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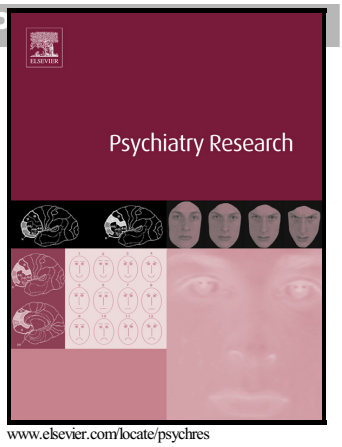

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Are UHR patients who present with hallucinations alone at lower risk of transition to psychosis?

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Abstract

The aim of this study was to investigate whether Ultra High Risk for psychosis (UHR) patients who present with hallucinations alone at identification as UHR are at lower risk of transition to psychosis than UHR patients who present with symptoms other than hallucinations or hallucinations plus other symptoms.

Our primary dataset was a retrospective "case-control" study of UHR patients (N = 118). The second, independent dataset was a long-term longitudinal follow up study of UHR patients (N = 416). We performed a survival analysis using Log-rank test and Cox regression to investigate the relationship between symptom variables and transition to a psychotic disorder.

Hallucinations alone at baseline were not significantly associated with a reduced risk of transition to psychosis. In the case control study the presence of hallucinations

when found in the absence of any thought disorder and visual hallucinations in the absence of substance misuse was associated with a reduced risk of transition to psychosis. In the longitudinal follow-up dataset perceptual disturbance found in the absence of a disorder of affect or emotion was associated with an increased risk of transition to psychosis.

Key words: Hallucination, Schizophrenia, High- Risk, Prodromal

1. Introduction:

Hallucinations are sensory experiences that take place in the absence of corresponding external stimulation of the relevant sensory organ, in the awake state and with sufficient sense of reality that the individual attributes the event to being outside of their control (David, 2004). Hallucinations have traditionally been defined by the sensory modality in which they are perceived i.e. auditory, visual, gustatory, olfactory, somatic or tactile (Aleman and Laroi, 2008). Aleman and Laroi (2008) suggest that the hypotheses proposed to explain the underlying mechanism of hallucinations can be loosely divided into three categories (1) hallucinations as a disturbance in cognitive-perceptual processes (Slade and Bentall, 1988), (2) hallucinations as a disturbance of metacognitive processes (Frith., 1991; Bentall., 1990; Morrison et al., 1995) and (3) hallucinations as a disturbance of brain biochemistry and/ or structure (David et al., 1996; Woodruff et al., 1997; Allen et al., 2012). While evidence exists to support many of these hypotheses, the field is yet to reach scientific consensus (Aleman and Laroi, 2008; Dirk Blom and Sommer, 2012).

Hallucinations are a primary symptom of psychotic disorders such as schizophrenia in both ICD-10 and DSM-5 (World Health Organisation, 1992; American Psychiatric Association, 2013). 70% of patients with schizophrenia experience hallucinations, most commonly in the auditory modality, followed by visual hallucinations (Mueser et al., 1990). Hallucinations are reported in current psychiatry textbooks as key psychotic symptoms (Kraepelin, 1899; Jaspers, 1963; Saddock et al., 1989; Gelder et

al., 2009). Hallucinations also appear in screening tools to detect psychotic disorders (Bebbington and Nayani, 1995; Konings et al., 2006).

The 'Ultra High Risk' group (UHR), also referred to as the 'At Risk Mental State' (ARMS) or "clinical high risk" (CHR) group, are a group of help seeking adolescents or young adults identified using reliable measurement tools and clinical criteria as being at very high risk of developing a psychotic illness in the near future (Yung et al., 2003; Miller et al., 2003). This clinically defined population was found, in initial studies, to have a rate of "transition" to a frank psychotic disorder of around 40% in the first 12 months after presentation (Yung et al., 2003; Philips et al., 2000). However, more recently a reduction in the transition rates has been reported in the literature, with authors reporting transition rates as low as 12% in 12 months (Morrison et al., 2012). A meta-analysis by Fusar-Poli et al. (2012) found consistent transition rates of 22% after 1 year, 29% after 2 years, and 36% after 3 years. These rates are 200- 300 times higher than would be expected in a general population sample. The PACE 400 dataset is the first long-term follow-up of a UHR cohort, and this has estimated that the overall rate of transition was 34.9% over a 10-year period (95% CI, 28.7%- 40.6%). The highest risk of transition was in the first 2 years of entry into the service (Nelson et al., 2013). Factors which have been associated with an increased risk of transition to psychosis in UHR samples include long duration of symptoms before treatment (Yung et al., 2003), basic and negative symptoms (Mason et al., 2004; Simon et al., 2006; Haroun et al., 2006; Yung et al., 2005), schizotypal disorder (Ruhrmann et al., 2010) sleep disturbances (Ruhrmann et al., 2010) and substance abuse (Cannon et al., 2008). Three factors of particular interest are subthreshold positive symptoms, (Yung et al., 2003; Mason et al., 2004; Ruhrmann et al., 2010; Yung et al., 2005) poor functioning, (Yung et al., 2003; Mason et al., 2004; Ruhrmann et al., 2010; Yung et al., 2006) and having genetic risk with functional decline. These three factors were found to be significant predictors in the large North American Prodrome Longitudinal Study (Cannon et al., 2008) and replicated in an independent sample (Thompson et al., 2011). Hallucinations are included in the UHR (ARMS/ CHR) criteria in either sub-threshold or infrequent forms as indicating high and imminent risk for psychosis (Yung et al., 2003).

However, more recently general population studies have shown that psychotic

symptoms and subclinical psychotic symptoms [or "psychotic like experiences" (PLEs)], are common in the general population (van Os, 2001). These PLE's include hallucinations, delusions, thought disorder and negative symptoms. Most general population studies of PLEs have tended to focus on PLEs in general, without distinguishing between different types of PLE. However, hallucinations do appear to be the most prevalent PLE in general population samples (Horwood et al., 2008; Kelleher et al., 2012). Epidemiological studies estimate the prevalence of hallucinations to be between 5 and 15% in the general population (Tien, 1991; Johns et al., 2004). In adolescent and young adult (university) samples these estimates are higher with rates of between 6% and 37% reported in the literature (Dhossche et al., 2002; Altman et al., 1997; Barrett and Etheridge, 1992). However, Johns et al., (2002) found that only 25% of adults reporting hallucinations met diagnostic criteria for a psychotic disorder. Hallucinations in adolescent populations often appear to be common but transitory phenomena that do not persist into adulthood (De Loore et al., 2011).

Numerous studies have also found that there is a non-clinical population (i.e. people who have never been clinically referred or have never received a psychiatric or neurological diagnosis) who hear voices, which they experience as benign and are not associated with psychological distress, functional decline or psychiatric illness (Romme et al., 1989; Daalman et al., 2011). These voice hearers do not seek help from clinical services.

Hallucinations are also common in many non-psychotic psychiatric disorders and in a number of organic disorders. These include mood disorders where they are considered a marker of disorder severity (Choong et al., 2007) and borderline personality disorder where they are mostly auditory, distressing and tend to have a critical quality (Slotema et al., 2012).

As such, hallucinations, which were once considered a classic psychotic symptom, now appear to be common in general population samples, not necessarily associated with distress or help seeking and frequently occur in non-psychotic illnesses. It is in this context that we felt it timely to re-examine the clinical significance in the UHR population of hallucinations if they and they alone are the reason for assessing

someone as being at UHR. Only one, relatively small, study has reported that presence of auditory hallucinations at entry to the clinic was predictive of transition to psychosis (Mason et al., 2004), but this finding has not been replicated in larger cohorts (Ruhrmann et al., 2010; Woods et al., 2009; Nelson et al., 2013).

This exploration is particularly pertinent as it has been proposed that in a given individual, PLEs, like hallucinations might either be: (i) an expression of an underlying neurological / psychological vulnerability to a psychotic disorder; (ii) an 'incidental' attenuated psychotic symptom which is not necessarily associated with risk of psychosis but is associated with a non-psychotic illness that will remit once treated; or (iii) present in non-clinical normal individuals, and not associated with distress or disability or increased vulnerability to psychotic disorder (Yung et al., 2009). A possible analogy, which encapsulates (i) and (ii) is to consider a hallucination as being like a fever. Both a hallucination and a fever are common non-specific symptoms that exist on a continuum with normal, are associated with some distress and indicate some underlying pathology. However, this underlying illness may be relatively benign and short-lived or something more serious and enduring.

Much attention has been focused on the identification of clinical signs, symptoms or factors, which alone or in combination could enrich the identification of those at highest risk within the UHR population. However, little has been reported on the identification of clinical factors that alone or in combination may indicate a reduced risk of transition within the UHR population. In other areas of medical practice it is common for the presence of one symptom to be considered more or less significant when found in the absence of other symptoms or signs. An example would be a cough found in the absence of crepitations being considered less clinically concerning than when found with crepitations. In the UHR field, little consideration has been given to the clinical relevance of the presence of one particular symptom while in the absence of other specific symptoms, signs or clinical factors. This is important because 'relevant negatives' may offer additional insight into the clinical trajectory of UHR patients (Yung et al., 2012).

Historically the presence of visual hallucinations in the absence of other psychotic symptoms raised a query about organicity/ substance use (Teeple et al., 2009).

However, possible disparities in transition rates associated with different forms of perceptual disturbance, in the UHR population, is an under researched area.

1.2 Aims of this study:

The primary aim of this study was to investigate if the presence of hallucinations alone at baseline in UHR individuals is associated with a reduced risk of transition to psychosis compared to those who present with symptoms other than hallucinations. The secondary aims were twofold (a) to examine if hallucinations with/ without specific other symptoms e.g. hallucinations with or in the absence of thought disorder, were more or less likely to transition to psychosis (b) certain forms of hallucinations e.g. visual, tactile, olfactory are associated with an even lower level of risk of transition.

It is our primary hypothesis that those young people who are assessed as UHR on the basis of hallucinations alone are less likely to transition to psychosis than those young people presenting with other symptoms.

2. Methods:

We used data from two separate datasets collected at the Personal Assistance and Clinical Evaluation (PACE) clinic in Melbourne. Our primary dataset was a case control study which was developed to investigate whether specific clinical data characterised UHR patients who did and did not go on to develop a psychotic disorder (N=118). Our secondary dataset was the first long-term longitudinal follow-up of UHR individuals who had consented to research since 1993 (The PACE 400 study) (Nelson et al., 2013). We repeated some of the analyses in this dataset in an attempt to replicate and further validate our findings. There was some overlap of study participants. For the purposes of this paper these overlap participants (N=20) were excluded from the analyses of the PACE 400 data so as to ensure that the samples were independent. Ethical approval was received from the University of Melbourne to conduct both studies.

2.1 Design

2.1.1 Case control study

This was a retrospective "case-control" study of patients meeting the UHR criteria treated at PACE, a specialised UHR clinic (Yung et al., 2007). A consecutive series of patients who later developed a psychotic disorder ('cases') between 2003 and 2008 were identified and compared to a randomly selected sample from the clinic who had not developed a psychotic disorder within a defined time frame ('controls'). For more detailed information on the case control study design see Figure 1.

2.1.2 PACE 400 dataset

The PACE 400 study is a longitudinal follow up study. The sample consisted of all UHR patients who participated in research studies at the PACE clinic between 1993 and 2006 (N = 416). For more detailed information on the cohort and the measures see Nelson et al., 2013.

2.2 Setting

Both studies took place at the PACE clinic in Melbourne. The PACE clinic is a specialist clinic for patients meeting UHR criteria aged between 15 and 25 living in northwestern Melbourne. For full operationalised criteria see (Yung et al., 2003).

2.3 Participants & Samples

2.3.1 Case control study

Details of the case control participants and sample are illustrated in figure 1. Transition to psychosis (threshold psychotic disorder) in the clinic is determined using the CAARMS criteria in accordance with earlier studies (Yung et al., 2003; Yung et al., 2004). This operationalised definition of transition to first episode psychosis consists of daily frank positive psychotic symptoms for longer than one week (Yung et al., 2005). Cases and controls were not individually matched but they were from the same period of recruitment. Year of recruitment is known to be a strong predictor of development of a psychotic disorder (Nelson et al., 2013). There was 1 control per case. The time to follow-up ranged from 1.2 to 6.5 years with a median of 4.5 years.

2.3.2 PACE 400

The sample consisted of all UHR patients who participated in studies at the PACE clinic between 1993 and 2006 (N = 416). 396 patients from the PACE 400 sample were included in the analyses.

2.4 Symptom measures & procedure

2.4.1 Case control study

2.4.1.2 Symptom measures

An auditing tool was developed specifically to gather detailed information from the clinical file about cases and controls, from their time of referral to four weeks following initial contact with a PACE clinician (Appendix 1). The auditing tool gathered information on hallucinations, delusions, thought disorder, negative symptoms, dissociative symptoms, mood symptoms, anxiety symptoms and personality traits. For the assessment of psychotic symptoms we included all symptoms assessed in the Operational Criteria for Psychotic Illness (OPCRIT) tool (McGuffin et al., 1991). The OPCRIT is a 90-item computer based diagnostic tool which generates diagnoses according to 12 operational diagnostic systems. OPCRIT is widely used in order to make valid diagnoses of psychotic disorders using information obtained from clinical files and has good validity (McGuffin et al., 1991). We also included additional symptom items, especially those related to symptom content that are not adequately covered by the OPCRIT tool, such as specific hallucinatory symptom content. This provided a detailed assessment of attenuated psychotic and other psychotic like symptoms.

2.4.1.2 Assessment of psychosis diagnosis

The OPCRIT tool was used to assess diagnosis at transition to psychotic disorder. All relevant data in the file up to four weeks from the date of transition was included in order to produce an OPCRIT diagnosis.

2.4.1.3 Procedure

The auditing tool was completed for cases and controls by a research assistant using information from the patients' clinical file. To ensure completeness in the assessment of baseline symptomatology, we used data from the clinical notes from date of first contact with a PACE clinician until four weeks after first contact. All patients accepted into the PACE clinic received a thorough initial assessment which included the CAARMS and a full assessment of clinical symptoms. In the majority of cases relevant clinical symptoms were elicited in the initial assessment, however, in a small number of cases additional baseline symptomatology was elicited after this

assessment but within the first four weeks of contact with a PACE clinician.

For 'cases' that developed a psychotic disorder, the OPCRIT was also administered by auditing clinical notes dated from time of transition until four weeks afterwards. Only the DSM-IV diagnoses generated by the OPCRIT program were used. Consequently, the research assistant was not blind to the transition status of the individual. However, the research assistant was blind to the study hypothesis. The accuracy of the ratings of the presence/absence of the symptoms by the research assistant was regularly checked by one of the investigators (BN) following initial training by two investigators (AT and BN).

2.4.2 PACE 400

2.4.2.1 UHR status and symptom measures

The CAARMS is a semi-structured interview that measures positive, negative, disorganised and other common symptoms. It allows intensity, frequency and duration of symptoms to be measured using one instrument (Yung et al., 2005). The CAARMS data included information on the presence and intensity of perceptual abnormalities but did not include details of hallucinatory form i.e. whether hallucination is visual/ auditory or other. Psychosocial functioning was measured using the Global Assessment of Psychosocial Functioning (GAF) (APA, 1994).

2.5 Data analysis

The outcome of interest and the dependent variable was transition to a psychotic disorder.

In the case control study the independent variables were all symptom questions included in the audit tool. However, when there were small numbers of responses for items, it was necessary to combine or group symptoms. The number of responses to an item that was considered satisfactory for analysis was set at n=10 a priori. These groups were formed on the basis of conventional psychopathological descriptions (Sims, 1988), by consensus between three of the authors (BN, AT, AY) (see table 4). One group of 'other' hallucinatory symptoms comprising of olfactory, gustatory, somatic and tactile hallucinations was also formed.

In PACE 400 the independent variables were the symptom scales of the CAARMS and GAF score. The CAARMS includes subscales on perceptual disturbance, disorders of thought content, conceptual disorganisation, motor disturbance, and basic symptom subscales. The CAARMS subscales are listed in table 5.

Differences in socio-demographic characteristics in the case control study were examined with t-tests (age) and the chi-squared test (gender, intake group). In both studies, we performed a survival analysis using Log-rank test and Cox regression to investigate the relationship between symptom variables and transition to a psychotic disorder with time to transition as a time-to-event variable. In the case of binary factors, an exact log-rank test (based on the distribution of the sum of independent hypergeometric random variables) was used.

A hazard ratio of less than 1 was taken to indicate a reduced risk of transition to psychosis for the group defined by the independent variable when compared with the rest of the sample without this independent variable / combination of independent variables.

As there were a relatively large number of variables in both studies, any association of ≤ 0.1 in the univariate analysis was then subject to a multivariate analysis, controlling for other possible predictive symptom variables. We then repeated this multivariate analysis additionally adjusting for duration of symptoms, GAF score and intake group. These additional adjustments were made as duration of symptoms and intake group, are known to be associated with transition to a psychotic disorder in our population (Yung et al., 2004). In the PACE 400 sample, we also controlled for baseline year of entry into PACE clinic, which has previously been found to be strongly associated with risk of transition to psychosis (Nelson et al., 2013).

We considered using a Bonferroni correction to control for multiple analyses however; as we were assessing evidence about specific hypotheses this was considered inappropriate (Perneger, 1998).

3. Results:

3.1 Sample demographics

3.1.1 Case control study

The demographics of the sample are shown in Table 1. Males were significantly older than females (19.4 v 17.6 years, t=3.58, p=0.001). OPCRIT diagnoses for the case control study are reported in Thompson et al., 2013.

[Insert table 1 around here]

3.1.2 PACE 400

The average age at baseline in the cohort was 18.9 years old (SD 3.4 years) and 48% (n= 200) of the sample were male. Demographics of the full PACE 400 dataset are reported in Nelson et al., 2013.

3.2 Hallucinations and relationship to development of psychosis

3.2.1 Case control study

3.2.1.1 Univariate analysis

Hallucinations alone at baseline were not associated with a reduced risk of transition to psychosis in the case control study (hazard ratio 0.83, p=0.67). Any hallucination and no dissociation (hazard ratio 0.54, p=0.03), visual hallucinations with no ego boundary disorder (hazard ratio 0.61, p=0.044), visual hallucinations with no substance use (hazard ratio 0.48, p=0.045) were associated with significant hazard ratios < 1 indicating a reduced risk of transition to psychosis. Two other symptoms combinations were associated with hazard ratios with p values <0.1 and were included in the subsequent multivariate analyses.

The other hallucinations group was small (n = 12). We repeated the same analyses in this group however the numbers in each of the subgroups was n<10 and so we have not reported these findings due to concerns about their reliability.

[Insert table 2 around here]

3.2.1.2 Multivariate analysis

The presence of hallucinations when found in the absence of any thought disorder

(hazard ratio 0.58, *p*=0.045) and visual hallucinations in the absence of substance misuse (hazard ratio 0.45, *p*=0.045) was associated with a reduced risk of transition to psychosis (see table 3).

[Insert table 3 about here]

3.2.2 PACE 400

3.2.2.1 Univariate analysis

Hallucinations alone at baseline were not associated with a reduced risk of transition to psychosis in the longitudinal follow-up data set (hazard ratio 1.09, *p*=0.23). Perceptual disturbance in the absence of conceptual disturbance (hazard ratio 0.32, *p*=0.007) was associated with a hazard ratio of less than one indicating a reduced risk of transition to psychosis. While perceptual disturbance in the absence of a disorder of concentration, attention and memory (hazard ratio 1.98, *p*=0.02) was associated with a hazard ratio of greater than 1 indicating an increased risk of transition to psychosis. Three other symptom combinations had p values <0.10 and were included in the subsequent multivariate analyses (See table 4).

No significant relationship was found between intensity of perceptual disturbance as rated on the CAARMS and risk of transition or non-transition to psychosis (*r*= 0.23, *p*=0.54). See Table 4 for the results of the univariate analysis.

[Insert table 4 about here]

3.2.2.2 Multivariate analysis

Perceptual disturbance found in the absence of a disorder of affect or emotion (hazard ratio 1.68, *p*=0.04) and perceptual disturbance found in the absence of a disorder of concentration, attention or memory (hazard ratio 1.88, *p*=0.046) were found to be associated with an increased risk of transition to psychosis. (See table 5).

[Insert table 5 about here]

4. Discussion

4.1 Principal findings

UHR patients who present with hallucinations alone were not found to be at significantly lower risk of transition to psychosis in the case control study or in the PACE 400 sample.

The case control analyses suggest that hallucinations in the absence of thought disorder reduce the risk of transition to psychosis by around 40% as evidenced by a significant adjusted hazard ratio of 0.58 in the case control when compared with the rest of the UHR sample without this symptom combination. The univariate analysis in the PACE 400 dataset replicated these findings. However, this finding was no longer significant once other possible confounders in the PACE 400 sample were controlled for. Baseline year had a very significant effect on the hazard ratio for this symptom combination, resulting in a small increase in the hazard ratio itself, even though the p value fell below the level of statistical significance.

In the PACE 400 cohort, perceptual abnormalities occurring in the absence of a disorder of emotion or affect were found to be associated with a significantly increased risk of transition to psychosis. The disorder of emotion and affect subscale of the CAARMs rates both subjective emotional disturbance (including anhedonia and emotional blunting) and objective affective change (including blunting of affect, reduced prosody and inappropriate affect) at clinical interview. The finding that those people who report perceptual disturbances but have no evidence of a disorder of emotion or affect at clinical interview as rated on the CAARMs were at higher risk of transition to psychosis was initially surprising as it appeared to conflict with previous research which reported that co-morbid depressive symptoms increased the risk of transition to psychosis (Yung et al., 2003). Furthermore, depression and anxiety symptoms are very common over the lifetime of a psychotic illness (Buckley et al., 2009). However, more recently a large multi-centre study and a meta analysis have found that co-morbid depressive and anxiety symptoms are not associated with an increased risk of transition to psychosis in the UHR population (Salokangas et al., 2012; Fusar-Poli et al., 2014;). It could be that many of those young people with

perceptual disturbance in the context of disorders of emotion and affect might be those with depressive disorders or emotionally unstable personality traits and some perceptual disturbance seen as secondary and a sequelae of these disorders whereas those with perceptual disturbance without disorders of emotion and affect may be more likely to develop a primary enduring psychotic disorder. This needs further study.

Perceptual abnormalities in the absence of impaired attention or subjective and objective cognitive changes were also found to be associated with a higher risk of transition to psychosis as evidenced by a significant adjusted hazard ratio of greater than 1 in the PACE 400 cohort. The cognition and attention subscale on the CAARMs includes assessment of subjective changes in concentration, attention, comprehension and memory and objective cognitive changes, which include inattentiveness during interview or during brief mental status testing, e.g. serial sevens. Previous research has not found an association between attention and increased risk of transition to psychosis (Francey et al., 2005). However, some cognitive deficits including impaired verbal fluency, verbal and visual memory, and working memory have consistently been associated with increased risk of transition to psychosis in the UHR population (Fusar-Poli et al., 2012). As such, the finding that perceptual disturbances found in the absence of disorders of cognition was associated with an increased risk of transition to psychosis was surprising. However, it likely that this brief and broad measure of cognition as included in this CAARMs subscale is not sufficiently sensitive to identify the particular cognitive deficits associated with transition. Rating on this sub scale which included memory, concentration and attention may also be affected by mood states.

Data from the case control study suggests that individual forms of hallucinations (e.g. auditory and visual) in isolation may not be associated with increased or reduced risk of transition to psychosis. However, visual hallucinations in the absence of substance use were associated with a 55% reduced likelihood of transition to psychosis as evidenced by a significant adjusted hazard ratio of 0.45 in the case control study. The finding that the use of psychotropic substances such as cannabis are associated with an increased risk of developing a psychotic illness is well documented (van Os, 2002; Arsenault et al., 2004; Barnett et al., 2007). Although in the PACE clinic where this

study was conducted a relationship between substance use and transition to psychosis has consistently not been found (Philips et al., 2002; Thompson et al., 2013b). The finding that UHR young people with visual hallucinations but who do not use illicit substances are less likely to transition to psychosis may point to an epigenetic influence of substance use on the risk of developing psychosis (Rutten et al., 2009)? It could also be that these young people do not have the neurobiological substrate that might be common to patients with psychosis and substance misuse. Substance use or absence of substance use did not significantly alter the hazard ratios of other forms of hallucinations. For 20% of the young people presenting with visual hallucinations, these were there only attenuated psychotic symptom.

4.2 Comparison with previous work

Only one study has reported that hallucinations were predictive of transition to psychosis (Mason et al., 2004). This cohort study had a smaller sample size (N = 74) than our case control study (N = 118), with a shorter follow-up period (mean of 26 months, SD +/- 9.2 compared to our mean of 48 months, SD +/- 21). Moreover, Mason and colleagues did not investigate specific forms of hallucinations or symptom combinations or whether risk of transition was decreased in those people who presented with hallucinations alone at baseline.

4.3 Strengths and limitations of the study

Case control study:

The main strength of the case control study is that it uses data from a comparatively large number of UHR individuals with baseline symptom data who subsequently developed a psychotic disorder (N = 59). Therefore, it has the benefit of increased power compared to other studies in the field where numbers of transitions are relatively low. It is possible but unlikely that some of our controls transitioned to psychosis after follow-up with our median time to follow up for the controls of 4.5 years with the range being 1.2 years to 6.5 years. However, Nelson et al. (2013) showed that transition to psychosis is highest in the first 2 years but continues up to five years after identification as UHR.

Using clinical files to extract the symptom data is associated with some limitations. While all initial assessments included a standardised in-depth clinical interview and the completion of the CAARMS, clinicians do not complete a standardised

assessment form. As such, we cannot be certain that data were not subject to bias due to some answers not being recorded systematically in the clinical files.

Not all symptoms were present in sufficient cases to allow investigation individually and therefore we needed to combine a number of symptoms into broader groups. We set a priori the prevalence of a symptom N=10.

PACE 400

The main strength of this study is that it is the first long-term follow up of a UHR cohort. The sample size and duration of follow up is large when compared with similar studies in this field. However, no detailed information on specific types or form of perceptual abnormalities was available in this data. The grouping called perceptual abnormalities included a wide spectrum of disturbance from illusions to frank hallucinations.

4.4 Clinical Implications

The data indicate that in the UHR population hallucinations on their own (i.e., in the absence of any other attenuated psychotic symptoms) are of clinical significance and should not be dismissed as incidental or insignificant. However, there may be certain combinations such as hallucinations in the absence of thought disorder, which may make transition to psychosis less likely and others such as hallucinations in the absence of disorders of emotion, and affect which make transition to psychosis more likely.

Returning to the analogy of temperature and fever. Like a fever, perceptual disturbance appears to be a non-specific clinical feature, which may represent the end point of a number of clinical pathways. It may be that like a fever the true clinical significance of a hallucination is defined less by to its own clinical features and better understood by the presence or absence of other signs and symptoms.

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References

Aleman, A., Laroi, F., 2008 Hallucinations: The Science of Idiosyncratic Perception. American Psychological Association, Washington, DC.

Allen, P., Modinos, G., Hubl, D., Shields, G., Cachia, A., Jardri, R., Thomas, P., Woodward, T., Shotbolt, T., Plaze, M., Hoffman, R., 2012 Neuroimaging Auditory Hallucinations in Schizophrenia: From Neuroanatomy to Neurochemistry and Beyond. Schizophrenia Bulletin 38, 695-703

Altman, H., Collins, M., Mundy, P., 1997 Subclinical hallucinations and delusions in nonpsychotic adolescents. Journal of Child Psychology and Psychiatry 38, 413- 420.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Publishing, Arlington, VA.

Arseneault, L., Cannon, M., Witton, J., Murray, R.M., 2004 Causal association between cannabis and psychosis: examination of the evidence. British Journal of Psychiatry 184, 110-7

Barnett, J.H., Werners, U., Secher, S.M., Hill, K.E., Brazil, R., Masson, K., Pernet, D.E., Kirkbride, J.B., Murray, G.K., Bullmore, E.T., Jones, P.B., 2007 Substance use in a population-based clinic sample of people with first-episode psychosis. British Journal of Psychiatry 190, 515-20

Barrett, T.R., Etheridge, J.B. 1992 Verbal hallucinations in normals: V Perceived reality characteristics. Applied Cognitive Psychology. 6, 379- 387

Bebbington, P.E., Nayani, T., 1995 The Psychosis Screening Questionnaire. International Journal of Methods Psychiatric Research 5, 11-19

Bentall, R.P., 1990 The Illusion of Reality: A Review and Integration of Psychological Research on Hallucination. Psychological Bulletin 107, 82- 95

Buckley, P.F., Miller, B.J., Lehrer, D.S., Castle D.J., 2009 Psychiatric Comorbidities and Schizophrenia Schizophrenia Bulletin 35, 383-402

Choong, C., Hunter, M.D., Woodruff P.W., 2007 Auditory hallucinations in those populations that do not suffer from schizophrenia. Current Psychiatry Reports 9, 206-12

Daalman, K, Boks, M.P.M., Diederen, K.M.J., de Weijer, A.D., Blom, J.D., Kahn, R.S., Sommer, I.E.C., 2011 The same or different? A phenomenological comparison of auditory verbal hallucinations in healthy and psychotic individuals. Journal of Clinical Psychiatry. 72, 320–25

David, A.S., 1994 The neuropsychological origin of auditory hallucinations. In A.S. David, J.C. Cutting (Eds.), The neuropsychology of schizophrenia. Hove: Erlbaum

David, A.S., 2004 The cognitive neuropsychiatry of auditory verbal hallucinations: an overview. Cognitive Neuropsychiatry 9, 107- 23

de Leede-Smith, S., Barkus, E., 2013 A comprehensive review of auditory verbal hallucinations: lifetime prevalence, correlates and mechanisms in healthy and clinical individuals. Frontiers in Human Neuroscience 7, 367

De Loore, E., Gunther, N., Drukker, M., Feron, F., Sabbe, B., Deboutte, D., van Os, J., Myin-Germeys, I., 2011 I Persistence and outcome of auditory hallucinations in adolescence: a longitudinal general population study of 1800 individuals. Schizophrenia Research 127, 252-6.

Dirk Blom, J., Sommer, I. 2011 Hallucinations. Research and practice Springer-Verlag, New York Inc

Dhossche, D., Ferdinand, R., Van der Ende, J., Hofstra, M.B., Velhulst, F. 2002 Diagnostic outcome of self reported hallucinations in a community sample of adolescents. Psychological Medicine 32, 619- 627

Fergusson, D.M., Poulton, R., Smith, P., Bouden, J. 2006 Cannabis and psychosis. British Medical Journal 332, 172-175

Francey, S.M., Jackson, H.J., Phillips, L.J., Wood, S.J., Yung, A.R., McGorry, P.D. 2005 Sustained attention in young people at high risk of psychosis does not predict transition to psychosis. Schizophrenia Research 79, 127-36.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., McGuire, P., 2012 Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Archives of General Psychiatry 69, 220-229.

Fusar-Poli, P., Deste, G., Smieskova, R., Yung, A.R., Howes, O., Stieglitz, R., Vita, A., McGuire, P., Borgwardt, S., 2012 Cognitive Functioning in Prodromal Psychosis: A Meta analysis. Archives of General Psychiatry 69, 562-571

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., McGuire, P.K., 2014 Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophrenia Bulletin 40,120-31

Gelder, M., Andreasen, N., Lopez-Ibor, J., Geddes, J., 2009 The New Oxford Textbook of Psychiatry (2nd edn). Oxford University Press

Horwood, J., Salvi, G., Thomas, K., Duffy, L., Gunnell, D., Hollis, C., Lewis, G., Menezes, P., Thompson, A., Wolke, D., Zammit, S., Harrison, G., 2008 IQ and non-clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort. British Journal of Psychiatry 193, 185-91

Jaspers, K. 1963 General Psychopathology (trans. J. Hoenig & M.W. Hamilton). Manchester: Manchester University Press. Reprinted (1997) in two volumes in Baltimore, MD, by Johns Hopkins University Press

Johns, L.C., Nazroo, J.Y., Bebbington, P., Kuipers, E., 2002 Occurrence of hallucinatory experiences in a community sample and ethnic variations. British Journal of Psychiatry 180, 174–78

Johns, L.C., Cannon, M., Singleton, N., Murray, R.M., Farrell, M., Brugha, T., Bebbington, P., Jenkins, R., Meltzer, H., 2004 Prevalence and correlates of self- reported psychotic symptoms in the British population. British Journal of Psychiatry 185, 298–305

Kelleher, I., O' Connor, D., Clarke, M.C., Devlin, N., Harley, M., Cannon, M., 2012 Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. Psychological Medicine 9: 1-7

Konings, M., Bak, M., Hanssen, M., van Os, J., Krabbendam, L. 2006 Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatrica Scandinavia 114, 55-61

Kraepelin, E., 1899 Psychiatrie: ein Lehrbuch für Studirende und Aertze (6th edn). Leipzig: Barth Verlag. Reprinted (1990) as Psychiatry: A Textbook for Students and Physicians (ed. J. M. Quen; trans. H. Metoiu & S. Ayed). Canton, MA: Science History Publications.

Larøi, F., 2012 How do auditory verbal hallucinations in patients differ from those in non-patients? Frontiers in Human Neuroscience. 6, 25

Mason, O., Startup, M., Halpin, S., Schall, U., Conrad, A., Carr, V., 2004 Risk factors for transition to first episode psychosis among individuals with "at-risk mental states." Schizophrenia Research 71, 227-37

McGuffin, P., Farmer, A., Harvey, I. 1991 A polydiagnostic application of operational criteria in studies of

psychotic illness. Development and reliability of the OPCRIT system. Archives General Psychiatry 48, 764-70

Miller, T.J., McGlashan, T.H., Rosen, J.L., Somjee, L., Markovich, P.J., Stein, K., Woods, S.W., 2003 Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin 29, 703-15

Morrison, A.P., Haddock, G., Tarrier, N., 1995 Intrusive thoughts and auditory hallucinations: A cognitive approach. Behavioural and Cognitive Psychotherapy 23, 265–280

Mueser, K.T., Bellack, A.S., Brady, E.U., 1990 Hallucinations in schizophrenia. Acta Psychiatrica Scandinavica 82, 26-29

Nelson, B., Yuen, K., Yung, A.R., 2011 Ultra high risk (UHR) for psychosis criteria: are there different levels of risk for transition to psychosis? Schizophrenia Research 125, 62-8

Nelson, B., Yuen, H., Wood, S.J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D.L., Brewer, W.J., Francey, S.M., Amminger, G.P., Thompson, A., McGorry, P.D., Yung, A.R., 2013 Long-term Follow-up of a Group at Ultra High Risk ("Prodromal") for Psychosis: The PACE 400 Study. JAMA Psychiatry 70, 793-802

Ohayon, M., 2000 Prevalence of hallucinations and their pathological associations in the general population. Psychiatric Research 97, 153–64

Perneger, T.V., 1998 What's wrong with Bonferroni adjustments? British Medical Journal 316, 1236–38

Phillips, L.J., Yung, A.R., McGorry, P.D., 2000 Identification of young people at risk of psychosis: Validation of personal assessment and crisis evaluation clinic intake criteria. Australian and New Zealand Journal of Psychiatry 34, *Supplement*, 164-69

Phillips, L.J., Curry, C., Yung, A.R., Yuen, H.P., Adlard, S., McGorry, P.D., 2002 Cannabis use is not associated with the development of psychosis in an 'ultra' high-risk group. Australian and New Zealand Journal of Psychiatry 36, 800-6

Romme, M.A., Escher, A.D. 1989 Hearing voices. Schizophrenia Bulletin. 15, 209-16

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R.K., Heinimaa, M., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Juckel, G., Heinz, A., Morrison, A., Lewis, S., von Reventlow, H.G., Klosterkötter, J., 2010 Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. Archives of General Psychiatry 67, 241-51.

Rutten, B.P.F., Mill, J., 2009. Epigenetic Mediation of Environmental Influences in Major Psychotic Disorders. Schizophrenia Bulletin 35,1045–1056

Saddock, B.J., Saddock, V.A., Ruiz, P., 2009 Kaplan and Sadock's Comprehensive Textbook of Psychiatry. 9th Edition. Lippincott Williams & Wilkins.

Salokangas, R.K., Ruhrmann, S., von Reventlow, H.G., Heinimaa, M., Svirskis, T., From, T., Luutonen, S., Juckel, G., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Schultze-Lutter, F., Klosterkötter, J.: EPOS group. 2012 Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophrenia Research 138, 192-7

Simon, A,E., Dvorsky, D.N., Boesch, J., Roth, B., Isler, E., Schueler, P., Petralli, C., Umbricht, D., 2006 Defining subjects at risk for psychosis: a comparison of two approaches. Schizophrenia Research. 81, 83-90.

Slade, P.D., Bentall, R.P., 1988 Sensory Deception: Towards a Scientific Analysis of Hallucinations. London: Croom Helm

Slotema, C.W., Daalman, K., Blom, J.D., Diederen, K.M., Hoek, H.W., Sommer, I.E. 2012 Auditory verbal hallucinations in patients with borderline personality disorder are similar to those in schizophrenia. Psychological Medicine. 42, 1873-8

Sommer, I.E.C., Daalman, K., Rietkerk, T., Diederen, K.M., Bakker, S., Wijkstra, J., Boks, M.P. 2010 Healthy individuals with auditory verbal hallucinations who are they? Psychiatric assessments of a selected sample of 103 subjects. Schizophrenia Bulletin. 36, 633–41

Tien, A.Y., 1991 Distributions of hallucinations in the population. Social Psychiatry and Psychiatric Epidemiology 26, 287-292.

Teeple, R.C., Caplan, J.P., Stern, T.A., 2009 Visual hallucinations: differential diagnosis and treatment. Primary Care Companion Journal Clinical Psychiatry 11, 26-33

Thompson, A., Nelson, B., Bruxner, A., O' Connor, K., Mossaheb, N., Simmons, M.B., Yung, A.R., 2013 Does specific psychopathology predict development of psychosis in ultra high-risk (UHR) patients? Australian and New Zealand Journal of Psychiatry 47, 380-90

Thompson, A., Nelson, B., Yung, A., 2011 Predictive validity of clinical variables in the "at risk" for psychosis population: international comparison with results from the North American Prodrome Longitudinal Study. Schizophrenia Research 126, 51-7

van Os, J., Hanssen, M., Bijl, R.V., Vollebergh, W. 2001 Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison *Archives of General Psychiatry* 58, 663-68

van Os, J., 2002 Cannabis Use and Psychosis: A Longitudinal Population-based Study. American Journal of Epidemiology 156, 319-327.

van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2009 A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychological Medicine 39, 179–95

Woodruff, P.W.R., Wright, I.C., Bullmore, E.T., Brammer, M., Howard, R.J., Williams, S.C.R., Shapleske, J., Rossell, S., David, A.S., McGuire, P.K., Murray, R.M. 1997 Auditory hallucinations and the temporal cortical response to speech in schizophrenia: a functional magnetic resonance imaging study. American Journal of Psychiatry 154: 1676–1682.

World Health Organisation. 1992. ICD- 10 Classification of mental and behavioural disorder: Clinical descriptions and diagnostic guidelines. Geneva.

Yung, A.R., Phillips, L.J., Yuen, H.P., Francey S.M,, McFarlane. C,A,, Hallgren. M., McGorry, P.D., 2003 Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group Schizophrenia Research 60, 21-32

Yung, A.R., Philips, L.J., Yuen, H.P., McGorry, P.D. 2004 Risk Factors for psychosis in an ultra high risk group: psychopathology and clinical features. Schizophrenia Research 67, 131-42

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005 Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Australian and New Zealand Journal of Psychiatry 39, 964-71

Yung, A.R., Nelson, B., Baker, K., Buckby, J.A., Baksheev, G., Cosgrave, E.M., 2009 Psychotic-Like Experiences in a Community Sample of Adolescents: Implications for the Continuum Model of Psychosis and Prediction of Schizophrenia. Australian and New Zealand Journal of Psychiatry 43, 118-28

Yung, A.R., Woods, S., Ruhrmann, S., Addington, J., Schultze-Lutter, F., Cornblatt, B.A., Amminger, G.P., Bechdolf, A., Birchwood, M., Borgwardt, S., Cannon, T.D., de Haan, L., French, P., Fusar-Poli, P., Keshavan, M., Klosterkötter, J., Kwon, J.S., McGorry, P.D., McGuire, P., Mizuno, M., Morrison, A.P., Riecher-Rössler, A., Salokangas, R.K., Seidman, L.J., Suzuki, M., Valmaggia, L., van der Gaag, M., Wood, S.J., McGlashan, T.H., 2012 Whither the Attenuated Psychosis Syndrome? Schizophrenia Bulletin 38, 1130-34

Table1

Case control study: Demographics of total sample, cases and controls at baseline

	Total sample n= 118	**Cases n= 59**	**Controls n=59**	**P value ^**
Age, mean (SD)	18.3 (2.7)	18.6 (2.6)	18 (2.9)	0.54 +
Gender, female (%)	69 (58.5)	34 (57.6)	35 (59.3)	0.71
Highest Education, number (%) #				
Secondary yr 7-10	48 (41.4)	24 (41.4)	24 (42.9)	0.52
Secondary yr 11-12	50 (43.1)	25 (43.1)	25 (44.6)	0.53
Tertiary commenced	16 (13.8)	9 (15.5)	7 (12.5)	0.23
Occupation, number (%)				
Full time/part time	16 (13.6)	5 (8.5)	7 (11. 9)	0.25

work Full time/part time student	57 (48.3)	28 (47.5)	29 (49.2)	0.20
Unemployed	50 (42.4)	26 (44.1)	21 (35.6)	0.08
Duration of psychotic symptoms, mean in weeks (SD) ^	35 (44.4)	34.1 (48.2)	36.1 (41.2)	0.86
Duration of mood symptoms, mean in weeks (SD) ~	31 (40.5)	31.2 (43.5)	31.4 (38.1)	0.65
Living status, number (%)				
Not with parents	39 (33.1)	17 (28.8)	22 (37.3)	0.06
With parents	79 (67.0)	42 (71.2)	37 (62.7)	0.06
Hx of substance use, number (%) >	66 (56.9)	35 (59.3)	31 (54.4)	0.30
UHR Intake group, number (%)				
Trait	32 (27.1)	19 (32.2)	13 (22.0)	0.01*
APS	104 (88.1)	53 (89.8)	52 (88.1)	0.56
BLIPS	4 (3.4)	3 (5.1)	1 (1.7)	0.04*
APS& BLIPS	1 (0.8)	1 (1.7)	-	-
APS & Trait	20 (16.9)	15 (25.4)	5 (4.2)	0.001*
APS & Trait & BLIPS	1(0.8)	-	1 (1.7)	-

N= 118 unless otherwise stated #N=114 ^n=113 ~n=112 >n=116
+ p value associated with t test
^ p value associated with chi-squared test
*statistical significance set at p<0.05

Table 2

Case control study: Prevalence of hallucinations with associated hazards ratios (and p value) of developing a psychotic disorder

Symptom items	**Number with item present (%)**	**Hazards Ratio (95% CI)**	**P value ***
Any Hallucination (n=80)			
Any hallucination only	14 (11.9)	0.83 (0.36, 1.94)	0.67
Any hallucination with:			
+ any delusion	56 (47.5)	1.54 (0.73, 3.26)	0.26
No delusion	24 (20.3)	0.58 (0.29, 1.20)	0.14
+ any thought Disorder ^	19 (16.1)	1.14 (0.58, 2.25)	0.72
No thought disorder	61 (51.7)	0.65 (0.39, 1.08)	0.09*
+ ego boundary Disorder ^^	63 (53.3)	1.62 (0.84, 3.12)	0.15
No ego boundary Disorder	17 (14.4)	0.66 (0.39, 1.12)	0.12
+ negative symptoms	33 (28)	0.64 (0.35, 1.19)	0.16

^^^			
No negative symptoms	48 (40.7)	0.97 (0.58, 1.64)	0.92
+ dissociation	10 (8.5)	0.96 (0.39, 2.41)	0.93
No dissociation	70 (59.3)	0.54 (0.31, 0.94)	0.03*
+ substance use	48 (40.7)	1.18 (0.70, 1.98)	0.53
No substance use	32 (27.2)	0.56 (0.30, 1.06)	0.07*
Auditory Hallucinations (n=60)			
Auditory hallucination only	12 (10.2)	0.84 (0.51, 1.40)	0.52
Auditory hallucination with:			
+ any delusion	40 (33.9)	1.49 (0.64, 3.48)	0.35
No delusion	20 (16.9)		
+ any thought Disorder	10 (8.5)	1.49 (0.64, 3.48)	0.35
No thought disorder	50 (42.4)	0.73 (0.44, 1.24)	0.25
+ ego boundary Disorder	14 (11.9)	1.51 (0.74, 3.01)	0.26
No ego boundary Disorder	46 (39.0)	0.69 (0.42, 1.13)	0.14
+ negative symptoms	23 (19.5)	2.10 (0.72, 6.09)	0.16
No negative symptoms	37 (31.4)	0.87 (0.5, 1.52)	0.63
+ dissociation	4 (3.4)	0.94 (0.23, 3.85)	0.93
No dissociation	56 (47.5)	0.85 (0.51, 1.41)	0.52
+ substance use	36 (30.5)	1.19 (0.70, 2.04)	0.52
No substance use	24 (20.3)	0.66 (0.33, 1.35)	0.26
Visual Hallucinations (n=55)			
Visual hallucination only	7 (5.9)	1.22 (0.44, 3.37)	0.70
Visual hallucination with:			
+ any delusion	31(26.3)	0.68 (0.41, 1.15)	0.14
No delusion	14 (11.9)	0.56 (0.23, 1.41)	0.22
+ any thought Disorder	16 (13.6)	1.08 (0.51, 2.28)	0.84
No thought disorder	39 (33.1)	0.62 (0.34, 1.10)	0.10
+ ego boundary Disorder	13 (11.0)	1.40 (0.66, 2.95)	0.38
No ego boundary Disorder	42 (35.6)	0.61 (0.35, 0.95)	0.044*
+ negative symptoms	21(17.8)	0.55 (0.25, 1.20)	0.13
No negative symptoms	34 (28.8)	0.93 (0.53, 1.70)	0.80
+ dissociation	8 (6.8)	1.04 (0.38, 2.90)	0.95
No dissociation	47 (39.8)	0.67 (0.39, 1.14)	0.14
+ substance use	30 (25.4)	1.08 (0.61, 1.93)	0.78
No substance use	25 (21.2)	0.48 (0.29, 1.01)	0.045*

*statistical significance set at p<0.05 however p<0.1 was subject to subsequent multivariate analysis

^**Thought disorder group** included neologisms, thought blocking, loosening of associations or derailment and tangentiality, flight of ideas and racing thoughts, circumstantiality, perserveration or echolalia and poverty of speech.

^^**Delusion of ego boundary group** included passivity, thought insertion, thought withdrawal, thought broadcast, thoughts being read, made thoughts or feelings.

^^^**Negative symptoms group** included alogia, avolition, apathy, anhedonia, affective flattening.

Table 3:

Case control study

Adjusted analysis of the joint significance of variables that were associated with a p value of predictors ≤ 0.1 in the univariate analysis (Table 2)

Symptom items	**Hazards Ratio (95% CI)**	**P value ***
Any hallucination with		
No thought disorder	0.58 (0.33, 0.98)	0.045*
No dissociation	0.58 (0.33, 1.02)	0.06
No substance use	0.55 (0.28, 1.06)	0.08
Visual hallucination with		
No ego boundary disorder	0.59 (0.32, 1.07)	0.08
No substance use	0.44 (0.20, 0.98)	0.045*

*statistical significance set at p<0.05 however p<0.1 was subject to subsequent multivariate analysis

Table 4
PACE 400
Frequency of perceptual abnormalities and frequency of perceptual abnormalities in combination with other CAARMS scales and the associated hazards ratios (and p value) of developing a psychotic disorder.

CAARMS scales	**Number with item present (%)** **N= 396**	**Hazards Ratio (95% CI)**	**P value ***
Any Perceptual abnormality	300 (75.6)	1.09 (0.95, 1.27)	0.23
Perceptual abnormality only	119 (29.6)	1.31 (0.87, 1.96)	0.20
Perceptual abnormality with:			
+ disorder of thought content	277 (68.9)	1.05 (0.67, 1.65)	0.83
No disorder of thought content	23 (6.1)	0.60	0.31

		(0.22, 1.62)	
+ conceptual disorganization	238 (59.2)	1.44 (0.94, 2.23)	0.11
No conceptual disorganization	61 (15.2)	0.32 (0.14, 0.73)	0.007*
+ motor disturbance	89 (22.1)	1.39 (0.90, 2.15)	0.14
No motor disturbance	209 (52.0)	0.69 (0.46, 1.03)	0.07*
+ disorders of emotion and affect	222 (55.2)	0.72 (0.49, 1.07)	0.11
No disorders of emotion and affect	76 (18.9)	1.41 (0.89, 2.24)	0.10*
+ impaired energy	248 (61.7)	0.75 (0.50, 1.12)	0.16
No impaired energy	50 (12.4)	1.42 (0.84, 2.39)	0.20
+ impaired tolerance to normal stress	299 (74.4)	0.92 (0.58, 1.49)	0.75
No impaired tolerance to normal stress	53 (13.2)	1.32 (0.78, 2.23)	0.30
+ disorder of concentration, attention and memory	268 (67.7)	0.69 (0.47, 1.02)	0.06*
No disorder of concentration, attention and memory	31 (7.7)	1.98 (1.10, 3.55)	0.02*
+ basic symptom: impaired emotional functioning	28 (7.0)	0.56 (0.23, 1.36)	0.20
+ basic symptom: impaired energy	16 (4.0)	0.69 (0.22, 2.17)	0.52
+ basic symptom: impaired motor functioning	13 (3.2)	0.92 (0.30, 2.99)	0.95
+ basic symptom: impaired bodily sensation	12 (3.0)	0.71 (0.17, 2.87)	0.71
+ basic symptom: impaired external perception	24 (6.0)	0.84 (0.37, 1.92)	0.68
+ basic symptom: impaired autonomic functioning	10 (2.5)	0.35 (0.05, 2.47)	0.29

* Statistical significance = $p<0.05$

Table 5
PACE 400

Adjusted analysis of the joint significance of variables that were associated with a p value of predictors ≤ 0.1 in the univariate analysis

CAARMS scales	**Hazards Ratio (95% CI)**	**P value ***
Perceptual abnormality with no conceptual disorganization	0.49 (0.17, 1.37)	0.18
Perceptual abnormality with disorder of concentration, attention and memory	0.84 (0.54, 1.31)	0.45
Perceptual abnormality with no motor disturbance	1.25 (0.80, 1.96)	0.33
Perceptual abnormality with no disorder of emotion and affect	1.68 (1.02, 2.76)	0.04*

Perceptual abnormality with no disorder of concentration, attention and memory	1.88 (1.01, 3.52)	0.046*

* Statistical significance = p<0.05

Figure 1 Case Control Methodology

Highlights

- The aim of this study was to investigate whether UHR patients who present with hallucinations alone at identification as UHR are at lower risk of transition to psychosis than UHR patients who present with no hallucinations or hallucinations plus other symptoms.
- Our primary dataset was a retrospective "case-control" study of UHR patients (N = 118). The second, independent dataset was a long-term longitudinal follow up study of UHR patients (N = 416).
- Hallucinations alone at baseline were not significantly associated with a reduced risk of transition to psychosis.
- In the longitudinal follow-up dataset perceptual disturbance found in the absence of a disorder of affect or emotion was associated with an increased risk of transition to psychosis.

6. Figure(s)

Figure 1