Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis

Eva Velthorst⁎, Dorien H. Nieman, Hiske E. Becker, Reinaud van de Fliert, Peter M. Dingemans, Rianne Klaassen, Lieuwe de Haan, Thérèse van Amelsvoort, Don H. Linszen

Department of Psychiatry, Academic Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 5 November 2008
Received in revised form 21 January 2009
Accepted 3 February 2009
Available online xxxx

Keywords:
Psychosis
Ultra high risk symptoms
Social withdrawal
Basic symptoms
GAF-score
Prediction of psychosis

ABSTRACT

Background: The chance of transition to psychosis in patients at Ultra High Risk for developing psychosis (UHR) is 10–15%. The aim of present study was to investigate differences in baseline clinical symptomatology, general level of functioning (GAF-score) and genetic risk between UHR patients who did (UHR+T) or did not (UHR+NT) make a transition to psychosis. Sharpening UHR inclusion criteria may aid in improving prediction of transition to psychosis.

Method: The study sample was taken from 285 patients who were examined within the Dutch Prediction of Psychosis Study (DUPS) at the Academic Medical Center of the University of Amsterdam, the Netherlands. Out of 73 included UHR subjects, 18 made a transition to psychosis. Psychopathology was investigated with the Structured Interview for Prodromal Syndromes, Bonn Scale for the Assessment of Basic Symptoms and GAF-score. The follow-up period of the study was three years.

Results: The UHR+T group showed more social anhedonia and withdrawal, more bizarre thinking and a lower GAF score at baseline than the UHR+NT group.

Conclusions: In agreement with the results of Cannon et al. [Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, M., McGlashan, T., Heinssen, R., 2008. Prediction of Psychosis in Youth at High Clinical Risk: A Multisite Longitudinal Study in North America. Arch. Gen. Psychiat. 65 (1) 28–37.], our study indicates that severity of specific symptoms at baseline is related to transition to psychosis in UHR subjects. These findings may contribute to a more accurate prediction of a first psychotic episode. Furthermore, symptoms that are increased at baseline in the UHR+T group could be a focus of cognitive behavioural therapy in the UHR period.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

The early phase of a psychosis has been considered as a critical period, which can disproportionately influence the long-term evolution of the disorder (Reading and Birchwood; 2005). In more recent research great importance is attached to an even earlier period. Yung et al. (1996, 2003) and Klosterkötter et al. (2005) described the assessment and treatment of pre-psychotic or 'ultra high risk' symptoms. The ultra high risk phase, retrospectively called prodromal phase, recognizable by subtle behavioural changes and a decline in functioning, occurs prior to the development of the characteristic signs and symptoms of the illness that permit definitive diagnosis and lasts on average between 1 and 5 years (Phillips et al., 2002; Yung et al., 2003).

Whereas Reading and Birchwood (2005) emphasize intervention during the first episode of psychosis, Yung et al. (2003) argue that intervention within the above mentioned ultra high risk phase of schizophrenia and related psychoses is indicated and may result in attenuation, delay or even prevention of the onset of psychosis in some vulnerable individuals. The identification of people with a psychotic vulnerability is needed to enable preventive approaches. How can this, often non-specific, phase be recognised?

⁎ Corresponding author. Academic Medical Center, Department of Psychiatry, Meibergdreef 5, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 8913671; fax: +31 20 8913536.
E-mail address: e.velthorst@amc.uva.nl (E. Velthorst).

0920-9964/$ – see front matter © 2009 Elsevier B.V. All rights reserved.

Please cite this article as: Velthorst, E., et al., Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.02.002
The Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne, Australia, initiated the formation of criteria for UHR for developing psychosis. Their criteria can be subsumed under three headings: Genetic risk and reduced functioning, Attenuated psychosis and Brief limited intermittent psychotic symptoms (BLIPS) (Yung et al., 2003).

With these three criteria, UHR patients used to have a chance between 10 and 40% of making the transition to psychosis (Yung et al., 2003, 2006a,b). More recent studies however show transition rates of 10 to 15%, which might partly reflect a reduction in duration of UHR symptoms prior to receiving help (Yung et al., 2007; Cannon et al., 2008).

Klosterkötter et al. (2001) emphasized the presence of ‘basic symptoms’ as an important risk-factor for the development of a first psychotic episode. Basic symptoms are self-reported disturbances in cognition and perception that were found to be predictive of a transition to psychosis over a 10 year follow up period. These symptoms include for example thought interference, thought pressure and thought blockages. Klosterkötter et al. reported that the absence of basic symptoms excludes a subsequent schizophrenia diagnosis with a probability of 96%.

In our naturalistic longitudinal cohort study we assessed UHR symptomatology and basic symptoms in a subsample of the 285 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. Part of this Dutch sample also participated in the European Prediction of Psychosis Study (EPoS, see for an earlier publication: Nieman et al., 2007). The follow up period in the study was three years. A previous comparable study found that certain symptoms contribute uniquely to the prediction of psychosis (Cannon et al., 2008). In their 2 1/2 year follow-up of 291 treatment-seeking UHR patients, they reported that genetic risk for schizophrenia with recent deterioration, higher levels of unusual thought content, higher levels of suspicion/paranoia, greater social impairment, and a history of substance abuse are key predictors of a subsequent psychosis. If replicated, these findings may contribute to a more accurate prediction of a first psychotic episode.

Therefore, following the study of Cannon et al. (2008), the present study focuses on the predictive value for transition to psychosis of baseline UHR symptoms. Furthermore, the predictive value of genetic risk with reduced functioning and recent deterioration (assessed with the GAF score) will be evaluated.

Within this framework the following question has been formulated: are differences in baseline clinical symptoms, genetic risk and GAF score present between UHR patients with a transition to a psychotic disorder (UHR+T) and UHR patients without a transition (UHR+NT) at three years follow up?

2. Methods

2.1. Participants

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 psychotic development.

Inclusion criteria were age between 12 and 35 years, being able and willing to give informed consent and falling in one of the following groups:

1. Genetic risk in combination with reduced functioning: subjects who have a first degree relative with a psychotic disorder, or who themselves have a schizotypical personality disorder and who have experienced a significant decrease in functioning during the past year (i.e. 30% reduction of GAF-score for at least one month).
2. Attenuated Positive Symptoms (APS): subjects who have experienced sub threshold, attenuated positive psychotic symptoms, defined by at least 1 of the following symptoms, appearing several times per week for at least 1 week within the last three months: unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication and odd behavior/appearance.
3. 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 last 3 months and resolving spontaneously within 1 week.
4. Basic symptoms: presence of at least 2 of the following 9 self-reported disturbed cognitive and perceptive basic symptoms of at least ‘moderate’ severity during the last 3 months: inability to divide attention, thought interference, pressure and -blockage, disturbances of receptive and of expressive speech, disturbance of abstract thinking, unstable ideas of reference, capitvation of attention by details of the visual field.

Exclusion criteria of this study were the presence or history of a psychotic disorder for more than one week, an IQ<85, symptoms due to a known general medical disorder or intoxication with drugs or alcohol. Patients were allowed to use cannabis, but they were excluded if they used any other drug or if the cannabis caused the UHR symptoms. To sort out the relation between cannabis use and psychotic symptoms, we asked the cannabis-using patients to stop taking drugs during the following month. Subsequently, they were assessed again with the SIPS to investigate if their symptoms remained. If the symptoms abated, the patient was not included the study. In addition, we asked if the symptoms ever occurred without cannabis use. ‘Cannabis use’ in past or present was defined as having used cannabis at least 5 times in a lifetime.

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. Informed consent of the participants was obtained after the nature of the procedures had been fully explained.

2.2. Instruments

The semi-structured interview, Structured Interview for Prodromal Syndromes (SIPS, Miller et al., 2002), 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 4 SIPS subscales that include five Positive Symptom items, six Negative Symptom items, four Disorganization Symptoms items and four General Symptom items. All symptoms are rated on a 7 point rating scale.
scale rating 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 to 5 range are considered as indicative of the UHR phase (APS). A score of 6 signifies psychosis or BLIPS (Miller et al., 2002). The two interviewers (DHN and RvdF) received a two-day training workshop by Dr. T. J. Miller, one of the SIPS authors, including a reliability check after approximately six months. The pairwise inter-rater concordance of the SIPS was 77% and determined acceptable by the training team.

The Bonn Scale for the Assessment of Basic Symptoms Prediction scale (BSABS-P, Klosterkötter et al., 1996) is developed to assess ‘basic symptoms’. The BSABS-P is a semi-structured interview that consists of 33 principal items and can be divided into 5 BSABS-subscales: Cognitive thought disorders, Additional symptoms with positive predictive value (i.e., thought perseveration and decreased ability to discriminate between ideas and perception, fantasy and true memories), Visual perception disorders, Acoustic perception disorders and Cognitive motor disorders. The symptoms are rated on a scale rating from 0 (not present/absent) to 6 (severe). The investigators received repeated training by one of the scales’ authors (Dr. F. Schultzze-Lutter). Concordance rate with expert rating (F.S.-L.) was 87.9%.

To determine the general level of functioning and the reduction in functioning, the GAF-score (American Psychiatric Association, 1994) was used. This score is derived of the GAF-scale, a retrospective scale which is rated by a psychiatrist from 1 to 100, for the current situation and for highest level in past year. 1 to 10, for example, signifies ‘a persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death’, whereas 91 to 100 on the other hand, stands for ‘Superior functioning in a wide range of activities, life’s problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.’ The decline in functioning is computed by the subtraction of the current GAF-score from the highest GAF-score in past year.

A transition to psychosis was operationalized as a continuation of BLIPS, i.e., as one or more psychotic symptoms persisted 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 (PANSS, Kay et al., 1987) for longer than one week. To establish a formal DSM-IV diagnosis, the SCID (Structured Clinical Interview for DSM-IV, Spitzer et al., 1992) was administered to all patients after transition to psychosis.

### 2.3. Procedure

After their referral to DUPS, putative UHR patients were invited for a first interview with a psychiatrist and a psychologist. In this approximately two hour lasting face to face interview, subjects were asked about their lifelong history of complaints, family history of psychiatric disorders, drug- and medicine use. Subsequently, in a standardized order, the SIPS and BSABS-P were administered.

Simultaneously, in another interview the parents or guardians were asked about the lifelong development of their child. The SOPS and BSABS-P were scored and each subject was discussed in a staff meeting. When considered at ‘ultra high risk’, the patients were asked to sign a written informed consent before participating in the DUPS project.

#### Table 1

Sociodemographic variables of the UHR+T and UHR+NT group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UHR+T (n=18)</th>
<th>UHR+NT (n=55)</th>
<th>Statistics</th>
<th>df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean,(SD), y</strong></td>
<td>20.4 (1.9)</td>
<td>18.7 (3.9)</td>
<td>t=1.7</td>
<td>72</td>
<td>.10</td>
</tr>
<tr>
<td><strong>Male, No. (%)</strong></td>
<td>13 (72.2)</td>
<td>34 (62.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cannabis use, No. (%)</strong></td>
<td>5 (31.3)</td>
<td>32 (58.2)</td>
<td>χ²=3.4</td>
<td>1</td>
<td>.07</td>
</tr>
<tr>
<td><strong>Genetic risk, No. (%)</strong></td>
<td>7 (38.9)</td>
<td>11 (20.0)</td>
<td>χ²=2.6</td>
<td>1</td>
<td>.11</td>
</tr>
<tr>
<td><strong>Global functioning, mean±SD, score</strong></td>
<td>45.8 (8.4)</td>
<td>51.4 (11.7)</td>
<td>t=-2.2</td>
<td>40</td>
<td>.03</td>
</tr>
</tbody>
</table>

**Inclusion symptoms**

| Attenuated symptoms, No. (%)            | 4 (22.2)     | 17 (30.9)     |            |      |         |
| Attenuated + basic symptoms, No. (%)   | 8 (44.4)     | 29 (52.7)     |            |      |         |
| BLIPS, No. (%)                         | 1 (5.6)      | 0             |            |      |         |
| BLIPS+attenuated, No. (%)              | 0            | 2 (3.6)       |            |      |         |
| BLIPS+attenuated + basic s., No. (%)   | 1 (5.6)      | 4 (7.3)       |            |      |         |
| BLIPS+basic symptoms, No. (%)          | 2 (11.1)     | 0             |            |      |         |
| Genetic risk & reduced functioning + basic symptoms, No. (%) | 0 | 1 (1.8) | | | |
| Genetic risk and reduced functioning + attenuated symptoms, No. (%) | 1 (5.6) | 0 | | | |
| Genetic risk and reduced functioning + attenuated + basic symptoms, No. (%) | 1 (5.6) | 2 (3.6) | | | |

**Comorbid diagnoses**

| Affective disorder, No. (%)           | 8 (44.4)     | 21 (38.2)     | χ²=.22     | 1    | .64     |
| Anxiety disorder, No. (%)            | 4 (22.2)     | 8 (14.5)      |            |      |         |
| Substance abuse (in rem.), No. (%)   | 3 (16.7)     | 8 (14.5)      |            |      |         |
| Development disorder, No. (%)        | 3 (16.7)     | 3 (5.5)       |            |      |         |
| Dissociative disorder, No. (%)       | 1 (5.6)      | 1 (1.8)       |            |      |         |
| None/postponed, No. (%)              | 6 (33.3)     | 13 (23.6)     |            |      |         |
| Others, No. (%)                      | 0            | 7 (12.7)      |            |      |         |

UHR+NT = Ultra high risk without transition, UHR+T = Ultra high risk with transition.
No. = number of subjects.

Comorbid diagnoses were assessed using the Structured Clinical Interview for DSM disorders (Spitzer et al., 1992).

Please cite this article as: Velthorst, E., et al., Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.02.002
this naturalistic longitudinal cohort study, subjects were followed up for three years. They were referred back to their referring mental health institution. Some received treatment, 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, they were seen for a SIPS interview at 9, 18 and 24 months and interviewed by telephone at 36 months.

2.4. Statistical analysis

In current study, the differences in scores on the two questionnaires and one rating scale (SIPS, BSABS-P and GAF-score) between the two groups were examined with two-tailed t-tests. For the items social anhedonia and withdrawal, decreased expression of emotion, additional symptoms with a positive value and current GAF-score a t-test with pooled variance was used because SD was significantly unequal between the two groups. A p-value <0.05 was considered statistically significant. The possible difference between groups in sex was evaluated using a chi-square test. With a Spearman’s rank order correlation, we looked at the strength of the relationship between the most robust variables. A multivariate algorithm that optimizes prediction of conversion to psychosis was derived from a Cox proportional hazards model.

3. Results

Table 1 lists the demographics of the included group. The included group consisted of 73 subjects (47 men, mean age 19.2, SD 3.9). Of these 73 UHR subjects, 18 (25%) made a transition to a psychosis (13 men, mean age, 20.4, SD 3.9) and 55 did not (34 men, mean age 18.7, SD 3.8). The mean interval between inclusion and transition of this group was 11.9 months (Range=2.00–36.00, SD=8.6). Eight subjects (11%) were lost to follow up. The patients with follow-up information did not differ significantly from those lost to follow up in terms of sex, age, severity of positive and negative symptoms, basic symptoms, global functioning and family predisposition.

Table 2 lists the mean scores on the SOPS of the two groups. Two-tailed t-tests showed that there were no overall differences in positive symptoms between the UHR+T group and the UHR+NT group at baseline.

There was a significant difference between negative symptoms in the UHR+T group and the UHR+NT group at baseline. This difference is mainly caused by a significant higher score on item N1 of the SIPS ‘social anhedonia and withdrawal’ by the UHR+T group (t=3.1, p=.004) compared to the UHR+NT group.

Although no significant differences were noticeable between the UHR+NT group and the UHR+T group in all disorganisation symptoms taken together, a difference was found in one of its symptoms, namely D2 ‘bizarre thinking’ (t=2.1, p<.05). This means that more subjects, who eventually made a transition to psychosis, already scored higher on this SIPS item than the subjects who did not make the transition to psychosis.

We found trends on the SIPS P2 item ‘suspiciousness’ (t=1.7, p=.09) and on the Negative symptoms item N3 ‘decreased expression of emotion’ (t=1.9, p=.07) with the UHR+T group reporting slightly more suspiciousness and decreased expression of emotion at baseline than the UHR+NT group.

Table 3 lists the mean scores on the BSABS in the two groups. None of the BSABS symptoms showed increased severity in the UHR+T group compared to the UHR+NT group. Several basic symptoms were even less severe in the UHR+T group compared to the UHR+NT group.

Concerning the analyses of differences in general functioning at baseline, we only found a significant difference in current GAF-score, with a lower score in the UHR+T group compared to the UHR+NT group (t=−2.2, p=.03). Both the difference in amount of decline in functioning (3.73) and the difference in GAF-score highest in the past year (2.46) between the two groups were not significant.

Table 4 indicates the strength of the relationship between the variables that showed a difference at baseline between the UHR+T and the UHR+NT group. The most significant correlation at the .01 level was found between ‘Social anhedonia and withdrawal’ and ‘Decreased expression of emotion’.

Using the Backward Stepwise method of the Cox proportional hazard model, it can be concluded that reporting social
anhedonia and withdrawal symptoms is the best predictor for a subsequent psychosis in our UHR group (Wald = 4.5, p = .03, RR = 1.3).

4. Discussion

Our study finds striking similar results as the study of Cannon et al. (2008). As well as the Cannon et al. study, our results show that the UHR subjects who later make the transition to psychosis have increased social anhedonia and withdrawal as assessed with the SIPS compared to the UHR subjects that do not make the transition to psychosis. In addition, our results concerning the lower general level of functioning and the higher amount of bizarre thinking in the subjects that later make a transition to psychosis are comparable with the results of Cannon et al. We found trends for increased suspiciousness and decreased expression of emotion in the UHR + T group. Although no conclusions can be drawn upon these latter relative powerless findings, we believe that they do give some clinical valuable information as they point in the same direction as the larger 2008 Cannon et al. study.

Especially withdrawal from social interaction may be an important factor in the development of a psychosis. Because thoughts are not tested in social interaction, social withdrawal might contribute to the development and maintenance of delusional ideas and suspiciousness. Moreover, social withdrawal occurs at the expense of psychosocial development and it might reinforce other negative symptoms such as alogia and decreased expression of emotion. Otherwise, alogia and decreased expression of emotion may reinforce social withdrawal. Not only was the difference at baseline between the UHT + NT and the UHR + T groups statistically significant, it was also clinically discernable in retrospect.

Johnstone et al. (2005) also found social withdrawal to be predictive of a first psychosis. Addington et al. (2007) reported that social functioning in UHR patients was at the level of first episode schizophrenia patients.

Social anhedonia and withdrawal may partly reflect a depressive state. However, the absence of a difference in comorbid affective disorders as opposed to the significant difference in social anhedonia and withdrawal between the UHR + T and UHR + NT groups, suggests that social anhedonia and withdrawal does not merely indicate a depressive state. In addition, there was no significant difference in mean score on the SIPS item ‘Dysphoric mood’ between both groups. Disentanglement of negative symptoms and depression remains an issue.

Cognitive behavioural therapy is a promising method for intervening in the UHR period (Morrison et al., 2004). An important focus in cognitive behavioural therapy for UHR patients should be reducing social anhedonia and withdrawal and reducing suspiciousness, as these symptoms are often related. Furthermore, antidepressive medications may improve negative symptoms and may even prevent psychosis (Cornblatt et al., 2007; Fusar-Poli et al., 2007).

In contrast with the 2001 study of Klösterkotter, we did not find significant more basic symptoms at baseline in the UHR + T group compared to the UHR + NT group. This contradiction may be contributable to their older patient group (mean = 29.7 years old at baseline) and longer follow-up period. In our study, basic symptoms do not predict psychosis within a follow up period of three years.

In the present study, cannabis users did not have a higher transition rate than non-cannabis users. Although Cannon et al. (2008) found a history of substance abuse to be predictive of conversion to psychosis, they did not find any specific subclass of their substances tested (i.e., alcohol, hypnotics, cannabis, amphetamines, opiates, cocaine and hallucinogen) to be significantly associated with risk. Our finding might also be attributable to the fact that we did not make a distinction between present and past use. Yung et al. (2006b) reported on differences in current GAF-score within a similar group. In line with Yung et al. and Cannon et al. (2008) our study found that low functioning at baseline was significantly associated with later psychosis within the UHR group. Conversely, we did not find any differences in amount of decline and highest GAF score in the past year. Thus, the UHR + T subjects functioned comparable to the UHR + NT subjects at some point in the year before inclusion in the DUPS study.

In the present study, eight subjects were lost to follow up. Therefore, we cannot be certain about their current state of functioning. A transition to psychosis is highly unlikely, since we asked the practitioner who referred the patients to contact us when they suspected a psychosis. In addition, many patients in the Amsterdam region are referred to our Adolescent Clinic in case of psychosis.

In a commentary on the Cannon et al. (2008) study, Yung (2008) underlined that although the findings can be helpful in narrowing down the UHR inclusion criteria, it should be noticed that the predictive value of the newly found predictors of transition to psychosis in the general population is most likely much lower because of the reduction in sensitivity. Yung states that these criteria should therefore not be applied in the general population. More research is needed to determine the value of the newly found predictors as valid UHR inclusion criteria.

Our study shows that a few differences are present at baseline in reported symptoms between those patients who eventually do and do not make the transition to psychosis. Our study is the first to replicate the Cannon et al. (2008) reported results. Especially the amount of negative symptoms merits specific attention in the future. Adding the negative item social anhedonia and withdrawal to the UHR inclusion criteria may improve prediction of transition to psychosis in UHR patients.

Role of the funding source

This study was supported by a grant for the Dutch Prediction of Psychosis Study from ZON-MW (ZorgOnderzoek Nederland/NWO-Medische Wetenschappen, project # 2630.0001) and a grant from the European Commission had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Author Dorien Nieman was involved in the design of the study, statistical analysis and wrote part of the first draft of the manuscript. Hiske Becker included patients in the study and did clinical assessments concerning transition to psychosis. Reinaud van de Fliert recruited patients into the study and did clinical assessments. Peter Dingemans was involved in management of the Ultra High Risk project. Rianne Klaassen included patients in the study and did clinical assessments. Lieuwie de Haan and Thérèse van Amelsvoort read the manuscript carefully and commented on it. Don Linszen was supervisor of the Ultra High Risk project. Eva Velthorst was involved in data
collection and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
All authors declare that they have no conflicts of interest.

Acknowledgement
We thank Erik Wagemans for his help with the data.

References


