Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Further examination of the reducing transition rate in ultra high risk for psychosis samples: The possible role of earlier intervention

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ARTICLE INFO

Article history:
Received 15 January 2016
Received in revised form 21 April 2016
Accepted 25 April 2016
Available online xxxx

Keywords:
Prodrome
Ultra high risk
Early intervention
Psychosis

ABSTRACT

Background: The rate of transition to psychotic disorder in ultra high risk (UHR) patients has declined in recent cohorts. The reasons for this are unclear, but may include a lead-time bias, earlier intervention, a change in clinical characteristics of cohorts, and treatment changes.
Aims: In this paper we examined the two possibilities related to reduction in duration of symptoms prior to clinic entry, i.e., lead-time bias and earlier intervention.
Method: The sample consisted of all UHR research participants seen at the PACE clinic, Melbourne between 1993 and 2006 ($N = 416$), followed for a mean of 7.5 years (the 'PACE 400' cohort). Duration of symptoms was analysed by four baseline year time periods. Analysis of transition rate by duration of symptoms was restricted to more homogenous sub-samples (pre-1998 and pre-2001) in order to minimize confounding effects of change in patient characteristics or treatments. These cohorts were divided into those with a short and long duration of symptoms using a cut-point approach.
Results: Duration of symptoms prior to entry did not reduce significantly between 1993 and 2006 ($p = 0.10$). The group with a short duration of symptoms showed lower transition rates and did not catch up in transition rate compared to the long duration of symptoms group.
Discussion: These data suggest that, while earlier intervention or lead-time bias do not fully account for the declining transition rate in UHR cohorts, it appears that earlier intervention may have exerted a stronger influence on this decline than length of follow-up period (lead-time bias).

1. Introduction

The development of criteria for identifying help-seeking young people at risk of schizophrenia and other psychotic disorders has introduced a potent paradigm for researching risk factors, illness biomarkers and pathogenetic mechanisms, as well as conducting preventive intervention trials (Fusar-Poli et al. 2013; Yung et al. 2012a). These "ultra high risk" (UHR) criteria, also referred to as "clinical high risk" or "prodromal" criteria, are based around attenuated positive psychotic symptoms, brief psychotic symptoms and trait vulnerability due to schizotypal personality disorder or family history of psychotic disorder (Yung et al. 1996; Yung et al. 2003; Yung et al. 2004), in addition to being help-seeking and in the adolescent to young adult age range (the highest period of risk for psychosis).

The UHR criteria have been widely used (Cannon et al. 2008; McGlashan et al. 2007) with rates of psychosis onset ("transition" or "conversion") found to range between 8 and 54% within 1–2.5 years (Cannon et al. 2008; Cornblatt et al. 2003; Mason et al. 2004; Miller et al. 2002; Morrison et al. 2012; Ruhrmann et al. 2003; Ruhrmann et al. 2010; Yung et al. 2003). However, there is evidence of a decline in transition rates in more recent UHR cohorts with rates as low as 8–28% in one year (Amminger et al. 2010; Demjaha et al. 2012; Morrison et al. 2012; Simon and Umbricht; Velthorst et al. 2009; Yung et al. 2007). Consistent with this, a recent meta-analysis indicated a significant relationship between transition rates and year of journal article publication, with more recent publications reporting lower transition rates (Fusar-Poli et al. 2012). In our medium to long-term follow-up study of 416 UHR cases ("PACE 400"; Nelson et al. 2013) recruited over a 13 year period (1993–2006) we found a strong effect of more recent cohorts having a lower transition rate than older cohorts, consistent with an earlier publication from our group (Yung et al. 2007). We argued that there may be multiple (possibly overlapping) reasons for

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http://dx.doi.org/10.1016/j.schres.2016.04.040
0920-9964/

this. The first two of these reasons relate to reduction in duration of symptoms prior to clinic entry.

1. Lead-time bias. This refers to patients in more recent cohorts possibly being referred to treatment earlier in the course of their symptoms and therefore requiring a longer observation or follow-up period to register transitioned cases. The shorter "window of observation" would give the false impression of more recent cohorts having lower transition rates. This implies that extending this window of observation by following patients from recent cohorts for a longer period of time may reveal comparable transition rates to earlier cohorts.
2. Earlier intervention. A shorter duration of symptoms prior to entry in more recent cohorts may have allowed intervention to be *more effective* in delaying or preventing transition to psychosis, consistent with the clinical staging model in psychiatry (McGorry et al. 2006).
3. Change in sample characteristics. More recent cohorts may inherently be at lower risk of psychosis due to differences in clinical characteristics of UHR cohorts over the years (e.g., symptom dimensions, neurocognitive functioning, etc.). This may be related in part to sampling patterns associated with referral pathways and identification approaches (Fusar-Poli et al. 2015; Wiltink et al. 2015).
4. Treatment changes. It is possible that standard treatment for UHR patients has become more effective over the years in delaying or preventing transition to psychosis.

There has been considerable discussion in the literature about the issue of the declining transition rate in high risk samples with regards to implications for the validity of the UHR criteria (van Os and Linscott 2012), for effectively researching pathogenetic mechanisms driving psychosis onset (Nelson et al. 2014a, 2014b), the proposal to include Attenuated Psychosis Syndrome in the DSM-5 (Yung et al. 2012b), and for the identification of sufficiently enriched samples for preventive intervention trials (McGorry et al. 2009). A central limitation noted in several recent UHR intervention trials has been the reasonably low transition rates in the treatment groups being compared (McGorry et al. 2013b; Morrison et al. 2012). It is important to understand the reasons for the reducing transition rate as this will assist in introducing measures to enrich UHR samples.

The purpose of the current report is to use the PACE 400 data set to examine the plausibility of the first two reasons listed above (lead time bias and earlier intervention) and to examine which of these two possibilities might be more likely to be influencing the transition rate. The analytic approach is exploratory rather than hypothesis driven. We have used the same data set to examine the third reason (change in clinical characteristics of the samples) in another report (Hartmann et al. 2016). This analysis indicated that although there was some change in clinical characteristics over the years (greater array of attenuated psychotic symptoms and higher thought disorder in earlier cohorts) this was not substantial enough to fully account for the declining transition rate. Also, a previous report from our group indicated that a reduction in duration of symptoms prior to clinic entry may play a role in the reducing transition rate (Yung et al. 2007). We therefore decided to examine the first two possibilities listed above, both of which are related to a possible reduction in duration of symptoms prior to clinic entry, in greater detail. This paper extends on the previous report from our group (Yung et al. 2007) by using a larger sample with a substantially longer follow-up time. Reason four (change in treatment) will be the subject of future work.

2. Method

2.1. Setting and sample

Full details of the PACE 400 study are provided in Nelson et al. (2013). The PACE clinic is a specialist clinic for UHR patients. The catchment area of the service includes northwestern metropolitan Melbourne, Australia. The age range accepted to PACE over the time period of the baseline studies was 15–30 years. Young people are accepted to PACE if they meet criteria for at least one of three UHR groups: Attenuated Psychotic Symptoms (APS), Brief Limited Intermittent Psychotic Symptoms (BLIPS) and Trait groups (see Nelson et al. 2013). Exclusion criteria for PACE are presence of a current or past psychotic disorder, known organic cause for presentation, and past neuroleptic exposure equivalent to a total continuous haloperidol dose of >15 mg.

The sample consisted of all UHR patients who participated in studies at the PACE clinic between 1993 and 2006 ($N = 416$). Seven studies - three intervention (Berger et al. 2012; McGorry et al. 2002; Yung et al. 2011) and four cohort (Phillips et al. 2009; Thompson et al. 2007; Yung et al. 1996; Yung et al. 2003) studies - were conducted over this period.

2.2. Measures

2.2.1. UHR status

From 1993 to 1999 UHR status at baseline was assessed using both the Brief Psychiatric Rating Scale (BPRS)/Comprehensive Assessment of Symptoms and History (CASH)/Global Assessment of Functioning (GAF) method (Yung et al. 1996; Yung et al. 2003) and the Comprehensive Assessment of At Risk Mental States (CAARMS)/GAF method (Yung et al. 2005) while the concurrent validity of the CAARMS was being established. From 1999 the CAARMS replaced the BPRS/CASH as the means of establishing UHR status.

2.2.2. Outcome measures

Psychosis status: The main outcome of interest was transition to psychotic disorder. This was defined as at least one fully positive psychotic symptom several times a week for over one week. From 1993 to 1999 psychosis threshold was determined using both the BPRS/CASH and the CAARMS while the concurrent validity of the CAARMS was being established. From 1999 the CAARMS replaced the BPRS/CASH for determination of psychosis status. The CAARMS allows intensity, conviction, frequency, recency and duration of symptoms to be assessed using one instrument and has well-defined anchor points. The CAARMS has good to excellent reliability (Yung et al. 2005). If CAARMS data were not available for determination of psychosis status (e.g., due to not being able to locate the participant), then the State public mental health records were accessed.

2.2.3. Baseline variables

A range of clinical, neurocognitive and neurobiological assessments were conducted in this cohort (see (Nelson et al. 2013) for full details). "Duration of symptoms prior to treatment" refers to the duration between the first noted change from premorbid state, retrospectively determined using all available information (self report and informant report), and date of acceptance into the PACE clinic, as per our previous research (Nelson et al. 2013; Yung et al. 2007). Accordingly, the variable is more inclusive than attenuated psychotic symptoms – it refers to the onset of any psychiatric symptoms that eventually led to referral to the PACE clinic, in line with the fact that the early stage of the psychosis prodrome tends to be characterized by non-specific symptomatology, including mood disturbance, anxiety and basic symptoms. The CAARMS (Yung et al. 2005) was used to operationalise this variable, as per our previous research. If accounts of first onset of any psychiatric symptom varied between patient and informant (generally, family members), then the patient estimation was used, given that patients themselves can more accurately provide the date of first subjective change and that insight is not generally impaired in this cohort (Yung et al. 2007). Psychosocial functioning was measured using the Global Assessment of Functioning (GAF; APA, 1994) and the Quality of Life Scale (QLS; Heinrichs et al. 1984). Baseline year was divided into four time periods, as per previous analyses: 1993–1997, 1998–2000, 2001–2003 and 2004–2006. The aim was to have time periods equally spaced but with

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a reasonable and reasonably equal number of participants in each period.

2.2.4. Procedure

A previously developed tracking system (Henry et al. 2007) was used to locate and recontact participants. The steps followed were accessing 1) the National Death Index: to determine if any participant had died since last contact; 2) Research files; 3) Public mental health service record systems; 4) National Electoral Roll (as it is compulsory in Australia to enrol to vote); 5) Telephone directory; 6) Previous contacts; 7) Internet-based searching. If individuals did not consent to face-to-face assessment, they were asked if they would consent to a brief telephone or written assessment, enabling collection of a minimum data set.

2.2.5. Statistical analysis

As both lead-time bias and earlier intervention are related to shorter duration of symptoms, descriptive statistics, analysis of variance and chi-square tests were used to investigate if duration of symptoms has decreased over the years. Also, if lead-time bias was operating, then the transition rate of those with shorter durations of symptoms would be expected to catch up with the transition rate of those with longer durations of symptoms. Survival analysis was used to investigate whether there was evidence for such a catch-up.

3. Results

3.1. Follow-up

At follow-up, 311 of the 416 subjects (75%) were available for interview (268 (64.4%) face-to-face, 40 (9.6%) telephone, 3 (0.7%) written). Forty-nine people (11.8%) refused follow-up and a further 47 (11.3%) could not be located. Those who were not interviewed were evenly spread across the baseline year cohorts.

3.2. Lead time bias and earlier intervention as possible reasons for the declining transition rate

Both lead-time bias and earlier intervention are related to shorter durations of symptoms prior to referral (henceforth 'duration of symptoms'). In order for these two reasons to be valid reasons for declining transition rates, one would expect that the duration of symptoms would have decreased over the years. Therefore, duration of symptoms was examined by baseline year time period. Data were unavailable for the 1993 and 1994 cases (17 cases in total). Therefore the first baseline year time period consisted of cases between 1995–1997. Table 1 shows descriptive statistics of duration of symptoms broken down by the four baseline year time periods.

These values indicate a decrease in duration of symptoms over the first three baseline year time periods but not in the fourth. A log transformation was applied to the duration of symptoms data in order to remove skewness and to stabilise the standard deviations. An ANOVA was conducted on this log-transformed data, resulting in a p-value of 0.10, indicating that there was not a significant decrease in duration of symptoms by baseline year time period.

Duration of symptoms by baseline year time period was also examined using a cut-point approach (short v long duration of symptoms). Based on the Table 1 median values, 365 days (1 year) was used as a cut-point, because this value is close to the median values and ensures reasonable sample sizes in each category. Also, from a clinical point of view, duration of symptoms longer than a year would generally be regarded as a substantial duration of untreated symptoms. Table 2 shows the percentage of cases with a duration of symptoms longer than 1 year in each of the baseline year time periods.

These percentages show a drop in duration of symptoms from the first to the second time period, but no substantial change after that point. A chi square test comparing the four baseline year time period yielded a p-value of 0.19. Consistent with the comparison of mean values, this analysis does not support the notion of a substantial decrease in duration of symptoms over the baseline year cohorts.

3.3. Lead time bias versus earlier intervention

While the above analysis indicates that lead-time bias and earlier intervention have not exerted a *strong* influence on the declining transition rate, as both possibilities are based on a reduction of duration of symptoms prior to referral, they may nevertheless have played a role. We therefore conducted further analyses in order to disentangle their relative impact on the transition rate.

Our recent report (Hartmann et al. 2016) indicated that patient characteristics have changed over the time frame of baseline recruitment of the sample (1993–2006). This might also be the case for treatments in this patient population. It is therefore not suitable to use data from this entire time frame to differentiate between the influence of a lead-time bias and earlier intervention. Restricting the analysis to a more homogenous sample (in terms of recruitment time frame) minimises the possible confounding effects of these other factors (change in patient characteristics or treatments). In order for a lead-time bias to be identified, data is required on a sample with a long follow-up period, so that one can observe whether those with a short duration of symptoms "catch up" in transition rate with those with a longer duration of symptoms. For these reasons, we limited analysis to two cohorts: participants recruited before 1998 (cohort 1) and participants recruited before 2001 (cohort 2). Cohort 1 is a more homogenous sample, maximising the reduction of the possible confounding effects, but has a smaller sample size and number of transitions ($n = 108$, number of transitions $= 49$). While cohort 2 may be a slightly less homogeneous sample because of the longer time period of baseline recruitment, it consists of a larger sample and a larger number of transitions ($n = 184$, number of transitions $= 76$), increasing statistical power. We examined if the two cohorts provided similar results (i.e., a form of sensitivity analysis).

As above, a cut-point approach was used to define short and long duration of symptoms. Cohort 1 and cohort 2 were divided into those with a duration of symptoms less than and greater than one year (see Table 3).

Figs. 1 and 2 show the survival curves of transition rates for cohort 1 and cohort 2 respectively.

Fig. 1 shows that the curve of the short duration of symptoms group shows lower transition rates and no sign of catching up with the long duration of symptoms group. The p value of the difference between the two curves is 0.04, supporting the observation that the short duration of symptoms group does not catch up with the long duration of symptoms group. Fig. 2, corresponding to cohort 2, shows a similar

Table 1
Duration of symptoms (days) by baseline year time periods.

Baseline year time periods	Mean	Median	Min	Max	SD	n
1995–1997	557.1	293.5	3	7286	897.9	108
1998–2000	482.6	180	1	5491	817.5	76
2001–2003	312.2	182	6	2072	354.1	109
2004–2006	444.8	240	16	2325	499.8	90

Table 2
Percentage of cases with duration of symptoms >1 year by baseline year time period.

Baseline year time period	% of cases with duration of symptoms >1 year
1995–1997	43.5
1998–2000	30.3
2001–2003	31.2
2004–2006	35.6

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Table 3
Number of cases and transitions for short and long duration of symptoms groups by cohort.

	Cohort 1 (1995–1997)		Cohort 2 (1995–2000)	
	n	Number (%) of transitions	n	Number (%) of transitions
Short duration of symptoms	61	22 (36%)	114	37 (32%)
Long duration of symptoms	47	27 (57%)	70	39 (56%)

Note: Short duration of symptoms = symptom duration <1 year; long duration of symptoms = symptom duration >1 year.

pattern. Both figures indicate that the short duration of symptoms group does not appear to "catch up" in transition rate with the long duration of symptoms group, suggesting that earlier intervention is a stronger or more plausible reason than lead-time bias for the declining transition rate over the years.

As a further attempt to gauge the reliability of the above results, the analysis was repeated in the following ways:

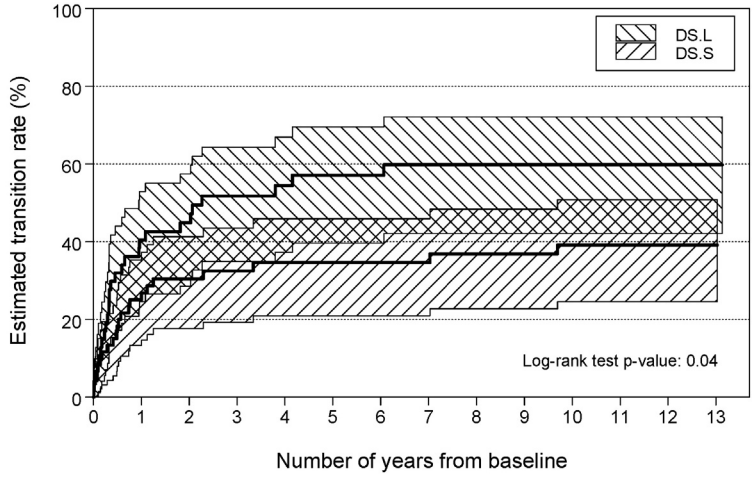
1. Two different cut-points for duration of symptoms (1.5 years and 2 years) were used.
2. Adjusting the survival curves for GAF score, based on the fact that GAF has previously been found to be a strong predictor of transition in this cohort (Nelson et al. 2013).
3. Analysing baseline year as a continuous variable rather than in categories.

In all these analyses, very similar results were obtained to those reported above (analysis available upon request).

4. Discussion

In this paper, we examined the possibilities of a lead-time bias and earlier intervention in the course of emerging symptoms as contributing to the declining transition rate in UHR samples. The analysis indicated that duration of symptoms prior to referral has not reduced substantially in UHR patients seen at our clinic between 1993 and 2006, suggesting that neither lead-time bias or earlier intervention fully account for the declining transition rate, as both of these reasons are based on a substantial reduction in duration of symptoms prior to referral. This finding is in contrast to a previous report from our group (Yung et al. 2007), a discrepancy which may be due to the fact that the current study included a larger sample with a longer baseline recruitment period (13 years compared to 5 years). By limiting our analysis to a more homogenous sub-group in terms of recruitment time frame (and thereby minimising the influence of other possible confounding factors) we identified earlier intervention in the course of symptoms as being more likely to have contributed to the decline in transition rate than follow-up period (lead-time bias). Those with a shorter duration of symptoms prior to referral did not catch up in transition rate to those with a longer duration of symptoms, suggesting that earlier intervention may have played a role in reducing the risk of developing psychotic disorder in these patients. In fact, patients with a long duration of symptoms (>1 year) displayed a strikingly high transition rate compared to those with a shorter duration of symptoms (56% compared to 32%, see Table 3). While neither lead-time bias or earlier intervention seem to *fully* account for the reducing transition rate, there is greater evidence for the contribution of earlier intervention than time period of observation (lead-time bias).

Another possible interpretation of the current finding that those with a shorter duration of symptoms had a lower transition rate is that it is not that earlier intervention influenced the illness trajectory, but rather that these cases were more likely to be experiencing transient symptoms that would in fact have resolved without intervention. These cases may not have met UHR criteria if assessed at a later time point (a form of "length time bias")(Yung et al. 2007). In contrast, those with a longer duration of symptoms may be a different type of clinical presentation – namely, a young person with persistent symptoms associated with distress, impairment and help-seeking. Persistent psychotic experiences associated with functional impairment have previously been found to be associated with longitudinal progression along the psychosis continuum (as in the psychosis proneness-persistence-impairment model (van Os et al. 2009)), which may be reflected in the higher transition rate in this "long duration of symptoms" group. The only way of parsing these possibilities (earlier intervention versus length time bias) would be to analyse outcomes of help-seeking UHR patients



Note.
DS.L = Long duration of symptoms.
DS.S = Short duration of symptoms.

Fig. 1. Survival curves of transition rates and 95% confidence bounds by duration of symptoms groups for the 1993–1997 cohort.

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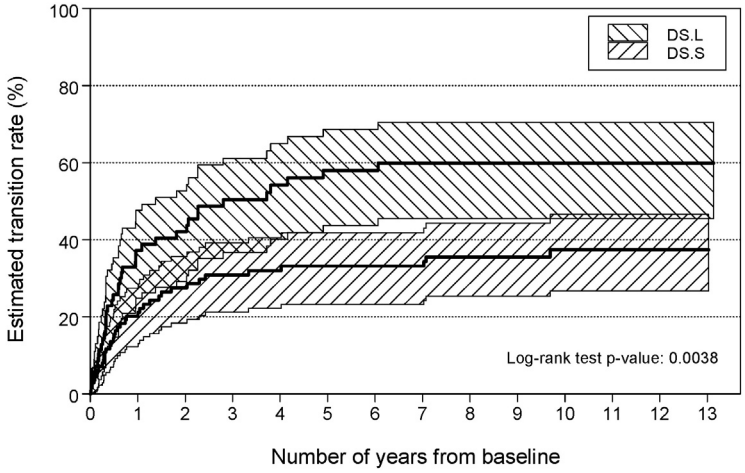

Note.
DS.L = Long duration of symptoms.
DS.S = Short duration of symptoms.

Fig. 2. Survival curves of transition rates and 95% confidence bounds by duration of symptoms groups for the 1993–2000 cohort.

with a short duration of symptoms who go on and do not go on to receive treatment, a study design which presents practical and ethical challenges.

Notwithstanding this issue, the current findings suggest that the significance of minimising the duration of untreated psychosis (DUP) in first episode psychosis (Marshall et al. 2005; Norman and Malla 2001; Norman et al. 2005), as recently observed again in the RAISE study (Kane et al. 2015), may also be critical in the UHR population in the form of minimising the duration of untreated illness (DUI). That is, identifying and providing intervention as early as possible in the course of attenuated psychotic symptoms may have an impact on the trajectory of illness, averting the transition to fully-fledged psychotic disorder. Therefore, increased awareness and assessment of attenuated psychotic symptoms in primary care, effective referral pathways and access to appropriate clinics is important. In the Australian context, the "headspace" youth mental health services make an important contribution to this identification of subthreshold psychotic symptoms in primary care (Rickwood et al. 2007; Rickwood et al. 2014). Similar youth mental health service models have been established in Ireland and the UK (McGorry et al. 2013a). Awareness campaigns targeting general practitioners and other services that manage young people with mental health problems, such as youth centres and student counselors, may be appropriate. Reynolds and colleagues (Reynolds et al. 2015) reported that a two-hour session in training GPs to identify people at high clinical risk of psychosis or with first episode psychosis led to a significant increase in referrals to the relevant specialised early psychosis teams. This approach should be coupled with an enrichment strategy based on screening for attenuated psychotic symptoms in help-seeking young people, such as the use of short screening instruments (e.g., the Prodromal Questionnaire-16; Ising et al. 2012).

However, as we have previously argued (Nelson et al. 2013), awareness campaigns must be balanced against the potential problem that such campaigns will spread into the non-help-seeking community. Psychotic experiences are reasonably common in the general population (van Os et al. 2009), especially in adolescents (Kelleher et al. 2012; Scott et al. 2009; Yung et al. 2009), with one study finding that between 0.09 and 8% of a general population sample of adolescents met criteria for a risk syndrome, depending on varying disability criteria (Kelleher et al. 2012). Extending early detection to these populations (e.g., by screening for psychotic experiences in schools or over the internet) may identify a large number of young people, many with transient psychotic experiences, most of whom are not distressed by or seeking help for these experiences. Although such a screening strategy may detect some people genuinely at risk (Schimmelmann et al. 2011), particularly if the psychotic experiences are severe and persistent (Kaymaz et al. 2012), it would result in poor specificity.

The optimal balance of sensitivity and specificity depends on the population being considered and the particular goals of a research study or clinical service. As mentioned at the outset, fairly high transition rates (high specificity) are required in UHR cohorts in order to test interventions and elucidate aetiological mechanisms driving onset of fully-fledged psychotic disorder. Enrichment strategies based on refining psychosis risk factors are therefore required. However, in a broad population of help-seeking young people specificity of detection for psychosis risk may be less important, with the emphasis being on providing interventions as early as possible to improve clinical outcomes (Purcell et al. 2015a; Purcell et al. 2015b), regardless of underlying psychosis risk. This approach is consistent with recent suggestions to broaden risk identification beyond psychosis into a pluripotential risk identification strategy (Johannessen and McGorry 2010; McGorry and van Os 2013), in line with the clinical staging model (McGorry 2007, 2013).

The retrospective nature of assessing onset of symptoms may be considered a limitation, given that it may be vulnerable to biases introduced by current mental state and memory difficulties. However, this method of assessing duration of symptoms is the standard approach used in the prodrome field (Nelson et al. 2013; Schultze-Lutter et al. 2015; Yung et al. 2007) and alternative approaches to assessing this variable do not seem feasible given that this is generally the first contact UHR patients have with clinical services (Wiltink et al. 2015).

5. Conclusions

The reducing transition rate in UHR samples seems to be a complex phenomenon not reducible to a single cause. Contributing, and possibly interacting, factors identified to date include changing clinical characteristics (Hartmann et al. 2016), recruitment strategies (Fusar-Poli et al. 2015; Wiltink et al. 2015), and reduction in duration of symptoms prior to identification (Yung et al. 2007). The current report shows that earlier intervention in the course of symptoms may be exerting a stronger influence on the reducing transition rate than the time window of observation ("lead time" bias). The possible contributions of changes in treatment and "length time" bias should be investigated in future work.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Nelson and Yung designed the study and wrote the protocol. Yuen undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Role of the funding source

We acknowledge the funding support of the National Health and Medical Research Council (NHMRC) Program grants 350241 and 566529 (awarded to PM, ARY and SJW) and the Colonial Foundation. JAH was supported by a Rubicon Fellowship from the Netherlands Organisation for Scientific Research (NWO 825.15.015), BN was supported by an NHMRC Career Development Fellowship (1027532), SJW was supported by an NHMRC Clinical Career Developmental Award (359223), and ARY was supported by an NHMRC Senior Research Fellowship (566593). AL was supported by a NHMRC Early Career Fellowship (1072593).

Acknowledgment

The authors would like to acknowledge the contribution of the research participants.

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Please cite this article as: Nelson, B., et al., Further examination of the reducing transition rate in ultra high risk for psychosis samples: The possible role of earlier intervention, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.04.040

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Please cite this article as: Nelson, B., et al., Further examination of the reducing transition rate in ultra high risk for psychosis samples: The possible role of earlier intervention, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.04.040