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Original Article

Investigation of Neurocognitive Deficits, Quality of Life, and Functional Performance in Ultra-High-Risk Individuals Compared to Familial High-Risk Individuals for Schizophrenia

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Abstract

Objective: This study aimed to investigate neurocognitive functioning, quality of life, and global functional performance in Ultra-High Risk (UHR) individuals compared to Familial High-Risk (FHR) individuals for developing schizophrenia.
Method: An observational cross-sectional study was conducted using a convenient sampling method at Roozbeh Hospital in Tehran, Iran, from June 2017 to January 2020. The study included 40 UHR individuals based on the Structured Interview for Psychosis Syndrome (SIPS) interview, as well as 34 FHR individuals due to genetic risk. Neurocognitive functioning, quality of life, and global functional performance were assessed by using the Cambridge Automated Neuropsychological Test Battery (CANTAB) and Controlled Oral Word Association Test (COWAT), Quality of Life Scale (QLS), and Global Assessment of Functioning (GAF).
Results: UHR individuals for schizophrenia demonstrated significant lower scores in phonemic and semantic verbal fluency ($t = 6.218$, $P < 0.001$; $t = 4.184$, $P < 0.001$, respectively), more total errors for spatial working memory ($t = -5.874$, $P < 0.001$), and fewer problems solved in minimum moves in Stocking of Cambridge (SOC) ($t = -2.706$, $P < 0.01$) compared to FHR individuals. Intra-Extra Dimension (IED) did not differ significantly between the two groups. Moreover, the study indicated significant GAF decline ($F = 79.257$, $P < 0.001$) and lower total score on the QLS ($t = -10.655$, $P < 0.001$) in UHR compared to FHR individuals.
Conclusion: It is possible to differentiate UHR individuals from FHR individuals through neurocognitive, quality of life, and global functioning assessment.

Key words: *Cognition; Neuropsychology; Prodromal Signs; Psychosis; Schizophrenia*

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Schizophrenia is a debilitating disorder often with a long prodromal stage (1). The prodromal state of schizophrenia is accompanied by an increased risk for developing the full-blown disease (2). Early risk assessment in these individuals is beneficial for proper management (3). The ultra-high risk state for schizophrenia (UHR) is a clinical description for the prodromal state of schizophrenia (4). UHR individuals can be identified by Structured Interview for Psychosis Syndrome (SIPS). It is a common psychometric tool for identifying UHR individuals based on their symptoms, individual traits, and general function level, which is assessed by means of a semi-structured interview (5). Moreover, familial high-risk individuals (FHR) are at increased risk irrespective of the UHR criteria (6). In recent decades, many studies have evaluated the significance of a positive family history in making individuals more vulnerable to schizophrenia. Conversely, the UHR or clinically high-risk group can be considered an almost recent concept. Therefore, comparing the clinical and genetic risk groups is expected to elucidate key prognostic features of the schizophrenia prodrome.

The state of cognitive deficits contributes to the functional outcomes of individuals with schizophrenia (7). Current diagnostic tools on schizophrenia (ICD11, DSM5) include sections on cognitive impairments among the related clinical findings (8). The most prominent deficits in the neurocognitive domains in schizophrenia are known to take place in working memory and executive functioning (9). Notably, neurocognitive impairments often predate the main psychopathological symptoms of schizophrenia (10). UHR individuals also manifest deficits in several neurocognitive domains (11). Moreover, some neurocognitive impairments previously demonstrated prognostic significance in determining the subsequent risk of disease transition (12). Global functional performance and quality of life (QoL) are the major constituents in psychiatric therapies (13). Although several studies have previously performed the prognostic risk assessment in UHR and FHR individuals, there has been limited direct comparison between these two groups (14). Therefore, comparing the severity of neurocognitive impairments, the quality of life, and the functional outcomes is expected to enable the identification of the key prognostic markers in the prodromal state of the disease.

The principal objective of this study was to investigate neurocognitive performance including Spatial Span (SSP), Spatial Working Memory (SWM), Stocking of Cambridge (SOC), and Intra-Extra Dimensional Set Shifting (IED), Verbal Fluency, QoL, and functional performance in UHR and FHR individuals. We aimed to test if there are higher levels of cognitive deficits, lower QoL, and poorer cognitive performance in the UHR group compared to FHR individuals.

Materials and Methods

Participants

This was an observational cross-sectional study with a convenient sampling method. Participants were identified from the medical records of outpatient or inpatient units of Roozbeh Hospital, Tehran, from June 2017 to January 2020. Two groups were defined initially: first-degree relatives of patients with clinical diagnosis of schizophrenia, and help-seeking individuals. Medical record files of admitted patients from Inpatient Psychiatric wards of Roozbeh Hospital were explored. All first-degree relatives of the individuals with schizophrenia in the 15-39 age group were selected. The second group participants were recruited from help-seeking individuals referring to Emergency Department with a recorded history of at least one psychotic symptom with sub-threshold duration or/and frequency (not meeting the criteria for any psychotic disorder), as evaluated by a psychiatric specialist. Individuals were identified from the records and contacted by telephone. Participants from both groups were primarily included if they met these criteria: age between 15 to 39 years, education level of at least junior high school, no documented history of clinical schizophrenia, or any other related psychotic diseases or history of taking any anti-psychotic medications, and not using psychoactive drugs within the previous year. The aim and procedure of the study were briefly explained to each person, and those who agreed to participate in the study were recruited by obtaining both oral and written informed consent.

All individuals were investigated using the Structured Interview for Psychosis Syndrome (SIPS) scale for the identification of the UHR group, conducted at Roozbeh by a well-trained resident of psychiatry. Individuals who neither met UHR criteria nor had positive familial history were excluded from the study. A summary of symptom severity scales as well as the results of the Global Assessment of Functioning (GAF) for each person were reported. Neurocognitive assessments were performed for all included individuals in the laboratory of Cognitive Science Studies, at Roozbeh Hospital. Working memory and executive functioning were evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB), and verbal fluency with the Controlled Oral Word Association Test (COWAT). An additional interview was performed for the assessment of QoL and scored using Quality of Life Scale (QLS). All interviews were recorded to ensure the completion of interviews, while informed consent was obtained from all participants.

Procedure

Psychopathology Measures

The UHR individuals were identified using SIPS scale, which is a semi-structured interview tool that includes the Scale of Prodromal Symptoms (SOPS), family-history questionnaire, Schizotypal Personality Disorder Checklist, and an adapted form of the GAF scale (5). The SOPS, as a part of the SIPS, comprises of positive,

negative, disorganization, and general symptoms, as well as a summary of the SIPS syndrome criteria. It is a 19-item scale used for addressing the severity of each symptom, if present. The SIPS has been used for two decades with good indicators of its reliability and validity and has been previously employed in a sample of Iranian population (5, 15). In this study individuals were interviewed and scored from 0-6 using version 5.6.1 of the SIPS interview (16) by a trained psychiatry resident. Symptoms with a severity rating of 3-6 were further investigated regarding the symptom onset, frequency, worsening, and the presence of schizotypal personality disorders and reported. As a distinct variable in our study, GAF results were separately recorded (see below). Based on SOPS scores, individuals were included if they belonged to at least one of the following categories: Brief Intermittent Psychotic Syndrome (BIPS), Attenuated Positive Symptom Syndrome (APS) or Genetic Risk and Deterioration Syndrome (GRDS).

Neurocognitive Performance

Neurocognitive assessment tests were conducted using the CANTAB and COWAT. The CANTAB is a standardized assessment tool that was originally developed by the University of Cambridge in 1992. Due to their completely visuospatial property, these tools do not pose any language barriers or engaging problems as a result of psychopathologies. Therefore, the CANTAB is suitable for appraisal of patients from different cultural backgrounds and comprises insignificant cultural interference in information-obtaining tasks. These tests were standardized in a 3000 population (17). The results are reported as mean and standard deviation (SD), which are utilizable for comparative objectives.

In this study, the SSP, SWM, SOC, and IED tests were performed. The SSP test evaluates the reliability of working memory performance in terms of span length, mean time to first response, mean time to last response, total errors, and total usage errors as the dependent variables. The SWM test was used as a measure of accuracy in working memory errors in 4-, 6-, and 8- boxes conditions, with results recorded as within errors and total errors. SOC and IED are measures of executive functioning. SOC was recorded for 2- to 5-move mean initial thinking time and mean subsequent thinking time, and the number of problems solved in minimum moves. The IED test was applied to identify impairments in set-shifting ability. The dependent variables in IED included completed stage errors and trials, stages completed, and total trials.

Verbal fluency performance was investigated using the COWAT. This test assesses individual performances on phonemic and semantic word finding (18, 19). Phonemic verbal fluency was evaluated by instructing the individuals to make as many words as possible with a specified alphabet within one minute – no more than one person's name. Moreover, participants were asked to say animal names as many as possible to assess semantic verbal fluency. The dependent variable in this task was the mean number of acceptable words in the two conditions. All tests were observed by an interviewer and the results were recorded.

Global Assessment of Functioning

GAF is a modified form of the GAF scale originally introduced by Hall 1995 (20). This scale evaluates the global functional performance in mental illnesses, rated from 0-100. In this study, the modified version of the GAF scale from the SIPS scale was used. The results were recorded as the current and last year's performance levels for symptomatic UHR (BIPS + APS), GRDS, and FHR groups .

Quality of Life

All participants underwent a semi-structured interview for investigating their QoL and scored based on the QLS (21, 22). This is a 21-item scale specialized for individuals with schizophrenia that focuses on determining the QoL regarding interpersonal, instrumental, intrapsychic, and commonplace productive functioning and has been successfully validated for the Iranian population in a recent study (22). Each item includes a number of suggested questions and are open to be further investigated as needed. Afterward, a score from 0 to 6 is given, standing for a range from absent to completely adequate performance. In this study, interviews were performed for each participant, and scores were recorded for each category.

Statistical Analyses

Data analysis was performed using the Statistical Package for Society Sciences (SPSS) version 23.0. Test results were reported as quantitative variables using mean and standard deviation for each group. Bivariate analyses (UHR vs. FHR) were conducted using two-tailed student t-tests. Moreover, the analysis of variance (ANOVA) test was used for GAF results in three groups: BIPS + APS, GRDS, and FHR.

Ethical Aspects

The study was conducted in accordance with the principles of the Declaration of Helsinki (1996) and the current Good Clinical Practice guidelines. The purpose and an overview of the study were explained to the individuals during the initial contact. For those who agreed to participate, all the necessary information was provided, prior to signing written informed consents. The information of the participants was used anonymously and solely for the purpose of the study. The original names were only available to the main researcher. This study was approved by the ethics committee of Tehran University of Medical Sciences (TUMS) and was supported by TUMS with the code IR.TUMS.MEDICINE.REC.1398.313.

Results

Study Population

A total number of 132 individuals initially attended the study, including 59 from the genetic risk group and 73 from the help-seekers group. Some individuals were

excluded due to the following reasons: two from the genetic risk group due to a previous history of psychotic disorders, two from the genetic risk group and five from the help-seekers because of recent consumption of stimulant drugs, seven from the genetic risk group and thirteen from the help-seekers group owing to prior anti-psychotic drugs consumption. Afterward, an additional 29 individuals were excluded during the SIPS interview for not meeting either the UHR or HR criteria.

Our final sample consisted of 40 UHR individuals (UHR group, 54%) based on the SIPS interview, and 34 high-risk individuals due to genetic risk (FHR group, 46%). Among 74 participants, 28 (70%) and 24 (70.6%) were women in the UHR and FHR groups, respectively, and the difference was not significant (chi = 0.003, P = 0.956). The mean ages of the participants were 27.48 ± 5.34 and 26.59 ± 4.85 years in the UHR and FHR groups, respectively. There was no significant difference between the two groups (t = 0.743, P = 0.460).

Neurocognitive Domains

Verbal Fluency

Ultra-high-risk participants obtained significantly lower scores for phonemic verbal fluency compared with the FHR group. Moreover, a significantly lower number of words were generated by the UHR individuals in the semantic fluency test in comparison with the FHR participants (Table 1).

Table 1. Individual Performances in Phonemic and Semantic Verbal Fluency for Ultra-High Risk for Schizophrenia (UHR) (N = 40) vs. Familial High-Risk for Schizophrenia (FHR) (N = 34) Individuals

Items	Parameter	Mean	SD	t	P-Value
Phonemic	UHR	8.25	2.362	6.218	< 0.001
	FHR	12.09	2.948		
Semantic	UHR	13.55	3.714	4.184	< 0.001
	FHR	17.38	4.163		

Abbreviations: UHR: Ultra-High Risk for Schizophrenia; FHR: Familial High-Risk for Schizophrenia.

Working Memory

Span length was significantly lower in the UHR group compared to the FHR group. Individual performances on mean time to first response, mean time to last response, total errors, and total usage errors exhibited no significant differences. Results for individual performances on SSP are listed in Table 2.

The Spatial Working Memory test was conducted in three conditions – 4-, 6-, and 8-box. Total errors for SWM were significantly different between the two groups, with significantly poorer results for the UHR group (t = -5.874, P < 0.001). However, the within errors difference was not significant (t = -1.809, P = 0.075).

Executive Functioning

SOC test was performed to assess executive functioning. The results obtained for mean initial thinking time in 2-, 3-, and 5-moves were only non-significantly different. However, performance was significantly lower in mean initial thinking time in 4-moves for the UHR group vs. the FHR group (t = -2.592, P = 0.012). Furthermore, mean subsequent thinking times were invariably greater for UHR individuals. The number of problems solved in minimum moves was significantly less in the UHR group versus the FHR group (t = -2.706, P < 0.01). The results are presented in Table 2 in which no significant difference was reported between the two groups in any of IED domains.

Quality of Life

The total score of QoL was 75.17 ± 9.99 for the UHR group and 98.88 ± 8.96 for the FHR group, indicating significantly lower levels for the former group (t = -10.655, P < 0.001). Subcategories also invariably showed significantly lower levels of QoL for the UHR compared to FHR group. Specifically, differences are present for interpersonal relationship (t = -9.523, P < 0.001), instrumental role (t = -10.111, P < 0.001), intrapsychic foundation (t = -8.756, P < 0.001) and common objects and activities (t = -4.568, P < 0.001). A summary of results is listed in Table 3.

Global Assessment of Functioning

For all participants, GAF was investigated for the current status, the highest value over the last year, and the difference in terms of decline. Analysis was performed for three risk groups with a significantly weaker pattern for the UHR compared to the FHR group. Specifically, significant impairments for UHR subgroups were evident for current GAF (F = 61.692, P < 0.001), highest GAF (F = -4.838, P = 0.011), and GAF decline (F = 79.257, P < 0.001) compared to FHR. The results are represented in Table 4.

Table 2. Results of Neurocognitive Assessment by Using CANTAB for Ultra-High Risk for Schizophrenia (UHR) vs. Familial High-Risk for Schizophrenia (FHR) Individuals

Test	Variables	UHR (N = 40) Mean ± SD	FHR (N = 34) Mean ± SD	t	P-Value
Spatial Span					
	Span length	4.9 ± 1.12	6.03 ± 1.29	4.018	**< 0.001**
	Mean time to first response	3181.35 ± 637.41	3099.91 ± 529.33	-0.591	0.556
	Mean time to last response	4001.42 ± 728.21	3982.55 ± 630.05	-0.118	0.906
	Total errors	13.18 ± 5.47	13.62 ± 5.71	0.340	0.735
	Total usage errors	1.85 ± 1.64	1.82 ± 1.54	-0.071	0.944
Stocking of Cambridge					
	Mean initial thinking time: 2-moves	1344.24 ± 1287.44	1032.98 ± 1036.67	-1.121	0.266
	Mean initial thinking time: 3-moves	3203.03 ± 2563.85	2022.17 ± 1600.50	-2.370	**0.021**
	Mean initial thinking time: 4-moves	2879.36 ± 1831.34	193.20 ± 1232.34	-2.592	**0.012**
	Mean initial thinking time: 5-moves	2881.67 ± 2178.36	2824.22 ± 3085.24	-0.092	0.927
	Mean subsequent thinking time: 2-moves	468.21 ± 640.37	86.39 ± 232.93	-3.431	**0.001**
	Mean subsequent thinking time: 3-moves	484.58 ± 805.46	93.07 ± 339.96	-2.736	**0.009**
	Mean subsequent thinking time: 4-moves	1516.90 ± 1616.06	598.04 ± 682.67	-3.232	**0.002**
	Mean subsequent thinking time: 5-moves	1475.33 ± 1634.57	541.25 ± 1213.51	-2.771	**0.007**
	Problems solved in minimum moves	6.02 ± 2.21	7.11 ± 1.17	2.706	**0.009**
Intra-Extra Dimension (IED)					
	Completed stage errors	9.700 ± 5.482	9.176 ± 6.233	-0.489	0.626
	Completed stage trials	63.925 ± 20.520	66.205 ± 7.441	-0.654	0.516
	Stages completed	8.200 ± 2.344	8.882 ± 0.447	1.797	0.079
	Total errors	10.800 ± 6.131	10.911 ± 7.166	0.072	0.943
	Total trials	66.475 ± 19.144	69.147 ± 10.719	0.723	0.472

Abbreviations: CANTAB: The Cambridge Neuropsychological Test Automated Battery; UHR: Ultra-High Risk for Schizophrenia; FHR: Familial High-Risk for Schizophrenia.

Table 3. Quality of Life for Ultra-High Risk for Schizophrenia (UHR) vs. Familial High-Risk for Schizophrenia (FHR) Individuals

Variables	UHR (N = 40) Means ± SD	FHR (N = 34) Means ± SD	t	P-Value
Interpersonal relationship	3.836 ± 0.526	4.916 ±.434	9.523	< 0.001
Instrumental role	2.537 ± 0.649	4.044 ±.626	10.111	< 0.001
Intrapsychic foundation	3.593 ± 0.526	4.641 ±.493	8.756	< 0.001
Common objects and activities	4.612 ± 0.571	5.308 ±.738	4.568	< 0.001
Intrapsychic foundation plus Common objects and activities	3.809 ± 0.536	4.778 ±.434	8.445	< 0.001
Total score	75.17 ± 9.99	98.88 ± 8.96	10.655	< 0.001

Abbreviations: UHR: Ultra-High Risk for Schizophrenia; FHR: Familial High-Risk for Schizophrenia.

Table 4. Global Assessment of Functioning Performances for Ultra-High Risk for Schizophrenia (UHR) vs. Familial High-Risk for Schizophrenia (FHR) Individuals

Variables	BIPS & APS (N = 26) Means ± SD	GRDS (N = 14) Means ± SD	FHR (N = 34) Means ± SD	F	P-Value
GAF(current)	43.65 ± 8.78	41.07 ± 6.84	68.53 ± 11.71	61.692	< 0.001
GAF(highest)	67.50 ± 9.19	69.64 ± 7.19	74.44 ± 9.02	4.838	0.011
GAF(decline)	23.84 ± 8.40	28.57 ± 4.56	5.91 ± 6.06	79.257	< 0.001

Abbreviations: UHR: Ultra-High Risk for Schizophrenia; FHR: Familial High-Risk for Schizophrenia; BIPS: Brief Intermittent Psychotic Syndrome; APS: Attenuated Positive Symptom Syndrome; GRDS: Genetic Risk and Deterioration Syndrome.

Discussion

In this study, we investigated the comparative performances of individuals with clinical increased risk and those with genetic risk for schizophrenia in several cognitive and functional domains. The UHR group demonstrated significantly impaired functioning in most of the neurocognitive subdomains related to executive functioning, working memory, and verbal fluency compared to individuals in the FHR group. Specifically, we identified significant between-group differences in both phonemic and semantic domains of verbal fluency performances. Additionally, the UHR individuals were found to experience relatively lower levels of QoL in all subdomains. Moreover, they performed significantly poorer in both the current and previous general functioning compared to the genetically at-risk group.

Verbal fluency is a potential predictor of conversion rates of at-risk groups to the full-blown disease (23). Deficits in this function herald an increasing risk for the persistence of negative symptoms in individuals with schizophrenia (24). Previous studies on at-risk individuals have mainly investigated declines in the semantic category of verbal fluency (23). In this study, we also included the phonemic subdomain to investigate the two at-risk groups. Remarkably, UHR individuals demonstrated significant decline in both categories compared to FHR individuals. In a similar design, Magaud *et al.* obtained no significant differences in phonological fluency (25). However, their study used non-specific inclusion criteria for the comparison group, unlike the selection of FHR individuals in this work. Our findings designate a possible prognostic value of phonemic verbal fluency in determining the risk of developing schizophrenia among the at-risk groups. Future studies are needed to identify the state of impairments in verbal fluency in UHR and FHR individuals compared to normal individuals.

Working memory function significantly declines in individuals with schizophrenia (26). The dorsolateral prefrontal cortex (DLPFC) is the cortical center responsible for performing working memory tasks (27). Recently, altered activation levels in DLPFC have been demonstrated to be associated with the severity of disorganization features among individuals with schizophrenia (28). Additionally, performance in working memory is a well-established prognostic marker with respect to the risk of conversion in UHR individuals (29). A meta-analysis study identified working memory function as the only domain that significantly differed

between UHR and FHR individuals (30). In the present study, significant impairments were denoted in some parameters of spatial working memory in the UHR individuals compared to the FHR group. These findings suggest the potential utility of working memory performance in determining the prognosis among the at-risk groups for schizophrenia. Future studies involving a long-term follow-up might be helpful to delineate the importance of these impairments in predicting the rate of transition to the full-blown psychosis.

Ultra-high-risk individuals for schizophrenia have significant impairments in planning and problem-solving skills compared to normal controls (31). These functions are the two subdomains of executive functioning associated with the patients' functional outcomes (32). In this study, the problem-solving ability and subsequent thinking times were significantly impaired in the UHR compared to FHR individuals, whereas initial thinking time differed only in one test condition. In a number of previous studies, UHR individuals demonstrated comparable performances to the individuals with first-episode schizophrenia (31). Cognitive flexibility is another related subdomain of executive functioning in schizophrenia. Previous studies identified significant declines in cognitive flexibility in UHR individuals compared to normal controls, but non-significant differences with first-episode schizophrenia (33). Our results replicated such comparable performance in cognitive flexibility for the two at-risk groups. These findings might denote shortages of the current methods on executive function assessment in distinguishing the prodromal and clinical state.

In a recent meta-analytic study of UHR individuals, lower QoL scores were associated with impaired cognitive performance and the severity of psychiatric symptoms (24). Similarly, the current study demonstrated significantly lower levels of QoL in UHR individuals compared to the FHR group. Despite the presence of similar results for UHR in comparison with normal controls (34), previous research has paid less attention to their QoL relative to genetically at-risk individuals. Adjunctively, the functional outcomes in individuals with schizophrenia are closely related to QoL (35). In this study, we obtained significant impairments in GAF for the UHR group compared to the FHR group. Functional performance and QoL have crucial roles in studying psychiatric disorders due to their impact on clinical decision-making (36).

Limitation

Nevertheless, several limitations were present in the conduction of this study. Firstly, this study lacked normal control participants. As a result, we could not derive interrelations between the clinical findings and functional outcomes in order to interpret the observed differences. Moreover, follow-up data were not included in this study, thereby limiting the identification and comparison of the actual risks of conversion. Another limitation was the lack of corrections for age and sex differences. Nonetheless, we identified several factors that significantly differed between the two groups that might be useful for further investigations. Future longitudinal studies are needed to focus on the role of each domain of neurocognitive function in predicting the rate of transition to the first episode of full-blown psychosis.

Conclusion

In summary, this study compared two at-risk groups for developing schizophrenia regarding their performance across several neurocognitive domains and their states in functional outcomes. The results indicate that it is possible to differentiate UHR individuals from FHR individuals through neurocognitive, quality of life, and global functioning assessment. Future longitudinal studies are required to focus on the role of each domain of neurocognitive function in predicting the rate of transition to the first episode of full-blown psychosis.

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Conflict of Interest

None.

References

1. Häfner H. From Onset and Prodromal Stage to a Life-Long Course of Schizophrenia and Its Symptom Dimensions: How Sex, Age, and Other Risk Factors Influence Incidence and Course of Illness. Psychiatry J. 2019;2019:9804836.
2. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res. 2003;60(1):21-32.
3. Yung AR. Treatment of people at ultra-high risk for psychosis. World Psychiatry. 2017;16(2):207-8.
4. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull. 1996;22(2):353-70.
5. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal

symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003;29(4):703-15.
6. Cardno AG, Marshall EJ, Coid B, Macdonald AM, Ribchester TR, Davies NJ, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry. 1999;56(2):162-8.
7. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull. 2000;26(1):119-36.
8. Valle R. Schizophrenia in ICD-11: Comparison of ICD-10 and DSM-5. Rev Psiquiatr Salud Ment (Engl Ed). 2020;13(2):95-104.
9. Reichenberg A. The assessment of neuropsychological functioning in schizophrenia. Dialogues Clin Neurosci. 2010;12(3):383-92.
10. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 2009;23(3):315-36.
11. Pukrop R, Schultze-Lutter F, Ruhrmann S, Brockhaus-Dumke A, Tendolkar I, Bechdolf A, et al. Neurocognitive functioning in subjects at risk for a first episode of psychosis compared with first- and multiple-episode schizophrenia. J Clin Exp Neuropsychol. 2006;28(8):1388-407.
12. Seidman LJ, Shapiro DI, Stone WS, Woodberry KA, Ronzio A, Cornblatt BA, et al. Association of Neurocognition With Transition to Psychosis: Baseline Functioning in the Second Phase of the North American Prodrome Longitudinal Study. JAMA Psychiatry. 2016;73(12):1239-48.
13. Karow A, Wittmann L, Schöttle D, Schäfer I, Lambert M. The assessment of quality of life in clinical practice in patients with schizophrenia. Dialogues Clin Neurosci. 2014;16(2):185-95.
14. Üçok A, Direk N, Koyuncu A, Keskin-Ergen Y, Yüksel Ç, Güler J, et al. Cognitive deficits in clinical and familial high risk groups for psychosis are common as in first episode schizophrenia. Schizophr Res. 2013;151(1-3):265-9.
15. Hormozpour M, Amini H, Pajouhanfar S, Faghankhani M, Rahmani A, Sharifi V. Transition to Psychosis: Evaluation of the First-Degree Relatives of Patients with Schizophrenia . Iran J Psychiatry. 2016;11(1):15-23.
16. McGlashan TH, Miller TJ, Woods SW, Hoffman RE, Davidson L. Instrument for the assessment of prodromal symptoms and states. Early intervention in psychotic disorders. 2001:135-49.
17. Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J R Soc Med. 1992;85(7):399-402.
18. Ross TP, Calhoun E, Cox T, Wenner C, Kono W, Pleasant M. The reliability and validity of qualitative scores for the Controlled Oral Word Association Test. Arch Clin Neuropsychol. 2007;22(4):475-88.
19. Ghasemian-Shirvan E, Molavi Shirazi S, Aminikhoo M, Zareaan M, Ekhtiari H. Preliminary Normative Data of Persian Phonemic and Semantic Verbal Fluency Test. Iran J Psychiatry. 2018;13(4):288-95.
20. Hall RC. Global assessment of functioning. A modified scale. Psychosomatics. 1995;36(3):267-75.
21. Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull. 1984;10(3):388-98.
22. Masoomi M, Shadloo B, Nedjat S, Bahrami Z, Sharifi V, Amini H. Validity and reliability of the Persian version of the “Quality of Life Scale” in schizophrenia. IJPBS. 2018;12(3).
23. Becker HE, Nieman DH, Dingemans PM, van de Fliert JR, De Haan L, Linszen DH. Verbal fluency as a possible predictor for psychosis. Eur Psychiatry. 2010;25(2):105-10.
24. Yung AR, Nelson B, McGorry PD, Wood SJ, Lin A. Persistent negative symptoms in individuals at Ultra High Risk for psychosis. Schizophr Res. 2019;206:355-61.
25. Magaud E, Kebir O, Gut A, Willard D, Chauchot F, Olie JP, et al. Altered semantic but not phonological verbal fluency in young help-seeking individuals with ultra high risk of psychosis. Schizophr Res. 2010;123(1):53-8.
26. Forbes NF, Carrick LA, McIntosh AM, Lawrie SM. Working memory in schizophrenia: a meta-analysis. Psychol Med. 2009;39(6):889-905.
27. Barbey AK, Koenigs M, Grafman J. Dorsolateral prefrontal contributions to human working memory. Cortex. 2013;49(5):1195-205.
28. Smucny J, Dienel SJ, Lewis DA, Carter CS. Mechanisms underlying dorsolateral prefrontal cortex contributions to cognitive dysfunction in schizophrenia. Neuropsychopharmacology. 2022;47(1):292-308.
29. Wood SJ, Pantelis C, Proffitt T, Phillips LJ, Stuart GW, Buchanan JA, et al. Spatial working memory ability is a marker of risk-for-psychosis. Psychol Med. 2003;33(7):1239-47.
30. Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatr Scand. 2014;130(1):1-15.
31. Anda L, Brønnick KK, Johannessen JO, Joa I, Kroken RA, Johnsen E, et al. Cognitive Profile in Ultra High Risk for Psychosis and Schizophrenia: A Comparison Using Coordinated Norms. Front Psychiatry. 2019;10:695.
32. Burgess PW. Theory and methodology in executive function research. Methodology of frontal and executive function: Routledge; 2004. p. 87-121.
33. Hwang WJ, Lee TY, Shin WG, Kim M, Kim J, Lee J, Kwon JS. Global and Specific Profiles of Executive Functioning in Prodromal and Early Psychosis. Front Psychiatry. 2019;10:356.
34. Kim KR, Song YY, Park JY, Lee EH, Lee M, Lee SY, et al. The relationship between psychosocial functioning and resilience and negative symptoms in individuals at ultra-high risk for psychosis. Aust N Z J Psychiatry. 2013;47(8):762-71.

35. Woon PS, Chia MY, Chan WY, Sim K. Neurocognitive, clinical and functional correlates of subjective quality of life in Asian outpatients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(3):463-8.
36. Eack SM, Newhill CE. Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis. Schizophr Bull. 2007;33(5):1225-37.