Word count: 3,533
Tables: 2
Figures: 2

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

James B. Kirkbride Ph.D.,[1 2]* Yasir Hameed MRCPsych,[3] Gayatri Ankireddypalli M.D. MRCPsych,[4] Konstantinos Ioannidis MRCPsych,[2 5] Carolyn M. Crane M.Sc.,[5] Mukhtar Nasir MRCPsych,[3] Nikolett Kabacs M.D.,[5] Antonio Metastasio M.D. MRCPsych,[3] Oliver Jenkins MRCPsych,[3] Ashkan Espandian M.D.,[5] Styliani Spyridi Ph.D. MRCPsych,[5] Danica Ralevic MRCPsych,[3] Suneetha Siddabattuni MRCPsych,[3] Ben Walden MRCPsych,[3] Adewale Adeoye MPH MBBS,[3] Jesus Perez M.D. Ph.D.,[2 5] Peter B. Jones Ph.D. FMedSci[2 5]

[1]PsyLife group, Division of Psychiatry, UCL, London, W1T 7NF
[2]Department of Psychiatry, University of Cambridge, Cambridge, CB2 0SZ
[3]Norfolk & Suffolk Foundation Trust, Norwich, Norfolk, NR6 5BE
[4]North Essex Partnership NHS Foundation Trust, Chelmsford, Essex, CM2 0QX
[5]Cambridgeshire & Peterborough Foundation Trust, and NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East of England, Cambridge, Cambridgeshire, CB21 5EF

*Corresponding author: Dr James Kirkbride, Sir Henry Dale Fellow, Division of Psychiatry, 6th Floor Maple House, 149 Tottenham Court Road, UCL, London, W1T 7NF, UK. j.kirkbride@ucl.ac.uk Tel: +44 (0) 20 7679 9297.

Disclosures & acknowledgements

None of the authors have any conflicts of interest to declare.

James Kirkbride was supported by a Sir Henry Wellcome Research Fellowship from the Wellcome Trust (grant number: WT085540), through which the SEPEA study (www.sepea.org) was established. Dr James Kirkbride is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (grant number: 101272/Z/13/Z). Peter Jones directs the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East of England. Jesus Perez was supported by NIHR grant RP-PG-0606-1335. Funders had no involvement in the preparation of this manuscript.

We would like to thank the Cambridgeshire & Peterborough (CPFT) and Norfolk & Suffolk Foundation Trusts (NSFT) for sponsoring this research. We are indebted to all service users and staff at the six EIP services where the SEPEA study took place: CAMEO North (Peterborough, CPFT), CAMEO South (Cambridge, CPFT), the West Norfolk Early Intervention Service (Kings Lynn, NSFT), the Central Norfolk Early Intervention Team (Norwich, NSFT), the Great Yarmouth & Waveney Early Intervention Service (Great Yarmouth, NSFT) and the former Suffolk Early Intervention Psychosis Service (Stowmarket, NSFT). We are also grateful to staff at the *NIHR Clinical Research Network: Eastern* (formerly the Mental Health Research Network) for the invaluable support provided to the study, and the dedicated help of all assistant psychologists and Clinical Studies Officers who contributed to data collection. In addition to assistance in OPCRIT assessment from several authors of this paper, we are grateful to Drs Eva Aguilar (CPFT), Poornima Chandrappa (NSFT), Louise Colledge (CPFT), Ben Davies (CRN: Eastern), Jeanine Gambin (CPFT), Martina Gariga (CPFT), Maria Gonzalez (CPFT), Clare Knight (CPFT), Santvana Pandey (NSFT) and Swathi Theegala (CPFT), Rebecca Webster (CPFT), Antonio Zambrana (CPFT) for their assistance with OPCRIT completion.

Abstract

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

Method: We identified all new first episode psychosis cases, 16-35 years old, presenting to Early Intervention Psychosis services in the East of England, during 2 million person-years follow-up. Presence of International Classification of Diseases, Tenth Revision, F10-33 psychotic disorder was confirmed using OPCRIT. We estimated incidence rate ratios [IRR] following multivariable Poisson regression, adjusting for age, sex, ethnicity, socioeconomic status, neighborhood-level deprivation and population density.

Results: Of 1,005 referrals, 687 participants (68.4%) fulfilled epidemiological and diagnostic criteria for first episode psychosis (34.0 new cases per 100,000 person-years; 95%CI: 31.5-36.6). Median age-at-referral was similar (p=0.27) for men (22.5 years; interquartile range: 19.5-26.7) and women (23.4 years; 19.5-29.1); incidence rates were highest for men and women before 20 years old. Rates increased for ethnic minority groups (IRR: 1.4; 95%CI: 1.1-1.6), with lower socioeconomic status (IRR: 1.3: 95%CI: 1.2-1.4) and in more urban (IRR: 1.4; 95%CI: 1.0-1.8) and deprived neighborhoods (IRR: 2.1; 95%CI: 1.3-3.3) after adjustment for confounders.

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

Background

Early Intervention in psychosis now arguably represents the gold standard of care for people in their first episode of psychosis (1). This care model incorporates pharmacological and psychological interventions, family and social support, supported employment and physical healthcare checks, delivered by a multidisciplinary team for up to 5 years. The rationale for early intervention derives from observations that reducing the duration of untreated psychosis may improve clinical, functional and social outcomes in the short- to medium-term (2–8). This effect is most robust for schizophrenia spectrum disorders (2–4), with much less evidence in regard to the affective psychoses (9). Since Early Intervention Psychosis service provision is founded on evidence-based healthcare (10), this should include the provision of robust estimates of incidence of psychotic disorders to inform healthcare commissioners about local variation in service need. Unfortunately, psychosis epidemiology is predominantly informed by an older literature, conducted prior to the widespread introduction of these services (11; 12), almost exclusively based in urban settings (13). This research has revealed important heterogeneity in incidence by person (14–18) and place (19; 20), generating new directions for etiological research (21–23). However, national implementation efforts being developed in countries such as Denmark (24), Australia (25) and Canada (26), and currently undergoing revision in the UK (27), require accurate, relevant estimates about the epidemiology of psychotic disorders in populations served by Early Intervention Psychosis services. Such data will also be critical in countries such as the USA, where early intervention initiatives are gaining traction (28–31), but where 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 Early Intervention Psychosis services. Consistent with earlier epidemiology (11; 13), we hypothesized that the incidence of psychotic disorders, including non-affective psychoses, would decline with age and greater socioeconomic status, and be higher amongst men, black and minority ethnic groups and in more deprived, urban neighborhoods. In line with previous findings (13; 20), we also hypothesized that affective psychoses would show less variation across these domains.

Method

Design & setting

We identified all people aged 16-35 years old who presented to six Early Intervention Psychosis services in a defined catchment area, over 3.5 years from 1 August 2009. These services were implemented on the basis of a national implementation guide (32) as the sole referral point for suspected psychosis for people up to 35 years old. Services accepted referrals 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 and Norfolk and Suffolk NHS Foundation Trust (Supplemental Figure 1). In 2011, the catchment area had an estimated population of 2.4m people (4.5% of the English population) (33), of whom 24.0% were 16-35 years old. The catchment area contained 530 administrative neighborhoods with a median population of 3,992 people (interquartile range [IQR]: 2,426-5,935). The region is varied in terms of its sociodemographic characteristics and population density (Supplemental Figure 1).

Inclusion criteria

We applied the following inclusion criteria to all participants referred to Early Intervention Psychosis services in our study:

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

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

Diagnostic outcomes

We used a two-stage diagnostic procedure to confirm presence of an International Classification of Diseases, Tenth Revision, psychotic disorder (ICD-10 F10-33). In the first stage, we asked the clinician responsible for care to provide a clinical diagnosis six months after acceptance into care, and at service discharge (median follow-up: 2.3 years; IQR: 1.2-3.0). In the second stage, we obtained

research-based diagnoses at these time points using OPCRIT (34), a reliable diagnostic instrument (34; 35), which produces ICD-10 diagnoses according to 90 standardized symptom items (36). We trained a panel of clinicians (N=25) to rate OPCRIT items from 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 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, confirmed by OPCRIT assessment.

We classified participants according to their final OPCRIT diagnosis, as follows: all clinically-relevant psychotic disorders (F10-33), non-affective psychoses (F20-29), schizophrenia (F20), other non-affective psychoses (F21-29), substance-induced psychoses (F10-19), affective psychoses (F30-33), bipolar disorder (F30-31) and psychotic depression (F32-33). Since OPCRIT does not distinguish substance-induced psychoses from other non-affective psychoses, we relied on a clinical diagnosis of substance-induced psychosis at 6 months after acceptance (n=8), discharge (n=2) or both (n=19) for people who received an OPCRIT diagnosis of "ICD-10 other non-organic psychoses" (i.e. F21-29 & F1X.5). Incepted participants without any OPCRIT-confirmed psychotic disorder were excluded from the *incidence sample* (Figure 1).

Exposure and confounder variables

Sociodemographic information, including birthdate, sex, ethnicity, marital status, birth country, postcode, employment status, and main, current or last occupation and parental occupations was collected at first referral, 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 2011 Census of Great Britain. Here, we created a dichotomous ethnicity variable (black and minority ethnic groups versus white British) to examine initial variation. We classified birth country as UK- or foreign-born. We classified participant socioeconomic status according to current, or if unemployed for less than two years, main or last occupation, according to a standard methodology (37; 38) as follows: professional & managerial occupations; 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 socioeconomic status similarly, taking the higher occupation of both parents, where available.

We geocoded participants to their neighborhood at initial referral to obtain measures of their social environment. We defined multiple deprivation as the proportion of households in each neighborhood classified as deprived on at least two of four indicators from the 2011 census (employment, education, health, living environment; Supplemental Table 1). We categorized multiple deprivation on an equal-interval scale (7.7-18%; 18.1-28%; 28.1-38%; 38.1-47.1%). We estimated population density for each neighborhood based on the total 2011 census population divided by area, expressed as people per square mile. We categorized population density according to the proportion of neighborhoods: below the median (48-587 people per square mile); in the 50^{th}-75^{th} percentile (588-4653); 76^{th}-95^{th} percentile (4,654-11,099); 96^{th}-100^{th} percentile (11,100-21,970).

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 multiplied population estimates by 3.5 to obtain person-years at-risk over the study period, and stratified the data by age group (16-24,25-29,30-35 years), sex, ethnicity and participant socioeconomic status.

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 differences in sociodemographic characteristics between cases and the population at-risk. For all psychotic disorders (F10-33), non-affective psychoses (F20-29) and affective psychoses (F30-33), we then fitted multivariable Poisson regression models to examine potential differences in incidence by age group (three-category), sex, ethnicity, participant socioeconomic status and Early Intervention Psychosis service setting, after mutual adjustment for all remaining variables. Forward-fitting modelling was used to determine the most parsimonious model, assessed via likelihood ratio test [LRT-χ^2]. Where variation in incidence between services was detected, we then examined whether this was attributable to multiple deprivation or population density, using multilevel Poisson models, fitted with neighborhood-level random intercepts. In these analyses, we excluded participants of no fixed

abode (n=28). Incidence rates were presented per 100,000 person-years. 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 Early Intervention Psychosis services with a suspected first episode of psychosis during 2.02m person-years at-risk, of whom 899 (89.5%) were accepted into 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 person-years, respectively (Supplemental Figure 2). One-hundred-and-one participants (10.0%) did not meet epidemiological criteria (Figure 1), leaving 798 people in our incepted sample, of whom 687 (86.1%) were diagnosed with an OPCRIT-confirmed ICD-10 psychotic disorder (F10-33). This corresponded to a crude incidence of 34.0 new cases per 100,000 person-years (95%CI: 31. 5-36. 6). Most incidence cases received a diagnosis of schizophrenia (F20; 50.9%) or other non-affective psychotic disorder (F21-29; 32.5%), giving a crude incidence of 28.3 per 100,000 person-years (95%CI: 26.1-30.8) for non-affective psychotic disorders. The incidence of affective psychotic disorders (F30-33) was lower (4.2 per 100,000 person-years; 95%CI: 3.4-5.1); the majority of these (77.4%) were bipolar affective psychoses (Figure 1). The incidence of probable substance-induced psychosis was low (1.5 per 100,000 PYAR; 95%CI: 1.0-2.1).

Baseline characteristics and descriptive epidemiology

In our incidence sample, median age-at-referral did not differ between men (22.5; IQR: 19.5-26.7) and women (23.4; IQR: 19.5-29.1; Mann-Whitney U-test: Z=1.1; p=0.27). We observed weak evidence (Kruskal-Wallis χ^2=5.0 on 2 degrees of freedom [df]; p=0.08) of differences in median age-at-referral between affective (23.6 years; IQR: 20.0-27.3), non-affective (22.6 years; IQR: 19.6-27.4) and probable substance-induced psychoses (21.0 years; IQR: 17.7-24.7). Two-thirds of cases (n=459; 66.8%) were men (Table 1), although there was also weak evidence that this pattern differed between non-affective (67.7% men), affective (57.1% men) and probable substance-induced

psychoses (76.7% men) (χ^2-test on 2df=5.1; p=0.08). Compared with the population at-risk, cases were more likely to be men, younger, from an ethnic minority background, single, unemployed, of lower socioeconomic status and from more deprived and densely populated neighborhoods (all 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=21.1: 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 peak rates 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=15.4; p=0.02), but differed for affective psychoses (LRT-χ^2 on 6df=9.5 p=0.15), 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, socioeconomic status and setting, following mutual adjustment for each other (Table 2, Adjustment 1). For example, rates were 1.47 times higher in ethnic minority participants (95%CI: 1.23-1.76) compared with the white British group, increased with lower socioeconomic status and varied between Early Intervention Psychosis services. Further multilevel modelling suggested that variation in incidence across the region was associated with both neighborhood-level population density and multiple deprivation, after adjustment for all other covariates (Table 2, Model 2). We observed evidence that this relationship was nonlinear, with excess rates restricted to the most densely populated (IRR 1.37; 95%CI: 1.02-1.84) and deprived neighborhoods (IRR: 2.11; 95%CI 1.34-3.32) in the study.

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 (IRR in most versus least deprived neighborhoods: 2.74; 95%CI: 1.71-4.39) remained consistently associated with neighborhood-level incidence (Supplemental Table 3). There was some evidence that patterns of risk differed for the affective psychoses, despite a smaller sample (N=84). Rates were more similar for men and women (IRR for men: 1.27; 95%CI: 0.82, 1.96) and less strongly associated with socioeconomic status, after adjustment for other confounders (Supplemental Table 2). While affective psychoses rates varied between services, this was not associated with either neighborhood-level variable (Supplemental Table 3).

Discussion

In this, the largest epidemiological study of first episode psychosis conducted since Early Intervention Psychosis 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. In particular, our findings (i) reveal substantial incidence rates of all clinically-relevant psychotic disorders in young people; (ii) demonstrate that median age-at-first-referral is similar for young men and women before 35 years old, with 50% of cases presenting by 23 years old, and; (iii) we extend previous knowledge to show that incidence in more rural populations in England, which have received less research, varies by classic individual- and neighborhood-level social and economic determinants of health, particularly for non-affective disorders; affective psychoses showed less variation overall.

Methodological considerations

Our study was based on referrals to Early Intervention Psychosis services from multiple sources, including other mental health services within the National Health Service, and self-referrals. Our findings should therefore be interpreted based on administrative or first contact incidence. We were unable to perform a leakage study to detect potentially missed cases, which could have led us to under-estimate the true incidence in the catchment area. Nonetheless, Early Intervention Psychosis services are the sole referral point for young people with suspected psychotic symptoms, and actively engaged in outreach and promotion in the East of England. In England, there is very little private mental healthcare for psychosis, reducing risk of leakage. The epidemiological characteristics of our sample were consistent with other major first episode psychosis studies (39; 40), implying that our study design did not introduce substantial under-ascertainment overall, or differentially by sociodemographic subgroups. Although the excess incidence in black and minority ethnic groups was smaller than normally reported (13), there is no evidence that such groups are less likely to be referred to Early Intervention Psychosis services, despite differing care pathways (41–43). Furthermore, a separate paper from our study (*in submission*) demonstrates that rates for specific ethnic groups are in line with excesses more typically observed (13). Our modest IRRs for this group, overall, are probably driven by the large proportion of non-British white migrants in this population (52.2%), whose overall psychosis risk is similar to the white British population (40). We did not measure the duration of untreated psychosis in our sample, but this could only have affected the

estimation of incidence rates if it had changed rapidly over the short follow-up period of our study (3.5 years); this is unlikely, particularly given services were well-established in our catchment area.

We cannot generalize our findings to people younger than 16 years old. This remains an important, underexplored epidemiological research issue, given that early intervention and more general youth mental health services, often accept cases from 14 years old or younger; limited evidence suggests incidence is very rare (44; 45). Our catchment area was considerably more rural than those previously studied in England. Generalizability to other settings will depend on the exact composition of their catchment areas, and we did not have data on very rural areas (i.e. less than 48 inhabitants per square mile). Nonetheless, variation in population density across our catchment area included the values for median population densities of 37 of 50 U.S. states (46).

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 (47). 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 research-based criteria for psychotic disorder to our initial sample. OPCRIT diagnoses were assessed by trained clinicians, with good inter-rater reliability based on a small sample of twenty real-world case vignettes. The proportion of people who received a clinical diagnosis in the incepted sample, who also met OPCRIT-criteria for psychotic disorder was high (positive predictive value = 687/722 i.e. 95.2%), demonstrating good concurrent validity in line with previous research (36). We presented results for all clinically-relevant disorders given current interest in this broad psychosis phenotype. Rates of affective psychotic disorders were lower than typically reported in adults (i.e. up to 64 years old) in England (13), though were consistent with observations elsewhere in Europe (48). Given that the incidence of such disorders show less decline with age, and may even peak after 45 years old (13; 49), lower rates 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 Early Intervention Psychosis services in a large, diverse rural and urban population in the East of England. Referral rates to such services approached 50 people per 100,000 person-years, with services subsequently accepting nearly nine out of ten referrals onto caseloads. We estimated that the true incidence of psychotic disorder seen through these services was closer to 34 new cases per 100,000 person-years. This difference highlights important challenges faced by policymakers, commissioners and practitioners in developing, deploying and delivering effective early intervention services.

Previous influential commissioning guidelines have used uniform estimates of narrowly-defined schizophrenia incidence – closer to 15 per 100,000 person-years – based on an older epidemiology, as a basis for caseload and workforce calculations (32). However, in practice, Early Intervention Psychosis services may be mandated to intervene on a broader spectrum of psychoses, including other non-affective and affective psychotic disorders, as well as other mental health disorders where psychotic-like symptoms can present. In a US context, where Early Intervention Psychosis services are currently gaining momentum (29; 30), service provision is primarily predicated on the treatment of non-affective psychoses. If, however, earlier intervention in the critical period for psychosis generates greater diagnostic uncertainty (50), this will inevitably result in a higher proportion of undifferentiated psychopathologies at first referral. Our data highlight some of the pragmatic realities in implementing Early Intervention Psychosis services, which will accept a proportion of people who do not meet full research-based criteria for non-affective psychotic disorder (29.1% of the incepted sample), in addition to 10.5% of people referred to but not accepted by services. Such groups would still require a degree of psychiatric triage and signposting, for which services need to be additionally resourced to effectively implement the fidelity criteria upon which they are predicated (5). We have provided robust estimates of referral, acceptance, inception and incidence rates in a diverse population, which can be used as part of a wider suite of evidence to inform service provision across the full spectrum of psychoses (51), not limited to schizophrenia.

Meaning of the findings epidemiological implications

Our findings extend previous epidemiological research to show that incidence of psychotic disorders varies by sociodemographic and environmental characteristics in more rural settings than typically studied (11; 13). As expected, incidence rates were lower, overall, than reported in more urban populations in England. For example, recent rates for young people presenting to Early Intervention Psychosis services in highly-urban Southeast London (29,267 people per square mile) were 54.6 per

100,000 person-years (95%CI: 49.5-60.2) (52), higher than reported here. Nonetheless, crude rates of psychotic disorders in our most urban and deprived communities overlapped with such estimates, which persisted after adjustment for age, sex, ethnicity and individual-level socioeconomic status. The nonlinear associations we observed between population density, deprivation and psychosis incidence in our mixed rural and urban population imply that a threshold of exposure to environmental factors may be necessary to increase risk. These findings accord with limited previous research on this issue (53). However, it remains unclear whether associations between environmental characteristics and psychosis risk reflect genuine etiological variance, or arise from selection factors, including familial aggregation of shared genetic or environmental experiences, which perpetuate downward social drift (22). These processes may not be mutually exclusive, but lead to the intergenerational accumulation of deleterious risk factors which subsequently affect a number of adverse health and social outcomes, including schizophrenia and other psychoses. Further longitudinal studies are required to disentangle the potential role of social causation from drift or selection. Although we could not establish causation directly, our results demonstrate 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 effective early intervention services for psychosis.

References

1. McGorry PD: Early Intervention in Psychosis: Obvious, Effective, Overdue [Internet]. J. Nerv. Ment. Dis. 2015; 203:310–318Available from: http://journals.lww.com/jonmd/Fulltext/2015/05000/Early_Intervention_in_Psychosis__Obvious,.2.aspx

2. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T: Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review [Internet]. Arch. Gen. Psychiatry 2005; 62:975–983Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16143729

3. Perkins DO, Gu H, Boteva K, Lieberman JA: Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis [Internet]. Am. J. Psychiatry 2005; 162:1785–1804Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16199825

4. Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J: Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis [Internet]. Br. J. Psychiatry 2014; 205:88–94Available from: http://bjp.rcpsych.org/bjprcpsych/205/2/88.full.pdf

5. Csillag C, Nordentoft M, Mizuno M, Jones PB, Killackey E, Taylor M, Chen E, Kane J, McDaid D: Early intervention services in psychosis: from evidence to wide implementation. [Internet]. Early Interv. Psychiatry 2015; [cited 2015 Dec 1] Available from: http://www.ncbi.nlm.nih.gov/pubmed/26362703

6. Bertelsen M, Jeppesen P, Petersen L, Thorup A, Ohlenschlaeger J, le Quach P, Christensen TO, Krarup G, Jorgensen P, Nordentoft M: Five-Year Follow-up of a Randomized Multicenter Trial of Intensive Early Intervention vs Standard Treatment for Patients With a First Episode of Psychotic Illness: The OPUS Trial [Internet]. Arch. Gen. Psychiatry 2008; 65:762–771Available from: http://archpsyc.ama-assn.org/cgi/content/abstract/65/7/762

7. Craig TKJ, Garety P, Power P, Rahaman N, Colbert S, Fornells-Ambrojo M, Dunn G: The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis [Internet]. Br. Med. J. 2004; 329:1060–1067Available from: http://www.bmj.com/content/329/7474/1067.abstract

8. Hegelstad WT, Larsen TK, Auestad B, Evensen J, Haahr U, Joa I, Johannesen JO, Langeveld J, Melle I, Opjordsmoen S, Rossberg JI, Rund BR, Simonsen E, Sundet K, Vaglum P, Friis S, McGlashan T: Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome [Internet]. Am J Psychiatry 2012; 169:374–380Available from: http://www.ncbi.nlm.nih.gov/pubmed/22407080

9. Henry LP, Amminger GP, Harris MG, Yuen HP, Harrigan SM, Prosser AL, Schwartz OS, Farrelly SE, Herrman H, Jackson HJ, McGorry PD: The EPPIC follow-up study of first-episode psychosis: longer-term clinical and functional outcome 7 years after index admission. [Internet]. J. Clin. Psychiatry 2010; 71:716–28[cited 2016 Apr 11] Available from: http://www.ncbi.nlm.nih.gov/pubmed/20573330

10. McGorry PD: Truth and reality in early intervention [Internet]. Aust. N. Z. J. Psychiatry 2012; 46:313–316Available from: http://anp.sagepub.com/content/46/4/313.short

11. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D: A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. [Internet]. BMC Med. 2004; 2:1–22Available from: http://www.biomedcentral.com/1741-7015/2/13

12. Saha S, Chant D, Welham J, McGrath J: A Systematic Review of the Prevalence of Schizophrenia [Internet]. PLoS Med. 2005; 2:e141Available from: http://dx.doi.org/10.1371%2Fjournal.pmed.0020141

13. Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, Murray RM, Jones PB: Incidence of Schizophrenia and Other Psychoses in England, 1950–2009: A Systematic Review and Meta-Analyses [Internet]. PLoS One 2012; 7:e31660Available from: http://dx.doi.org/10.1371/journal.pone.0031660

14. Fearon P, Kirkbride JB, Morgan C, Dazzan P, Morgan K, Lloyd T, Hutchinson G, Tarrant J, Lun Alan Fung W, Holloway J, Mallett R, Harrison G, Leff J, Jones PB, Murray RM: Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study [Internet]. Psychol. Med. 2006; 36:1541–1550Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16938150

15. Bourque F, van der Ven E, Malla A: A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants [Internet]. Psychol Med 2011; 41:897–910Available from:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20663257

16. Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, Susser ES: Advancing paternal age and the risk of schizophrenia [Internet]. Arch. Gen. Psychiatry 2001; 58:361–367Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11296097

17. Jones P, Rodgers B, Murray R, Marmot M: Child development risk factors for adult schizophrenia in the British 1946 birth cohort [Internet]. Lancet 1994; 344:1398–1402Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7968076

18. Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G: Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review [Internet]. Lancet 2007; 370:319–328Available from: http://www.sciencedirect.com/science/article/B6T1B-4P8SSFV-13/2/f728309b253836eacc2783edb499fec5

19. Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, Andersen PK, Melbye M: Effects of family history and place and season of birth on the risk of schizophrenia [Internet]. N. Engl. J. Med. 1999; 340:603–608Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10029644#

20. March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, Susser E: Psychosis and Place [Internet]. Epidemiol Rev 2008; 30:84–100Available from: http://epirev.oxfordjournals.org/cgi/content/abstract/mxn006v1

21. Akdeniz C, Tost H, Streit F, Haddad L, Wust S, Schafer A, Schneider M, Rietschel M, Kirsch P, Meyer-Lindenberg A: Neuroimaging evidence for a role of neural social stress processing in ethnic minority-associated environmental risk [Internet]. JAMA Psychiatry 2014; 71:672–680Available from: http://www.ncbi.nlm.nih.gov/pubmed/24740491

22. Sariaslan A, Larsson H, D'Onofrio B, Långström N, Fazel S, Lichtenstein P: Does Population Density and Neighborhood Deprivation Predict Schizophrenia? A Nationwide Swedish Family-Based Study of 2.4 Million Individuals [Internet]. Schizophr. Bull. 2015; 41:494–502Available

from: http://schizophreniabulletin.oxfordjournals.org/content/41/2/494

23. Di Forti M, Lappin JM, Murray RM: Risk factors for schizophrenia -- All roads lead to dopamine [Internet]. Eur. Neuropsychopharmacol. 2007; 17:S101–S107Available from: http://www.sciencedirect.com/science/article/B6T26-4N5F0G5-4/2/11aa0b9d40e00476c38a953b30d62e3c

24. Nordentoft M, Melau M, Iversen T, Petersen L, Jeppesen P, Thorup A, Bertelsen M, Hjorthøj CR, Hastrup LH, Jørgensen P: From research to practice: how OPUS treatment was accepted and implemented throughout Denmark [Internet]. Early Interv. Psychiatry 2015; 9:156–162Available from: http://dx.doi.org/10.1111/eip.12108

25. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ: EPPIC: an evolving system of early detection and optimal management [Internet]. Schizophr. Bull. 1996; 22:305–326Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8782288

26. Malla A, Lal S, Vracotas NC, Goldberg K, Joober R: Early intervention in psychosis: specialized intervention and early case identification [Internet]. Encephale 2010; 36 Suppl 3:S38–45Available from: http://www.ncbi.nlm.nih.gov/pubmed/21095391

27. Department of Health & NHS England: Achieving Better Access to Mental Health Services by 2020 [Internet]. London: 2014. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/361648/mental-health-access.pdf

28. Caplan B, Zimmet S V, Meyer EC, Friedman-Yakoobian M, Monteleone T, Jude Leung Y, Guyer ME, Rood LL, Keshavan MS, Seidman LJ: Prevention and recovery in early psychosis (PREP((R))): building a public-academic partnership program in Massachusetts, United States [Internet]. Asian J. Psychiatr. 2013; 6:171–177Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23466116

29. Srihari VH, Tek C, Pollard J, Zimmet S, Keat J, Cahill JD, Kucukgoncu S, Walsh BC, Li F, Gueorguieva R, Levine N, Mesholam-Gately RI, Friedman-Yakoobian M, Seidman LJ, Keshavan MS, McGlashan TH, Woods SW: Reducing the duration of untreated psychosis and its impact in the U.S.: the STEP-ED study [Internet]. BMC Psychiatry 2014; 14:335Available from: http://www.ncbi.nlm.nih.gov/pubmed/25471062

30. Kane JM, Robinson DG, Schooler NR, Mueser KT, Penn DL, Rosenheck RA, Addington J, Brunette MF, Correll CU, Estroff SE, Marcy P, Robinson J, Meyer-Kalos PS, Gottlieb JD, Glynn SM, Lynde DW, Pipes R, Kurian BT, Miller AL, Azrin ST, Goldstein AB, Severe JB, Lin H, Sint KJ, John M, Heinssen RK: Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. [Internet]. Am. J. Psychiatry 2015; appiajp201515050632[cited 2015 Oct 21] Available from: http://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.2015.15050632

31. Dixon LB, Goldman HH, Bennett ME, Wang Y, McNamara KA, Mendon SJ, Goldstein AB, Choi C-WJ, Lee RJ, Lieberman JA, Essock SM: Implementing Coordinated Specialty Care for Early Psychosis: The RAISE Connection Program. [Internet]. Psychiatr. Serv. 2015; 66:691–8[cited 2016 Mar 1] Available from: http://www.ncbi.nlm.nih.gov/pubmed/25772764

32. Department of Health: Mental health policy implementation guide [Internet]. London: National Health Service; 2001. Available from: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/dh_4009350

33. Office for National Statistics: 2011 Census: Aggregate data (England and Wales) [Internet]. 2011; Available from: http://infuse.mimas.ac.uk.

34. McGuffin P, Farmer A, Harvey I: A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system [Internet]. Arch Gen Psychiatry 1991; 48:764–770Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1883262

35. Williams J, Farmer AE, Ackenheil M, Kaufmann CA, McGuffin P: A multicentre inter-rater reliability study using the OPCRIT computerized diagnostic system [Internet]. Psychol Med 1996; 26:775–783Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8817712

36. Craddock M, Asherson P, Owen MJ, Williams J, McGuffin P, Farmer AE: Concurrent validity of the OPCRIT diagnostic system. Comparison of OPCRIT diagnoses with consensus best-estimate lifetime diagnoses [Internet]. Br J Psychiatry 1996; 169:58–63Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8818369

37. Office for National Statistics: The National Statistics Socio-economic Classification (NS-SEC rebased on the SOC2010) [Internet]. 2010; 2015Available from: http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/soc2010-volume-3-ns-sec--rebased-on-soc2010--user-manual/index.html

38. Office for National Statistics: Standard Occupational Classification 2010 (SOC2010) [Internet]. 2010; Available from: http://www.ons.gov.uk/ons/guide-method/classifications/current-standard-classifications/soc2010/index.html

39. Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP, Mallett RM, Harrison GL, Murray RM, Jones PB: Heterogeneity in Incidence Rates of Schizophrenia and Other Psychotic Syndromes: Findings From the 3-Center ÆSOP Study [Internet]. Arch. Gen. Psychiatry 2006; 63:250–258Available from: http://archpsyc.ama-assn.org/cgi/content/abstract/63/3/250

40. Kirkbride JB, Barker D, Cowden F, Stamps R, Yang M, Jones PB, Coid JW: Psychoses, ethnicity and socio-economic status [Internet]. Br. J. Psychiatry 2008; 193:18–24Available from: http://bjp.rcpsych.org/cgi/content/abstract/193/1/18

41. Ghali S, Fisher HL, Joyce J, Major B, Hobbs L, Soni S, Chisholm B, Rahaman N, Papada P, Lawrence J, Bloy S, Marlowe K, Aitchison KJ, Power P, Johnson S: Ethnic variations in pathways into early intervention services for psychosis. [Internet]. Br. J. Psychiatry 2013; 202:277–83[cited 2016 Jan 11] Available from: http://bjp.rcpsych.org/content/202/4/277.long

42. Bhui K, Stansfeld S, Hull S, Priebe S, Mole F, Feder G: Ethnic variations in pathways to and use of specialist mental health services in the UK. Systematic review [Internet]. Br J Psychiatry 2003; 182:105–116Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12562737

43. Islam Z, Rabiee F, Singh SP: Black and Minority Ethnic Groups' Perception and Experience of Early Intervention in Psychosis Services in the United Kingdom [Internet]. J. Cross. Cult. Psychol. 2015; 46:737–753[cited 2016 Jan 12] Available from: http://jcc.sagepub.com/content/46/5/737.abstract

44. Okkels N, Vernal DL, Jensen SOW, McGrath JJ, Nielsen RE: Changes in the diagnosed incidence of early onset schizophrenia over four decades [Internet]. Acta Psychiatr. Scand. 2012;

127:62–68Available from: http://dx.doi.org/10.1111/j.1600-0447.2012.01913.x

45. Tiffin PA, Kitchen CEW: Incidence and 12-month outcome of childhood non-affective psychoses: British national surveillance study. [Internet]. Br. J. Psychiatry 2015; 206:517–8[cited 2016 Feb 29] Available from: http://www.ncbi.nlm.nih.gov/pubmed/25792697

46. United States Census Bureau: Resident Population Data - 2010 Census [Internet]. 2010; [cited 2016 Mar 2] Available from: http://www.census.gov/2010census/data/apportionment-dens-text.php

47. Office for National Statistics: Coverage assessment and adjustment methods [Internet]. 2012; 1–18[cited 2015 Dec 10] Available from: http://www.ons.gov.uk/ons/guide-method/census/2011/census-data/2011-census-user-guide/quality-and-methods/coverage-assessment-and-adjustment-methods/index.html

48. Lasalvia A, Bonetto C, Tosato S, Zanatta G, Cristofalo D, Salazzari D, Lazzarotto L, Bertani M, Bissoli S, De Santi K, Cremonese C, De Rossi M, Gardellin F, Ramon L, Zucchetto M, Amaddeo F, Tansella M, Ruggeri M: First-contact incidence of psychosis in north-eastern Italy: influence of age, gender, immigration and socioeconomic deprivation. [Internet]. Br. J. Psychiatry 2014; 205:127–34[cited 2015 Nov 28] Available from: http://bjp.rcpsych.org/content/205/2/127.long

49. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H: Individual and familial risk factors for bipolar affective disorders in Denmark [Internet]. Arch. Gen. Psychiatry 2003; 60:1209–1215Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14662553

50. McGorry PD, Killackey E, Yung A: Early intervention in psychosis: concepts, evidence and future directions [Internet]. World Psychiatry 2008; 7:148–156Available from: http://www.ncbi.nlm.nih.gov/pubmed/18836582

51. Kirkbride JB, Jackson D, Perez J, Fowler D, Winton F, Coid JW, Murray RM, Jones PB: A population-level prediction tool for the incidence of first-episode psychosis: translational epidemiology based on cross-sectional data [Internet]. BMJ Open 2013; 3Available from: http://bmjopen.bmj.com/content/3/2/e001998.abstract

52. Bhavsar V, Boydell J, Murray R, Power P: Identifying aspects of neighbourhood deprivation associated with increased incidence of schizophrenia [Internet]. Schizophr Res 2014; 156:115–121Available from: http://www.ncbi.nlm.nih.gov/pubmed/24731617

53. Croudace TJ, Kayne R, Jones PB, Harrison GL: Non-linear relationship between an index of social deprivation, psychiatric admission prevalence and the incidence of psychosis [Internet]. Psychol. Med. 2000; 30:177–185Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10722188

Table 1: Socio-demographic characteristics of people with first episode psychosis and the population at-risk

Variable[1]	Cases		Person-years		Crude incidence[2]	
	N	%	N	%	Rate	(95%CI)
Total	687	(100.0)	2,021,663	(100.0)	34.0	(31.5, 36.6)
Age group						
16-17	78	(11.4)	170,125	(8.4)	45.8	(36.7, 57.2)
18-19	115	(16.7)	201,184	(10.0)	57.2	(47.6, 68.6)
20-22	161	(23.4)	311,294	(15.4)	51.7	(44.3, 60.4)
23-25	118	(17.2)	320,537	(15.9)	36.8	(30.7, 44.1)
26-28	84	(12.2)	311,749	(15.4)	26.9	(21.8, 33.4)
29-31	76	(11.1)	318,756	(15.8)	23.8	(19.0, 29.9)
32-35	55	(8.0)	388,021	(19.2)	14.2	(10.9, 18.5)
χ^2 *on 6df: 127.4; p-value*:	*p<0.01*					
Sex						
Women	228	(33.2)	989,434	(48.9)	23.0	(20.2, 26.2)
Men	459	(66.8)	1,032,229	(51.1)	44.5	(40.6, 48.7)
χ^2 *on 1df: 68.2; p-value*:	*p<0.01*					
Ethnicity						
White, British	514	(74.8)	1,623,031	(80.3)	31.7	(29.0, 34.5)
Black & minority ethnic groups	173	(25.2)	398,632	(19.7)	43.4	(37.4, 50.4)
χ^2 *on 1df: 13.0; p-value*:	*p<0.01*					
Country of birth						
UK-born	578	(84.1)	1,656,512	(81.9)	34.9	(32.2, 37.9)
Foreign-born	109	(15.9)	365,152	(18.1)	29.9	(24.7, 36.0)
χ^2 *on 1df: 2.2; p-value*:	*p=0.14*					
Employment status						
Employed	154	(22.4)	1,292,656	(63.9)	11.9	(10.2, 14.0)
Student	119	(17.3)	419,633	(20.8)	28.4	(23.7, 33.9)
Looking after home or family	29	(4.2)	104,727	(5.2)	27.7	(19.2, 39.8)
Long term sick or disabled	164	(23.9)	89,332	(4.4)	183.6	(157.5, 213.9)
Unemployed	218	(31.7)	114,309	(5.7)	190.7	(167.0, 217.8)
Retired	-	-	1,007	(0.05)	-	
Missing	3	(0.4)	-	-	-	
χ^2 *on 4df: 1600; p-value*:[3]	*p<0.01*					
Participant socioeconomic status						
Professional & managerial	71	(10.3)	493,675	(24.4)	14.4	(11.4, 18.1)
Intermediate occupation	80	(11.6)	333,806	(16.5)	24.0	(19.2, 29.8)
Routine & manual	272	(39.6)	668,782	(33.1)	40.7	(36.1, 45.8)
Long-term unemployed, students & unclassifiable	264	(38.4)	525,400	(26.0)	50.2	(44.5, 56.7)
χ^2 *on 3df: 115.3; p-value*:	*p<0.01*					
Parental socioeconomic status[4]						
Professional & managerial	204	(29.7)	-		-	
Intermediate occupation	155	(22.6)	-		-	
Routine & manual	189	(27.5)	-		-	
Long-term unemployed, students & unclassifiable	139	(20.2)	-		-	

Marital status[5]						
Single	611	(88.9)	109,677	(61.0)	-	
Married or civil partnership	61	(8.9)	54,131	(30.1)	-	
Widowed, divorced or dissolved	15	(2.2)	15,954	(8.9)	-	
χ^2 *on 2df: 224.7; p-value*:	*p<0.01*					
Early Intervention Psychosis service						
North Cambridgeshire	91	(13.2)	309,302	(15.3)	29.4	(24.0, 36.1)
South Cambridgeshire	161	(23.4)	443,730	(21.9)	36.3	(31.1, 42.3)
West Norfolk	37	(5.4)	110,989	(5.5)	33.3	(24.2, 46.0)
Central Norfolk	147	(21.4)	498,222	(24.6)	29.5	(25.1, 34.7)
Great Yarmouth & Waveney	80	(11.6)	160,825	(8.0)	49.7	(40.0, 61.9)
Suffolk	171	(24.9)	498,596	(24.7)	34.3	(29.5, 39.3)
χ^2 *on 5df: 17.3; p-value*:	*p<0.01*					
Neighborhood population density (People per square mile)[6]						
48-587 (Below median)	135	(20.5)	543,010	(26.9)	24.9	(21.0, 29.4)
588-4,653 (50-75th percentile)	181	(27.5)	549,365	(27.2)	32.9	(28.5, 38.1)
4,654-11,099 (76-95th percentile)	218	(33.1)	634,887	(31.4)	34.3	(30.1, 39.2)
11,100-21,970 (96-100th percentile)	125	(19.0)	294,533	(14.6)	42.4	(35.6, 50.6)
χ^2 *on 3df: 19.3; p-value*:	*p<0.01*					
Neighborhood multiple deprivation (% households)[6]						
7.8-18.0%	161	(24.4)	623,332	(30.8)	25.8	(22.1, 30.1)
18.1-28.0%	288	(43.7)	862,013	(42.6)	33.4	(29.8, 37.5)
28.1-38.0%	159	(24.1)	456,966	(22.6)	34.8	(29.8, 40.6)
38.1-47.1%	51	(7.7)	79,352	(3.9)	64.3	(48.8, 84.6)
χ^2 *on 3df: 34.0; p-value*:	*p<0.01*					

[1]χ^2-test reports evidence that the distribution of people with first episode psychosis differs from population-at-risk for a given variable, based on appropriate Pearson χ^2 statistics and degrees of freedom (*df*)
[2]Per 100,000 person-years at risk
[3]Test based on all categories except "retired" & "missing" where there was insufficient data
[4]Not available for denominator
[5]Population data only was only available by marital status and age (16-35 years) for the "Household Reference Person", i.e. head of household, not all individuals in population at-risk. Incidence rates not estimated
[6]N=28 cases of no fixed abode were excluded because they could not be geocoded to a neighborhood

Table 2: Multivariable Poisson regression of all clinically-relevant psychosis

Variable	Unadjusted		Adjustment 1		Adjustment 2	
	IRR	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Sex (men vs women)	1.93	(1.65, 2.26)†	1.90	(1.62, 2.22)†	1.87	(1.59, 2.20)†
Age group						
16-24	Ref		Ref		Ref	
25-29	0.57	(0.47, 0.68)†	0.66	(0.54, 0.80)†	0.65	(0.53, 0.80)†
30-35	0.33	(0.27, 0.41)†	0.41	(0.32, 0.52)†	0.42	(0.33, 0.53)†
Ethnicity						
White British	Ref		Ref		Ref	
Black & minority ethnic groups	1.37	(1.15, 1.63)†	1.47	(1.23, 1.76)†	1.35	(1.12, 1.63)†
Participant socioeconomic status						
Professional & managerial	Ref		Ref		Ref	
Intermediate occupations	1.67	(1.21, 2.29)†	1.58	(1.14, 2.17)†	1.59	(1.15, 2.19)†
Routine & manual occupations	2.83	(2.18, 3.67)†	2.28	(1.74, 2.97)†	2.09	(1.60, 2.74)†
Long-term unemployed, students & unclassifiable	3.49	(2.69, 4.54)†	2.26	(1.70, 2.99)†	2.19	(1.65, 2.92)†
Early Intervention Psychosis service						
North Cambridgeshire	Ref		Ref		Ref	
South Cambridgeshire	1.23	(0.95, 1.59)	1.24	(0.96, 1.61)	1.54	(1.12, 2.12)†
West Norfolk	1.13	(0.77, 1.66)	1.14	(0.78, 1.67)	1.21	(0.79, 1.84)
Central Norfolk	1.00	(0.77, 1.30)	1.02	(0.78, 1.33)	1.11	(0.83, 1.50)
Great Yarmouth & Waveney	1.69	(1.25, 2.28)†	1.69	(1.24, 2.29)†	1.47	(1.05, 2.08)†
Suffolk	1.17	(0.90, 1.50)	1.21	(0.94, 1.56)	1.34	(1.00, 1.80) †
Neighborhood population density (People per square mile)‡						
48-587 (Below median)	Ref		-		Ref	
588-4,653 (50-75th percentile)	1.32	(1.04, 1.67)†	-		1.25	(0.98, 1.59)
4,654-11,099 (76-95th percentile)	1.36	(1.08, 1.71)†	-		1.17	(0.91, 1.49)
11,100-21,970 (96-100th percentile)	1.71	(1.30, 2.26)†	-		1.37	(1.02, 1.84)†
Neighborhood multiple deprivation (% households)‡						
7.8-18.0%	Ref		-		Ref	
18.1-28.0%	1.27	(1.04, 1.56)†	-		1.36	(1.08, 1.72)†
28.1-38.0%	1.36	(1.07, 1.72)†	-		1.37	(1.02, 1.83)†
38.1-47.1%	2.46	(1.71, 3.54)†	-		2.11	(1.34, 3.32)†

IRR: incidence rate ratio

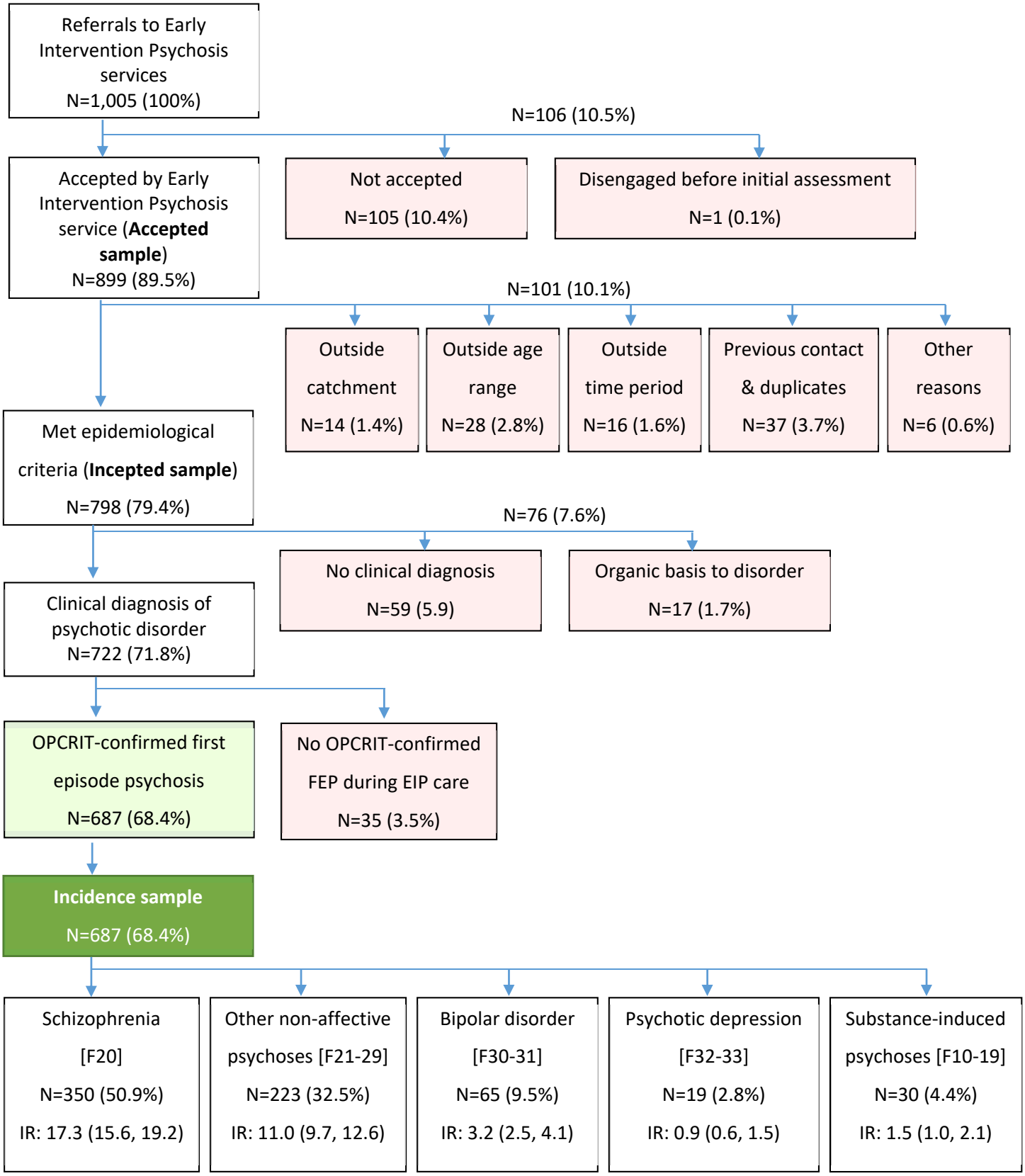
†p≤0.05

‡Analyses based on N=659 cases. Excluding N=28 cases of no fixed abode

Adjustment 1 is based on the full sample (N=687), mutually adjusted for all variables listed

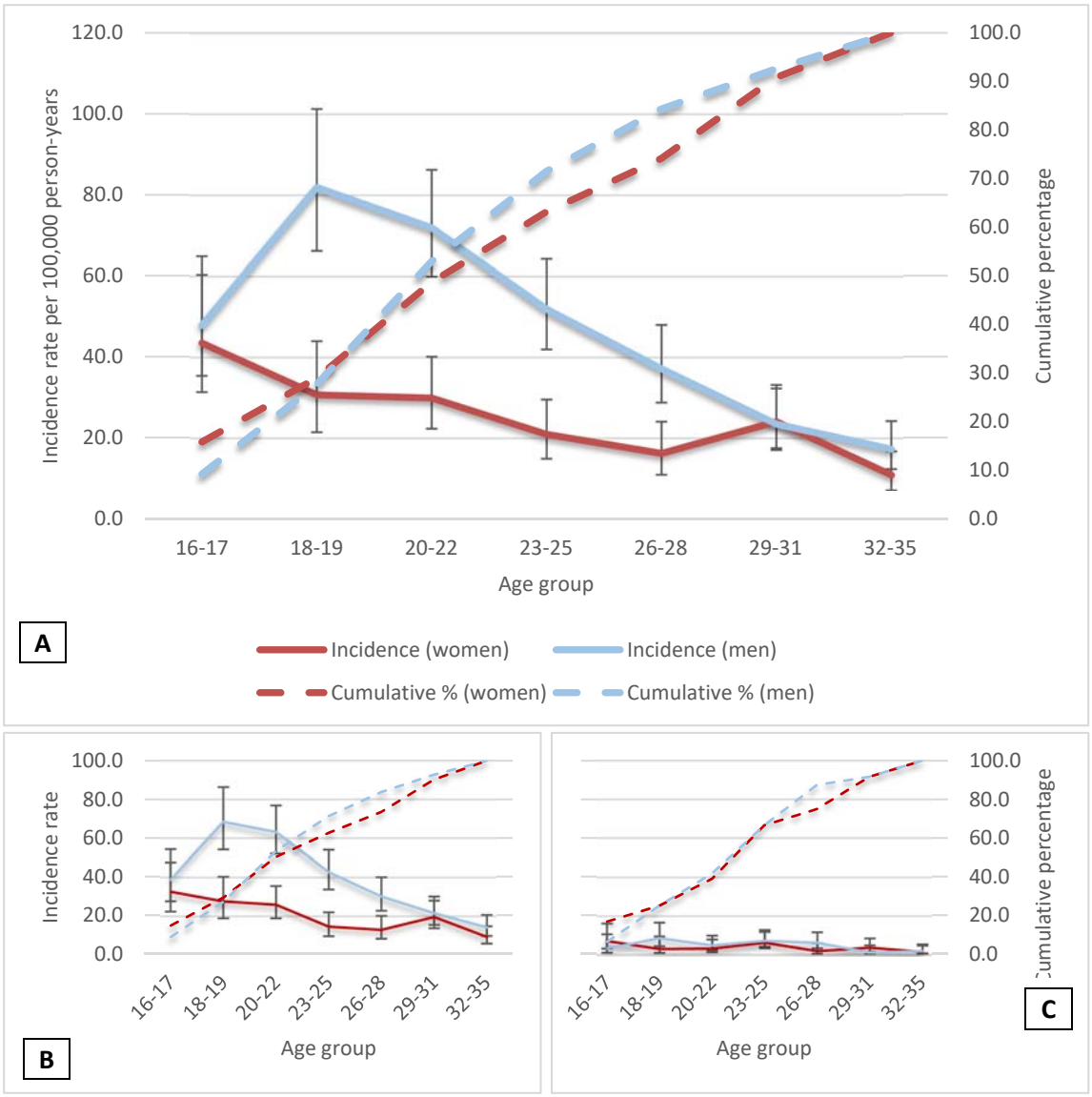
Adjustment 2 is based on the restricted sample N=659. IRR are mutually adjusted for all variables listed.

Figure 1: Flow diagram of referrals to Early Intervention in Psychosis services



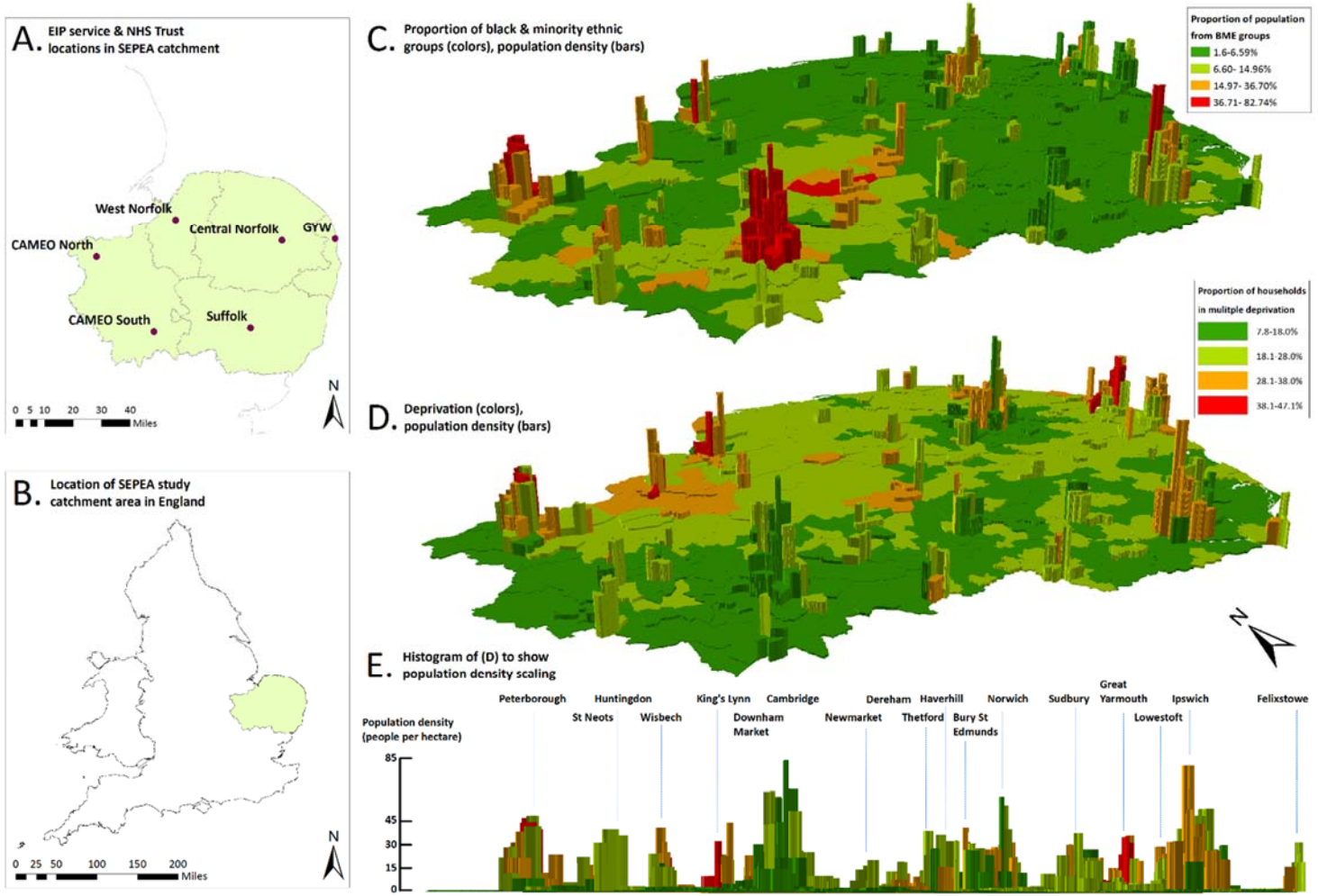
Legend: IR: Crude incidence rate per 100,000 person-years with 95% confidence intervals.

Figure 2: Age-sex specific incidence rates of selected psychotic disorders with 95% confidence intervals and cumulative percentage of cases presenting to Early Intervention Psychosis services



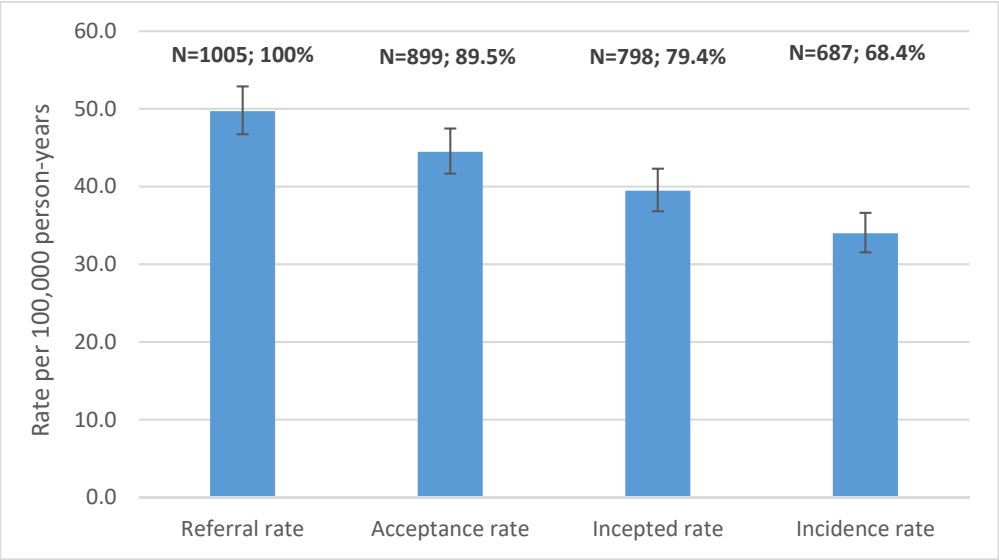
Legend: Crude incidence per 100,000 person-years and cumulative proportion of participants presenting to Early Intervention Psychosis services, by age and sex, with 95% confidence intervals (error bars) for (A) all clinically-relevant psychotic disorders, (B) non-affective psychotic disorders and (C) affective psychotic disorders. Likelihood ratio test [LRT] p-values for an age-sex interaction in Poisson regression models were (A) LRT-χ^2 on 6df=21.1: p<0.01, (B) LRT-χ^2 on 6df=15.4: p=0.02 and (C) LRT-χ^2 on 6df=9.5: p=0.15. All graphs are plotted on the same scale to show relative differences in crude incidence between disorders.

Supplemental Figure 1: Location, Early Intervention Psychosis service provision and selected catchment area characteristics



Legend: A. Location of six Early Intervention Psychosis services in the SEPEA catchment area. GYW: Great Yarmouth & Waveney. CAMEO is the Early Intervention Psychosis provider in Cambridge & Peterborough. **B.** Location in England. **C.** Proportion of black & minority ethnic groups (colors) and population density (bars) in 530 small area neighborhoods. Categorized in centiles relative to the proportion of ethnic minority groups 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 2011 Census of Great Britain. See also Supplemental Table 1.

Supplemental Figure 2: Rate of contact in Early Intervention Psychosis services by contact type



Legend
Referral rate: Number of referrals per 100,000 person-years
Acceptance rate: Number of referrals accepted by Early Intervention Psychosis 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 first episode psychosis, per 100,000 person years

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

Environmental	Description	Catchment (N=530)		Rest of England (N=7,159)		Median difference^		
variable		**Median**	**IQR**	**Median**	**IQR**	**Diff.**	**95%CI**	**p-value**
Population density	People per square mile	588	(209-4,653)	3,646	(573-8,976)	-3,583	(-4,347, -2,818)	<0.01
Ethnicity	% of population from black and minority ethnic groups	5.5	(3.5-11.1)	6.7	(4.0-15.7)	-1.2	(-1.8, -0.5)	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)	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.

^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.

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 (p<0.01). Median differences in neighborhood-level ethnic composition (-1.2%; 95%CI: -1.8, -.05; p=0.01) and multiple deprivation (-0.7%; 95%CI: -1.8, 0.3; p=0.14) between the SEPEA region and the rest of England were small, but only met statistical significance for the former. 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: Multivariable Poisson analysis of non-affective and affective psychotic disorders by major sociodemographic characteristics

Variable	Non-affective psychoses				Affective psychoses			
	N	%	IRR†	95%CI	N	%	IRR†	95%CI
Total cases	571	(100.0)	-		84	(100.0)	-	
Sex								
Women	185	(32.3)	Ref		36	(42.9)	Ref	
Men	388	(67.7)	1.97	(1.65, 2.35)‡	48	(57.1)	1.27	(0.82, 1.96)
Age group								
16-24	368	(64.2)	Ref		51	(60.7)	Ref	
25-29	118	(20.6)	0.64	(0.52, 0.81)‡	24	(28.6)	0.72	(0.43, 1.22)
30-35	87	(15.2)	0.45	(0.35, 0.58)‡	9	(10.7)	0.24	(0.11, 0.51)‡
Ethnicity								
White British	434	(75.7)	Ref		53	(64.3)	Ref	
Black & minority ethnic groups	139	(24.3)	1.41	(1.15, 1.71)‡	30	(36.7)	2.30	(1.44, 3.68)‡
Participant socioeconomic status								
Professional & managerial	58	(10.1)	Ref		12	(14.3)	Ref	
Intermediate occupation	63	(11.0)	1.53	(1.07, 2.19)‡	13	(15.5)	1.55	(0.70, 3.42)
Routine & manual	232	(40.5)	2.41	(1.80, 3.24)‡	31	(36.9)	1.47	(0.74, 2.92)
Long-term unemployed, students & unclassifiable	220	(38.4)	2.37	(1.73, 3.24)‡	28	(33.3)	1.17	(0.56, 2.44)
Early intervention psychosis service								
N. Cambridgeshire	71	(12.4)	Ref		18	(21.4)	Ref	
S. Cambridgeshire	130	(22.7)	1.29	(0.96, 1.73)	29	(34.5)	1.19	(0.65, 2.16)
West Norfolk	28	(4.9)	1.10	(0.71, 1.70)	5	(6.0)	0.85	(0.31, 2.31)
Central Norfolk	129	(22.5)	1.14	(0.85, 1.53)	13	(15.5)	0.51	(0.25, 1.04)
Great Yarmouth & Waveney	63	(11.0)	1.68	(1.19, 2.37)‡	14	(16.8)	1.73	(0.85, 3.53)
Suffolk	152	(26.5)	1.37	(1.03, 1.82)‡	5	(6.0)	0.19	(0.07, 0.51)‡

IRR: incidence rate ratio
†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^			
	N	%	IRR†	95%CI	N	%	IRR†	95%CI
Total cases	548	(100.0)	-		83	(100.0)		-
Neighborhood population density (People per square mile)								
48-587 (Below median)	110	(20.1)	Ref		19	(22.9)	Ref	
588-4,653 (50-75th percentile)	154	(28.1)	1.31	(1.01, 1.70)‡	20	(24.1)	0.77	(0.39, 1.53)
4,654-11,099 (76-95th percentile)	185	(33.8)	1.20	(0.92, 1.57)	24	(28.9)	0.99	(0.49, 2.01)
11,100-21,970 (96-100th percentile)	99	(18.1)	1.30	(0.95, 1.77)	20	(24.1)	1.59	(0.74, 3.44)
Neighborhood multiple deprivation (% households)								
7.8-18.0%	129	(23.5)	Ref		28	(33.7)	Ref	
18.1-28.0%	243	(44.3)	1.47	(1.15, 1.89)‡	33	(39.8)	0.81	(0.43, 1.51)
28.1-38.0%	132	(24.1)	1.46	(1.07, 2.00)‡	17	(20.5)	0.67	(0.28, 1.58)
38.1-47.1%	44	(8.0)	2.74	(1.71, 4.39)‡	5	(6.0)	0.44	(0.12, 1.57)
Early Intervention Psychosis service								
North Cambridgeshire	70	(12.8)	Ref		18	(21.7)	Ref	
South Cambridgeshire	121	(22.1)	1.68	(1.19, 2.38)‡	28	(33.7)	1.00	(0.48, 2.11)
West Norfolk	27	(4.9)	1.12	(0.70, 1.79)	5	(6.0)	1.00	(0.34, 2.94)
Central Norfolk	126	(23.0)	1.28	(0.93, 1.76)	13	(15.7)	0.50	(0.23, 1.09)
Great Yarmouth & Waveney	61	(11.1)	1.41	(0.97, 2.05)	14	(16.9)	2.10	(0.94, 4.71)
Suffolk	143	(26.1)	1.58	(1.15, 2.17)‡	5	(6.0)	0.18	(0.06, 0.50)‡

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