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A case-control study
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Premorbid adjustment in individuals at ultra-high risk for developing psychosis: a case-control study

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Abstract

Objective: Deterioration in premorbid adjustment is related to ultra-high risk (UHR) individuals developing psychosis, but it has not been examined how UHR individuals’ development differs compared to healthy controls. This study investigates differences in premorbid adjustment between UHR individuals and a healthy control group.

Method: 48 UHR individuals and 50 healthy controls matched on group level for age, gender and parents’ socioeconomic status were included in the study. Both groups were assessed with the Premorbid Adjustment Scale (PAS). Based on the PAS scores, composite social and academic scales were computed.

Results: Compared to the healthy controls the UHR individuals’ social and academic premorbid adjustment declined across age periods. Social premorbid adjustment declined particularly between late adolescence and adulthood. Academic premorbid adjustment declined particularly between childhood and early adolescence. The UHR individuals had more premorbid adjustment difficulties on both the social and academic scale, and on the individual PAS scales.

Conclusion: From childhood UHR individuals have lower levels of social and academic premorbid adjustment compared to healthy controls, and the difficulties increase with age. As such, social and academic premorbid adjustment could be an important focus for early intervention.

Keywords

Psychosis; ultra-high risk; prodrome; premorbid adjustment; psychosocial factors

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1. Introduction

Psychosis entails severe psychosocial consequences for the affected individual (1), causes distress among relatives (2) and is among the most expensive mental disorders for society (3). Therefore, characterization and identification of the individual’s developing psychosis is highly relevant.

A substantial amount of studies have investigated psychosocial factors such as premorbid adjustment in patients experiencing first episode psychosis. It has been found that these patients have difficulties in social and academic premorbid adjustment when compared to healthy controls (4, 5). Additionally, for these patients, poor premorbid adjustment is associated with more negative symptoms, poor quality of life, increased risk of relapse and cognitive impairment (6-11).

Since the prodromal phase can only be ascertained retrospectively, the term ultra-high risk (UHR) for developing psychosis has been introduced to refer to a subthreshold syndrome or genetic vulnerability that can lead to subsequent psychosis (12). It is in this early phase that poor social and role functioning often appears (13, 14). Some researchers have been investigating the development of psychosocial difficulties amongst youth assessed as UHR. In their sample Niendam and colleagues (15) found that about half of the UHR individuals had improved in social and role functioning after eight months, whereas the other half showed a continuously low level or had declined further. Cornblatt, Auther (16) found that compared to a non-clinical group, the UHR individuals presented with impaired social and role functioning at baseline, and in their study, social functioning remained at a low level at the 12-month follow-up. Additionally, low baseline levels of social functioning have been found to predict later development of psychosis (17). Therefore, psychosocial difficulties seem
to be a serious and persistent problem for individuals at UHR and might affect the
development of psychosis.

Investigating the level of social and role functioning before the UHR status
using retrospective methods has not been done as extensively. Social and role
functioning prior to the UHR characterization is often denoted as premorbid
adjustment. Dragt and colleagues (18) found that sociability and withdrawal, as well as
social-sexual aspects during early adolescence predicted later development of
psychosis. Similarly, Tarbox, Addington (19) found that deficits in social premorbid
adjustment predicted later development of psychosis, and when combined with
baseline symptoms of suspiciousness the prediction was further increased. In line with
this, Mason, Startup (20) observed that multiple factors of premorbid adjustment,
including social or academic factors, predicted the development of psychosis. In
Addington, Penn (21) the UHR individuals’ development in premorbid adjustment
resembled the gradual worsening pattern seen in first episode and multi-episode
schizophrenia patients. However, during adulthood, the UHR individuals performed
better than the two other groups.

None of the above-mentioned studies (18-21) included a healthy control group
when investigating UHR individuals’ premorbid adjustment difficulties. Some recent
studies have found lower psychosis transition rates than previously observed (reviewed
in 22). In order to guide future research towards variables that might improve the
prediction of psychosis, we compared the development of the whole UHR group (not
only the ones developing psychosis) to a non-clinical group. It is worth stressing the
importance of not only focusing on transition to psychosis but also focusing more
highly on the individuals’ level of functioning.
The current methods used to identify individuals with increased risk for developing psychosis are primarily based on the presence of attenuated psychotic symptoms (23, 24). These symptoms are observed, on average, one year before the onset of the psychotic episode (25). By assessing premorbid adjustment, we hope to identify factors that appear even earlier than the attenuated psychotic symptoms, hereby making it possible to intervene earlier in the pathologic development.

The aim of our study was to determine if individuals at UHR for developing psychosis at baseline differed in their social and academic premorbid adjustment characteristics when compared to healthy controls (Hypothesis 1). Furthermore, we examined whether UHR individuals showed a gradual increase in premorbid adjustment deficits across all PAS age periods, a pattern that was not expected for the healthy controls (Hypothesis 2). Finally, we analysed whether the changes in scores from one PAS age period to the next were greater for the UHR individuals compared to the healthy controls (Hypothesis 3).

2. Methods

The presented data are from the Prodromal Project conducted at the Mental Health Centre Copenhagen (Denmark). Data were collected between September 2009 and August 2014. The study was approved by the Regional Ethics Committee of the Capital Region, Denmark (H-D-2009-013). All participants gave signed informed consent.
2.1 UHR individuals

Fifty UHR individuals were enrolled at the Mental Health Centre Copenhagen, and 48 of these underwent assessment with the Premorbid Adjustment Scale (PAS). The UHR individuals in Nordholm, Poulsen (26)’s study are from the same cohort. The participants were referred from services in the Capital Region of Denmark such as psychiatric hospitals, community mental health services, psychotherapy outpatient departments, and from collaborating research projects that they did not meet inclusion criteria for. Since there are no specific UHR services in Denmark, the UHR individuals are typically treated in the general mental health system for their primary symptoms, such as anxiety and depression. The project was a supplement to this standard treatment. Inclusion was based on the Comprehensive Assessment of At-Risk Mental States (CAARMS; 27). The CAARMS is a semi-structured interview designed to assess the psychopathology thought to indicate imminent development of a first-episode psychotic disorder, and to determine if the individual meets the criteria for being at ultra-high risk for the onset of a first psychotic disorder. The individuals had to be between 18 and 40 years old and fulfil the UHR criteria for at least one of the following subgroups. The Attenuated Psychotic Symptoms (APS) group encompasses individuals who have symptoms that deviate from normal phenomena but that are not yet strictly psychotic. The Brief Limited Intermittent Psychotic Symptoms (BLIPS) group refers to individuals who have symptoms of psychotic intensity but have a total duration of less than seven days and resolve spontaneously. The Trait and State Risk Factor Group defines a group of individuals who have some trait risk factor for psychotic disorder. This can be either a schizotypal personality disorder or a family history of psychotic disorder in a first-degree relative. Other inclusion criteria related to level of functioning. This was measured with the Social and Occupational
Functioning Assessment Scale (SOFAS; 28), which evaluates the individual's level of social and occupational functioning on a scale of 1-100. All UHR individuals had to be help-seeking and have a decline in functioning (a 30% reduction or more for at least one month) or a sustained low level of functioning (a score of 50 or below for at least one year). Additional background information regarding the patients’ mental health was acquired using the Structural Clinical Interview for DSM Disorders, Research Version, Patient Edition (SCID-I/P; 29) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; 30) but were not used in this specific study. All assessors underwent SCID-I training and were certified. They also participated in formal CAARMS training. A team of two to three mental health specialists comprising of a psychologist and up to two medical doctors assessed the individuals for eligibility.

2.2 Exclusion criteria

The following exclusion criteria were used in both the UHR and healthy control group: past history of a treated or untreated psychotic episode of one week’s duration or longer, organic brain disease (e.g., epilepsy, inflammatory brain disease), any physical illness with psychotropic effect (if not stabilized), current treatment with mood stabilizers or methylphenidate, having received more antipsychotic medication than equivalent to a total lifetime dose of 50 mg haloperidol, existing diagnosis of a serious developmental disorder (e.g., Asperger's syndrome, the participants’ primary psychiatrist was asked to assess for a developmental disorder if the researchers suspected a participant to have the diagnosis), IQ below 70 assessed with the Wechsler Adult Intelligence Scale – Third Edition (31), documented history of developmental
delay or intellectual disability, current pregnancy, or symptoms that are entirely explained by acute intoxication.

2.3 Healthy controls

Fifty healthy controls were found by advertising on a webpage, where healthy controls can apply for participation in studies. They all lived in the Capital Region of Denmark and they did not have any first-degree relatives with a current or previous psychiatric diagnosis. They underwent the SCID-I/P, and the SCID-II, CAARMS and SOFAS to rule out current or previous psychiatric disorders and ensure the UHR criteria were not met. The controls were group matched with the UHR individuals for gender, age, and parents’ socioeconomic status (SES), and received payment for their participation.

2.4 Premorbid adjustment

A Danish translation of the Premorbid Adjustment Scale (PAS, 32) was administered to all participants at baseline. The PAS is an interview-based rating schedule designed to assess functioning retrospectively, particularly social and academic premorbid adjustment factors. PAS defines the “premorbid” period as ending six months before first psychiatric contact or six months before the appearance of florid psychotic symptoms. For UHR individuals that were not part of the BLIPS subgroup, the criterion of first psychiatric contact was used and the individuals were instructed only to report experiences ending six months before the psychiatric contact. The predictive and concurrent validity of the PAS has shown to be satisfactory (33). The scale is divided into five premorbid adjustment subscales: 1) Sociability and withdrawal, 2) Peer relationships, 3) Achievements in school, 4) Adaptation to school and 5) Ability to form interpersonal and sexual relationships. Each subscale consists of one item.
Additionally, the scale divides the former mentioned areas of premorbid adjustment into four life periods: Childhood (up to 11 years), early adolescence (age 12–15), late adolescence (age 16–18), and adulthood (age 19 and beyond). For Achievements in school and Adaptation to school there is no adulthood age period. Based on the subject’s own statements, each item is rated on a 7-point scale from 0–6, where 0 indicates healthy function and 6 denotes maximum adjustment deficits. The original edition of the PAS (32) includes a General section, however due to concerns regarding the validity of this section (34) we decided not to use it.

2.5 Premorbid adjustment scoring and missing values

The PAS includes standard scoring instructions (32), however a range of other methods have been used when scoring the PAS (35). We chose a method of scoring that would reduce the number of statistical tests required, in order to minimize the risk of multiplicity. A general social score was calculated by taking the mean of the Sociability and withdrawal subscale, and the Peer relationships subscale. Similarly, a general academic score was calculated by taking the mean of the Achievements in school and Adaptation to school subscales. These averaged scores were calculated for all participants for each of the age periods creating a compound social scale and an academic scale (see also 19). The results below reflect the analysis of the available cases (i.e., no missing data); a sensitivity analysis using multiple imputation is reported in the online appendix. Because there was too much data missing for the socio-sexual scale of the PAS, this subscale was excluded from all analyses.

2.6 Statistical analyses
The data were analysed with IBM SPSS Statistics version 23. To test the mean difference in premorbid adjustment between the UHR individuals and healthy controls, which relates to Hypothesis 1, an ANCOVA model was used. The model was adjusted for age, gender, and the parents’ socioeconomic status. The significance level for the group differences was set to 5% two-tailed. To reduce multiplicity a hierarchical approach was chosen, where a significant test result would lead to analysis of the chronologically preceding age period. We chose to begin with the adulthood age period and move backwards in time, because 1) the adulthood age period was closest to most of the individuals’ current age, thereby making this age period the one that was least affected by a recall bias, and 2) the literature suggests that the UHR status gradually develops over time (12) so, if we had started from childhood and found no difference in that age group, we would have been forced to stop the analyses. This could have led us to overlooking significant and relevant differences in adolescence and adulthood. Furthermore, an analysis of the individual underlying scales was performed (Figure 1). For example, if the social composite scale for one of the age periods revealed a significant result, further analysis of the variables composing the scale (i.e. Sociability and withdrawal and Peer relationships) was performed.

Regarding the assumption of normality, we assumed normally distributed residuals because the PAS scores are sums of individual items, and this is stated by the central limit theorem.

Hypothesis 2 and 3 aimed at examining whether the development of the UHR individuals differed from the development of the healthy controls. The hypotheses were examined by performing two separate repeated measures ANOVAs with the social and academic composite scales. We used the repeated measure analyses to show if the trajectory of the scores between UHR individuals and healthy controls differed
across all age periods (Hypothesis 2). The repeated measures also contained three contrasts for the social scale (four age periods) and two contrasts for the academic scale (three age periods). To imitate a developing pattern, the analyses moved forward from the childhood age period and compared the change from one age period to the next (Hypothesis 3). For example, the first contrast would regard the change in UHR individuals’ premorbid adjustment level between the childhood and adolescence age period, and analyse if this change differed from the healthy controls’ change across the same age period. The significance level for the overall and contrast differences were set to 5% two-tailed and Huynh-Feldt corrected F-tests are reported.

3. Results

3.1 Sample characteristics

Demographic characteristics of the 48 UHR individuals and the 50 healthy controls are presented in Table 1. As expected due to group matching, no differences were found between the UHR individuals and healthy controls in age, gender, and parents’ SES.

3.2 Differences in the composite social and academic scales

Differences in premorbid adjustment were found between the UHR individuals and the healthy controls on the composite social scale and academic scale. The UHR individuals reported more premorbid adjustment deficits than the healthy controls for all age periods.

The covariate-adjusted means from for with the social and academic scales are presented in Figure 2.
For the individual PAS scales, the results are presented in Table 2 and graphs of the average PAS items are presented in Figure 3. Significant differences appeared for all of the individual PAS items for all age periods.

3.5 Premorbid adjustment decline in UHR individuals

For the social composite scale there was a significant interaction between participants and age periods, $F(2.6, 188.4) = 10.36, p = .001$. This indicates that across all of the four age periods of the social scale, the UHR individuals’ trajectory was, at the general level, different to that of the healthy controls’. Pairwise contrasts for the social scale revealed that the decline in premorbid adjustment ratings from childhood to early adolescence (highlighted by A in Figure 2), $F(1, 72) = 4.38, p = .040$ and late adolescence to adulthood (highlighted by C in Figure 2), $F(1, 72) = 10.46, p = .002$, was significantly more pronounced for the UHR individuals than for the healthy controls. There was no significant difference in the UHR individuals’ development compared to the healthy controls’ development between early adolescence and late adolescence (B, Figure 2).

For the academic composite scale a significant interaction between participants and age periods appeared, $F(2, 180) = 9.50, p < .001$, which implies that across all three age periods of the academic scale, UHR individuals and healthy controls generally have different trajectories. An investigation of the differences at adjacent age periods revealed that the decline in premorbid adjustment from childhood to early adolescence (D, Figure 2), $F(1, 90) = 15.43, p < .001$, was significantly greater for the UHR individuals than for the healthy controls. Between early adolescence and late adolescence (E, Figure 2) no significant change was found.
4. Discussion

To the best of our knowledge, this study is the first to compare premorbid adjustment differences between UHR individuals and healthy controls. Specific findings are as follows: 1) UHR individuals had significantly more premorbid adjustment deficits compared to healthy controls. The differences appeared in all social and academic areas for all age periods. 2) Compared to the healthy controls’ development, the UHR individuals showed a decline in social and academic premorbid adjustment across the age periods. The UHR individuals’ decline for the social scale particularly occurred between late adolescence and adulthood, and for the academic scale the decline occurred especially between childhood and early adolescence.

4.1 The presence of premorbid adjustment deficits

The results show that UHR individuals differ in social and academic premorbid adjustment compared to healthy controls. Based on UHR individuals’ own reports, social and academic difficulties are present already from childhood and they persist through adolescence and into adulthood. Previous studies have revealed that measurements of functioning, such as the Global Assessment of Functioning (36), are a predictor of psychosis and have therefore been included in the UHR criteria (12, 37). The present study suggests that lower social and academic functioning appears in the premorbid period before the UHR status is determined. Therefore, poor premorbid adjustment might be a distinct characteristic of UHR individuals, like the lower levels of functioning. Premorbid adjustment can potentially be used to guide future research toward areas that may improve the prediction of psychosis. Additionally, by measuring psychosocial functioning prospectively, Cornblatt, Carrion (17) revealed that
particularly social deficits were a risk factor for psychosis. They therefore underlined the importance of focusing on social functioning in early intervention.

An important focus of future research that examines social and academic functioning, should be to specify more specific areas where UHR individuals experience difficulties. The items in the PAS give broad characteristics of an individual’s previous social and academic life, but they do this without catching the nuances of these contexts. Scales used to measure autistic traits (38), temperament reactions (39), or emotional functioning (40) could be used to achieve more precise measurements of the abilities that impair social functioning. More detailed assessments would increase the possibilities of developing better UHR criteria models, targeting the specific areas in which the young people experience difficulties.

4.2 The development during the early and late adolescence age periods

Figure 2 and Figure 3 reveal that little change appeared in the UHR individuals’ level of premorbid adjustment between early and late adolescence for both the social and academic scale. This could signify a stable period in the UHR individuals’ development. However, this greatly contradicts what is known about adolescence as a period in which individuals experience a high level of change (41, 42). It is more plausible that the stability during early and late adolescence found in this study reflects a methodological limitation of the PAS instrument. Separating memories between the early and late adolescence age periods might have been difficult for the participants and this could have caused similar scores for both periods.
4.3 Strength and limitations of the methodology

A strength of this study is that, in contrast to what has been done in previous studies, it compares the UHR individuals to healthy controls (18-21). Thereby, we have been able to reveal that the UHR individuals have a deteriorating developmental pattern of premorbid adjustment abilities compared to a non-clinical population. However, since the study is cross sectional, we have not been able to determine whether low premorbid adjustment increases the risk for developing a psychosis.

We choose to use healthy controls that did not meet the criteria for any current or previous psychiatric disorders. Neither could they have any first-degree relative with a current or previous diagnosis. This means that the healthy controls possibly perform better than the population in general, which is likely to have biased our results. Therefore, the premorbid adjustment difference between the UHR individuals and healthy controls might be larger, than if the UHR individuals were compared to the population in general.

We did not match the controls for years of education because the participants were expected to perform worse at school. This is because the illness often starts during the period of their education. Matching for education could have biased the results because highly intelligent UHR patients would have been selected, thereby hiding relevant differences in the academic subscales. SES, that includes the parents’ education as a proxy, was used instead of years of education.

The PAS (32) has the disadvantage of having a retrospective design. Although predictive and concurrent validity of the PAS has been established (33), it is important to keep in mind how unstable and inaccurate human memory can be (43). However, as Tarbox, Addington (19) mentions, using retrospective assessments on UHR individuals avoids two types of recall bias. Firstly, it assesses life periods close to the individuals’
age, secondly, the individuals are not psychotic at the time of the interview. A further
disadvantage of the PAS is that it uses a one-item measurement in order to investigate
a wide set of psychosocial abilities and is therefore not particularly specific. For
example, one does not know if lack of peer relationships is caused by communicative
disabilities, reduced initiative, social cognitive deficits or other factors. In addition to
the retrospective design, the PAS also has some weaknesses when used to rate young
people or individuals who have had an early contact with the psychiatric system. For
example, some of our UHR individuals were younger than 19 years and could
therefore not be rated on the adolescent age period. Furthermore, if an UHR individual
early in their life had been in contact with the psychiatric system, for example seen a
psychiatrist at age 15, then the late adolescence and adulthood age periods should not
be rated. This is because of the PAS’s definition of the premorbid period. The
sensitivity analysis with multiple imputation (see online appendix), however, largely
supports the findings in the available cases reported here.

Having experienced reduced functioning in the year up to assessment is part of
the CAARMS criteria for all of the UHR groups, which means that our results might
have been biased due to selection criteria, making it more likely to find significant
results. It is worth stressing that this overlap only occurs for the adulthood age period,
leaving the antecedent age periods unaffected.

4.4 Conclusion

Altogether, the differences in premorbid adjustment between UHR individuals and
healthy controls indicate that poor premorbid adjustment is a characteristic trait of
UHR individuals. Therefore, future research would benefit from investigating
psychosocial difficulties in UHR individuals, and maybe lead to finding variables that
can increase the prediction of psychosis. Furthermore, premorbid adjustment deficits seem to appear at a young age and increase as the UHR individuals grow older.

Therefore, premorbid adjustment could be a relevant target for early intervention.

References


Figure 1. Progression of the ANCOVA analyses
Figure 2. Development of social and academic premorbid adjustment deficits. The differences between UHR individuals and healthy controls were significant at all time points. A, B, C, D and E marks each of the pairwise contrasts for the repeated measure ANOVA.
Figure 3. Development of premorbid adjustment in the individual PAS scales. The differences between UHR individuals and healthy controls were significant at all time points.
Table 1. Demographic characteristics of UHR individuals and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>UHR</th>
<th>Controls</th>
<th>Group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>48</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>23.7 (4.6)</td>
<td>23.5 (4.4)</td>
<td>( t = 0.16, p = .872 )</td>
</tr>
<tr>
<td>Gender, female (%)</td>
<td>27 (56%)</td>
<td>28 (56%)</td>
<td>( \chi^2 = 0.00, p = 1.000 )</td>
</tr>
<tr>
<td>Parents’ SES (A/B/C)</td>
<td>30/18/0</td>
<td>30/20/0</td>
<td>( \chi^2 = 0.06, p = .838 )</td>
</tr>
</tbody>
</table>

Note: UHR, ultra-high risk; SES, socioeconomic status. Based on income and education, parents’ socioeconomic status was categorized in three groups where A is the highest and C is the lowest.
Table 2. Premorbid adjustment differences (with 95% confidence intervals) between UHR individuals and healthy controls available

<table>
<thead>
<tr>
<th>Component scales and individual PAS scales</th>
<th>Developmental period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adulthood (≥ age 19 years)</td>
</tr>
<tr>
<td>Social scale</td>
<td>2.2 (1.8 to 2.6)</td>
</tr>
<tr>
<td>Sociability and withdrawal</td>
<td>2.3 (1.8 to 2.8)</td>
</tr>
<tr>
<td>Peer relationships</td>
<td>2.1 (1.7 to 2.5)</td>
</tr>
<tr>
<td>Academic scale</td>
<td>Not part of the PAS instrument</td>
</tr>
<tr>
<td>Achievements in school</td>
<td>Not part of the PAS instrument</td>
</tr>
<tr>
<td>Adaptation to school</td>
<td>Not part of the PAS instrument</td>
</tr>
</tbody>
</table>

Note: UHR, ultra-high risk; PAS, Premorbid Adjustment Scale. Analyses adjusted for age, gender and parental socioeconomic status. Positive differences in favour of controls.