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Declining transition rates to psychotic disorder in "ultra-high risk" clients: Investigation of a dilution effect

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ABSTRACT

During recent years, a decrease has been noted in the rate of transition of ultra-high risk (UHR) clients to a psychotic disorder. Although important to the concept of the at-risk mental state, the reasons for this decline remain largely unknown. We investigated the possibility of a 'dilution effect' in contributing to the decline, i.e. if later UHR cohorts present with less severe clinical intake characteristics than earlier cohorts.

Firstly, clinical intake characteristics of a large UHR sample (n = 397) were compared across baseline year epochs (1995–2006). Characteristics showing significant differences were included in a Cox-regression to examine if they could explain the decline in transition rates. Secondly, because later cohorts show lower transition rates, 'more stringent' UHR-criteria were retrospectively applied to these cohorts (post-2000, n = 219), investigating if this resulted in a higher transition rate.

Results indicated that earlier cohorts presented with (1) a larger array of attenuated psychotic symptoms, (2) higher ratings on conceptual disorganization (formal thought disorder) and (3) a higher proportion of individuals with trait risk factor (all $P < .001$). However, these factors could not fully account for the decline in transition rates. Applying more stringent UHR-criteria to the post-2000-subsample did not substantially change the rate of transition.

Our study suggests that later UHR cohorts presented with different clinical intake characteristics than earlier cohorts. While this may have contributed to the observed decrease in transition rates to psychosis, it does not appear to fully account for this decline, suggesting other factors have also impacted on transition rates over time.

1. Introduction

During the mid-1990s, substantial research attention was directed towards the development of criteria enabling the reliable identification of young individuals at 'ultra-high risk' (UHR) for a psychotic disorder (Miller et al., 2002; Yung et al., 1996; Yung et al., 2003). The resulting criteria, applying to help-seeking young individuals, require the presence of at least one of the following clinical presentations: attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS, i.e., full-blown psychotic symptoms that resolve within a week without treatment), or a trait risk factor (schizotypal personality disorder or having a first-degree relative with a psychotic disorder), in addition to a marked decrease in functioning or chronic low functioning. These criteria are assessed using semi-structured interviews specifically developed for this purpose, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS, Yung et al., 2005) and the Structural Interview of Prodromal Symptoms (SIPS, Miller et al., 2003).

In the initial years of applying these criteria, approximately 40% of those identified as UHR subsequently developed a first-episode psychosis (FEP; referred to as "transition" or "conversion") within 12 to 30 months (Cannon et al., 2008; Mason et al., 2004; Miller et al., 2002; Yung et al., 2003). However, a steady decrease in transition rates of UHR clients has been observed across continents and institutions, declining to a 12-month rate of approximately 15% (Nelson et al., 2013; Simon and Umbricht, 2010; Simon et al., 2014; Yung et al., 2006; Yung et al., 2007; Ziermans et al., 2011). This decrease has also been empirically verified in a meta-analysis (Fusar-Poli et al., 2012).

Labelling and treating individuals as being at 'high risk' for psychosis (Keith and Matthews, 1991; McGlashan et al., 2007; Miller et al., 2002), when in fact they may never be at increased risk of developing a psychotic disorder, is a contentious issue (Carpenter, 2009; Ruhrmann et al., 2010; Woods et al., 2009; Yung et al., 2010a; Yung et al., 2010b).

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Although these young individuals are distressed and help-seeking, calling for early intervention and preventive treatment, they may not be at risk for psychosis specifically (Lin et al., 2015). Therefore, it is crucial to identify the factors underlying the apparent decline in transition rates.

It has been argued that the decline could be explained by (i) a treatment effect (an improvement in clinical care provided to the UHR population reducing the transition rate) (Fusar-Poli et al., 2012; Nelson et al., 2013; Simon et al., 2014; Wiltink et al., 2015; Yung et al., 2007); (ii) a length time bias (an individual briefly meets the UHR criteria, but symptoms resolve quickly: he/she never would have met the criteria if assessed at a later point) (Yung et al., 2007); (iii) a lead time bias (increased community awareness of the concept of an at-risk state driving referrals to specialized services *earlier* in the illness course) (Nelson et al., 2013; Yung et al., 2007); and/or (iv) a combination of the latter two (improved care at an earlier stage of illness). Evidence for these hypotheses stems from studies showing that duration of symptoms prior to first contact with a clinical service has decreased over the years (Yung et al., 2007) and transition rates appear to be lower in individuals engaging in specific focused interventions (i.e., psychological therapy or antipsychotic medication) (Fusar-Poli et al., 2012). While these factors certainly contribute to the decline in transition rates to psychosis, they do not appear to fully account for it (Nelson et al., 2013).

As the concept of at-risk mental states has gained extensive community awareness over the years, the so-called dilution effect has been postulated (Yung et al., 2007). An increased attentiveness to at-risk mental states may have been associated with less selective referral patterns, leading in turn to a possible 'dilution' of the pool of young people who are screened using the UHR criteria (Nelson et al., 2013; Wiltink et al., 2015; Yung et al., 2007). Such a dilution increases the probability that individuals are included who will not develop psychosis, the 'false positives' (Fusar-Poli et al., 2012; Nelson et al., 2013; Yung et al., 2007). The present study builds on these ideas we first articulated in 2007 (Yung et al., 2007). It seeks to systematically investigate the influence of a possible dilution effect on the decline in transition rates by examining the clinical intake characteristics of UHR clients across earlier and later cohorts. Specifically, the present study aimed to answer the following questions:

(1) Do later UHR cohorts show less severe clinical characteristics at intake in terms of number and intensity of APS, level of general functioning, and presence of trait risk factor for psychotic illness compared to earlier cohorts? If so, do these contribute to explaining the drop of transition rates over the years?
(2) Would the transition rates of later cohorts be higher and comparable to earlier cohorts if more stringent criteria (requiring higher intensity and frequency ratings for APS in order to obtain UHR status) were applied retrospectively?

2. Materials and methods

2.1. Setting and sample

The sample comprised a cohort of young people referred to as the 'PACE 400' cohort and previously described in Nelson et al. (2013). This cohort consists of young individuals attending the UHR-specialized PACE Clinic (Melbourne, Australia) and participating in one of seven research studies (Berger et al., 2012; McGorry et al., 2002; Phillips et al., 2009; Thompson et al., 2007; Yung et al., 1996; Yung et al., 2011; Yung et al., 2003) conducted between 1995 and 2006 in this centre. All research studies were approved by the local ethics committee and written informed consent was obtained before study enrolment. Help-seeking young people were accepted into the clinic if they were aged between 15 and 30 years and met at least one of the three UHR groups (i.e. APS, BLIPS, Trait; see Table 1). Exclusion criteria for PACE are a past or current psychotic episode, past neuroleptic exposure corresponding to a total continuous dose of more than 15 mg of haloperidol, or a known organic cause for presentation. For a detailed description of the sample, see Nelson et al. (2013).

To investigate whether more stringent criteria applied retrospectively to later cohorts result in transition rates similar to those of earlier cohorts (Aim 2), only individuals allocated to PACE using the most recent version of the CAARMS, introduced in 2000, were selected ('post-2000 subsample').

2.2. Procedure

UHR status and clinical intake characteristics were assessed upon intake to the PACE clinic. UHR individuals were divided into four groups according to their year of entry to PACE: 1995–1997, 1998–2000, 2001–2003, and 2004–2006 (see Nelson et al., 2013). This grouping produced equally spaced periods with an adequate number of participants in each period and is herein referred to as baseline year epoch.

Transition status was ascertained as far as possible for all participants at follow-up (see Nelson et al. (2013) for full details of the procedure of transition ascertainment). Transition to psychosis was defined as the presence of one full positive psychotic symptom daily for at least one week, as assessed with the CAARMS; if no CAARMS data were available, state public mental health records were consulted.

2.3. Measures

2.3.1. UHR status

The Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005), a semi-structured interview designed to assess UHR criteria, was used in conjunction with the Global Assessment of Functioning (GAF) (Jones et al., 1995) to establish UHR and transition status (see Table 1, third column, for an overview of the UHR criteria). The more stringent criteria were determined a priori by the researchers and applied retrospectively to post-2000 cohorts (Aim 2). They are shown in the fourth column of Table 1. These more stringent criteria required higher intensity and frequency ratings for APS in order to obtain UHR status (see Section 2.3.2.1).

2.3.2. Clinical characteristics at intake

2.3.2.1. Attenuated psychotic symptoms (APS). Attenuated psychotic symptoms were assessed using the CAARMS subscales 'disorders of thought content' (TC), 'perceptual abnormalities' (PA), and 'conceptual disorganization' (CD). The variable 'intensity of APS' ranged from 0 (not present) to 4 (severe) for TC, PA and CD. There was a change in CAARMS scoring when a new version was introduced in 2000. In order to make the two versions compatible for joint analyses for Aim 1, the post-2000 'intensity' score (0–6) was converted into the old CAARMS conviction scale (0–4).

The variable 'number of APS' ranged from 0 to 3, with 0 indicating the absence of any APS and 3 the presence of all three APS (TC, PA, and CD) in an individual participant. The absence of a symptom to a clinically significant degree on each of the three APS subscales was defined as low intensity rating (0–2) and presence as high intensity rating (3–4). The number of APS was computed using this definition.

2.3.2.2. General functioning. General functioning was assessed using the GAF (Jones et al., 1995) resulting in scores ranging from 0 to 100.

2.3.2.3. Trait risk factor. Family history (first degree) of psychosis was assessed using a shortened version of the Family Interview for Genetic Studies (FIGS) (Maxwell, 1992), while the presence of schizotypal personality disorder was defined according to DSM-IV (American Psychiatric Association, 2000). This variable was dichotomous (yes/no).

Table 1
Ultra-high-risk criteria.

Group	Criteria	Operationalized in the CAARMS[a] as	Adapted Operationalization for the present investigation ('more stringent')
Attenuated positive psychotic symptoms (APS)	Presence of ≥1 of the following symptoms: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, odd thinking and speech, odd behaviour, and appearance At least several times a week Present within the past year Present for ≥1 week and ≤5 years	CAARMS subscales Disorders of Thought Content (TC), Perceptual Abnormalities (PA), Disorganized Speech (DS) Group A: Severity Scale Score 3–5 (TC), 3–4 (PA), and/or 4–5 (DS) PLUS Frequency Scale Score 3–6 (TC, PA and/or DS) for ≥1 week OR Frequency Scale Score 2 (TC, PA and/or DS) Group B: Severity Scale Score 6 (TC and/or DS) and/or 5–6 (AP) PLUS Frequency Sale Score 1 (TC, PA and/or DS)	CAARMS[a] subscales Disorders of Thought Content (TC), Perceptual Abnormalities (PA), Disorganized Speech (DS) Group A: Severity Scale Score 4–5 (TC), 4 (PA), and/or 4–5 (DS) PLUS Frequency Scale Score 4–6 (TC, PA and/or DS) for ≥1 week OR Frequency Scale Score 3 (TC, PA and/or DS) Group B: Severity Scale Score 6 (TC and/or DS) and/or 5–6 (AP) PLUS Frequency Sale Score 3 (TC, PA and/or DS)
Brief limited intermittent psychotic symptoms (BLIPS)	Transient psychotic symptoms: presence of ≥1 of the following: ideas of reference, magical thinking, perceptual disturbance, paranoid ideation, and odd thinking or speech Duration of episode: <1 week At least several times per week Symptoms resolve spontaneously Must have occurred within the past year	CAARMS subscales Disorders of Thought Content (TC)[a], Perceptual Abnormalities (PA)[a], Disorganized Speech (DS)[a] Intensity Scale Score 6 (TC), 6 (DS), and/or 5–6 (PA) PLUS Frequency Scale Score 4–6 (TC, DS, and/or AP)	n/a
Trait and state risk factors	Schizotypal personality disorder in the identified individual or a first-degree relative with a psychotic disorder Significant decline in mental state or functioning, maintained for at least ≥1 month and ≤5 years Decline in functioning must have occurred within the past year	SCID-II (Schizotypal personality disorder) Family questionnaire (family history of psychosis) 30% decline in GAF	n/a

[a] The severity scale of the early version of CAARMS varied between 0 and 4. The UHR criteria of the early version were operationalized in a similar manner as what is shown here.

2.4. Statistical analyses

With regards to Aim 1, clinical intake characteristics were compared across the baseline year epochs using ANOVA (continuous measures) or chi-square tests (categorical measures). To investigate if identified statistical differences in clinical intake characteristics could account for the observed decline in transition rates, these variables were included as covariates in Cox regression analyses with baseline year as a predictor. If changes in the clinical intake characteristics accounted for the reduction in transition rate over the years, then the previously identified significant results for baseline year should decrease in level of significance or even disappear after adjusting for these characteristics. The Cox regression analyses additionally controlled for duration of symptoms before contact with PACE, as this has previously been shown to be significantly associated with transition to psychosis (Nelson et al., 2013; Yung et al., 2006; Yung et al., 2007; Yung et al., 2005).

With regards to the second aim, existing CAARMS-based criteria for determining UHR status were made more stringent and applied retrospectively to the post-2000 sample. Subsequently, the rate of transition to psychotic disorder, derived by survival analysis (Kaplan–Meier estimation) was compared when applying original vs. new UHR criteria.

All analyses were conducted using S-Plus and SPSS. The threshold for α was set at .05.

3. Results

3.1. Sample

The PACE 400 cohort consisted of 416 young individuals (Nelson et al., 2013). For Aim 1 of the present study, 19 individuals (18 individuals participating in an early PACE study in 1993 and one other participant) were excluded as they did not have CAARMS data. Consequently, a total of 397 young individuals, participating in research studies at PACE between 1995 and 2006, were included for Aim 1. The mean age at intake was 18.8 years (SD: 3.4) and 53.1% were female. Mean time to follow-up was 7.3 years (SD: 3.1, range: 2.4 to 13.1 years). From this sample, 105 individuals were known to have transitioned to a psychotic disorder. 98.5% of the transitions were determined by the CAARMS and 1.5% by public state records. Additional sample characteristics are displayed in Table 2 and a breakdown of DSM-IV diagnoses at baseline is provided in Table 3.

For Aim 2, a total of 219 individuals were included in the post-2000 subsample. The mean age at intake was 18.2 years (SD: 3.0) and 57.5% were female. Mean time to follow-up was 4.9 years (SD: 1.3, range: 2.4 to 8.7 years). From this subsample, 32 individuals were known to have transitioned to a psychotic disorder. 98.6% of the transitions were determined by the CAARMS and 1.4% by public state records. Additional subsample characteristics are displayed in Table 2.

3.2. Clinical intake characteristics across baseline years

Table 4 provides the summary statistics of the UHR characteristics broken down by baseline year epochs. GAF, CD, and trait risk factor differed significantly between baseline year epochs. Later year epochs were associated with lower intensity ratings on CD, a lower percentage

Table 2
Sample characteristics at PACE intake.

Characteristic	Total sample	'Post-2000' subsample
N	397	219
Age at baseline, M (SD)	18.8 (3.4)	18.2 (3.0)
Gender		
Male, N (%)	186 (46.9)	93 (42.5)
Female, N (%)	211 (53.1)	126 (57.5)
Intake group		
Trait risk factor, N (%)	115 (29.0)	50 (22.8)
BLIPS, N (%)	56 (14.1)	15 (6.8)
APS, N (%)	315 (79.3)	186 (84.9)
Time to PACE[a], M (SD)	446.4 (678.8)[b]	372.5 (434.4)[d]
Baseline GAF, M (SD)	58.3 (11.1)[c]	56.1 (8.7)

BLIPS = brief limited intermittent psychotic symptoms; APS = attenuated positive psychotic symptoms.
[a] Time to PACE = time between symptom onset and first contact with the PACE clinic (days).
[b] Missing for 15 participants (n = 382).
[c] Missing for 1 participant (n = 396).
[d] Missing for 13 participants (n = 206).

Table 3
DSM-IV baseline diagnosis across baseline year epochs.

Baseline year epoch	DSM-IV diagnostic category[a]					Total, N (%)
	No diagnosis, N (%)	Depressive disorders, N (%)	Anxiety disorders, N (%)	Substance-related disorders, N (%)	Other disorders, N (%)	
1995–1997	12 (20.3)	27 (45.8)	11 (18.6)	3 (5.1)	6 (10.2)	59 (100)
1998–2000	9 (11.7)	50 (65.0)	8 (10.4)	4 (5.2)	6 (7.8)	77 (100)
2001–2003	5 (4.4)	68 (59.1)	12 (10.4)	2 (1.7)	28 (24.4)	115 (100)
2004–2006	16 (16.8)	69 (72.6)	6 (6.3)	0 (0)	4 (4.2)	95 (100)
Total, N (%)	42 (12.1)	214 (61.9)	37 (10.7)	9 (2.6)	44 (12.7)	346 (100)[b]

$X(12) = 46.10$, $P < .001$.
[a] As assessed by the Structured Clinical Interview for DSM IV Disorders (SCID-I) (First et al., 1996).
[b] Missing for 51 participants.

of participants presenting with a positive trait risk factor, and lower GAF score.

Table 5 provides the percentage frequencies of number of APS (i.e., what per cent of the sample presented with 0, 1, 2 or all 3 APS). Later years were associated with a lower percentage of individuals presenting with a higher number of APS.

3.3. Aim 1: does a change in clinical intake characteristic account for the reduction in transition rate over the years?

The results of the Cox regression analyses are shown in Table 6, Part 1. As expected and previously reported (Nelson et al., 2013), baseline year emerged as a highly significant predictor of transition (model a). It was of interest to investigate whether this variable remained a significant predictor after adjusting for the characteristics which appeared to have changed over the years (see Section 3.2). Models b and c indicate that adjusting for CD, either exclusively (model b) or in combination with other previously identified predictors (Nelson et al., 2013) (model c), did decrease the level of significance of baseline year, but it remained significant. The same was true for the variable trait risk factor. Adjusting for trait risk factor, either exclusively (model d) or in combination with other previously identified predictors (Nelson et al., 2013) (model e) appeared to have no effect on baseline year as a predictor. Thus, while the decreasing trend of CD and decreasing proportion of individuals presenting with the trait risk factor may have some influence on the declining transition rates over the years, its influence is at best small. In model f, all the relevant predictors are combined. The results lead to the same conclusion as above. In Table 6, Part 2, detailed results for the full model f are provided.

With regard to the decreasing trend in the number of APS over the years (Table 5), we asked a similar question: could this difference in number of APS fully or partially explain the decline in transition rates over the years? To answer this question, Cox regression analysis was again employed. The results are shown in Table 7. Although number of APS is a significant predictor of transition, either exclusively (model a) or in combination with other relevant predictors (model b), baseline year remained a significant predictor of transition.

3.4. Aim 2: more stringent UHR criteria retrospectively applied to the later cohorts

Of the 219 UHR participants who were recruited from the year 2000 onwards, 32 (14.6%) were known to have transitioned to a psychotic disorder over a mean period of 4.9 years. Applying retrospectively the 'more stringent' criteria (Table 1, fourth column), only 125 of these 219 individuals would be considered UHR+. Of these 125, 21 (16.8%) were known to have transitioned. Thus, we see a slight increase in the proportion of transitioned cases (14.6% to 16.8%). However, 11 transitioned cases were excluded based on these 'more stringent' criteria. Table 8 provides the estimated transition rates derived from the Kaplan–Meier procedure at different time points. As can be seen from the table, transition rates increased slightly after the more stringent criteria were applied.

4. Discussion

The present study investigated the possibility of a 'dilution effect' as a factor in explaining the decreasing proportion of UHR clients who transition to a psychotic disorder over the years. That is, we tested the hypothesis that individuals from later UHR cohorts present with less severe clinical characteristics compared to earlier cohorts, representing a group of young people still classified as UHR according to the criteria, but being less likely to develop a psychotic disorder.

As expected, a number of clinical intake characteristics varied across the baseline year epochs. Compared to earlier cohorts, later cohorts presented with a lower degree of conceptual disorganization and a lower proportion of individuals with the trait risk factor. However, these differences were not substantial enough to account for the decline in transition rate. A similar picture emerged for the number of APS: although the number of APS has changed across baseline years (i.e., later cohorts presented with a smaller number of APS) and number of APS was a significant predictor of transition to psychosis, these differences could not fully account for the decline in transition rates over the years.

Similarly, increasing the threshold required to reach UHR status in the post-2000 subsample was associated with only a slight increase in

Table 4
Summary statistics of the UHR intake characteristic, broken down by baseline year epochs.

Baseline year epoch	UHR intake characteristic					N
	Disorders of thought content, mean (SD)	Perceptual abnormalities, mean (SD)	Conceptual disorganization, mean (SD)	Trait risk factor, %	General functioning, mean (SD)	
1995–1997	2.0 (1.0)	2.1 (1.6)	2.1 (1.1)	34.9	62.5 (14.6)	108
1998–2000	2.0 (1.2)	2.3 (1.5)	2.2 (1.0)	44.2	58.3 (9.8)	77
2001–2003	2.1 (0.9)	2.3 (1.3)	1.5 (0.9)	25.2	56.0 (8.8)	115
2004–2006	1.8 (0.9)	2.5 (1.1)	1.0 (1.0)[b]	14.4	56.2 (8.4)	97
P-value[a]	0.164	0.249	$<1 \times 10^{-15***}$	$9 \times 10^{-5***}$	$2 \times 10^{-5***}$	–

[a] P-value of ANOVA of chi-square test, comparing baseline year epochs.
[b] Missing for one participant (n = 296).
*** $P < .001$.

Table 5
Percentage frequencies of number of attenuated positive symptoms.

Baseline year epochs	% frequency of number[a] of APS				n	P-value[b]
	0 APS	1 APS	2 APS	3 APS		
1995–1997	18.5	44.4	28.7	8.3	108	$4 \times 10^{-9***}$
1998–2000	28.6	22.1	33.8	15.6	77	
2001–2003	38.3	36.5	23.5	1.7	115	
2004–2006	38.5	53.1	8.3	0	96	

APS = attenuated positive psychotic symptoms.
[a] 'Number' varying from 0 to 3; 0 = absence (low intensity ratings: score 0–2) on all three APS (Disorders of Thought Content, Perceptual Abnormalities, Conceptual Disorganization) and 3 = presence (high intensity ratings: score 3–4) on all three APS.
[b] P-value of chi-square test, comparing the baseline year epochs.
*** P < .001.

transition rate (10.5% to 12.4% over 2 years), still much lower than the original transition rates observed in early cohorts. Furthermore, this slight gain in specificity came at the expense of sensitivity, as the adjusted UHR threshold yielded a substantial number of 'false negatives', i.e., young individuals who would not have been identified as UHR, but who would have progressed to psychosis.

Taken together, the results indicate that earlier UHR cohorts may have presented with a different clinical profile with a greater array of symptoms than later UHR cohorts and that this may have contributed to, but not be the only reason for, the declining transition rate. It may be that young people presenting at PACE over the years did differ in other clinical features not assessed here, such as distress associated with symptoms (Power et al., 2015), basic self-disturbance (Nelson et al., 2012), and substance use patterns (Phillips et al., 2002), further contributing to the change in psychosis risk. Prior research has shown that the duration of symptoms before first contact with the UHR clinic (Yung et al., 2007) seem to contribute to the decline in transition rates, but not as primary factors. Earlier referral combined with provision of more effective treatment may have resulted in the prevention of transition of those identified as being at risk. Indeed, interventions in UHR patients have been shown to be effective (Fusar-Poli et al., 2012; Marshall and Rathbone, 2011; Stafford et al., 2013) and, consistent with the staging model (McGorry, 2007, 2010), potentially more effective when delivered in earlier stages. The care and treatment routinely provided to UHR patients at PACE changed considerably over the years, progressing from a system mostly focussing on monitoring to a comprehensive integrated case management system with psychotherapy.

Table 7
P-values of Cox regression analysis: Number of APS.

Model	Number of APS	Baseline year	General functioning	Time PACE[a]
a	$3 \times 10^{-4***}$	$3 \times 10^{-5***}$	–	–
b	0.028*	$2 \times 10^{-7***}$	$2 \times 10^{-6***}$	0.002**

APS = attenuated positive psychotic symptoms.
[a] Duration of symptoms before contact with PACE clinic.
*** P < .001.
** P < .01.
* P < .05.

Nonetheless, the results of the present study may provide some useful insights into UHR sample enrichment. That is, number of APS emerged as a significant predictor of transition. This finding suggests that future research could stratify samples according to number of APS.

The finding that individuals from earlier years with a higher transition rate presented with higher ratings on the CAARMS subscale 'Conceptual Disorganization' aligns with the results of other studies. We previously showed that the symptom cluster 'communicational-cognitive-behavioural disorganization' was the strongest predictor of transition to psychosis (Raballo et al., 2011), a result which was supported by a similar study (Demjaha et al., 2012). Likewise, conversion to psychosis was exclusively (DeVylder et al., 2014) or best (Armando et al., 2015) predicted by disorganized communication in several UHR samples. Recent studies from the US are consistent with these findings (Addington et al., 2015) (Cornblatt et al., 2015). Taken together, these studies indicate that thought disorder/conceptual disorganization may constitute a robust clinical predictor of transition in UHR samples.

It has been argued that there are two different causal pathways to psychosis: an affective, 'good-outcome' pathway and a negative symptom/cognitive, 'poor-outcome' pathway (Myin-Germeys and van Os, 2007). We could speculate that individuals from early UHR cohorts, being higher in thought disorder, were more representative of the

Table 6
Cox regression analyses predicting transition.

Part 1: P-values

Model	Baseline year	Conceptual disorganization	Trait risk factor	General functioning	Time PACE[a]
a	$3 \times 10^{-7***}$	–	–	–	–
b	$10 \times 10^{-5***}$	0.312	–	–	–
c	$7 \times 10^{-9***}$	0.807	–	$4 \times 10^{-8***}$	0.001**
d	$3 \times 10^{-7***}$	–	0.724	–	–
e	$2 \times 10^{-10***}$	–	0.260	$1 \times 10^{-8***}$	0.002**
f[b]	$4 \times 10^{-9***}$	0.943	0.271	$2 \times 10^{-8***}$	0.002**

[a]Duration of symptoms before contact with PACE clinic.
[b]For model specifications of the final model, see part 2.
***P < .001; **P < .01.

Part 2: Detailed results: final model (f)

Predictors	Coefficient	Standard error	Hazard ratio	95% confidence interval for hazard ratio	
				Lower limit	Upper limit
Baseline year epoch[a]					
1998–2000	−0.517	0.243	0.60	0.37	0.96
2001–2003	−1.539	0.300	0.22	0.12	0.39
2004–2006	−2.006	0.407	0.14	0.06	0.30
Conceptual disorganization	−0.007	0.104	0.99	0.81	1.22
Trait risk factor	−0.248	0.228	0.78	0.50	1.22
GAF	−0.052	0.009	0.95	0.93	0.97
Time PACE[b]	0.00030	0.000082	1.03[c]	1.01	1.05

[a]Baseline year epoch is a factor with 1995–1997 as the reference level.
[b]Duration of symptoms before contact with PACE clinic.
[c]The hazard ratio for Time PACE is for a difference of 100 days.

Table 8
Kaplan–Meier estimated transition rates for original vs. more stringent criteria at various time points.

	Time from baseline	Estimated transition rate (%)	95% confidence interval	Cumulative number of transitions
Original criteria (n = 219)	1 year	9.4	5.3–13.3	19
	2 years	10.5	6.1–14.7	21
	3 years	14.5	9.4–19.4	28
	4 years	16.0	10.5–21.1	30
	5 years	18.1	11.9–23.9	32
More stringent criteria (n = 125)	1 year	11.4	5.3–17.0	13
	2 years	12.4	6.1–18.3	14
	3 years	17.6	10.0–24.5	19
	4 years	20.2	11.9–27.7	21
	5 years	20.2	11.9–27.7	21

cognitive pathway endophenotype, while individuals from later UHR cohorts were more representative of the affective pathway endophenotype. This speculation seems supported by the higher proportion of individuals presenting with a depressive disorder in more recent years (Table 3), but is contradicted by a study showing that comorbid depression and anxiety diagnoses had no effect of risk of transition (Fusar-Poli et al., 2014). Future studies should examine the presence and potential impact of affective disturbance and stress sensitivity in UHR cohorts across epochs.

The present study showed that the proportion of individuals presenting with the trait risk factor decreased over the years. This finding may reflect a change in referral patterns and identification strategies over the years. Indeed, there is evidence for altered referral patterns in PACE from 1996 to 2000, as reflected in a shift of referrals stemming from (mental) health professionals to non-professional sources such as family members (Wiltink et al., 2015). Likewise, a changed identification process at entry to the clinical service, actively screening for psychosis risk in a broader group of help-seeking young people, may have 'picked up' on APS to a greater extent than a family history of psychotic illness. These factors may have contributed to the UHR groups represented progressively tilting away from the trait risk group.

Unexpectedly, general functioning as measured by the GAF decreased across baseline year epochs. This finding was unanticipated, as it is well-known that poor functioning and decline in functioning are risk-factors for psychosis (Nelson et al., 2013; Yung et al., 2006). As the GAF score is determined by a conglomeration of different factors (Gaite et al., 2005), it is difficult to ascertain exactly which factors have contributed to the change in GAF scores over the baseline year epochs. One possibility, which would be consistent with our previous speculation regarding different pathways to psychosis, is the higher proportion of mood disorders in later cohorts (Lin et al., 2015). It may be that the greater predominance of these disorders in later cohorts, which may relate to change in service structure and different referral patterns to PACE over the years (Wiltink et al., 2015), contributed to the lower GAF scores in these cohorts. Alternatively, it is possible that a greater proportion of young individuals from later cohorts resided in socially deprived areas with corresponding lower functioning scores. Although speculative, this is consistent with the shift that occurred in the PACE clinic catchment area over the years, from a Statewide catchment area to being limited to northwestern metropolitan Melbourne, which includes a greater concentration of socially deprived suburbs (O'Donoghue et al., 2014).

4.1. Limitations

The results of the present study have to be interpreted in light of a number of limitations. Firstly, two different versions of the CAARMS were used over the years. Due care was put into making these versions compatible in scoring (i.e., converting a 0–6 scale to a 0–4 scale), however we cannot exclude the possibility that this may have impacted the results. Furthermore, the investigation of the observed 'decline in transition rate' is inherently a retrospective question and was studied using existing data. It therefore comes with limitations associated with retrospective investigations.

Finally, by investigating the clinical intake characteristics over the years, the present study is only an indirect assessment of a dilution effect. The dilution is presumably rooted in the growth and broadening of clinical services, a change of identification and screening processes, and different referral structures, which are difficult to directly assess.

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Contributors
Conceived and designed the studies: PMc, ARY, AL, SJW, and BN. Analysed the data: HPY. Led the manuscript drafting: JAH and BN. Wrote and revised the manuscript: JAH, HPY, PMc, ARY, AL, SJW, SL, and BN. All authors contributed to and have approved the final manuscript.

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

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