormalities at baseline were associated with later transition to psychosis (CHR-T vs. CHR-NT). Models for each region of interest were controlled for age at baseline, site, ethnicity, and sex. To further explore psychopathology of CHR in our sample, we fitted LMMs to investigate the difference in positive and negative symptoms, and global functioning between CHR-T and CHR-NT groups in the absence of MRI data. In these models, group (CHR-T vs CHR-NT), time, and their interaction were considered the fixed effects of interest, and we controlled for age at baseline, sex, and ethnicity. The random effects were the same as mentioned above.

To adjust for multiple comparisons, we used false discovery rate (FDR) correction. All 50 *P*-values from the baseline analysis and main fixed effects of LMM were included in the correction. All *P*-values reported are uncorrected; however, we indicate which are significant after FDR correction with an asterisk.

Sensitivity Analyses

A small number ($n = 20$) of CHR participants received antipsychotic treatment, which is thought to have an impact on brain structure.[37,38] We therefore conducted a sensitivity analysis, repeating all analyses above after excluding participants who had used antipsychotics. A separate FDR correction was performed, including all *p*-values in the antipsychotics' sensitivity analyses. In the EU-GEI high-risk study, the Childhood Trauma Questionnaire (CTQ[39]) was administered to obtain childhood adversity information. In the current sample, CHR individuals experienced more childhood trauma compared to HC, which could be a possible confounder. We therefore conducted an additional sensitivity analysis including total CTQ score (range from 25 to 125) as a covariate when comparing baseline brain volume between CHR and HC. When examining the association between baseline brain volumes and positive symptoms, we performed a sensitivity analysis excluding CHR individuals who transitioned, and this was only undertaken for brain regions associated with transition to psychosis. Finally, when examining the relationship between transition status and the trajectory of symptoms and functioning, we conducted a sensitivity analysis excluding symptom and functioning measures after the point of transition.

Results

Sample Characteristics

226 CHR and 65 HC participants from the EU-GEI high risk study who had a baseline MRI scan that passed quality control were included in the analyses. The number of CHR individuals in the MRI comparison to HC was smaller ($n = 159$ CHR) because we only included the 4 sites that recruited HC to ensure the analysis was not confounded by scanner. When we examined clinical variables in the CHR group, all sites were included with $n = 226$ CHR. Table 1 contains data from the entire sample while Table S2 includes the subset of 4 sites that recruited HCs. In both the whole sample and the sub-sample of 4 sites, there was no significant difference in sex, age or ethnicity, however HC had significantly more years of education and there were significant group differences in socioeconomic status (Table 1 and Table S2). During follow-up, 48 individuals in the CHR group transitioned into psychosis. There was no significant difference in baseline demographics between those who later transitioned to psychosis (CHR-T, $n = 48$) and those who did not (CHR-NT, $n = 178$) except for socioeconomic status ($P = .039$) and a higher proportion of antipsychotic users in the CHR-T group ($P = .004$, Table S3).

Baseline Brain Volume Differences between CHR and HC

At baseline, CHR individuals had significantly lower total GM and fusiform gyrus volume than HC. There was no significant difference between CHR and HC in ACC, hippocampus or insula volume (Table 2).

Association of Baseline Brain Volumes on Longitudinal Symptoms and Later Transition in CHR

For the 226 CHR individuals with symptom ratings, 53 were assessed at 1 time point only, 65 were assessed at 2

Table 1. Baseline Demographic and Clinical Information

	CHR ($n = 226$)	HC ($n = 65$)	χ^2/U	*P*
Sex female (%)	108 (48%)	31 (48%)	0.0002	.989
Ethnicity (White/Black/Other)	163/22/41	42/10/13	1.963	.375
Age	22.58 ± 0.32	22.95 ± 0.51	0.955	.340
Years in education[a]	14.49 ± 0.22	16.08 ± 0.35	3.99	**<.001**
Father's socioeconomic status at participants' birth (Salariat/Intermediate/Working Class)[b]	66/62/60	30/20/5	12.501	**.002**
CTQ[c]	49.23 ± 1.04	34.44 ± 1.33	-7.703	**<.001**
Current cannabis use, *n* (%)[d]	64 (37%)	18 (42%)	0.412	.521
Antipsychotic use, *n* (%)[e]	20 (9%)			
Baseline SANS[f]	20.24 ± 14.12			
Baseline CAARMS positive[g]	10.09 ± 4.12			
Baseline GAF disability[h]	54.52 ± 12.33			

Abbreviations: CHR: clinical high risk; HC: healthy control [a]Years in education is available for 199 CHR and 64 HC; [b]Father's socioeconomic status is available for 181 CHR and 55 HC; [c]CTQ: the Childhood Trauma Questionnaire, baseline data is available for 211 CHR and 64 HC; [d]Current cannabis use is available for 175 CHR and 43 HC; [e]Antipsychotic use is available for 217 CHR; [f]SANS: The Scale for the Assessment of Negative Symptoms, baseline data is available for 219 CHR; [g]CAARMS: Comprehensive Assessment of At-Risk Mental States, baseline data available for 225 CHR; [h]GAF disability: Global Assessment of Functioning, baseline data is available for 222 CHR. Bold values (e.g., $P < 0.001$) indicate statistically significant results.

Table 2. Comparison of Brain Volumes of CHR vs HC at Baseline

	CHR ($n = 159$)	HC ($n = 65$)			
	Brain volume (ml) mean ± SD	***Brain volume (ml) mean ± SD***	***b***	***95% CI***	***P***
Total GM	664.923 ± 5.642	692.983 ± 8.473	-13.99	-23.52 to -4.45	**.004** *,[a]
ACC	8.517 ± 0.125	8.988 ± 0.194	-0.350	-0.710 to 0.010	.057
Hippocampus	8.408 ± 0.063	8.608 ± 0.091	-0.155	-0.331 to 0.021	.084
Fusiform gyrus	20.133 ± 0.221	21.300 ± 0.391	-0.663	-1.272 to -0.054	**.033**
Insula	14.660 ± 0.138	15.243 ± 0.243	-0.383	-0.782 to 0.016	.060

*$P < .05$ after false discovery rate correction; [a]Corrected $P = .008$; CHR: clinical high risk; HC: healthy control; GM: gray matter; ACC: anterior cingulate cortex. Models adjusted for age, scanner, ethnicity, total intracranial volume and sex. Bold values (e.g., $P < 0.001$) indicate statistically significant results.

timepoints, 75 were assessed at 3 timepoints and 33 were assessed at 4 timepoints.

No significant interaction effect between baseline brain volume and time was observed, indicating that there was no time-related change associated with baseline brain volume. There was a significant effect of baseline total GM volume and hippocampus volume on CAARMS positive symptoms (Table 3, Figure S2), indicating that lower total GM and hippocampus volumes at baseline were associated with higher CAARMS positive symptoms scores over follow-up assessments, when controlling for time. Time effects were significant for all regions, indicating that positive symptoms improved over time when brain volumes were held constant.

No significant association was observed between baseline brain volumes and negative symptoms (Table S4), or global functioning Table S5). Time effects were significant for both scales, indicating that both negative symptoms and functioning improved over time.

Logistic regression showed that baseline hippocampus volume was associated with later transition (Odds ratio: 0.588, $P = .041$, 95% CI: 0.353 to 0.979), indicating that CHR individuals with higher baseline hippocampus volume were less likely to transition into psychosis (Table 4).

Effect of Transition Status on Longitudinal Symptom Ratings

To further explore longitudinal change in symptoms and functioning between CHR-T and CHR-NT, we examined positive, negative symptoms, and global functioning. This analysis was in the absence of neuroimaging data and included 226 individuals (178 CHR-NT and 48 CHR-T, Figure S3). Transition status had a significant main effect on SANS ($P = .038$) and GAF ($P = .048$), indicating that CHR-T individuals exhibited more negative symptoms and worse functioning compared to CHR-NT individuals. No difference was observed in CAARMS positive symptoms. A significant time effect was found for all three measures (all $P < .001$), which was potentially driven by the larger CHR-NT

Table 3. Association of Baseline Brain Volumes on the Trajectory of Positive Symptoms in CHR Individuals Using Linear Mixed Models

Brain Volume (mL)	CAARMS positive symptoms					
	Estimated between-individual effect of baseline brain volume			Estimated between-individual effect of time (per 1 year follow-up)		
	b	*95% CI*	*P*	*b*	*95% CI*	*P*
Total GM	-0.010	-0.019 to -0.001	**.029**	-1.284	-1.641 to -0.927	<**.001**[*,b]
ACC	-0.108	-0.423 to 0.208	.504	-1.293	-1.650 to -0.936	<**.001**[*,b]
Hippocampus	-1.109	-1.740 to -0.477	**.001**[*,a]	-1.278	-1.634 to -0.921	<**.001**[*,b]
Fusiform gyrus	-0.187	-0.397 to 0.023	.080	-1.287	-1.643 to -0.930	<**.001**[*,b]
Insula	-0.246	-0.545 to 0.053	.107	-1.292	-1.648 to -0.935	<**.001**[*,b]

[**]$p<.05$ after false discovery rate correction; [a]Corrected $P = .002$; [b]Corrected $P = .002$; CAARMS: Comprehensive Assessment of At-Risk Mental States; GM: total gray matter volume; ACC: anterior cingulate. Bold values (e.g., $P < 0.001$) indicate statistically significant results.

Table 4. Associations between Baseline Brain Volumes and Later Transition

	CHR-T (*n* = 178)	CHR-NT (*n* = 48)			
	Brain volume (ml) mean ± SD	*Brain volume (ml) mean ± SD*	*Odds ratio*	*95% CI*	*P*
Total GM	673.907 ± 10.526	670.138 ± 5.385	0.997	0.990 to 1.004	.380
ACC	8.532 ± 0.241	8.665 ± 0.117	0.894	0.699 to 1.143	.371
Hippocampus	8.233 ± 0.099	8.487 ± 0.063	0.588	0.353 to 0.979	**.041**
Fusiform gyrus	20.453 ± 0.386	20.243 ± 0.213	0.989	0.847 to 1.155	.890
Insula	14.786 ± 0.280	14.776 ± 0.136	0.897	0.712 to 1.131	.358

[*]$P < .05$ after false discovery rate correction; CHR-T: participants who later transitioned to psychosis; CHR-NT: participants who did not transition; GM: gray matter; ACC: anterior cingulate cortex. Models adjusted for age, site, ethnicity and sex. Bold values (e.g., $P < 0.001$) indicate statistically significant results.

group improving in symptoms and functioning over time. Finally, there was a significant interaction effect of transition status x time, for positive symptoms, negative symptoms, and functioning (all $P < .001$). This result showed that CHR-T individuals experienced worsening symptoms and global functioning over time, while CHR-NT individuals tended to improve (see Figure 1 and Table S6).

Sensitivity Analyses

We re-ran all analyses excluding 20 CHR (11 CHR-NT and 9 CHR-T) participants who had used antipsychotics at baseline and additional 9 CHR (5 CHR-NT and 4 CHR-T) participants with missing medication history data. The results still showed significant smaller total GM volume in CHR participants ($b = 13.640$, 95% CI: -23.464 to -3.816, $P = .007$, Table S7). The previous reductions for the fusiform gyrus were no longer significant but showed a trend finding ($P = .055$). Regarding the baseline volume and its association with symptoms and functioning trajectory, the association between baseline hippocampus volume and positive symptoms remained significant, but this was no longer the case for total GM volume. In addition, we observed a new interaction effect between baseline ACC volume and time, indicating that individuals with higher baseline ACC volume were likely to have reduced positive symptom score over time (Table S8). No significant impact of baseline brain volume on SANS or GAF was observed as before (Tables S9 and S10). No volumetric difference was observed between CHR-T and CHR-NT (Table S11), however, the different trajectories of CAARMS positive symptom, SANS and GAF between transition and non-transition participants remained consistent with the main analyses (Table S12).

When CTQ was included as a covariate in the model when comparing CHR to HCs, it was a significant predictor ($P = .025$) only when comparing baseline fusiform gyrus volume between CHR and HC. When we adjusted for CTQ there was no longer a statistical difference at fusiform gyrus volume between the 2 groups ($b = -0.242$, 96% CI: -0.953 to 0.470, $p=.503$). As CTQ was not a significant predictor (and therefore not a confounder) for the other brain regions, we did not perform an adjustment for these analyses.

We first examined the association between baseline hippocampus volume and longitudinal CAARMS positive severity score in those who did not transition to psychosis, to avoid the potential impact of transition,

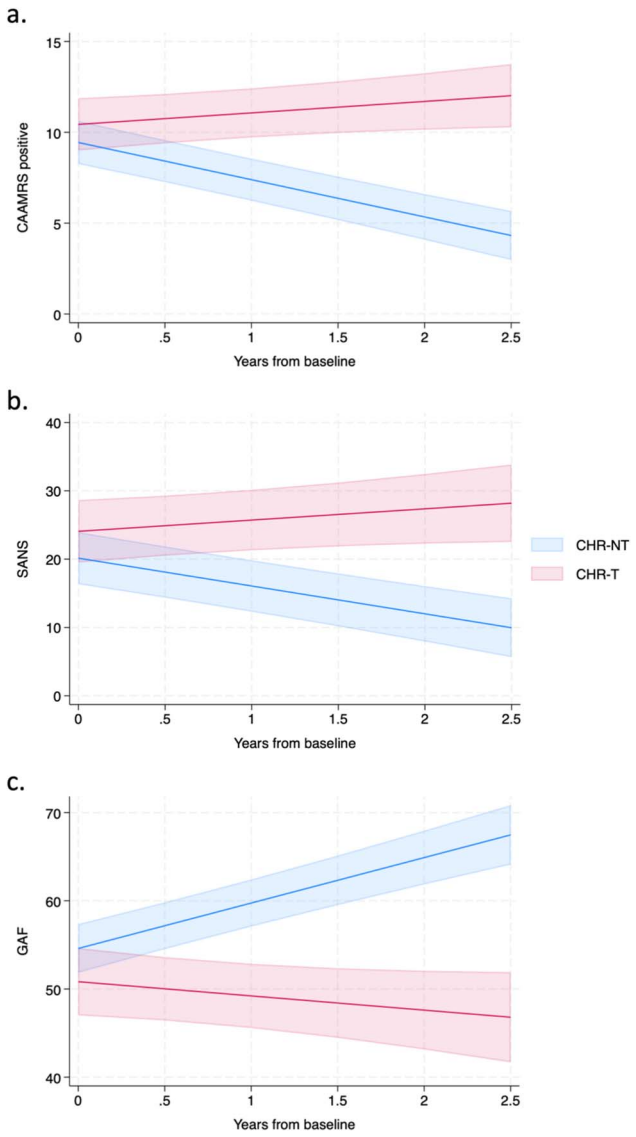

Figure 1. Linear Mixed Model for CAARMS Positive (a), SANS (b) and GAF (c) from Baseline to 2.5 Years of Follow-Up. SANS: The Scale for the Assessment of Negative Symptoms; CAARMS: Comprehensive Assessment of At-Risk Mental States; GAF: Global Assessment of Functioning; CHR-T: Individuals who transitioned to psychosis during follow-up; CHR-NT: Individuals who did not transition to psychosis during follow-up.

and the results were similar (for between-individual effect of baseline hippocampus volume $b = -0.89$, $P = .011$). We also examined the trajectory difference in positive and negative symptoms and global functioning and removed all assessments recorded in CHR-T individuals after transition; all CHR-NT timepoints were retained. 48 (out of 105) observations were excluded for CAARMS positive symptoms; 51 (out of 106) observations were excluded for SANS; 44 (out of 99) observations were excluded for GAF. A significant time × transition status for SANS ($b = 6.930$, 95% CI: 3.378 to 13.481, $P = .038$) remained as seen in the main analysis, but there was no longer a significant trajectory difference in CAARMS positive symptoms or GAF (Table S13 and Figure S4).

Discussion

In the present study, we examined baseline brain volume differences between CHR individuals and HCs, as well as the association between baseline brain volumes and symptoms, functioning, and transition over a 2-year follow-up. We found that CHR individuals exhibited lower total GM volume compared to HCs, as well as reduced volume in fusiform gyrus, with the total GM volume differences surviving FDR correction for multiple comparisons. Additionally, we observed that CHR individuals with lower total GM and hippocampus volume at baseline had higher CAARMS positive score in general, with the result for the hippocampus volume remaining significant after FDR correction. Lower hippocampus volume at baseline was also found to be predictive of transition. Excluding patients who had used antipsychotics at baseline or were missing data had a minor impact on the results and suggested that the ACC might predict changes in positive symptom severity in non-medicated CHR individuals. To the best of our knowledge, this is the first report of baseline brain volumes being associated with positive symptom severity over time in CHR individuals. Finally, we report that those within the CHR group who later transitioned to psychosis showed a worsening trajectory of positive & negative symptoms and functioning. Excluding observations recorded after transition lessened these effects and only the difference in trajectory of negative symptoms remained significant.

Baseline Brain Volume Differences between CHR and HC

We chose brain regions based on previous literature, and our findings of CHR volume reductions align with a number of previous studies. Lower fusiform volume in CHR individuals compared to HC is supported by a North American Prodrome Longitudinal Study (NAPLS) paper[40] as well as a meta-analysis by Ding et al.[32] The ENIGMA CHR study did not investigate total GM volume; however, it revealed significantly reduced ICV, mean CT, and total surface area.[5] When we controlled for childhood trauma, the fusiform gyrus volume was not significantly different between CHR and HC. Childhood trauma was not taken into account in the CHR studies mentioned above; however, studies investigating childhood trauma and brain structure have revealed that higher CTQ scores have been associated with lower fusiform volume[41] and surface area.[42] These results suggest that childhood trauma may need to be taken into consideration when investigating brain structures in CHR.

Association of Baseline Brain Volumes on Longitudinal Symptoms and Later Transition in CHR

Our results indicate that CHR individuals with lower total GM and hippocampus volume at baseline may experience more severe positive symptoms, with the hippocampus finding being more robust as it survived correction for multiple comparisons. Over the entire CHR sample, positive symptoms improved over time; however, those with lower baseline hippocampus volume consistently had more positive symptoms compared to their peers. The impact of baseline brain volumes on symptom trajectory using LMMs in CHR individuals has not been extensively reported. However, other analysis methods have found some support for these findings, for example, a longitudinal study by Ho et al.[43] also reported reduced hippocampal subfield volumes in those who had persistent sub-clinical symptoms or transitioned, compared to those who remitted. Conversely, a cross-sectional study of CHR individuals by Sasabayashi et al.[44] did not observe any association between subcortical brain volumes, including the hippocampus, and positive symptoms. Padmanabhan et al.[45] reported decreased total GM volume was associated with increased positive symptoms in a combined sample of patients with schizophrenia, schizoaffective, and bipolar disorder. The association reported by Padmanabhan et al. diminished when medication was controlled for, which was consistent with our study, where no correlation between total GM and positive symptoms was found after removing individuals with antipsychotic usage. Thus, while it appears that there may be a weak medication-dependent association with total GMV, the hippocampal finding was more robust.

When comparing baseline GM volume between CHR-T and CHR-NT, there are heterogeneous results in previous studies. The ENIGMA CHR study found widespread lower CT, but did not find any subcortical volume difference between CHR-T and CHR-NT[5]. The Shanghai-At-Risk-for-Psychosis (SHARP) Study analyzed participants who transitioned after 1 year of follow-up and found that CHR-T individuals had reduced baseline CT of the banks of superior temporal sulcus, Heschl's gyrus, and pars triangularis.[46] Our results only showed a significant finding for hippocampal volume, but the *P*-value was close to the threshold and was associated with a small effect size. This mirrors other reported findings for CHR-T vs CHR-NT comparisons for brain structure, which tend to have a small effect size.[5,47] Although the hippocampus abnormalities have been reported in a number of structural and functional MRI studies in schizophrenia, there is a lack of robust evidence that it can predict transition to psychosis.[48] In our study, individuals with lower hippocampal volume also had higher CAARMS positive scores throughout the follow-up period; thus, low hippocampal volume may be a marker for later transition and persistent positive symptoms. However, as the MRI data included in this analysis were baseline-only, we could not characterize within-person structural change over time, and further longitudinal studies with large samples may be required to confirm whether regional structure change interacts with symptom trajectory and precedes transition.

Effect of Transition Status on Longitudinal Symptom Ratings

We further explored the course of clinical symptoms and global functioning between those who transitioned to psychosis and those who did not. We found the CHR-NT group had less severe positive and negative symptoms as well as improved functioning during the 2-year period. This trajectory of symptoms is consistent with Velthorst et al.[49] who showed that positive and negative symptoms, as well as functioning, improved over time in CHR-NT individuals. Furthermore, a meta-analysis by Salazar de Pablo et al.[50] reported improvements in attenuated psychotic symptoms, negative symptoms, and functioning in a CHR-NT group. However, heterogeneity within CHR-NT is evident. In NAPLS-3, 3 symptom trajectories were identified: remission, partial remission, and persistent.[51] Conversely, in the CHR-T group, we reported that symptoms and functioning remained stable or worsened slightly over time. Previous studies have examined the trajectories of symptoms and functioning in CHR-T individuals; Hengartner et al.[52] recorded functioning, positive and negative symptoms, while Tran et al.[53] focused on negative symptoms. Both these studies showed an initial improvement over time in CHR-T individuals, which tended to level off. However, the heterogeneity in even CHR-NT was not easy to capture. When we included only assessments before transition, the significant trajectory difference remained consistent for SANS, but no significant difference was observed in CAARMS positive symptoms or GAF. This suggested that negative symptoms have the potential of being an early indicator for later transition. However, around half of the observations were excluded in the CHR-T group, and the remaining assessments were mostly within 1 1-year follow-up, which reduced the power of the analysis. Nevertheless, our results suggest that short-term change in symptoms might be a potential sign for the progression and an indicator for early intervention.

Limitations, Strengths, and Conclusion

Our study has some limitations. Firstly, for the positive symptom score we summed the CAARMS positive global ratings, which focus on the severity of symptoms, but we did not include duration and frequency of symptoms as these measures had more missing data. Secondly, as is common in longitudinal studies, our sample experienced attrition as participants were less likely to attend follow-up sessions. This can introduce attrition

bias into the results; to examine this further, we examined whether baseline demographics differed from participants who attended only baseline, or 2, 3, and 4 assessments. There was no difference in sex (P = .81), age at baseline (P = .054), CAARMS (p = .61), SANS (P = .39) or GAF (P = .97) but there were statistical differences in ethnicity (P = *.04*) and years in education (P = *.0001*). Lower years education have been associated with attrition in a number of other longitudinal studies,[54] however the reasons for this are still unclear.[55] Thirdly, this study only compared brain structure of CHR vs HC and CHR-T vs CHR-NT at baseline. Longitudinal MRI scans would clarify if changes in brain structure in the early phases of those at risk of psychosis may lead to better predictions of symptoms and functioning. Fourthly, when considering antipsychotics we conducted a sensitivity analysis excluding individuals using this medication and also those with missing medication data. However, residual confounding is a possibility and could occur when antipsychotic use was not accurately recalled by the participant. Lastly, CHR and HC were significantly different in term of their father's socioeconomic status and years of education. However, the latter could be a downstream influence, as CHR individuals may be less likely to participate in higher education because of their symptoms. As socioeconomic status was different between the groups, we considered including it as a covariate in an additional sensitivity analysis. However, we determined that socioeconomic status did not have a significant effect on any of the brain volumes of interest, so this sensitivity analysis was not included. In terms of strengths, the present study is a multicenter international study with diverse sites, so the sample is more representative globally. The sample size is reasonably large, increasing the statistical power of the analyses. Finally, all sites used ADNI-2 MRI sequences, which have been specifically developed for muti-center studies, and provided a standard, consistent protocol across sites for imaging analysis.

To conclude, our findings suggest that baseline regional brain volume could serve as an indicator for the persistence of positive symptoms and the future transition to psychosis in a sub-set of CHR individuals. We further demonstrate reduced total and regional GM volume in CHR individuals compared to HC at baseline. Future longitudinal MRI studies in CHR individuals will be crucial to further understand the progression of brain structure and its interaction with psychotic symptoms and functioning.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin online.

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Conflict of Interest

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References

1. Salazar de Pablo G, Radua J, Pereira J, et al. Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. *JAMA Psychiatry*. 2021;78:970-978. https://doi.org/10.1001/jamapsychiatry.2021.0830
2. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*. 2012;69:220-229. https://doi.org/10.1001/archgenpsychiatry.2011.1472
3. Kempton MJ, McGuire P. How can neuroimaging facilitate the diagnosis and stratification of patients with psychosis? *Eur Neuropsychopharmacol*. 2015;25:725-732. https://doi.org/10.1016/j.euroneuro.2014.07.006
4. Gifford G, Crossley N, Fusar-Poli P, et al. Using neuroimaging to help predict the onset of psychosis. *NeuroImage*. 2017;145:209-217. https://doi.org/10.1016/j.neuroimage.2016.03.075
5. ENIGMA. Association of Structural Magnetic Resonance Imaging Measures with psychosis onset in individuals at clinical high risk for developing psychosis: an ENIGMA working group mega-analysis. *JAMA. Psychiatry*. 2021;78:753-766. https://doi.org/10.1001/jamapsychiatry.2021.0638
6. Vissink CE, Winter-van Rossum I, Cannon TD, Fusar-Poli P, Kahn RS, Bossong MG. Structural brain volumes of individuals at clinical high risk for psychosis: a meta-analysis. *Biol Psychiatry Glob Open Sci*. 2022;2:147-152. https://doi.org/10.1016/j.bpsgos.2021.09.002
7. Luna LP, Radua J, Fortea L, et al. A systematic review and meta-analysis of structural and functional brain alterations in individuals with genetic and clinical high-risk for psychosis and bipolar disorder. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2022;117:110540. https://doi.org/10.1016/j.pnpbp.2022.110540
8. Lin A, Nelson B, Yung AR. 'At-risk' for psychosis research: where are we heading? *Epidemiol Psychiatr Sci*. 2012;21:329-334. https://doi.org/10.1017/S2045796012000388
9. Polari A, Lavoie S, Yuen H-P, et al. Clinical trajectories in the ultra-high risk for psychosis population. *Schizophr Res*. 2018;197:550-556. https://doi.org/10.1016/j.schres.2018.01.022
10. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat*. 2020;16:519-534. https://doi.org/10.2147/ndt.S225643
11. Cropley VL, Lin A, Nelson B, et al. Baseline grey matter volume of non-transitioned "ultra high risk" for psychosis individuals with and without attenuated psychotic symptoms at long-term follow-up. *Schizophr Res*. 2016;173:152-158. https://doi.org/10.1016/j.schres.2015.05.014

12. Tognin S, Richter A, Kempton MJ, et al. The relationship between Grey matter volume and clinical and functional outcomes in people at clinical high risk for psychosis. *Schizophrenia Bulletin Open*. 2022;3. https://doi.org/10.1093/schizbullopen/sgac040
13. Bersani FS, Minichino A, Fojanesi M, et al. Cingulate cortex in schizophrenia: its relation with negative symptoms and psychotic onset. A review study. *Eur Rev Med Pharmacol Sci*. 2014;18:3354-3367. https://doi.org/10.1111/j.1601-5215.2011.00640.x
14. Stevens FL, Hurley RA, Taber KH, Hurley RA, Hayman LA, Taber KH. Anterior cingulate cortex: unique role in cognition and emotion. *J Neuropsychiatry Clin Neurosci*. 2011;23:121-125. https://doi.org/10.1176/jnp.23.2.jnp121
15. Miyata J. Toward integrated understanding of salience in psychosis. *Neurobiol Dis*. 2019;131:104414. https://doi.org/10.1016/j.nbd.2019.03.002
16. Palaniyappan L, Liddle PF. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. *J Psychiatry Neurosci*. 2012;37:17-27. https://doi.org/10.1503/jpn.100176
17. Tian Y, Zalesky A, Bousman C, Everall I, Pantelis C. Insula functional connectivity in schizophrenia: subregions, gradients, and symptoms. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2019;4:399-408. https://doi.org/10.1016/j.bpsc.2018.12.003
18. Wylie KP, Tregellas JR. The role of the insula in schizophrenia. *Schizophr Res*. 2010;123:93-104. https://doi.org/10.1016/j.schres.2010.08.027
19. van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr Bull*. 2008;34:1066-1082. https://doi.org/10.1093/schbul/sbn117
20. Yung AR, Yung AR, Pan Yuen H, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Australian & New Zealand Journal of Psychiatry*. 2005;39:964-971. https://doi.org/10.1080/j.1440-1614.2005.01714.x
21. Mallett R. Sociodemographic schedule. *Section of Social Psychiatry, Institute of Psychiatry*. 1997;183:35.
22. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry*. 1989;155:49-52. https://doi.org/10.1192/S0007125000291496
23. Hall RC. Global assessment of functioning: a modified scale. *Psychosomatics*. 1995;36:267-275. https://doi.org/10.1016/S0033-3182(95)71666-8
24. Hedges EP, Dickson H, Tognin S, et al. Verbal memory performance predicts remission and functional outcome in people at clinical high-risk for psychosis. *Schizophrenia research. Cognition*. 2022;28:100222. https://doi.org/10.1016/j.scog.2021.100222
25. Jack CR Jr, Bernstein MA, Borowski BJ, et al. Update on the magnetic resonance imaging core of the Alzheimer's disease neuroimaging initiative. *Alzheimers Dement*. 2010;6:212-220. https://doi.org/10.1016/j.jalz.2010.03.004
26. Hedges EP, Dimitrov M, Zahid U, et al. Reliability of structural MRI measurements: the effects of scan session, head tilt, inter-scan interval, acquisition sequence, FreeSurfer version and processing stream. *NeuroImage*. 2022;246:118751. https://doi.org/10.1016/j.neuroimage.2021.118751
27. Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull*. 2012;39:1129-1138. https://doi.org/10.1093/schbul/sbs118
28. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl. Psychiatry*. 2012;2:e190. https://doi.org/10.1038/tp.2012.116
29. Si S, Bi A, Yu Z, et al. Mapping gray and white matter volume abnormalities in early-onset psychosis: an ENIGMA multicenter voxel-based morphometry study. *Mol Psychiatry*. 2024;29:496-504. https://doi.org/10.1038/s41380-023-02343-1
30. Picó-Pérez M, Vieira R, Fernández-Rodríguez M, De Barros MAP, Radua J, Morgado P. Multimodal meta-analysis of structural gray matter, neurocognitive and social cognitive fMRI findings in schizophrenia patients. *Psychol Med*. 2022;52:614-624. https://doi.org/10.1017/S0033291721005523
31. Chan RCK, Di X, McAlonan GM, Gong Q-y. Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. *Schizophr Bull*. 2009;37:177-188. https://doi.org/10.1093/schbul/sbp073
32. Ding Y, Ou Y, Pan P, et al. Brain structural abnormalities as potential markers for detecting individuals with ultra-high risk for psychosis: a systematic review and meta-analysis. *Schizophr Res*. 2019;209:22-31. https://doi.org/10.1016/j.schres.2019.05.015
33. Kuo SS, Pogue-Geile MF. Variation in fourteen brain structure volumes in schizophrenia: a comprehensive meta-analysis of 246 studies. *Neurosci Biobehav Rev*. 2019;98:85-94. https://doi.org/10.1016/j.neubiorev.2018.12.030
34. van Erp TGM, Hibar DP, Rasmussen JM, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry*. 2016;21:547-553. https://doi.org/10.1038/mp.2015.63
35. Detry MA, Ma Y. Analyzing repeated measurements using mixed models. *JAMA*. 2016;315:407-408. https://doi.org/10.1001/jama.2015.19394
36. Engqvist L. The mistreatment of covariate interaction terms in linear model analyses of behavioural and evolutionary ecology studies. *Anim Behav*. 2005;70:967-971. https://doi.org/10.1016/j.anbehav.2005.01.016
37. Navari S, Dazzan P. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychol Med*. 2009;39:1763-1777. https://doi.org/10.1017/S0033291709005315
38. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev*. 2013;37:1680-1691. https://doi.org/10.1016/j.neubiorev.2013.06.001
39. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abuse Negl*. 2003;27:169-190. https://doi.org/10.1016/s0145-2134(02)00541-0
40. Chung Y, Allswede D, Addington J, et al. Cortical abnormalities in youth at clinical high-risk for psychosis: findings from the NAPLS2 cohort. *Neuroimage Clin*. 2019;23:101862. https://doi.org/10.1016/j.nicl.2019.101862
41. Maier A, Gieling C, Heinen-Ludwig L, et al. Association of childhood maltreatment with interpersonal distance and social touch preferences in adulthood. *Am J Psychiatry*. 2020;177:37-46. https://doi.org/10.1176/appi.ajp.2019.19020212

42. Madden RA, Atkinson K, Shen X, et al. Structural brain correlates of childhood trauma with replication across two large, independent community-based samples. *European Psychiatry*. 2023;66:e19. https://doi.org/10.1192/j.eurpsy.2022.2347
43. Ho NF, Holt DJ, Cheung M, et al. Progressive decline in hippocampal CA1 volume in individuals at ultra-high-risk for psychosis who do not remit: findings from the longitudinal youth at risk study. *Neuropsychopharmacology.* 2017;42:1361-1370. https://doi.org/10.1038/npp.2017.5
44. Sasabayashi D, Takayanagi Y, Takahashi T, et al. Subcortical brain volume abnormalities in individuals with an At-risk mental state. *Schizophr Bull*. 2020;46:834-845. https://doi.org/10.1093/schbul/sbaa011
45. Padmanabhan JL, Tandon N, Haller CS, et al. Correlations between brain structure and symptom dimensions of psychosis in schizophrenia, schizoaffective, and psychotic bipolar I disorders. *Schizophr Bull*. 2014;41:154-162. https://doi.org/10.1093/schbul/sbu075
46. Del Re EC, Stone WS, Bouix S, et al. Baseline cortical thickness reductions in clinical high risk for psychosis: brain regions associated with conversion to psychosis versus non-conversion as assessed at one-year follow-up in the Shanghai-At-Risk-for-Psychosis (SHARP) study. *Schizophr Bull*. 2020;47:562-574. https://doi.org/10.1093/schbul/sbaa127
47. Fortea A, Batalla A, Radua J, et al. Cortical gray matter reduction precedes transition to psychosis in individuals at clinical high-risk for psychosis: a voxel-based meta-analysis. *Schizophr Res*. 2021;232:98-106. https://doi.org/10.1016/j.schres.2021.05.008
48. Walter A, Suenderhauf C, Harrisberger F, et al. Hippocampal volume in subjects at clinical high-risk for psychosis: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2016;71:680-690. https://doi.org/10.1016/j.neubiorev.2016.10.007
49. Velthorst E, Nieman DH, Klaassen RMC, et al. Three-year course of clinical symptomatology in young people at ultra high risk for transition to psychosis. *Acta Psychiatr Scand*. 2011;123:36-42. https://doi.org/10.1111/j.1600-0447.2010.01593.x
50. Salazar, de Pablo G, Soardo L, Cabras A, et al. Clinical outcomes in individuals at clinical high risk of psychosis who do not transition to psychosis: a meta-analysis. *Epidemiol Psychiatr Sci*. 2022;31:e9. https://doi.org/10.1017/S2045796021000639
51. Deng W, Chong B, Addington J, et al. Beyond the descriptive: a comprehensive, multidomain validation of symptom trajectories for individuals at clinical high risk for psychosis. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2025;10:195-202. https://doi.org/10.1016/j.bpsc.2024.08.020
52. Hengartner MP, Heekeren K, Dvorsky D, Walitza S, Rössler W, Theodoridou A. Course of psychotic symptoms, depression and global functioning in persons at clinical high risk of psychosis: results of a longitudinal observation study over three years focusing on both converters and non-converters. *Schizophr Res*. 2017;189:19-26. https://doi.org/10.1016/j.schres.2017.01.040
53. Tran T, Spilka MJ, Raugh IM, et al. Negative symptom trajectories in individuals at clinical high risk for psychosis: differences based on deficit syndrome, persistence, and transition status. *Schizophr Bull Open*. 2023;4. https://doi.org/10.1093/schizbullopen/sgad014
54. Young AF, Powers JR, Bell SL. Attrition in longitudinal studies: who do you lose? *Aust N Z J Public Health*. 2006;30:353-361. https://doi.org/10.1111/j.1467-842X.2006.tb00849.x
55. Reinwand DA, Crutzen R, Elfeddali I, et al. Impact of educational level on study attrition and evaluation of web-based computer-tailored interventions: results from seven randomized controlled trials. *J Med Internet Res*. 2015;17:e228. https://doi.org/10.2196/jmir.4941

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