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TITLE PAGE

Title: Outcomes following first episode psychosis – why we should intervene early in all ages, not only in youth

Running Title: Age limits for early intervention services: time to rethink?

Authors: JM Lappin & M Heslin, PB Jones, GA Doody, UA Reininghaus, A Demjaha, T Croudace, T Craig, K Donoghue, B Lomas, P Fearon, RM Murray, P Dazzan & C Morgan.

Corresponding Author: Julia M Lappin, Senior Lecturer, School of Psychiatry, University of New South Wales, Sydney, Australia. Email: j.lappin@unsw.edu.au Telephone: ++61293668610

Margaret Heslin, Honorary Lecturer, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Peter B Jones, Professor of Psychiatry, University of Cambridge, Cambridge, UK.

Gillian A Doody, Professor of Psychiatry, University of Nottingham, Nottingham, UK.

Ulrich A Reininghaus, Postdoctoral Research Fellow, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Arsime Demjaha, Honorary Lecturer, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Timothy Croudace, Professor of Applied Health Research, University of Dundee, Dundee, UK.

Thomas Jamieson-Craig, Professor of Psychiatry. Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Kim Donoghue, Postdoctoral Research Worker. Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Ben Lomas, Consultant Psychiatrist, Nottingham University Hospitals NHS Trust, University of Nottingham, Nottingham, UK.

Paul Fearon, Professor of Psychiatry, Trinity College Dublin, Ireland.

Robin M Murray, Professor of Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Paola Dazzan, Reader of Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Craig Morgan, Professor of Social Epidemiology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Department in which work was done: Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.

Abstract

Objective: To compare baseline demographics and ten-year outcomes of a first episode psychosis patient incidence cohort in order to establish whether current youth-focused age-based criteria for Early Intervention (EI) services are justified by patient needs.

Methods: Data on first episode psychosis patients from the AESOP-10 longitudinal follow-up study were used to compare baseline characteristics, and ten-year clinical, functional, and service use outcomes between those patients who would and would not have met age-based criteria for Early Intervention Services, in Australia or in the UK.

Results: 58% men and 71% women with first episode psychosis were too old to meet current Australian- Early Intervention age entry-criteria (χ^2 =9.1, p=0.003); while 21% men and 34% women were too old for UK- Early Intervention age-entry criteria (χ^2 =11.1, p=0.001). Ten-year clinical and functional outcomes did not differ significantly between groups by either Australian- or UK- Early Intervention age-entry criteria. Service use was significantly greater among the patients young enough to meet Early Intervention age-criteria [Australia: IRR=1.35 (1.19-1.52) p<0.001; UK: IRR=1.65 (1.41-1.93) p<0.001].

Conclusions: Current Early Intervention services are gender- and age-inequitable. Large numbers of patients with first episode psychosis will not receive Early Intervention care under current service provision. Illness outcomes at ten-years were no worse in first episode psychosis patients who presented within the age range for whom Early Intervention has been prioritised, though these patients had greater service use. These data provide a rationale to consider extension of Early Intervention to all, rather than just to youth.

Introduction

Specialist early intervention services (EIS) provide intensive support and management for younger individuals in the early years following their first psychotic illness. There is notable variability internationally in the upper age threshold selected for EI service provision: in Australia, services are typically offered up to age 25; in Singapore to age 40. In the UK, 35 years has been the recommended upper age cut-off for referrals (DoH, 2001) but recent NICE guidelines recommend that early intervention should be available to all, regardless of age (NICE, 2014).

Historically, EI services have been youth-focussed based on several principles: first, the zeitgeist that the majority of psychosis presents earlier in life. Second, prior to EIS development, evidence that there was delay among young people with emerging psychosis obtaining early treatment (Lincoln and McGorry, 1995), and finally, the theory that those who develop psychosis at a younger age suffer greater long-term impairment because the illness interrupts their social, personal and scholastic/occupational development (DoH, 2001).

Using data from the UK AESOP-10 study - a longitudinal follow-up of an incidence cohort of first episode psychosis patients - this study examined first, the baseline characteristics of first episode psychosis (FEP) individuals who would and would not meet current age-based criteria for EIS in Australia, or in the UK. Second, it tested the question whether ten-year clinical, functional and service use outcomes were worse in those who develop FEP at an age young enough to meet criteria for EI provision. It is important to emphasise that the cohort studied was treated in an *era prior to the establishment of EI services*; thus this is *not* an examination of the effectiveness of EI care. Rather, these analyses compare baseline characteristics and ten-year outcomes of all first episode psychosis patients in order to establish an evidence base for EI provision by testing the theory that those who develop psychosis at a younger age have worse outcomes than those who develop psychosis at an older age.

Methods

Setting

This paper is based on data from ÆSOP (Kirkbride et al, 2006) and ÆSOP-10 (Morgan et al, 2014), which are incidence and ten-year follow-up studies, respectively, of all individuals with a first episode of psychosis presenting for the first time to specialist mental health services in defined catchment areas in the UK between 1997 and 1999. Recruitment of ÆSOP cases ended before EI services were established in these areas.

Cases

Within tightly defined geographical areas in London and Nottingham, all cases with first episode of psychosis (codes F20–29 and F30–33 in ICD–10 (WHO, 1993)) who presented to specialist services were included in the incidence study. The Screening Schedule for Psychosis (Jablensky et al, 1992) was used to screen cases who presented to these services for eligibility and completed based on information from clinical notes, corroboration from mental health staff and, where possible, by interview with the participant.

Inclusion criteria for cases were: aged between 16 and 64 years with a first episode of psychosis and resident within the study catchment areas. Exclusion criteria were: evidence of psychotic symptoms precipitated by an organic cause; transient psychotic symptoms resulting from acute intoxication as defined by ICD–10 (WHO, 1993); previous contacts with mental health services for psychosis; and moderate or severe learning difficulties, or an IQ of less than 50 (WHO, 1993).

Follow-up

Cases were followed-up ten years after first contact with mental health services (detailed in Morgan et al (2014). At baseline, 532 incidence cases were identified. Of those, 387 had follow-up outcome data and thus made up the core analytic sample for outcome analyses (excluding those who had

died, emigrated or been excluded, plus those who did not have useable information on clinical course and outcome for at least eight years of follow-up). Within our analyses of outcomes, we excluded six further cases as they presented to services less than three weeks before EIS were launched in the London catchment area.

Measures

Baseline: Clinical and demographic data were collected from clinical records and, where possible, from interview. A shortened version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN version 2; WHO, 1994) was used to assess symptom presence and severity. This was used in conjunction with other clinical information (excluding diagnosis) to assign ICD-10 (WHO, 1993) psychotic diagnoses within research-team consensus meetings. Diagnoses were made blind to ethnicity and diagnosis from the clinical notes, as soon as possible after first contact. The Personal and Psychiatric History Schedule (WHO, 1996) was used to determine duration of untreated psychosis (DUP), defined as the period from onset of psychosis to first contact with statutory mental health services. Onset of psychosis was defined as the presence for one week or more of psychotic symptoms, further detailed in Morgan et al (2006).

Follow-up: The WHO Life Chart Schedule (Harrison et al, 2001; Sartorius et al, 1996; Susser et al, 2000) - designed to assess the long-term course of schizophrenia- was used to collate information at follow-up. It comprises four main areas: symptoms; treatment; residence; and work. It was adapted to include additional information on service use, including use of prescribed medication over follow-up. Information was derived for the Life Chart from multiple sources: case notes, interviews with cases, and informant information. Key variables have been defined previously elsewhere (Morgan et al, 2014). Course of illness was categorised as follows: remission within six months; episodic (no episode longer than six months' duration); continuous (no remission longer than six months' duration); or none of the above. Course type "none of the above" refers to an intermediate illness

course which was neither episodic not continuous; these individuals experienced both an episode that lasted longer than 6 months and a period of remission that lasted longer than 6 months during the follow-up.

The Life Chart was also used to record number of inpatient days; mental state at follow-up (in the last 30 days; psychotic or not psychotic); history of self-harm over follow-up; lifetime substance misuse (present/absent); and percentage of time employed over follow-up (dichotomised into under and over 25%). The Life Chart was presented at consensus meetings along with case note information so that decisions about all aspects of the Life Chart could be decided upon by consensus. The Global Assessment of Function (GAF) disability scale (Endicott et al, 1976) was used to assess function at follow-up; higher score indicates better level of general functioning. Treatment resistance was defined in line with modified Kane criteria for treatment resistance (Conley and Kelly, 2001).

Ethics

Full ethical approval for all aspects of the follow-up was provided by the local research ethics committees in South East London and Nottingham. All researchers had substantive or honorary contracts with either the South London and Maudsley National Health Service (NHS) Foundation Trust or the Nottingham Healthcare NHS Trust, the primary participating service providers.

Analyses

All data were analysed using STATA 11 (StataCorp, 2009). Age at first presentation to specialist services was used to assign subjects to FEP groups by age. Using chi-square tests, we compared clinical and sociodemographic characteristics between those ≤35years and those ≥ 36years (UK-EI age-criteria); these analyses were repeated for those ≤25years and those ≥ 26years (Australia-EI age-criteria).

We compared outcomes in those ≤35years and those ≥ 36years (UK-EI age-criteria) using, as appropriate, logistic (binary or multinomial), Poisson, or linear regression analyses. We adjusted analyses for gender, ethnicity, centre, and diagnosis to assess whether variations in outcome by age-group status were accounted for by these variables. Non-normally distributed continuous data were analysed using non-parametric bootstrap regressions (ordinary least squares). Bootstrap regressions were used as they produce the same coefficients as linear regression (and so are interpreted in the same way) but give more robust confidence intervals and therefore a more robust estimate of statistical significance. Analyses were repeated for those ≤25years and those ≥ 26years (Australia-EI age-criteria).

Results

532 incidence cases were identified at baseline and comprised the sample for determining who would have been eligible for EI service provision. Demographic characteristics are detailed in Table 1. Table 2 shows the number and percentage of cases who would and would not have met age-entry criteria for EIS in Australia (<=25years); and in the UK (<=35years); by gender, DUP, diagnosis, treatment resistance and substance use.

Baseline illness profiles and characteristics

Australia-EIS age-criteria. Of 532 cases, 196 (36.8%) would have met age entry criteria for EIS in Australia (χ^2 =9.1, df1, p=0.003) (Table 2). 42% of men were ≤25years, compared with only 29% of women aged ≤25 (χ^2 =11.0, df1, p=0.001). There was a greater proportion of patients aged≥ 26years who had a DUP>2years (19.4% compared to 7.7% in those ≤25years) (χ^2 =13.2, df1, p=0.001). There was a non-significant trend for greater proportion of depressive psychoses in the 26+years group (χ^2=5.8, df2, p=0.06). Treatment resistant illness was significantly more common in the ≤25years group (30.5% compared to 16.7% in those≤26years) (χ^2 =6.7, df1, p=0.009); as was substance misuse group (31.5% compared to 17.8% in those≥26years) (χ^2 =10.4, df1, p=0.001) (Table 2).

UK-EIS age-criteria. Of 532 cases, 391 (73.5%) would have met age entry criteria for EIS in UK. 62% of men were ≤35years, compared with only 38% of women aged ≤35 (χ^2 =11.0, df1, p=0.001) (Table 2). A total of 80 FEP cases presented with a DUP> 2years and in some services would not have been accepted by EIS. Of those ≤ 35years, 11.5% had a DUP over two years, compared to 24.8% of those≥36years (χ^2 =14.4, df1, p<0.001). Diagnostically, there were significantly higher proportions of manic psychoses in those ≤35years, and of depressive psychoses in those≥36years (χ^2=11.5, df2, p=0.003). There were significantly more cases of treatment resistant illness (χ^2 =8.3, df1, p=0.004) and of substance misuse (χ^2 =26.56, df1, p<0.001) in those ≤35years (Table 2).

Outcomes

The core analytic sample for analyses of outcomes at follow-up comprised 387 individuals (Morgan et al, 2014). For the analyses detailed here, six were excluded who presented less than three weeks before the introduction of EIS in the London catchment area for AESOP, giving a total sample of 381. Clinical, functional and service use outcomes are shown in Table 3 [Australia-based analyses] and Table 4 [UK-based analyses]. Adjusted analyses have been included to provide information about how key variables (gender; centre; diagnosis and ethnicity) impact on outcomes; unadjusted analyses are reported because they reflect the service use and outcomes of the populations as they would be presenting to EIS or other services, but it is important to note that for any given service, these outcomes would differ according to the demographics of the population being served.

Clinical Outcomes

Australia-EIS age-criteria. There were no differences between groups in course of illness (OR= 1.18, CI: 0.67-2.08); mental state at follow-up (OR= 1.00, CI: 0.61-1.62); or self-harm (OR= 1.17, CI: 0.63-2.16)(Table 3).

UK-EIS age-criteria. There was no difference between groups in course of illness over follow-up, with the highest proportion in both groups having a course that was neither episodic nor continuous (OR= 0.96, CI: 0.51-1.81), nor in mental state at follow-up (OR=1.28, CI: 0.75-2.20). More patients ≤35years engaged in self- harming behaviour over follow-up than those≥36years (OR=2.88, CI: 1.18-7.04, p=0.02) (Table 4).

Functional Outcomes

*Australia-EIS age-criteria. N*either GAF disability at follow-up (BMD= -1.19, CI: -5.63-3.24) nor employment over follow-up (OR=1.20, CI: 0.70-2.04) significantly differed between groups (Table 3).

UK-EIS age-criteria. Again, neither GAF disability at follow-up (BMD= -1.85, CI: -6.81-3.11) nor employment over follow-up (OR=1.87, CI: 0.96-3.65) significantly differed between groups (Table 4).

Service Use

Australia-EIS age criteria. There was a higher number of admissions (IRR=1.35, CI: 1.19-1.52, p<0.001) and greater proportion of follow-up in hospital in those ≤25years (BMD=4.02, CI: 1.51-6.54, p=0.02)(Table 3).

UK-EIS age-criteria. Those ≤35years were admitted to hospital over ten-year follow-up more often than those ≥36years (incidence rate ratio (IRR) =1.65, CI: 1.41-1.93, p<0.001). Proportion of follow-up spent in hospital was higher in those ≤35years (bootstrapped mean difference (BMD) =2.88%, CI: 0.54-5.22, p=0.14)(Table 4).

Discussion

This study uses data from a large observational cohort of first episode psychosis patients to explore the evidence base for prioritisation of early intervention (EI) service provision in first episode psychosis. The first striking finding is that current EI services are gender-inequitable: more than two thirds of women in Australia, and one third of women in the UK, are excluded from current EIS because they are too old. Evidence that men have an earlier onset of psychosis is well-replicated (Rabinowitz et al, 2006), and 20% of women with schizophrenia have illness onset after the fortieth year of life (Riecher-Rossler, 2007). Yet there has been an absence of acknowledgement that age cut-offs for EI services disproportionately negatively impact on women. This is concerning, given recent meta-analytic evidence that recovery rates in psychosis are similar in men and women (Jääskeläinen et al, 2013).

Based on this observational incidence cohort of first episode psychosis, current early intervention service provision would be available to only 36.8% of FEP patients in Australia, and to 73.5% in the UK. These findings concur well with evidence that 55% of FEP patients in Australia present after the typical EI service upper age limit of 25years (Selvendra et al, 2014). Similarly, Greenfield and co-workers (2016) recently described that following the extension of their UK-based EI service to age 65, 30% of subsequent referrals were aged over 35years (Greenfield et al, 2016). This evidence challenges the presently-held misapprehension that psychosis is an illness of young people. In fact, epidemiological evidence indicates that FEP presents across the age-span, and that with increasing age there are increased relative proportions of females affected (Hafner, 2003).

Duration of untreated psychosis of greater than two years was significantly *more* common in the patients too old to be accepted for EI care in either Australia or the UK. Because these data pre-date the establishment of EIS, this finding is not explained by successful earlier detection through interventions targeted at the younger age group. Clearly it is not only young people with emerging

psychosis who are delayed in obtaining early treatment (Lincoln and McGorry, 1995). These findings are concerning and suggest delayed help-seeking, and/or less adept detection of psychosis in this older age-group. While longer DUP is known to be associated with poorer outcomes, despite longer DUP being more common in the older group, outcomes were similar to those in the younger group. Various explanations are possible: the association between longer DUP and poorer outcomes at 1-2 years following FEP is of moderate effect size; studies over longer follow-up periods show mixed findings (Marshall et al, 2005). Further, the greater proportion of individuals with treatment resistant illness (with associated poorer outcomes) in the younger age group may explains the lack of difference in outcomes between groups, despite the difference in DUP.

Clinical and Functional Outcomes

There was no evidence that younger patients experienced poorer clinical outcomes: neither illness course nor likelihood of being psychotic at ten-year follow-up differed between those who were or were not below the age cut-offs. Nor was there any support for the hypothesis that patients presenting younger had poorer functional outcomes: neither employment nor disability (measured by GAF score) - differed between those who would and would not have met criteria for EIS in either Australia or UK. These findings indicate that older clients' clinical and functional needs are at least as great as those of younger clients.

Similar outcomes; different service use

Individuals young enough to meet current criteria for EIS in Australia or in the UK had greater service use: patients aged ≤25years spent proportionally longer in hospital during ten-year follow-up; and were admitted at a greater rate: number of admissions over time was 35% greater than in those ≥26years. This may in part be explained by markedly higher rates of comorbid substance use, and significantly higher rates of self-harm in the younger FEP group. Additionally, treatment resistant illness was significantly more prevalent in the younger FEP group, possibly contributing to the

observed higher service use. Yet despite this greater service use, there was no difference in the clinical and functional outcomes at follow-up.

Strengths of this study include the epidemiologically robust methods employed in AESOP10; previous studies of long-term course and outcome have focused on prevalence samples of patients with schizophrenia only (rather than all psychosis), which tend to have an over-representation of patients with poorer outcomes. Such studies have often applied an upper age cut-off well below 65years (reviewed in Morgan et al, 2014), which may artificially perpetuate the idea that FEP is an illness only of young people. In AESOP-10, clinical and functional outcomes were considered separately. Approximately 40% of patients with a non-affective disorder achieved symptomatic recovery (Morgan et al, 2014), in accordance with the rate of 47% reported by Robinson and coworkers in their 5-year follow-up of first-episode schizophrenia patients (Robinson et al, 2004). Functional recovery was left often achieved: only 22% of AESOP-10 clients were employed at 10-year follow-up (Morgan et al, 2014). These recovery rates are in keeping with those reported elsewhere: Jääskeläinen and coworkers' meta-analysis of clinical and social recovery rates in psychosis reported median rates of 13.5, with a range of 8% to 20% (Jääskeläinen et al, 2013).

Several limitations of this study should be acknowledged: first, as with all long-term follow-up studies, it is possible that selection or information bias might occur as a result of loss to follow-up/ missing data. As detailed in Morgan et al (2014), exhaustive tracing efforts resulted in follow-up of over 90% of the cohort, and analyses showed that there was no strong evidence of systematic bias. Second, the inferences made about the needs of patients of future EIS extend only to the age group of patients included here: 16-64years.

Conclusions

EIS have historically been youth-focussed, based on the premise that psychotic illness interferes at a key stage in a young person's development. We do not dispute that premise, but emphasise that psychosis impacts at all stages of life. Interestingly, the use of the term early intervention in psychosis has for many come to be synonymous with intervention in *youth* psychosis: the idea of intervening *early* should not be conflated with intervening *in the young*.

We recommend that consideration be given internationally to the extension of EIS provision to all on the basis of clinical need and gender- and age- equality. A significant proportion of people suffering psychotic illness for the first time are currently exempt from specialist services. Discussion is warranted about the potential to deliver early intervention to all. Possible service models include early intervention services which open to all ages, with a recognition that care offered will need to be tailored to different needs of different age groups. Alternatively, in Australia where there has been recent growth in youth-focussed mental health services, early intervention in psychosis could be managed both within these youth services, and additionally in a dedicated service for psychosis in adults over 25years. This would allow EI services to retain their youth focus, while also making necessary provision for older FEP patients with the same need for early intervention to optimise clinical and functional outcomes.

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TABLES

Table1: Sociodemographic and clinical characteristics of the entire sample (n=532)

Characteristics	Number (%)
London	327 (61.5)
Nottingham	205 (38.5)
Male	308 (57.9)
Female	224 (42.1)
Schizophrenia broad	385 (72.4)
Manic psychosis	71 (13.4)
Depressive psychosis	76 (14.3)
White British	232 (43.6)
Other White	37 (7.0)
Black Caribbean	140 (26.3)
Black African	65 (12.2)
Asian	26 (4.9)
Other	32 (6.0)
Age at baseline (years: median; IQR)	29.0 (22.0-36.0)
DUP (days: median; IQR)	59.5 (15.0-235.0)
Follow-up (years: median; IQR)	10.4 (9.3- 11.3)

IQR = interquartile range

Table 2: Unadjusted analyses comparing characteristics in patients who would and would not have met age-entry criteria for EI services in the UK (≤35years or ≥36years), or in Australia (≤25years or ≥26years)

	Australia-EIS cut-off			UK-EIS cut-off		
	≤25years n (%)	≥26years n (%)	p	≤35years n (%)	≥36years n (%)	p
Gender (n=532): Male Female	 130 (66.3) 66 (33.7)	 178 (53.0) 158 (47.0)	 χ^2=9.1, df1, p=0.003	 243 (62.1) 148 (37.9)	 65 (46.1) 76 (53.9)	 χ^2=11.0, df1, p=0.001
DUP (n=532): DUP < 2years DUP > 2years	 181 (92.4) 15 (7.7)	 271 (80.7) 65 (19.4)	 χ^2=13.2, df1, p<0.001	 346 (88.5) 45 (11.5)	 106 (75.2) 35 (24.8)	 χ^2=14.4, df1, p<0.001
Diagnosis (n=532): Non-affective Manic psychosis Depressive psychosis	 147 (75.0) 30 (15.3) 19 (9.7)	 238 (70.8) 41 (12.2) 57 (17.0)	 χ^2=5.8, df2, p=0.056	 287 (73.4) 59 (15.1) 45 (11.5)	 98 (69.5) 12 (8.5) 31 (22.0)	 χ^2=11.5, df2, p=0.003
Treatment Resistance (n=257): Non Treatment Resistant Treatment Resistant	 66 (69.5) 29 (30.5)	 135 (83.3) 27 (16.7)	 χ^2= 6.7, df1, p=0.009	 146 (74.1) 51 (25.9)	 55 (91.7) 5 (8.3)	 χ^2= 8.3, df1, p=0.004
Substance misuse (n=419): No Yes	 102 (68.5) 47 (31.5)	 222 (82.2) 48 (17.8)	 χ^2=10.4, df1, p=0.001	 222 (71.2) 90 (28.8)	 102 (95.3) 5 (4.7)	 χ^2=26.6, df1, p<0.001

Table 3: Differences in service use, clinical and functional outcomes between FEP patients who would and would not have met age-entry criteria for EI services in Australia (≤25years or ≥26years)

Outcome	**≤25years**	**≥26years**	**Unadjusted analyses**		**Adjusted analyses***	
			Odds Ratio (95% CI) *(unless otherwise indicated)*	P	Odds Ratio (95% CI) *(unless otherwise indicated)*	P
Number of admissions (n=334) (median[IQR])	3 (1-6)	2 (1-4)	**1.35 (1.19 to 1.52)[a]**	**<0.001**	1.33 (1.18 to 1.51)[a]	<0.001
Proportion of follow-up days as inpatient (n=360) (median[IQR])	3.0 (0.7-10.5)	1.9 (0.5-5.9)	**4.02 (1.51 to 6.54)[b]**	**0.02**	3.61 (1.07 to 6.15)[b]	0.005
Course of illness (n=340):						
Continuous	27 (22.5)	51 (23.2)	-		-	
Remission within 6 months	13 (10.8)	29 (13.2)	0.85 (0.38 to 1.89)	0.69	1.11 (0.48 to 2.59)	0.80
Episodic	22 (18.3)	47 (21.4)	0.88 (0.44 to 1.76)	0.73	1.03 (0.49 to 2.16)	0.93
None of the above	58 (48.3)	93 (42.3)	1.18 (0.67 to 2.08)	0.57	1.25 (0.68 to 2.27)	0.47
Mental state at follow-up (n=318):						
Non-psychotic	72 (65.4)	136 (65.4)	-		-	
Psychotic	38 (34.6)	72 (34.6)	1.00 (0.61 to 1.62)	0.99	0.82 (0.49 to 1.37)	0.44
Self-harm behaviour (n=319):						
No	93 (82.3)	174 (84.5)	-		-	
Yes	20 (17.7)	32 (15.5)	1.17 (0.63 to 2.16)	0.62	1.24 (0.66 to 2.34)	0.51
Employment (n=286):						
Employed less than 25% of follow-up	70 (69.3)	135 (73.0)	-		-	
Employed 25% or more of follow-up	31 (30.7)	50 (27.0)	1.20 (0.70 to 2.04)	0.51	1.32 (0.75 to 2.32)	0.33
GAF functioning (n=282) (mean; SD)	55.2 (17.6)	56.4 (18.6)	-1.19 (-5.63 to 3.24)[b]	0.60	0.18 (-4.12 to 4.34)[b]	0.94

IQR = Interquartile range; CI = confidence interval; p = p-value; SD = standard deviation. * Adjusted for baseline gender, centre, diagnosis and ethnicity.
[a] IRR Incidence Rate Ratio [b] Bootstrapped mean difference

Table 4: Differences in service use, clinical and functional outcomes between FEP patients who would and would not have met age-entry criteria for EI services in the UK (≤35years or ≥36years).

Outcome	**≤35years**	**≥36years**	**Unadjusted analyses**		**Adjusted analyses***	
			Odds Ratio (95% CI) *(unless otherwise indicated)*	P	Odds Ratio (95% CI) *(unless otherwise indicated)*	P
Number of admissions (n=334) (median[IQR])	3 (1-5)	2 (1-3)	**1.65 (1.41 to 1.93)[a]**	**<0.001**	1.59 (1.36 to 1.86)[a]	<0.001
Proportion of follow-up days as inpatient (n=360) (median[IQR])	2.6 (0.7-8.2)	1.2 (0.5-4.9)	**2.88 (0.54 to 5.22)[b]**	**0.02**	1.80 (-0.61 to 4.21)[b]	0.14
Course of illness (n=340):						
Continuous	59 (23.3)	19 (21.8)	-		-	
Remission within 6 months	31 (12.3)	11 (12.6)	0.91 (0.38 to 2.15)	0.83	1.30 (0.52 to 3.28)	0.57
Episodic	50 (19.8)	19 (21.8)	0.85 (0.40 to 1.77)	0.66	1.12 (0.51 to 2.49)	0.78
None of the above	113 (44.7)	38 (43.7)	0.96 (0.51 to 1.81)	0.89	1.07 (0.55 to 2.05)	0.85
Mental state at follow-up (n=318):						
Non-psychotic	151 (64.0)	57 (69.5)	-		-	
Psychotic	85 (36.0)	25 (30.5)	1.28 (0.75 to 2.20)	0.37	1.06 (0.60 to 1.88)	0.84
Self-harm behaviour (n=319):						
No	194 (80.8)	73 (92.4)	-		-	
Yes	46 (19.2)	6 (7.59)	**2.88 (1.18 to 7.04)**	**0.02**	3.37 (1.35 to 8.49)	0.01
Employment (n=286):						
Employed less than 25% of follow-up	151 (69.0)	54 (80.6)	-		-	
Employed 25% or more of follow-up	68 (31.1)	13 (19.4)	1.87 (0.96 to 3.65)	0.07	2.16 (1.06 to 4.37)	0.03
GAF functioning (n=282) (mean; SD)	55.5 (18.7)	57.3 (17.0)	-1.85 (-6.81 to 3.11)[b]	0.46	0.07 (-4.19 to 4.34)[b]	0.97

IQR = Interquartile range; CI = confidence interval; p = p-value; SD = standard deviation. * Adjusted for baseline gender, centre, diagnosis and ethnicity.
[a] IRR Incidence Rate Ratio [b] Bootstrapped mean difference