The lonely soul wanders: on the role of impaired social functioning in the prediction of a first psychosis

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THREE-YEAR COURSE OF CLINICAL SYMPTOMATOLOGY IN YOUNG PEOPLE AT ULTRA HIGH RISK FOR TRANSITION TO PSYCHOsis.

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ABSTRACT

Objective The investigation into the course of ultra high risk (UHR) symptomatology of those patients who eventually do not meet the psychosis-threshold criteria within the 3-year timeframe of the study.

Method The course of UHR symptoms, GAF score and employment status was investigated in 57 patients who did not make a transition to psychosis and who were examined within the Dutch Prediction of Psychosis Study in Amsterdam, the Netherlands.

Results At the 3-year follow-up, 75% of the patients who did not make a transition to psychosis had remitted from UHR status. With a Generalized Estimation Equation Model it was shown that this group recovered from positive (F = 52.7, P < 0.0001), negative (F = 24.3, P < 0.0001), disorganization (F = 14.4, P < 0.0001) and general symptoms (F = 25.0, P < 0.0001) within the timeframe of the study. In addition, the level of global functioning and likelihood of having a job and/or education significantly improved. The largest improvements occurred within the first year. UHR symptoms did not re-occur after improvement.

Conclusion With the current UHR criteria, a large percentage of the included subjects appear to have transitory complaints and dysfunctioning. A refinement of the UHR criteria may diminish the chance of including ‘false positives’ in future UHR studies.

Significant outcomes
- A substantial percentage of patients initially at ultra high risk (UHR) for psychosis report significantly fewer UHR symptoms within 1 year.
- Recovery is not limited to a reduction in symptomatology, but also involves improvement in global functioning as well as employment status.
- The large number of ‘false positives’ indicates the necessity of refining the current UHR criteria for psychosis.

Limitations
- Results are based on a limited sample size
- Transition to other comorbid disorders was not investigated
Introduction

Although our knowledge about the prodromal phase of schizophrenia is improving, with the current ‘UHR’ criteria (1), the reported transition rate from UHR state to psychosis dropped to 10 to 25 per cent in recent studies (2–5). The UHR criteria, which are mainly based on positive symptoms, have led to the inclusion of a considerable number of ‘false positives’ in UHR studies. Questions thus arose about the stability of psychotic-like symptoms in young people who eventually do not meet the psychosis threshold (6). The clinical positive symptoms reported for this group may in fact represent transitory age-specific symptoms rather than stable phenomena (6, 7). On the other hand, the symptoms of these patients may remain stable over the time span of the UHR studies.

So far, one study investigated the naturalistic course of clinical symptomatology in young UHR patients who did not convert into a full-blown psychosis, showing substantial clinical remission over a 1-year period (6). In their prospective study, Simon and Umbricht found the positive-negative-, disorganized- and general-item clusters of the Structured Interview for Prodromal Syndromes (SIPS) to decrease significantly in the non-converters.

In the absence of a protocolized intervention, the chance of remission to a non-risk state was over four-fold higher than the chance of transition to psychosis within a year of establishing UHR status (6). The results of their prospective study suggest that in the vast majority of young people initially at UHR, the reported problems are only temporary, or at least temporarily of clinical severity. Following Simon and Umbricht (6), the present naturalistic longitudinal cohort study focuses on the course of clinical symptomatology in UHR patients who do not reach the psychosis-threshold within the timeframe of the study (UHR Non-Transition; UHR-NT). In addition, we investigate the course of global functioning and employment status. We extended the follow-up period to 3 years, to capture any fluctuations in seemingly remitted symptoms.

Aims of the study

To replicate previous findings regarding the course of UHR symptomatology in a sample without a transition to psychosis with a longer follow-up period, to rule out transitory phenomena that may have occurred after 1 year. We hypothesized that a considerable number of patients would show reduced positive, negative, disorganization and general symptoms within 3-year follow-up, as well as a significant increase in global functioning (as assessed with the GAF-score). In addition, we expected the likelihood of having a job and/or education to be significantly improved compared to baseline.
Materials and Methods

Sample

Between August 2002 and July 2009, data were collected from 77 UHR patients; a subsample of the 285 help-seeking patients who were examined within the Dutch Prediction of Psychosis Study (DUPS) at the Adolescent Clinic of the Academic Medical Center (AMC) of the University of Amsterdam, the Netherlands. The main reasons for non-participation of the remaining 208 patients were the presence of a psychosis, symptoms not severe enough to meet UHR criteria, and a general refusal to participate in research activities. Part of our Dutch sample also participated in the European Prediction of Psychosis Study (EPOS, see earlier publications: 5, 8).

Prior to their referral to the AMC, all patients sought help for various complaints at local mental health services and other health services. The patients were referred to the DUPS project for a second opinion because the referring clinician suspected a development toward a psychosis. Inclusion criteria were ages in the range between 12 and 35 years, ability and willingness to give informed consent and falling in one or more of the following groups:

i) Genetic risk in combination with reduced functioning: subjects who have a first-degree relative with a psychotic disorder, or who themselves have a schizotypal personality disorder and who have experienced a significant decrease in functioning during the past year (i.e. 30% reduction in GAF score for at least 1 month).

ii) Attenuated Positive Symptoms (APS): subjects who have experienced subthreshold, attenuated positive psychotic symptoms, defined by at least one of the following symptoms appearing several times per week for at least one week within the previous 3 months: unusual thought content, delusional ideas, suspiciousness, persecutory ideas, grandiosity, perceptual abnormalities, hallucinations and disorganized communication.

iii) Brief limited intermittent psychotic symptoms (BLIPS): subjects who have experienced episodes of frank psychotic symptoms. BLIPS were defined by hallucinations, delusions or formal thought disorders occurring within the previous 3 months which resolved spontaneously within a week.
The exclusion criteria of this study were the presence or history of a psychotic disorder for more than one week, an Intelligence Quotient < 85, symptoms because of a known medical disorder or intoxication with drugs or alcohol. Patients were allowed to use cannabis, as is widely accepted in UHR research. However, if the patients used hard drugs, or if the cannabis caused the UHR symptoms, they were not included in the study. To establish the relation between cannabis use and UHR symptoms, we asked cannabis-using patients whether the symptoms ever occurred during periods of cannabis abstinence. If symptoms did not occur without cannabis use (as was the case in a few subjects), we asked those patients to stop taking cannabis during the following month. Because they were help seeking, the patients were usually motivated to do so.

Subsequently, they were assessed again with the SIPS to investigate if their symptoms were still present. If so, they were included in the study. If the symptoms abated, the patients were not included. ‘Cannabis use’ in the past or present was defined as having used cannabis at least five times in a lifetime (9). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Medical Ethical Committee of the AMC. The informed consent of the participants was obtained after the nature of the procedures had been fully explained.

Instruments

The semi-structured interview SIPS (10, 11) was used to determine the presence, severity and type of prodromal symptoms. The Scale Of Prodromal Symptoms (SOPS), the rating scale of the SIPS, has four subscales that include five positive, six negative, four disorganization and four general symptom items. All symptoms are rated on a seven-point rating scale ranging from 0 (Never, absent) to 6 (Severe / Extreme –and Psychotic for the positive items). The diagnosis of a prodromal state is based on the score at the positive items. Scores in the 3–5 range are considered to be indicative of the UHR phase (APS). A score of 6 signifies psychosis or BLIPS (9). Each interviewer (DHN, PD, and two other senior investigators) received a 2-day training workshop by Dr. T.J. Miller, one of the SIPS authors, including reliability check after approximately 6 months. The pairwise inter-rater reliability concordance of the SIPS was 77% and deemed acceptable by the training team.

The GAF score (12) was used to determine the global level of functioning. This score is derived from the GAF scale, a scale ranging from 1 to 100, both for the current situation and for the highest level in previous year.

A transition to psychosis was defined as the persistence of one or more positive psychotic symptoms for more than one week with a score of four or more on hallucinations, delusions or formal thought disorder on the Positive and Negative Syndromes Scale (13). The Structured Clinical Interview for DSM-IV (SCID-I; 14) was administered to all patients after transition to psychosis to establish a formal DSM-IV diagnosis.
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The treatment was documented using the Treatment Documentation Sheet (Patterson & Birchwood), an instrument designed for the EPOS project to assess treatments received during the previous 9 months. In our study, treatment was defined as any form of psychotherapy for at least five sessions and/or psychotropic medication prescription for at least 1 month in the previous 9 months.

Data of employment status were collected with the standardized Client Socio-demographic and Service Receipt Inventory (15). A meaningful employment status was defined as having a full or part-time job and/or study.

Procedure

After their referral to the AMC, putative UHR patients were invited for a first interview with a psychiatrist and a psychologist. In this face to face interview which lasted approximately 2 h, subjects were asked about their lifetime history of complaints, family history of psychiatric disorders, as well as drug and medicine use. Subsequently, the SIPS was administered. Simultaneously, in another interview, parents or guardians were separately asked about the lifetime development of their child.

All the diagnostic information for each subject was discussed in a staff meeting. Those patients considered to be at ‘UHR’ were asked to sign a written informed consent before participating in the DUPS project. Written informed consent was also obtained from parents or guardians if the participant was below the age of 18 years. They were referred back to their referring mental health professionals. Of these, some received treatment while others were only monitored. Patients, their parents or caretakers and the referring instances were asked to contact the DUPS project in case of increasing symptoms. In addition, a SIPS interview was carried out at 1-, 2- and 3-year follow-up.

Statistical analysis

All data were analysed using the spss statistical package for Windows (version 17.0; IBM Company, Chicago, IL, USA). Differences in age, clinical symptomatology and GAF score at baseline between those with and without follow-up data were examined by means of independent two-tailed t tests. Gender, treatment and cannabis use differences, as well as differences in family predisposition were analysed using Chi-square tests.

It was not possible to screen all UHR-NT patients at each assessment point. To correct for study drop-outs and missing assessments, we conducted a linear mixed model analysis. With this analysis, we measured the impact of time on the participants’ scores on the SOPS and GAF, across four different time points (at baseline, after 1-, 2- and 3-year follow-up).

A Generalized Estimating Equation model (GEE) was conducted to examine the development in employment status over time (i.e. the increase or decline in the likelihood of a significant job and/or study). Cannabis use was included as a covariate in the GEE and linear mixed model.
Results

Baseline characteristics

Table 1 displays the demographics of the included group. The included group consisted of 77 subjects (51 men, mean age 19.2, SD 3.8). Twenty patients (26%) had made a transition to a psychosis (14 men, mean age 20.2, SD = 4.0) and 57 had not (37 men, mean age 18.9, SD 3.7). The mean interval between inclusion and transition for this group was 13 months (Range = 2.00– 37.00, SD = 9.0).

Seven UHR-NT patients (12%) were lost to the follow-up after initial assessment.

The patients with follow-up information did not differ significantly at baseline from those lost to follow-up in terms of gender, age, severity of positive, negative, general and disorganization symptoms, global functioning and family predisposition. They did differ in cannabis use, with a higher percentage of cannabis users in the group lost to follow-up (-2 (1) = 5.0, P = 0.03). In total, 100% of the patients lost to follow-up (as opposed to 56% in the follow-up cohort) reported to have used cannabis at least five times during their lives.

Table 1: Baseline characteristics of the 77 followed-up patients with UHR status

<table>
<thead>
<tr>
<th>UHR-group (n=77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean; ± SD)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
</tr>
<tr>
<td>First-degree relative with psychosis (%)</td>
</tr>
<tr>
<td>Global functioning (mean; ± SD)</td>
</tr>
<tr>
<td>Cannabis use (n; %)</td>
</tr>
<tr>
<td>Employment status (n; %)</td>
</tr>
<tr>
<td>Paid/ self-employed</td>
</tr>
<tr>
<td>Unemployed</td>
</tr>
<tr>
<td>Student</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>SOPS (mean; ± SD)</td>
</tr>
<tr>
<td>Positive Symptom Subscale total</td>
</tr>
<tr>
<td>Negative Symptom Subscale total</td>
</tr>
<tr>
<td>Disorganized Symptom Subscale total</td>
</tr>
<tr>
<td>General Symptom Subscale total</td>
</tr>
</tbody>
</table>
Follow-up analysis

Table 2 lists the characteristics of the UHR-NT group (n = 57). We were able to conduct at least one follow-up assessment of 50 UHR-NT patient (87.8%). On average, 2.2 follow-up assessments were carried out at varying time points (SD=0.8, Range=1-3). Complete follow-up data were available for 23 UHR-NT patients (40.4%).

Of the 50 UHR-NT patients with a minimum of a single follow-up assessment, at least 17 patients (34%) received medication with or without psychotherapy at some point during the follow-up period. Eleven patients (22%) reported a period in which they received a protocolized form of psychotherapy without medication. At least 9 patients (18%) reported a period of therapy with medication, as well as a period in which they received therapy without medication. Thirteen patients did not have any kind of treatment in the period(s) between assessments. The most common types of prescribed medication were antidepressants (n = 12 patients), antipsychotics (n = 11), anxiolitics (n = 5) and methylphenidate (n = 5). The dose of prescribed antipsychotics varied from 50 to 200 mg chlorpromazine equivalents.

Table 2: Characteristics of the UHR-NT group (n=57)

<table>
<thead>
<tr>
<th>UHR-NT group (n=57)</th>
<th>Baseline</th>
<th>1-year follow-up</th>
<th>2-year follow-up</th>
<th>&gt;30 months follow-up</th>
<th>Statistics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global functioning ( M; ± SD)</strong></td>
<td>n=57</td>
<td>n=37</td>
<td>n=34</td>
<td>n=33</td>
<td>F=26.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>51.3 (12.0)</td>
<td>66.5 (12.8)</td>
<td>68.4 (12.0)</td>
<td>70.7 (11.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Employment status (No.; %)</strong></td>
<td>n=57</td>
<td>n=37</td>
<td>n=34</td>
<td>n=33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid/self employed or student</td>
<td>37 (72.5)</td>
<td>26 (83.9)</td>
<td>23 (74.2)</td>
<td>30 (83.3)</td>
<td>x²=11.0</td>
<td>.012</td>
</tr>
<tr>
<td>Unemployed/ other*</td>
<td>14 (27.5)</td>
<td>5 (16.1)</td>
<td>8 (25.8)</td>
<td>6 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SOPS (mean; ± SD)</strong>*</td>
<td>n=57</td>
<td>n=37</td>
<td>n=34</td>
<td>n=33</td>
<td>F=52.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Positive Symptom Subscale total</td>
<td>10.8 (3.7)</td>
<td>4.8 (3.3)</td>
<td>3.5 (2.9)</td>
<td>3.1 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative Symptom Subscale total</td>
<td>12.5 (7.3)</td>
<td>6.8 (5.8)</td>
<td>5.6 (6.1)</td>
<td>3.9 (6.1)</td>
<td>F=24.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Disorganized Symptom Subscale total</td>
<td>4.5 (2.8)</td>
<td>2.4 (1.7)</td>
<td>2.0 (1.5)</td>
<td>1.7 (1.8)</td>
<td>F=14.4</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* Other: sheltered employment, sickness leave, reintegration project
** Ranges: Positive = 0-30; Negative = 0-36, Disorganized = 0-24, General = 0-24. Cannabis use was included as a covariate in the model.
As expected, the results of the SOPS in the UHR-NT group showed a significant decline in positive (F (75) = 52.7, P < 0.0001), negative (F (75) = 24.3, P < 0.0001), disorganization (F (75) = 14.4, P < 0.0001), and general symptoms (F (77) = 25.0, P < 0.0001; see Fig. 1). Our results reveal that the largest decline in symptomatology occurs within the first year after baseline assessment. In addition, the GAF score significantly increased over time (F (78) = 26.3, P < 0.0001). No main or interaction effects of cannabis were found.

At the 3-year follow-up, 75% of the UHR-NT group had remitted from UHR status (i.e. no score of 3 or more on items P1 t • m P5 of the SIPS), while 25% still reported UHR symptoms. Of the patients who remitted from UHR status, 85.1% did also find a job and • or study. When examining the course of employment status, we found that the likelihood ratio for having a job and • or study increased at the 3-year follow-up (x² (4) = 11.0, P = 0.01). Despite the unexpected decline at the 2-year follow-up, our data indicate a significant increase in the number of young people with a full- or part-time job and • or study over 3 years. Here, we did find a main effect for cannabis use (x² (1) = 4.4, P = 0.04). Although the amount of studying and • or working of cannabis-using UHR-NT patients (61.4%) also increased with time, the frequency of a significant employment status within this group was consistently lower compared to the group who never used cannabis.

**Figure 1: Course of SOPS symptomatology in the UHR-NT group**
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Discussion

In this 3-year follow-up study of a cohort initially at UHR for developing a psychosis, we sought to investigate the course of clinical symptomatology and level of functioning of those who eventually did not make the transition to a psychosis. Our study indicates that a large part of the young helpseeking people show remission from UHR status 1 year after baseline assessment, which is in accordance with the results of Simon and Umbricht (6). We found the UHR-NT group to recover from positive, negative, disorganization and general symptoms within the first year of follow-up. In addition, the level of global functioning, as well as the likelihood of having a paid job and or being a student in this group significantly improved over time. The UHR symptoms did not reoccur after improvement during the 3-year follow-up.

The high remission rate in the UHR-NT group raises questions about the origin of the reported symptoms at baseline. As Simons et al. (6) already suggested, the baseline symptoms may in fact have represented transitory age-related psychotic-like experiences (7, 16). Transitory psychotic-like experiences such as extrasensory perceptions appear rather frequently in early adulthood (7, 17) possibly partly related to an inability to distinguish between relevant and irrelevant stimuli (17), as well as to stressful age-related events. In spite of the central role that the famous psychiatrist Klaus Conrad ascribed to “delusional mood” in the prodromal phase (18), it seems that even delusional mood does not necessarily result in a first psychotic episode.

Another explanation of the UHR symptom remission may be found in the early treatment received in the UHR-NT cohort. In spite of the naturalistic design of our study, most young people received treatment (psychotherapy and or treatment with medication) sometime during follow-up, and this might have contributed to the prevention of a worse outcome. However, the fact that most of the 20 UHR people who did make a transition to a psychosis also received some form of treatment contradicts this hypothesis. Moreover, as we rated the period with the highest level of symptoms somewhere since last assessment point, we do not know whether subjects improved because of the therapy. Randomized control trials to the effects of therapy are needed to unravel the cause and effect of any form of treatment. Although various randomized trials of the effects of medication on the development of a psychosis have already been carried out (19–21), at the moment definite conclusions about the efficacy of UHR interventions cannot be drawn (22). Preliminary results concerning the prescription of omega-3 fatty acids, however, seem promising and this subject is the focus of current research (23).

Alongside the ‘true positives’, it seems that with the current UHR criteria we include a large number of young people with transitory complaints. This issue fuels the need for further research into the core features of the prodromal phase of psychotic disorders. Yung et al. (16) already emphasized that certain psychotic-like experiences make a transition more likely when accompanied by distress, depression and disability. In addition, recent studies underlined the predictive value of negative symptoms as ‘social anhedonia and withdrawal’, and a lower level of global functioning (3, 4).
The addition of the criterion, a moderate score (≥3) on the item ‘social anhedonia and withdrawal’ to the current criteria (of a score of 3–5 or a score of 6 less than a week on at least one positive item of the SIPS), may contribute to a larger transition percentage in UHR groups.

**Limitations**

Our results should be considered in the context of some limitations. In our study, we did not assess comorbid disorders at each time point; therefore, it is unclear as to whether the complaints of the UHR-NT group in fact represented prodromal symptoms for the transition to other psychiatric disorders as a bipolar or a depressive disorder. However, the increased GAF score at follow-up seems to reflect only a modest occurrence of other severe psychiatric disorders.

A second limitation is our small sample size. Seven UHR-NT patients were lost to follow-up. Although we used a linear mixed model to correct for our unbalanced sample, we cannot completely rule out that we based our results upon a biased sample. A transition to psychosis in the patients lost to follow-up is unlikely however, as we asked the practitioner who referred the patients to contact us when they suspected a psychosis. In addition, most patients with a first psychotic episode in the Amsterdam region were referred to our Early Psychosis Department in case of psychosis.

To our knowledge, this study is the first to examine the course of clinical symptoms in a UHR group with a follow-up period of 3 years. With this relatively long follow-up period, we were able to reduce the possibility of missing fluctuating, and seemingly remitted symptoms. The most substantial improvement in clinical symptoms as well as in global functioning was seen in the first year after baseline assessment. As well as Simon and Umbricht (6) we believe that the complaints in the UHR-NT group most likely represented age related transitory dysfunction.

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