The epidemiology of first episode psychosis in early intervention in psychosis services: findings from the Social Epidemiology of Psychoses in East Anglia [SEPEA] study

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Abstract

Objective: Few studies have characterized the epidemiology of first episode psychoses [FEP] in rural or urban settings since the introduction of Early Intervention Psychosis [EIP] services. To address this, we conducted a naturalistic cohort study in England, where EIP services are well-established.

Method: We identified all potential FEP cases, 16-35 years old, presenting to EIP services in the East of England, during 3.5 years and 2m person-years follow-up. Presence of International Classification of Diseases, Tenth Revision, F10-33 psychotic disorder was confirmed using OPCRIT. We estimated crude and adjusted incidence rate ratios [IRR] following Poisson regression, by age, sex, ethnicity, socioeconomic status [SES], neighborhood-level deprivation and population density.

Results: Of 1,005 referrals to EIP services, 677 participants (67.4%) fulfilled epidemiological and diagnostic criteria for FEP (33.5 new cases per 100,000 person-years; 95%CI: 31.1-36.1). Median age-at-referral was similar (p=0.39) for men (22.6 years; interquartile range: 19.6-26.7) and women (23.4 years; 19.5-29.0); rates peaked before 20 years old. Rates increased for ethnic minority groups (IRR: 1.4; 95%CI: 1.1-1.6), with lower SES (IRR: 1.3: 95%CI: 1.2-1.4) and in more urban (IRR: 1.3; 95%CI: 1.0-1.7) and deprived neighborhoods (IRR: 2.2; 95%CI: 1.4-3.4) after mutual adjustment.

Conclusions: Pronounced variation in FEP incidence, peaking before 20 years old, exists in populations served by EIP services. Excess rates were restricted to the most urban and deprived communities, suggesting a threshold of socioenvironmental adversity may be necessary to increase incidence. This robust epidemiology can inform EIP service development in various settings, including rural populations, about likely population-level need.

Background

Early intervention in psychosis [EIP] now arguably represents the gold standard of care for people in their first episode of psychosis [FEP] (1). This care model incorporates pharmacological and psychological interventions, family and social support, supported employment and physical healthcare checks, delivered by a specialist multidisciplinary team for up to 5 years. EIP care aims to shorten duration of untreated psychosis, which when achieved is shown to improve long-term clinical, functional and social outcomes (2–8), particularly when care is maintained (9). EIP services are also more cost-effective than traditional psychosis care models (10). The foundation of effective EIP service provision is built on evidence-based healthcare (11). Fundamentally, this should include robust estimates of the incidence of psychotic disorders at the population-level, so healthcare commissioners have information local variation in service need to accurately inform caseload and workforce calculations. Unfortunately, psychosis epidemiology is predominantly informed by an older literature, conducted prior to the widespread introduction of EIP services (12; 13), almost exclusively based in urban settings (14). This research has revealed important heterogeneity in incidence by person (15–19) and place (20; 21), generating new directions for etiological research (22–24). However, national implementation efforts being developed in countries such as Denmark (25), Australia (26) and Canada (27), and currently undergoing revision in the UK (28), require accurate, relevant estimates about the current epidemiology of psychotic disorders in populations served by EIP services. Such data will also be critical in countries such as the USA, where local EIP initiatives are gaining traction (29–31), but little recent epidemiological data exists to inform service provision.

To address this gap, we established a naturalistic cohort study, known as the Social Epidemiology of Psychoses in East Anglia [SEPEA] study, in a diverse, mixed rural and urban setting in the East of England. We sought to precisely delineate the epidemiology of psychotic disorders since the introduction of EIP services. Consistent with earlier epidemiology (12; 14), we hypothesized that FEP incidence, including non-affective psychotic disorders, would decline with age and greater socioeconomic status [SES], and be higher amongst men, black and minority ethnic [BME] groups and in EIP services serving more deprived, urban populations in the catchment area. We also hypothesized that affective psychotic disorders would show less variation across these domains.

Method

Design & setting

We identified all people aged 16-35 years old who presented to six EIP services in a defined catchment area, over 3.5 years. EIP services were the sole referral point for suspected psychosis for people up to 35 years old. Services accepted from several sources, including self-referral, primary care, schools, universities, police and judicial services and other mental health services. The catchment area was concomitant with the boundaries of the Cambridgeshire and Peterborough NHS Foundation Trust [CPFT] and Norfolk and Suffolk NHS Foundation Trust [NSFT] (Supplemental Figure 1). At the time of the last Office for National Statistics [ONS] Census of Great Britain (2011), the catchment area had an estimated population of 2.4m people (4.5% of the English population) (32), of whom 24.0% were 16-35 years old. The catchment area contained 530 administrative neighborhoods (ONS Statistical Wards – median 2011 census population: 3,992; interquartile range [IQR]: 2,426-5,935). The region is varied in terms of deprivation, ethnicity and population density, with large rural areas punctuated by market towns and small cities, including Cambridge, Peterborough, Norwich and Ipswich (Supplemental Figure 1).

Case ascertainment

Case ascertainment commenced on 1st August 2009 in CPFT, 8th September 2009 in Suffolk and 28th September 2009 in Norfolk. We applied the following inclusion criteria to all participants referred to EIP services for the first time during this period:

1. Acceptance into EIP care due to suspected psychosis
2. 16-35 years old (except CPFT, where Cambridgeshire North and South services operated from 17 years old)
3. Resident in the catchment area, including those of no fixed abode
4. Absence of a moderate or severe learning disability, or an organic basis to disorder
5. No previous contact with health services for FEP

We collected baseline sociodemographic data on all participants who met these criteria (henceforth, the "*incepted sample*"), irrespective of later diagnosis. We followed this sample from referral until receipt of 3 years of standard EIP care, or discharge from the service, if earlier.

Diagnostic outcomes

We used a two-stage diagnostic procedure to confirm FEP diagnoses according to the International Classification of Diseases, Tenth Revision (ICD-10 F10-33). In the first stage, we asked the clinician responsible for care to provide a clinical ICD-10 diagnosis six months after EIP acceptance, and at service discharge (median: 2.2 years; IQR: 1.2-3.0). In the second stage, we obtained a research-based diagnosis at these two time points using OPCRIT (33), a reliable diagnostic instrument (33; 34), which produces valid ICD-10 diagnoses according to 90 standardized symptom items (35). We trained a panel of clinicians (N=25) to rate OPCRIT items from all available case note information. Excellent inter-rater reliability was achieved for any clinically-relevant psychotic disorder (F10-33: 92% agreement; IQR:92-100) and specific diagnoses (85%; IQR=81-90), based on completion of 20 anonymous case vignettes. Incepted participants were included in our *incidence sample* if they received an ICD-10 clinical diagnosis of psychotic disorder (F10-33) at either time point, subsequently confirmed by OPCRIT assessment.

We classified participants according to their final OPCRIT diagnosis, as follows: all clinically-relevant FEP (F10-33), non-affective psychoses (F20-29), schizophrenia (F20), other non-affective psychoses (F21-29), substance-induced psychoses [SIP] (F10-19), affective psychoses (F30-33), bipolar disorder (F30-31) and psychotic depression (F32-33). OPCRIT does not distinguish SIPs from other non-affective psychoses, which are grouped together under "ICD-10 other non-organic psychoses" (i.e. F21-29 & F1X.5). Therefore, in order to estimate probable SIPs within this category, we relied on the presence of a clinical SIP diagnosis at 6 months after acceptance (n=8), discharge (n=2), or both (n=19) time points. Incepted participants without any OPCRIT-confirmed FEP were excluded from the *incidence sample* (Figure 1).

Exposure and confounder variables

Sociodemographic information, including birthdate, sex, ethnicity, marital status, birth country, postcode at referral, employment status, and main, current or last occupation and parental occupations was collected by the clinical team, at first contact, using a standardized form. We classified age into seven categories (16-17, 18-19, 20-22, 23-25, 26-28, 29-31, 32-35) to permit fine-grained estimation of incidence by age and sex. Marital status was classified as single, married/civil partnership or widowed/divorced/dissolved. Ethnicity was self-ascribed to one of 18 categories from the ONS 2011 Census. Here, we created a dichotomous ethnicity variable (BME versus white British) to examine initial variation by ethnicity. We classified birth country as UK- or foreign-born.

We classified participant SES according to current, or if unemployed for less than two years, main or last occupation, according to standard ONS methodology (36; 37). Participant SES was categorized into four groups: professional & managerial, intermediate occupations (including small employers & self-employed), routine & manual occupations, and those not in employment (long-run unemployed, never worked, students, otherwise unclassifiable). We coded parental SES similarly, with the highest SES used if available for both parents.

We geocoded participants to their residential neighborhood at initial referral to investigate variation in incidence by two empirically-relevant environmental risk factors for psychosis, multiple deprivation and population density. We defined multiple deprivation as the proportion of households in each neighborhood classified on at least two of four deprivation indicators from the 2011 census (employment, education, health, living environment; Supplemental Table 1). We classified multiple deprivation on an equal-interval scale (7.7-18%; 18.1-28%; 28.1-38%; 38.1-47.1%). Population density was estimated as the total 2011 census population in each neighborhood divided by its area, expressed as people per hectare [pph] on an interval scale: 0-14.9, 15.0-29.9, 30.0-44.9, 45-84.8.

Population at-risk

The usual resident population at-risk, including students, was estimated from the 2011 Census, conducted 1st April 2011, which coincided with the mid-point of case ascertainment. We obtained commissioned ONS estimates of the population at-risk at neighborhood level, stratified by age (restricted to 16-24, 25-29, 30-35 years), sex, ethnicity and participant SES. We multiplied estimates by 3.5 to obtain person-years at-risk [PYAR] over the study period.

Statistical analyses

We first reported descriptive epidemiological characteristics of the sample, including crude incidence rates for each psychotic outcome and 95% confidence intervals [95%CI]. We used two-tailed Chi^2 [χ^2], Mann-Whitney U and Kruskal-Wallis χ^2 tests to analyze univariable differences in sociodemographic characteristics between FEP participants and the population at-risk. For all psychotic disorders (F10-33), non-affective psychoses (F20-29) and affective psychoses (F30-33), we fitted multivariable Poisson regression models to examine potential differences in incidence by age group (three-category), sex, ethnicity, participant SES and EIP service. Where variation in incidence

between EIP services was detected, we also examined whether rates varied by multiple deprivation and population density, using multilevel Poisson models, fitted with neighborhood-level random intercepts. We restricted these analyses to a subset of the cohort, excluding participants of no fixed abode (n=28). Model fit was assessed via likelihood ratio test [LRT-χ^2]. Incidence rates were presented per 100,000 PYAR. Analyses were conducted using Stata (version 13).

Ethics

Ethical approval was granted by Cambridgeshire III Local Research Ethics Committee (09/H0309/39).

Results

Case ascertainment and crude rates, by contact type

Over one thousand people (n=1,005) were initially referred to six EIP services with suspected FEP during 2.02m PYAR, of whom 899 (89.5%) were accepted into EIP care (Figure 1). This corresponded to crude referral and acceptance rates of 49.7 (95%CI: 46.7-52.9) and 44.5 (95%CI: 41.7-47.5) per 100,000 PYAR, respectively (Supplemental Figure 2). One-hundred-and-one participants (10.0%) did not meet our epidemiological criteria (Figure 1), leaving 798 people in our incepted sample, of whom 677 (84.8%) were diagnosed with an OPCRIT-confirmed ICD-10 psychotic disorder (F10-33). This corresponded to a crude incidence of 33.5 new cases per 100,000 PYAR (95%CI: 31.1-36.1). Most incidence participants received a diagnosis of schizophrenia (F20; 52.1%) or other non-affective psychotic disorder (F21-29; 31.2%), giving a crude incidence of 27.9 per 100,000 PYAR (95%CI: 25.7-30.3) for non-affective psychotic disorders. The incidence of affective psychotic disorders (F30-33) was lower (4.1 per 100,000 PYAR; 95%CI: 3.3-5.1); the majority of these (75.9%) were bipolar affective disorders (Table 1). Approximately 4.4% cases were diagnosed with probable substance-induced psychosis (1.5 per 100,000 PYAR; 95%CI: 1.0-2.1).

Baseline characteristics and descriptive epidemiology

Median age-at-referral did not differ between men (22.6; IQR: 19.6-26.7) and women (23.4; IQR: 19.5-29.0; Mann-Whitney U-test: Z=0.86; p=0.39). We observed weak evidence (Kruskal-Wallis χ^2=4.9 on 2 degrees of freedom [df]; p=0.09) of differences in median-age-referral between affective (24.0 years; IQR: 20.6-27.9), non-affective (22.6 years; IQR: 19.6-27.4) and probable substance-induced psychoses (21.3 years; IQR: 17.7-26.2). Two-thirds of FEP participants (n=451; 66.6%) were

men (Table 1), although this pattern differed between non-affective (68.8% men), affective (53.0% men) and probable substance-induced psychoses (75.9% men) (χ^2-test on 2df=8.8; p=0.01). FEP participants were more likely to be men, younger, from a BME background, single, unemployed, of lower participant SES and from more deprived and densely populated neighborhoods than the population at-risk, (Table 1; all χ^2 p<0.01), reflecting corresponding variation in crude incidence (Table 1). Further examination of incidence by age revealed classic effect modification by sex (Figure 2A; LRT-χ^2 on 6df=19.7: p<0.01), such that rates were higher for men than women until 29-31 years old, with a decline in incidence for both sexes from initial peaks in incidence at 18-19 years in men and 16-17 years old in women. These patterns were similar for non-affective psychoses (Figure 2B; LRT-χ^2 on 6df=16.7; p=0.01), but differed for affective psychoses (LRT-χ^2 on 6df=5.2 p=0.51), which were similar for men and women at all ages (Figure 2C).

Variation in the incidence of all clinically-relevant psychotic disorders

Incidence varied by age, sex, ethnicity, SES and EIP setting, following mutual adjustment in multivariable Poisson regression (Table 2, Adjustment 1). Thus, IRRs were 1.47 times higher in BME participants (95%CI: 1.23-1.76) compared with the white British group, increased with lower SES and varied between EIP services. For example, IRR were 1.62 (95%CI: 1.19-2.21) times higher in the EIP setting with the highest (Great Yarmouth & Waveney) versus lowest (North Cambridgeshire) incidence (Table 2, Adjustment 1). Further (multilevel) modelling suggested incidence increased progressively with greater neighborhood-level multiple deprivation after full model adjustment (Table 2, Adjustment 2); Compared with the most affluent neighborhoods, rates were 2.15 times greater (95%CI: 1.36-3.42) in neighborhoods with the highest proportion of households in multiple deprivation. Population density also independently increased psychosis risk, but this effect was weaker, and confined to the most-versus-least densely populated neighborhoods (IRR: 1.32; 95%CI: 1.00-1.74).

Variation in the incidence of non-affective and affective psychotic disorders

Incidence of non-affective psychoses followed similar patterns to those described above with respect to individual-level risk factors (Supplemental Table 2). However, only multiple deprivation was associated with neighborhood-level variation in incidence (Supplemental Table 3). There was some evidence that patterns of risk differed for the affective psychoses, despite a smaller sample (N=83). Rates were more similar for men and women (IRR for men: 1.07; 95%CI: 0.70, 1.65) and less strongly associated with SES, after adjustment for other confounders (Supplemental Table 2). While

affective psychoses varied by EIP setting, this was not associated with neighborhood-level multiple deprivation or population density (Supplemental Table 3).

Discussion

In this, the largest epidemiological study of FEP conducted since EIP services were introduced in England, we have precisely delineated heterogeneity in incidence in a mixed rural and urban population. Our findings should provide timely evidence for mental healthcare policymakers in various settings about the current burden of psychotic disorders in young people, and will aid clinical services in identifying individuals and populations most likely to experience FEP. In particular, our findings (1) reveal substantial incidence of all clinically-relevant psychotic disorders in young people presenting to EIP services; (2) demonstrate that the median age-at-first-referral is similar for young men and women before 35 years old, with 50% of FEP participants presenting by 23 years old, and; (3) extend previous knowledge to show that incidence in more rural populations, which have received less research, varies by classic individual- and neighborhood-level social and economic determinants of health, particularly for non-affective psychotic disorders; affective psychoses showed less variation overall.

Methodological considerations

Our study was based on referrals to EIP services from multiple sources, including self-referral, and so should be interpreted based on administrative incidence. We were unable to perform a leakage study to detect potentially missed cases, but we do not believe that our methodology led to systematic under-ascertainment; EIP services were the sole referral point for young people with suspected psychotic symptoms, and actively engaged in outreach and promotion. Further, the epidemiological characteristics of this sample were consistent with other FEP studies, suggesting broad representativeness to typical FEP cohorts. Excess incidence rates in BME groups reported here were smaller than normally reported (14), but we do not believe this was due to differential under-ascertainment of BME cases. In general, there is little evidence such groups are less likely to be referred to EIP services, despite differing care pathways (38–40). Furthermore, a separate paper from our study (*in submission*) has shown that incidence rates for specific ethnic groups, including people of black Caribbean, African, Pakistani and Bangladeshi origin, are in line with excesses more typically observed (14). Our modest IRRs for the BME group as a whole are probably driven by the large proportion of non-British white migrants included in the BME population at-risk (52.2%), whose overall FEP risk is similar to the white British population (41).

We cannot generalize our findings to people younger than 16 years old. The epidemiology of early onset psychosis remains an important, underexplored area requiring urgent epidemiological research, given that EIP and more general youth mental health services, often accept cases from 14 years old or younger; limited available evidence suggests incidence is very rare (42).

We obtained denominator data from the 2011 Census. While the true population at-risk is dynamic, any demographic changes in East Anglia over the 3.5 year period of our study would have been small, and unlikely to have substantially biased our results given the absolute rarity of psychotic disorders. The 2011 Census methodology minimized and adjusted estimates for non-response prior to publication (43). We could not adjust or inspect variation by factors including family history of psychiatric disorders or substance use, which are not routinely collected for the denominator.

We used a two-stage diagnostic procedure to apply strict research-based criteria for FEP to our initial sample. We presented results for all clinically-relevant FEP given current EIP interest in this broad psychosis phenotype. Rates of affective psychotic disorders, and particularly psychotic depression, were lower than typically reported in adults (i.e. up to 64 years old) in England (14), though were consistent with rates observed elsewhere in Europe (44). Given that the incidence of bipolar affective disorders show less decline with age, and may even peak after 45 years old (14; 45), the lower incidence reported in our young sample may be consistent with the underlying epidemiology.

Meaning of findings: implications for mental health services provision

Our findings highlight substantial demand for EIP services in a large, diverse rural and urban population in the East of England. Referral rates to EIP services approached 50 people per 100,000 PYAR, with services subsequently accepting nearly nine out of ten referrals onto caseloads. We estimated that the true incidence of FEP disorders seen through EIP services was closer to 33 new cases per 100,000 PYAR. This difference highlights important challenges faced by policymakers, commissioners and practitioners to develop, deploy and deliver effective EIP services.

Previous influential commissioning guidelines have used uniform estimates of narrowly-defined schizophrenia incidence – closer to 15 per 100,000 PYAR – based on an older epidemiology, as a

basis for caseload and workforce calculations (46). However, in practice, EIP services are mandated to intervene on the full spectrum of FEP, including other non-affective, affective psychotic and SIP disorders, as well as other mental health disorders where psychotic-like symptoms can present. Paradoxically, this issue is compounded by earlier intervention which inevitably leads to a higher proportion of undifferentiated psychopathologies presenting at initial referral. Our data suggested that EIP services are excellent at identifying true positive cases; 84.8% (n=677/798) of incepted participants in our study met OPCRIT-criteria for FEP. Nonetheless, 15.2% of cases incepted onto EIP caseloads (n=121/798) did not meet these criteria, in addition to 10.5% of initial referrals not accepted onto EIP caseloads. Both of these groups would have required psychiatric triage, signposting or longer periods of EIP assessment. While there is accumulating evidence that EIP services lead to better clinical, social and functional outcomes for people with psychosis than standard care (5), and are cost-effective in the long-term (10), these hard-fought gains may be eroded if services not resourced to effectively implement the fidelity criteria upon which they are predicated (5). This should include sufficient EIP resourcing to appropriately manage the full spectrum of referrals presenting with psychotic features, informed by accurate epidemiological estimates from EIP care.

In addition, commissioners need to be sensitive to different challenges faced by rural and urban service providers in upholding fidelity to the EIP care model. For example, the provision of EIP services in rural communities may be associated with various logistical issues not present in more urban populations (47), including geographical access-to-care, increased staff travel time, staff recruitment and the potential effects of mental health stigma in smaller, rural communities. We have provided robust estimates of referral, acceptance, inception and incidence rates in a diverse rural setting, which can be used as part of a wider suite of evidence to inform service provision (48).

Meaning of the findings epidemiological implications

Our findings confirm and extend previous epidemiological research showing that the incidence of psychotic disorders varies by sociodemographic and environmental characteristics. Our study was conducted in a more rural setting than most previous studies (12; 14). Our incidence rates were similar to those from a homogeneous rural population in Ireland (age-specific rates for 16-35 year olds obtained from study authors) (49). As expected, FEP incidence in our population was lower, overall, than reported in more urban populations. Recent rates for similarly-aged young people presenting to EIP services in highly-urban Southeast London, for example, suggests that crude

incidence was 54.6 per 100,000 person-years (95%CI: 49.5-60.2) (50), higher than reported here. Nonetheless, crude rates in the most densely-populated part of our region overlapped with this estimate, and there is evidence that such differences are further attenuated following standardization for ethnicity (51).

Our findings with regard to neighborhood-level population density and multiple deprivation were novel, given that these associations have not previously been confirmed in rural populations. Interestingly, while the relationship between incidence of all clinically-relevant psychotic disorders, including non-affective psychotic disorders, and these risk factors was in the expected direction, excess risk was predominantly restricted to the most deprived and densely populated neighborhoods in our catchment area. If true, these non-linear relationships imply that a threshold of exposure to environmental factors may be necessary before substantially increasing psychosis risk. These findings accord with limited previous observations in urban populations which have investigated possible nonlinear associations between deprivation and psychosis incidence (52). Despite some variation in the incidence of affective psychosis at EIP-level, there was little evidence this was associated with population density or multiple deprivation. It is presently unclear whether associations between environmental characteristics and FEP incidence reflect genuine etiological variance, or arise from selection factors, including familial aggregation of shared genetic or environmental experiences, which perpetuate downward social drift (23). One complex possibility is that these processes are not mutually exclusive but lead to intergenerational accumulation of deleterious risk factors which may affect a number of adverse health and social outcomes, including schizophrenia and other psychoses. Further longitudinal studies are required to disentangle the potential roles of social causation and drift or selection. Although we could not establish causation directly, our results provide further valuable evidence that our most more deprived and urban communities shoulder a disproportionate burden of psychosis morbidity at the population-level. This should be used to inform the provision of early intervention services for psychosis.

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Table 1: Socio-demographic characteristics of people with FEP and the population at-risk

Variable	FEP cases (%)	Person-years at- risk [PYAR] (%)	χ^2 test (df); p-value	Crude incidence rate per 100,000 PYAR (95%CI)
Total	677 (100.0)	2,021,663 (100.0)	-	33.5 (31.1, 36.1)
Age group				
16-17	73 (10.8)	170,125 (8.4)	χ^2=122.0 (6); p<0.01	42.9 (34.1, 54.0)
18-19	113 (16.7)	201,184 (10.0)		56.2 (46.7, 67.5)
20-22	158 (23.4)	311,294 (15.4)		50.8 (43.4, 59.3)
23-25	117 (17.3)	320,537 (15.9)		36.5 (30.5, 43.8)
26-28	85 (12.6)	311,749 (15.4)		27.3 (22.0, 33.7)
29-31	76 (11.3)	318,756 (15.8)		23.8 (19.0, 29.9)
32-35	53 (7.9)	388,021 (19.2)		13.7 (10.4, 17.9)
Sex				
Women	226 (33.4)	989,434 (48.9)	χ^2=65.6 (2); p<0.01	22.8 (20.0, 26.0)
Men	451 (66.6)	1,032,229 (51.1)		43.7 (39.8, 47.9)
Ethnicity				
White, British	506 (74.7)	1,623,031 (80.3)	χ^2=13.1 (2); p<0.01	31.2 (28.6, 34.0)
Black & minority ethnic groups	171 (25.3)	398,632 (19.7)		42.9 (36.9, 49.8)
Country of birth				
UK-born	570 (84.2)	1,656,512 (81.9)	χ^2=2.3 (2); p=0.13	34.4 (31.7, 37.4)
Foreign-born	107 (15.9)	365,152 (18.1)		29.3 (24.2, 35.4)
Employment status[1]				
Employed	153 (22.6)	1,292,656 (63.9)	χ^2=1600 (3); p<0.01	11.8 (10.1, 13.9)
Student	113 (16.7)	419,633 (20.8)		26.9 (22.4, 32.4)
Looking after home or family	29 (4.3)	104,727 (5.2)		27.7 (19.2, 39.8)
Long term sick or disabled	162 (23.9)	89,332 (4.4)		181.3 (155.5, 211.5)
Unemployed	217 (32.1)	114,309 (5.7)		189.8 (166.2, 216.9)
Retired	-	1,007 (0.05)		-
Missing	3 (0.4)	-		-
Participant SES				
Professional & managerial	70 (10.3)	493,675 (24.4)	χ^2=110.8 (3); p<0.01	14.2 (11.2, 17.9)
Intermediate occupation	80 (11.8)	333,806 (16.5)		24.0 (19.2, 29.8)
Routine & manual	270 (39.9)	668,782 (33.1)		40.4 (35.8, 45.5)
Long-term unemployed, students & unclassifiable	257 (38.0)	525,400 (26.0)		48.9 (43.3, 55.3)
Parental SES[2]				
Professional & managerial	203 (30.0)	-	-	-
Intermediate occupation	153 (22.6)	-		-
Routine & manual	182 (26.9)	-		-
Long-term unemployed, students & unclassifiable	139 (20.5)	-		-
Marital status[3]				
Single	603 (89.1)	109,677 (61.0)	χ^2=223.5 (2); p<0.01	-
Married or civil partnership	59 (8.7)	54,131 (30.1)		-

Widowed, divorced or dissolved		15 (2.2)	15,954 (8.9)		-
EIP service					
North Cambridgeshire		90 (13.3)	309,302 (15.3)	χ^2=15.4 (5); p<0.01	29.1 (23.7, 35.8)
South Cambridgeshire		161 (23.8)	443,730 (21.9)		36.3 (31.1, 42.3)
West Norfolk		37 (5.5)	110,989 (5.5)		33.3 (24.2, 46.0)
Central Norfolk		143 (21.1)	498,222 (24.6)		28.7 (24.4, 33.8)
Great Yarmouth & Waveney		76 (11.2)	160,825 (8.0)		47.3 (37.7, 59.2)
Suffolk		170 (25.1)	498,596 (24.7)		34.1 (29.3, 39.6)
People per hectare [Area N; %][4]					
0-14.9	[382; 72.1]	291 (44.8)	1,019,083 (50.4)	χ^2=20.8 (3); p<0.01	28.6 (25.5, 32.0)
15-29.9	[84; 15.8]	125 (19.3)	429,479 (21.2)		29.1 (24.4, 34.7)
30-44.9	[43; 8.1]	129 (19.9)	343,340 (17.0)		37.6 (31.6, 44.6)
45-84.8	[21; 4.0]	104 (16.0)	229,761 (11.4)		45.3 (37.3, 54.9)
Households in multiple deprivation (%) [Area N; %][4]					
7.8-18.0%	[180; 34.0]	161 (24.8)	623,332 (30.8)	χ^2=33.7 (3); p<0.01	25.8 (22.1, 30.1)
18.1-28.0%	[258; 48.7]	284 (43.8)	862,013 (42.6)		32.9 (29.3, 37.0)
28.1-38.0%	[81; 15.3]	153 (23.6)	456,966 (22.6)		33.5 (28.6, 39.2)
38.1-47.1%	[11; 2.1]	51 (7.9)	79,352 (3.9)		64.3 (48.8, 84.6)

FEP: first episode psychosis; PYAR: Person-years at-risk; SES: socioeconomic status; IQR: interquartile range; PPH: people per hectare; Area N: Number of neighborhoods (ONS statistical wards)

[1] χ^2-test based on all categories except "retired" & "missing" where there was insufficient data

[2] FEP participants were coded to their parental SES, not available for the denominator population. Incidence rates not estimated.

[3] Population data only was only available by marital status and age (16-35 years) in our catchment area for the "Household Reference Person", i.e. head of household, and not all individuals in population at-risk. Incidence rates not estimated.

[4] N=28 FEP participants of no fixed abode at first referral were excluded because they could not be geocoded to a neighborhood

Table 2: Incidence rate ratios of all clinically-relevant psychosis for major sociodemographic and environmental factors

Variable	Unadjusted IRR (95% CI)	Adjustment 1 IRR (95% CI)	Adjustment 2 IRR (95% CI)
Sex (men vs women)	1.91 (1.63, 2.24)†	1.88 (1.60, 2.20)†	1.85 (1.57, 2.18)†
Age group			
16-24	Ref	Ref	Ref
25-29	0.58 (0.48, 0.70)†	0.67 (0.54, 0.81)†	0.66 (0.54, 0.81)†
30-35	0.33 (0.27, 0.42)†	0.41 (0.33, 0.52)†	0.42 (0.33, 0.54)†
Ethnicity			
White British	Ref	Ref	Ref
Black & minority ethnic group	1.38 (1.16, 1.64)†	1.47 (1.23, 1.76)†	1.35 (1.11, 1.63)†
Participant SES			
Professional & managerial	Ref	Ref	Ref
Intermediate occupation	1.69 (1.23, 2.33)†	1.60 (1.16, 2.21)†	1.63 (1.18, 2.26)†
Routine & manual	2.85 (2.19, 3.70)†	2.31 (1.76, 3.02)†	2.17 (1.65, 2.85)†
Long-term unemployed, students & unclassifiable	3.45 (2.65, 4.49)†	2.24 (1.69, 2.98)†	2.21 (1.66, 2.96)†
EIP service			
North Cambridgeshire	Ref	Ref	Ref
South Cambridgeshire	1.25 (0.96, 1.61)	1.26 (0.97, 1.64)	1.54 (1.11, 2.12)†
West Norfolk	1.15 (0.78, 1.68)	1.15 (0.79, 1.69)	1.17 (0.77, 1.79)
Central Norfolk	0.99 (0.76, 1.28)	1.00 (0.77, 1.31)	1.09 (0.80, 1.47)
Great Yarmouth & Waveney	1.62 (1.20, 2.20)†	1.62 (1.19, 2.21)†	1.43 (1.01, 2.03)†
Suffolk	1.17 (0.91, 1.51)	1.22 (0.94, 1.57)	1.33 (0.99, 1.79)
People per hectare‡			
0-14.9	Ref	-	Ref
15-29.9	1.02 (0.82, 1.29)	-	0.95 (0.76, 1.20)
30-44.9	1.31 (1.04, 1.67)†	-	1.08 (0.84, 1.40)
45-84.8	1.63 (1.24, 2.14)†		1.32 (1.00, 1.74)†
Percentage households in multiple deprivation‡			
7.8-18.0%	Ref	-	Ref
18.1-28.0%	1.25 (1.02, 1.54)†	-	1.35 (1.07, 1.70)†
28.1-38.0%	1.31 (1.03, 1.66)†	-	1.35 (1.00, 1.82)†
38.1-47.1%	2.46 (1.70, 3.56)†	-	2.15 (1.36, 3.42)†

IRR: incidence rate ratio; SES: Socioeconomic status; EIP: Early Intervention Psychosis
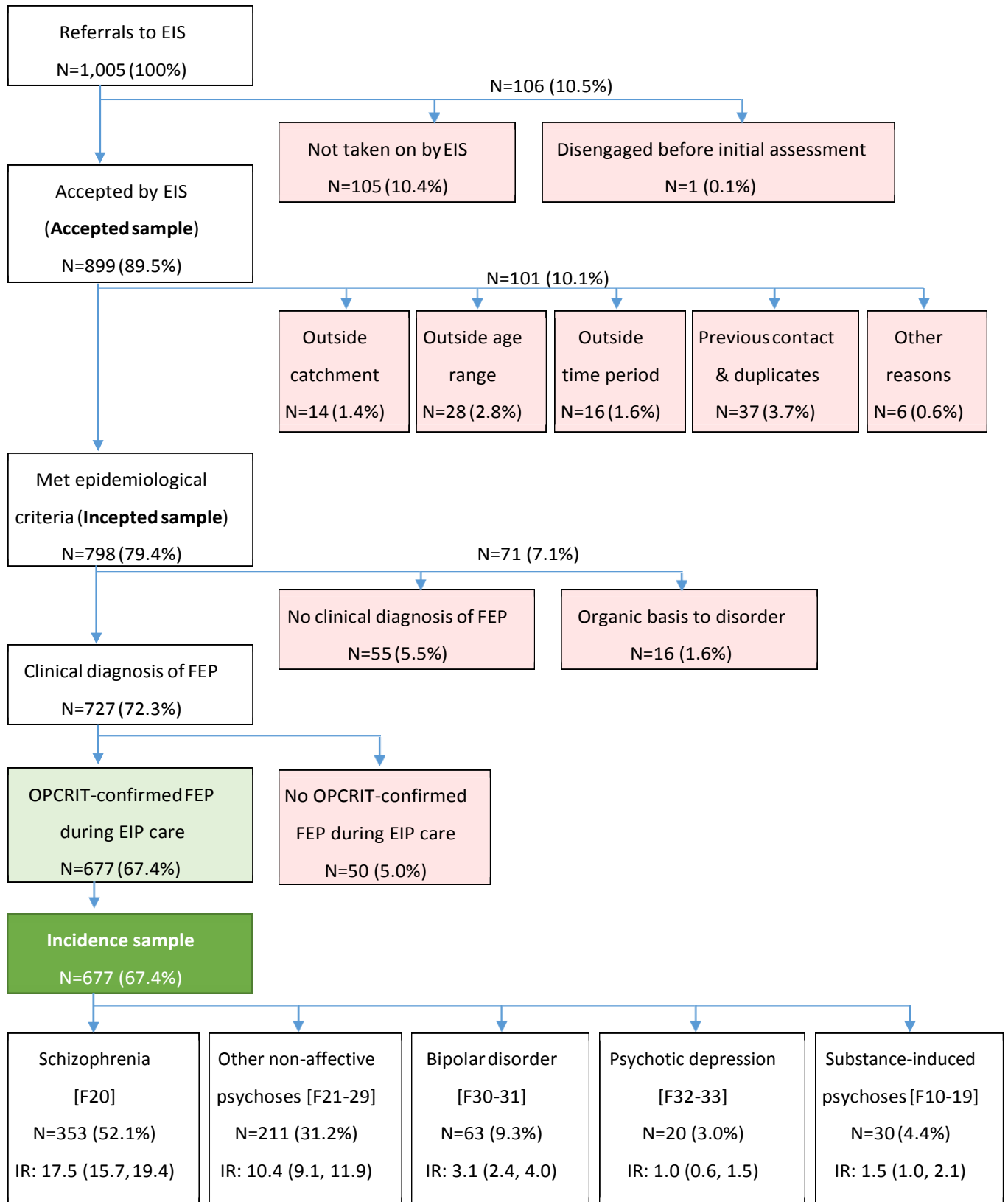
†p≤0.05

‡Analyses based on N=649 FEP participants. N=28 FEP participants were of no fixed abode at first referral and could not be geocoded to a small area neighborhood.

Adjustment 1 is based on the full sample (N=675), mutually adjusted for all variables listed

Adjustment 2 is based on the restricted sample N=649. IRR are mutually adjusted for all variables listed.

Figure 1: Flow diagram of referrals to EIP services in the SEPEA study

```
┌─────────────────────┐
│ Referrals to EIS    │
│ N=1,005 (100%)      │
└─────────────────────┘
```

N=106 (10.5%)

```
┌─────────────────────┐   ┌──────────────────────────────────┐
│ Not taken on by EIS │   │ Disengaged before initial        │
│ N=105 (10.4%)       │   │ assessment                       │
│                     │   │ N=1 (0.1%)                       │
└─────────────────────┘   └──────────────────────────────────┘
```

```
┌─────────────────────┐
│ Accepted by EIS     │
│ (Accepted sample)   │
│ N=899 (89.5%)       │
└─────────────────────┘
```

N=101 (10.1%)

```
┌────────────┐ ┌────────────┐ ┌────────────┐ ┌──────────────────┐ ┌────────────┐
│ Outside    │ │ Outside age│ │ Outside    │ │ Previous contact │ │ Other      │
│ catchment  │ │ range      │ │ time period│ │ & duplicates     │ │ reasons    │
│ N=14 (1.4%)│ │ N=28 (2.8%)│ │ N=16 (1.6%)│ │ N=37 (3.7%)      │ │ N=6 (0.6%) │
└────────────┘ └────────────┘ └────────────┘ └──────────────────┘ └────────────┘
```

```
┌──────────────────────┐
│ Met epidemiological  │
│ criteria (Incepted   │
│ sample)              │
│ N=798 (79.4%)        │
└──────────────────────┘
```

N=71 (7.1%)

```
┌──────────────────────┐   ┌──────────────────────────┐
│ No clinical diagnosis│   │ Organic basis to disorder│
│ of FEP               │   │ N=16 (1.6%)              │
│ N=55 (5.5%)          │   │                          │
└──────────────────────┘   └──────────────────────────┘
```

```
┌──────────────────────┐
│ Clinical diagnosis   │
│ of FEP               │
│ N=727 (72.3%)        │
└──────────────────────┘
```

```
┌──────────────────────┐   ┌──────────────────────────┐
│ OPCRIT-confirmed FEP │   │ No OPCRIT-confirmed      │
│ during EIP care      │   │ FEP during EIP care      │
│ N=677 (67.4%)        │   │ N=50 (5.0%)              │
└──────────────────────┘   └──────────────────────────┘
```

```
┌──────────────────────┐
│ Incidence sample     │
│ N=677 (67.4%)        │
└──────────────────────┘
```

```
┌────────────────┐ ┌──────────────────┐ ┌──────────────────┐ ┌──────────────────┐ ┌──────────────────┐
│ Schizophrenia  │ │ Other non-affect.│ │ Bipolar disorder │ │ Psychotic        │ │ Substance-induced│
│ [F20]          │ │ psychoses [F21-29]│ │ [F30-31]         │ │ depression       │ │ psychoses [F10-19]│
│ N=353 (52.1%)  │ │ N=211 (31.2%)    │ │ N=63 (9.3%)      │ │ [F32-33]         │ │ N=30 (4.4%)      │
│ IR: 17.5       │ │ IR: 10.4         │ │ IR: 3.1          │ │ N=20 (3.0%)      │ │ IR: 1.5          │
│ (15.7, 19.4)   │ │ (9.1, 11.9)      │ │ (2.4, 4.0)       │ │ IR: 1.0 (0.6,1.5)│ │ (1.0, 2.1)       │
└────────────────┘ └──────────────────┘ └──────────────────┘ └──────────────────┘ └──────────────────┘
```

Legend: IR: Crude incidence rate per 100,000 person-years with 95% confidence intervals.

Figure 2: Crude incidence of selected psychotic disorders by age and sex
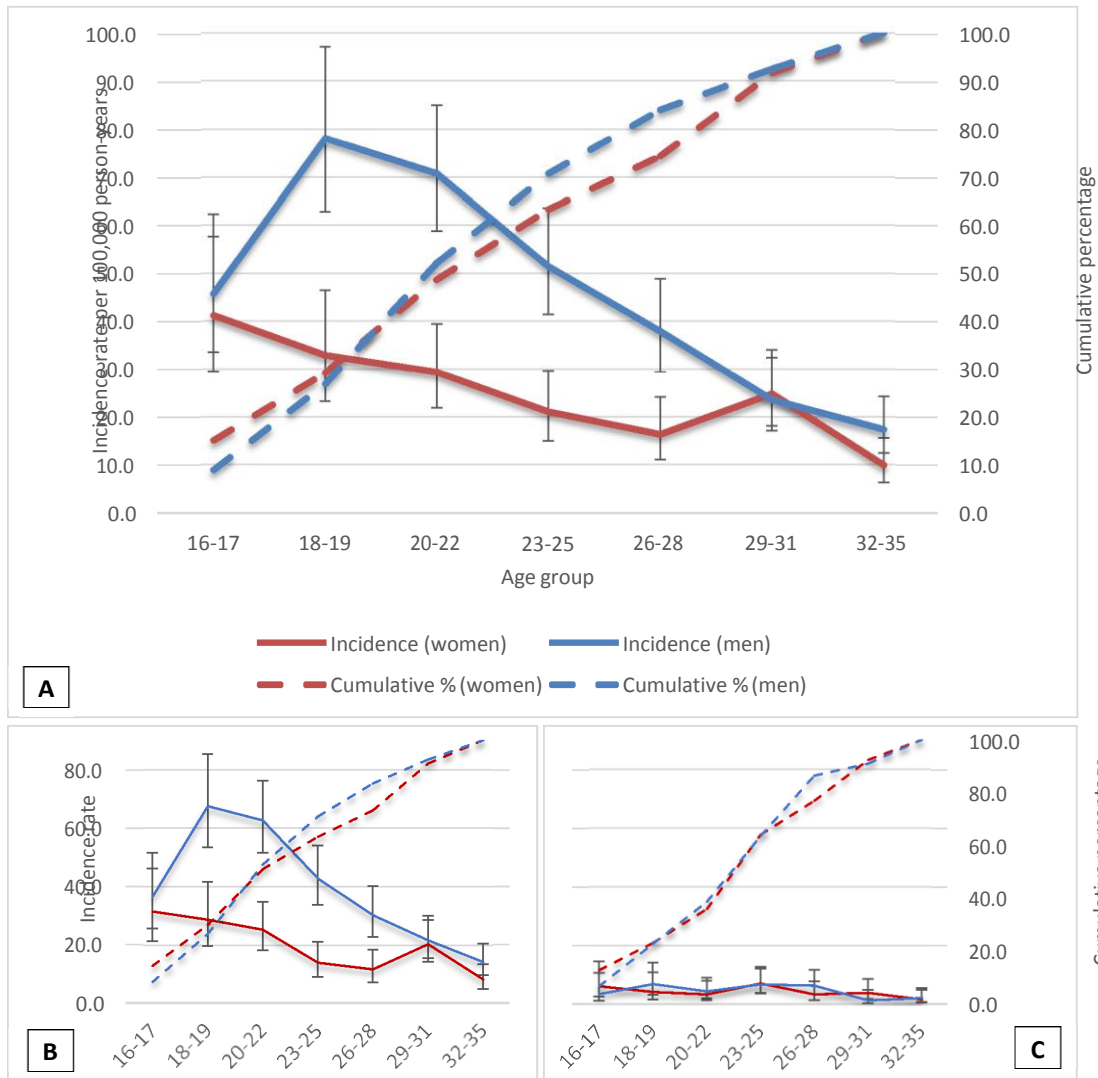
Legend: Crude incidence per 100,000 person-years and cumulative proportion of participants presenting to EIP services, by age and sex, for (A) all clinically-relevant psychotic disorders, (B) non-affective psychotic disorders and (C) affective psychotic disorders. LRT p-values for an age-sex interaction in Poisson regression models were (A) LRT-χ^2 on 6df=19.7: p<0.01, (B) LRT-χ^2 on 6df=16.7: p=0.01 and (C) LRT-χ^2 on 6df=5.2: p=0.51. All graphs are plotted on the same scale to show relative differences in crude incidence between disorders.

Supplementary Table 1: Neighborhood-level characteristics of the SEPEA catchment – description, summary and representativeness

Environmental variable	Description	SEPEA Median (IQR) N=530	Rest of England Median (IQR) N=7,159	Median difference^ (95%CI); p-value
Population density	People per hectare	2.3 (0.8-18.0)	16.8 (2.5-36.5)	-13.8 (-16.8, -10.8); p<0.01
Ethnicity	% of population of black & minority ethnicity	5.5 (3.5-11.1)	6.7 (4.0-15.7)	-1.2 (-1.8, -0.5); p=0.01
Multiple deprivation	% of households in 2 or more of the domains below:	20.6 (16.7-25.7)	21.4 (16.3-28.3)	-0.7 (-1.8, 0.3); p=0.14
Employment domain	% of households with at least one adult member reported as long-term sick or unemployed, not in full time study	N/A	N/A	-
Education domain	% of households without any member with at least "Level 2" education (≥5 GCSEs or equivalent) or in full-time study	N/A	N/A	-
Health & disability domain	% of households with at least one member's self-rated health as "bad" or "very bad", or with a limiting long-term health problem	N/A	N/A	-
Living environment domain	% of households with at least one of the following: (i) in overcrowding†; (ii) living in a shared dwelling‡, (iii) without central heating	N/A	N/A	-

IQR – Interquartile range; GCSE – General Certificate for Secondary Education, mandatory for children in 10th and 11th years of education. N/A: Domain-specific deprivation data not published by the Office for National Statistics [ONS].
^Obtained from quantile regression
† ONS definition of overcrowding based on number of rooms and people per household, weighted for age and relationship status.
‡A unit of accommodation shared by two or more households. See the ONS 2011 Glossary for full information on these measures:
http://www.ons.gov.uk/ons/guide-method/census/2011/census-data/2011-census-data/2011-first-release/2011-census-definitions/2011-census-glossary.pdf.
Accessed 14th January, 2016.

Legend: Neighborhood-level variation in population density, ethnicity and deprivation varied across the 530 neighborhoods in the SEPEA region. The SEPEA region was, however, substantially more rural than the rest of England (N=7,159) (p<0.01). Median differences in neighborhood-level ethnic composition (-0.7%; 95%CI: -1.8, 0.3) and multiple deprivation (-1.2%; 95%CI: -1.8, -.05) between the SEPEA region and the rest of England were small, but given the large number of neighborhoods (N=7689), met statistical significance for ethnic composition (p=0.01), though not multiple deprivation (p=0.14). ONS 2011 Census data were obtained from: Table QS119EW (deprivation); Table PHP01 (population density), and; Table KS201EW (ethnicity); see www.nomisweb.co.uk.

Supplementary Table 2: Incidence rate ratios of non-affective and affective psychotic disorders by major sociodemographic characteristics

Variable	Non-affective psychoses		Affective psychoses	
	Case (%)	IRR[†] (95% CI)	Case (%)	IRR[†] (95% CI)
Total cases	564 (100)	-	83 (100)	-
Sex				
Women	180 (31.9)	Ref	39 (47.0)	Ref
Men	384 (68.1)	2.00 (1.68, 2.39)[‡]	44 (53.0)	1.07 (0.70, 1.65)
Age group				
16-24	362 (64.2)	Ref	49 (59.0)	Ref
25-29	116 (20.6)	0.64 (0.51, 0.80)[‡]	25 (30.1)	0.80 (0.47, 1.35)
30-35	86 (15.2)	0.44 (0.34, 0.57)[‡]	9 (10.8)	0.26 (0.12, 0.55)[‡]
Ethnicity				
White British	427 (75.7)	Ref	55 (64.0)	Ref
BME group	137 (24.3)	1.41 (1.15, 1.72)[‡]	31 (36.0)	2.26 (1.41, 3.63)[‡]
Participant SES				
Professional & managerial	57 (10.1)	Ref	12 (14.5)	Ref
Intermediate occupation	64 (11.3)	1.58 (1.10, 2.26)[‡]	12 (14.5)	1.45 (0.65, 3.24)
Routine & manual	230 (40.8)	2.44 (1.81, 3.28)[‡]	31 (37.3)	1.52 (0.77, 3.03)
Long-term unemployed, students & unclassifiable	213 (37.8)	2.32 (1.69, 3.18)[‡]	28 (33.7)	1.23 (0.59, 2.57)
EIP service				
North Cambridgeshire	70 (12.4)	Ref	18 (21.7)	Ref
South Cambridgeshire	129 (22.9)	1.30 (0.97, 1.75)	30 (36.1)	1.23 (0.68, 2.23)
West Norfolk	28 (5.0)	1.11 (0.72, 1.73)	5 (6.0)	0.86 (0.32, 2.32)
Central Norfolk	127 (22.5)	1.14 (0.85, 1.53)	11 (13.3)	0.43 (0.20, 0.91)[‡]
Great Yarmouth & Waveney	59 (10.4)	1.60 (1.12, 2.27)[‡]	14 (16.9)	1.73 (0.85, 3.53)
Suffolk	151 (26.8)	1.38 (1.04, 1.84)[‡]	5 (6.0)	0.19 (0.07, 0.52)[‡]

IRR: incidence rate ratio; BME: Black & Minority Ethnic; SES: Socioeconomic status; EIP: Early Intervention Psychosis
†Adjusted for all other variables listed in table
‡p≤0.05

Supplementary Table 3: Neighborhood level variation in the incidence of non-affective and affective psychotic disorders

Variable	Non-affective psychoses		Affective psychoses	
	Case* (%)	IRR[†] (95% CI)	Case^ (%)	IRR[†] (95% CI)
Total cases	539 (100)	-	82 (100)	-
People per hectare[‡]				
0-14.9	242 (44.9)	Ref	38 (46.3)	Ref
15-29.9	110 (20.4)	1.00 (0.78, 1.27)	10 (12.2)	0.63 (0.30, 1.33)
30-44.9	106 (19.7)	1.04 (0.80, 1.36)	16 (19.5)	1.33 (0.66, 2.69)
45-84.8	81 (15.0)	1.20 (0.89, 1.61)	18 (22.0)	1.96 (0.98, 3.91)
Percentage households in multiple deprivation[‡]				
7.8-18.0%	130 (24.1)	Ref	28 (34.1)	Ref
18.1-28.0%	239 (44.3)	1.45 (1.13, 1.85)[‡]	33 (40.2)	0.82 (0.44, 1.52)
28.1-38.0%	126 (23.4)	1.44 (1.05, 1.97)[‡]	16 (19.5)	0.62 (0.26, 1.47)
38.1-47.1%	44 (8.2)	2.84 (1.76, 4.58)[‡]	5 (6.1)	0.39 (0.11, 1.35)
EIP setting				
North Cambridgeshire	69 (12.8)	Ref	18 (22.0)	Ref
South Cambridgeshire	120 (22.3)	1.68 (1.18, 2.38)[‡]	29 (35.4)	0.98 (0.47, 2.02)
West Norfolk	27 (5.0)	1.09 (0.68, 1.74)	5 (6.1)	0.98 (0.34, 2.83)
Central Norfolk	124 (23.0)	1.28 (0.92, 1.77)	11 (13.4)	0.41 (0.18, 0.91)[‡]
Great Yarmouth & Waveney	57 (10.6)	1.37 (0.93, 2.00)	14 (17.1)	2.05 (0.94, 4.50)
Suffolk	142 (26.3)	1.57 (1.14, 2.16)[‡]	5 (6.1)	0.18 (0.06, 0.51)[‡]

IRR: incidence rate ratio; EIP: Early Intervention Psychosis
[†]Adjusted for all other variables listed in table and age group (three-category), sex, ethnicity and participant SES, as described
[‡]p≤0.05
*25 FEP participants of no fixed abode was excluded from analysis
^One FEP participant of no fixed abode was excluded from these analysis

Supplemental Figure 1: Location, EIP service provision and selected catchment area characteristics
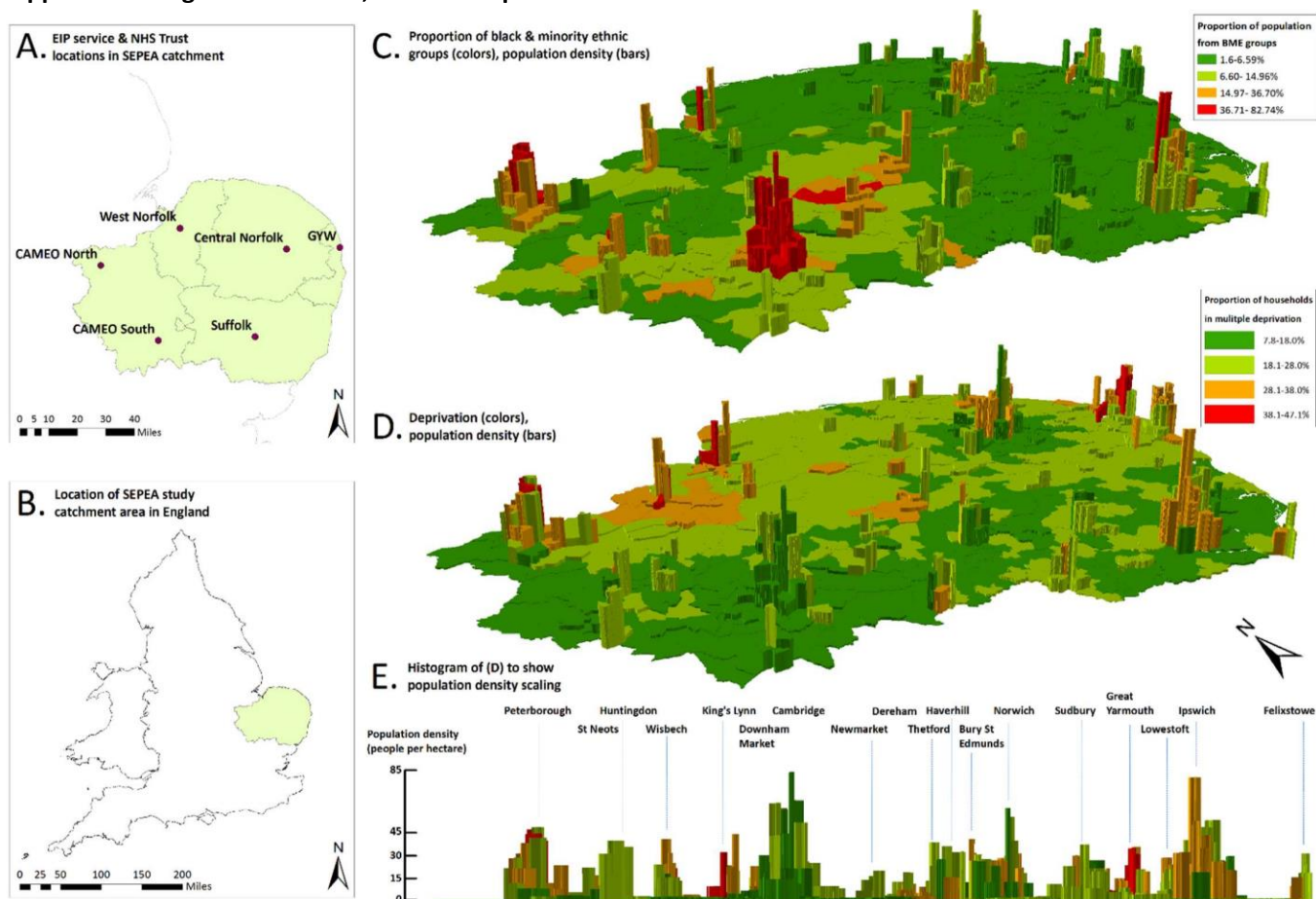
Legend: A. Location of six EIP services in the SEPEA catchment area. GYW: Great Yarmouth & Waveney. CAMEO is the EIP provider in Cambridge & Peterborough. **B.** Location in England. **C.** Proportion of black & minority ethnic [BME] groups (colors) and population density (bars) in 530 small area neighborhoods. Categorized in centiles relative to % BME in 7,689 English neighborhoods (i.e. up to median: 1.6-6.59%; 51st-75th centile: 6.60-14.96%; 76th-90th centile: 14.97-36.70%; 91st centile+: 36.71-82.7%). **D.** Proportion of households in multiple deprivation (colors), classified on 4-category interval scale used in analyses, and population density (bars). **E.** Histogram of (D.) showing population density scale and notable towns & cities in catchment. Colors correspond to multiple deprivation. Data from ONS 2011 Census. See also Supplemental Table 1.

Supplemental Figure 2: Rate of contact in EIP services by contact type
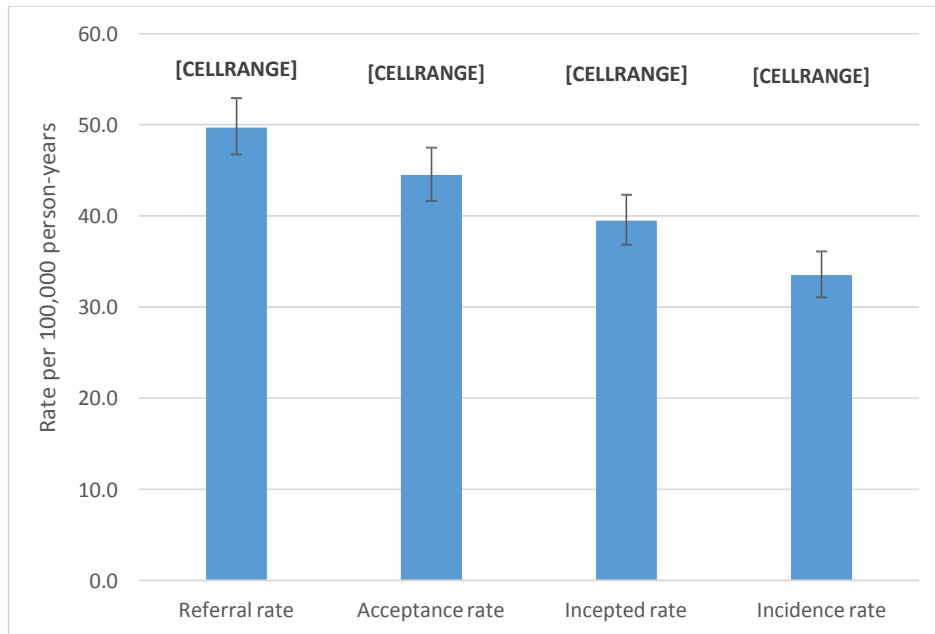
Legend
Referral rate: Number of referrals per 100,000 person-years
Acceptance rate: Number of referrals accepted by EIP services, per 100,000 person-years
Incepted rate: Number of accepted referrals who met epidemiological criteria, per 100,000 years
Incidence rate: Number of the incepted sample who received an OPCRIT-confirmed diagnosis for FEP, per 100,000 person years