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A population-level prediction tool for the incidence of first episode psychosis: translational epidemiology based on cross-sectional data

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Access to online data: Part of the development of this manuscript includes the visualisation of prediction data in map and tabular format on a website created for this project: www.psymaptic.org. We have password-protected relevant prediction data on these pages so only editors and peer reviewers can access this data until the peer review process is complete. We invite you to access these pages by visiting www.psymaptic.org and navigating to "*prediction>for peer reviewers*" on the top menu bar. From here, you can access the data as *prediction maps*, *national summary tables* or *downloadable data*. Please enter the password **pr2012** when prompted.

Abstract

Objectives: Mental health commissioners require precise information on local populations needs; these vary enormously according to social and demographic factors. We sought to develop a realistically complex population-based prediction tool for first episode psychosis [FEP] based on recent precise estimates of epidemiological risk.

Design & participants: Data from over 1000 FEP participants from two cross-sectional epidemiological studies were fitted to several different negative binomial regression models to estimate risk coefficients across combinations of different sociodemographic and socioenvironmental factors. We applied these coefficients to the population at-risk of a third, socioeconomically different region to predict the expected caseload over a 2.5 year period, where observed rates had been concurrently ascertained.

Main outcome measures: We compared observed counts with predicted counts (with 95% prediction intervals) at regional, EIS and local authority district [LAD] levels in East Anglia to establish the predictive validity of each model.

Setting: Empirical data from London, Nottingham and Bristol predicting counts in the population at-risk in the East Anglia region of the England.

Results: A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in EIS in East Anglia (95% PI: 459, 559) compared with 528 FEP participants observed over the same period. This model predicted correctly in 5 of 6 EIS (83.3%) and 19 of 21 LAD (90.5%). All models performed better than the current gold standard for early intervention in psychosis service commissioning in England (210 cases; 95% PI: 183-239).

Conclusions: We have developed a prediction tool for the incidence of psychotic disorder in England and Wales, and made this available as a free online tool (www.psymaptic.org) to provide mental healthcare commissioners with accurate forecasts based on a robust epidemiology and anticipated local population need. Our approach could potentially be applied to several other settings and disorders.

Background

Commissioners of health and social care require precise information on the health needs of their local populations.[1] Recent policy promotes the importance of mental health care alongside physical health, recognising the intimate relationship between the two.[2] Many people with severe mental health disorders have dire physical health[2]; they suffer an average of 15-20 life-years lost, with premature deaths predominately attributable to cardiovascular disease.

Mental health disorders alone represent the leading disease burden in the UK (22.8%).[3] They contribute substantially to healthcare expenditure and societal costs even before physical ill health is taken into account. The Centre for Mental Health estimated total costs of mental health to British health services and society at £105 billion in 2009/10,[4] a figure expected to double over the next 20 years.[2] These are serious challenges compounded by a paucity of information on which to commission appropriate services. Early intervention in psychosis services [EIS] offer a useful example of failure to arm commissioners with adequate information to map services to local need. EIS are a major evidence-based innovation, systematically commissioned throughout England and Wales over the past decade.[5] When EIS intervention is sustained there is evidence that people with psychosis achieve better functional and social outcomes.[6 7] Such services are also highly cost-effective.[4 8 9] However, EIS were originally commissioned on an anticipated rate of 15 new cases of any psychotic disorder per 100,000 people per year in the Department of Health's Mental Health Policy Implementation Guide [MH-PIG],[5] a figure at least three times lower than reported thereafter.[10-12] The error came from confusing schizophrenia, a particular constellation of psychotic symptoms with chronicity built into its definition, with all psychotic disorders requiring care. This was compounded by the fact that recent evidence concerning the rich epidemiological profile of first episode psychosis [FEP][13] was not translated into commissioning guidance.

We describe the development and validation of a population-level prediction tool capable of accurately estimating expected incidence of psychiatric disorder in a given population, underpinned by well-characterised epidemiological models. Applied to FEP as proof-of-concept, we show it is possible to precisely predict expected incidence in a given population, where the observed count of cases was within the prediction intervals forecast by our models. We applied our most precise prediction model to the population of England and Wales to provide health commissioners with a translational epidemiological prediction tool to underpin information-based service planning.

Methods

Our prediction models were based on epidemiological data from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [ÆSOP] and the East London First Episode Psychoses [ELFEP] studies,[14 15] two recent, methodologically-similar FEP studies. We fitted various count-based regression models with sociodemographic and socioenvironmental factors, well-established in the literature to be associated with the incidence of psychotic disorder.[16 17] We first established the relative *internal validity* of each model by estimating internal model fit diagnostics to assess how well each model fitted the empirical data (henceforth referred to as the *prediction sample*). We next sought to estimate the *external validity* of each model by applying model-based parameter coefficients to the population structure of a deliberately different region of England, East Anglia (referred to as the *validation sample*). This out-of-sample prediction technique allowed us to obtain the expected incidence of disorder in this region forecast by each model, which we compared with observed rates simultaneously ascertained in this region via the ongoing Social Epidemiology of Psychoses in East Anglia [SEPEA] study.[12] We performed various model fit diagnostics to identify which, if any, model demonstrated utilisable predictive capability.

Empirical data underlying prediction models (*prediction sample*)

Case ascertainment (numerator)

The designs of the ÆSOP and ELFEP studies have been described in detail elsewhere,[14 15] with features relevant to the present paper summarised here. Case ascertainment took place over two years in ELFEP (Newham: 1996-8; Tower Hamlets & Hackney: 1998-2000) and the Southeast London and Nottingham centres of the ÆSOP study (1997-9), and over the first 9 months of 1997 in Bristol (ÆSOP). All service bases were screened regularly for potential new contacts aged 16-64 years (18-64 in ELFEP) resident within these catchment areas. Leakage studies were conducted to identify participants missed by this initial screen, but meeting inclusion criteria for FEP.[14 15] All participants who received an ICD-10 F10-39 diagnosis for psychotic disorder following assessment via the Schedules for Clinical Assessment in Neuropsychiatry were included in the incident sample, except those with an organic medical basis to their disorder or profound learning difficulty. Data on age-at-contact, sex and ethnicity were collected on included participants. We geocoded participants' residential postcode at first contact to their corresponding local authority district [LAD] to allow us to model possible neighbourhood effects

associated with the incidence of psychotic disorder, such as population density or socioeconomic deprivation.

Population at-risk

We estimated the population at-risk from which participants originated using the 2001 Census of Great Britain, adjusted for study duration, and stratified by age group (16-17, 18-19, then 5-year age bands), sex and ethnicity. Ethnicity was based on self-ascription according to one of ten categories derived from the census: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white & black Caribbean, other mixed ethnic backgrounds and all other ethnicities.

Socioenvironmental variable estimation

We estimated LAD -level deprivation using the 2004 Index of Multiple Deprivation [IMD] in England, which estimated domains of deprivation using measures predominantly collected close to the time of our case ascertainment periods (see Box 1).[18] We z-standardised English LAD IMD scores to have a mean of zero and standard deviation of one, and extracted IMD z-scores for the 14 LADs in the ÆSOP and ELFEP studies. To inspect whether any particular deprivation domain was a better predictor of psychosis incidence than IMD, we also considered LAD-level income deprivation, employment deprivation and the extent of deprivation in our models (). We also estimated population density, by dividing LAD usual resident population by its area (in hectares), using ArcGIS 9.3 software.

<Box 1 about here>

Observed data for external validation of prediction models (*validation sample*)

The observed numerator (participant) and denominator (population at-risk) data for our *validation sample* was obtained from the SEPEA study, an ongoing study of the incidence of psychotic disorders incepted over three years (2009-12) through one of six EIS covering 20 LAD and a subsection of one LAD (the town of Royston, Hertfordshire) in Norfolk (three EIS: West, Central and Great Yarmouth & Waveney), Suffolk (one EIS) and Cambridgeshire, Royston & Peterborough (CAMEO North and South EIS).[12]

Case ascertainment

To establish the incepted incidence of first episode psychosis as seen through EIS, entry criteria for the SEPEA study were:

- Referral to an EIS in East Anglia for suspected first episode of psychosis
- Aged 16-35 years old at first referral to EIS (17-35 years in CAMEO services)
- Resident within the catchment area at first referral
- First referral during case ascertainment period (2009-12)

At six months after referral, or discharge from the service, whichever was sooner, we asked the clinician responsible for the care of the participant to provide an ICD-10 F10-39 psychiatric diagnosis using all information available. We excluded participants without a clinical FEP diagnosis, or participants presenting with an organic basis to disorder or profound learning disability. For remaining participants, basic sociodemographic and postcode information was recorded and classified in the same way as in the *prediction sample*. We included participants presenting to EIS during the first 2.5 years of the ongoing SEPEA study.

Population at-risk

We estimated the population at-risk of East Anglia using the latest (2009) mid-year census estimates published by the Office for National Statistics [ONS] at LAD-level, by age group, sex and ethnicity.[19] These estimates used the 2001 census base, adjusted for immigration, births and deaths each year. It was not possible to obtain 2009 mid-year estimates for Royston, because data were only published at the LAD-level, not by town. Here, we thus used denominator data from the 2001 census data, published for Royston in order to estimate the population at-risk. We do not believe this would have substantially invalidated our results as this town represented 0.6% of the overall population at-risk (n=9,555) in the SEPEA study. Denominator data were multiplied by 2.5 to account for person-years of exposure in the *validation sample*.

Socioenvironmental variable estimation

For each LAD in the SEPEA study we obtained corresponding socioenvironmental variables to those included in our *prediction sample,* using updated data collected as close to the SEPEA study case ascertainment period as possible. Population density was estimated using 2009 mid-term population estimates. Our measures of deprivation were derived from the IMD 2010,[20] which was estimated in an

analogous way to 2004 data, but collected from data sources obtained immediately prior to the SEPEA study.

Statistical techniques

Dataset generation

We constructed a dataset for the regression analysis of count data by pooling numerator and denominator data from the ÆSOP & ELFEP studies (the *prediction sample*). Data were stratified by age group, sex, ethnicity and LAD, such that each stratum represented the total count of cases in a unique sociodemographic group for a given LAD, with a corresponding estimate of the population at-risk, treated as an offset in our models. Our socioenvironmental measures (population density, deprivation) were adjoined to the dataset for each LAD.

Population at-risk data from the *validation sample* were stratified in the same way and retained in a separate database. Count of cases (which we wished to predict into, given the model) were entered as missing.

Prediction models

We used the *prediction sample* data to fit negative binomial regression models to obtain parameter coefficients of incidence for the sociodemographic and socioenvironmental factors included in each model. We considered the internal and external predictive capabilities of six models, all of which contained age group, sex, an age-sex interaction term and ethnicity. Model 1 contained no further covariates. Model 2 also included IMD. We replaced IMD with either income, employment or the extent of deprivation, respectively, in models 3-5. Model 6 included population density. Initial exploration of the *prediction sample* data indicated the presence of possible over-dispersion (variance (δ^2=1.37) exceeded mean (μ=0.4) count of cases) so negative binomial regression was preferred to Poisson regression since it explicitly models any over-dispersion with an extra dispersion parameter.

Internal model cross-validation & prediction

We assessed internal model validity in three ways. First we used Akaike's Information Criterion [AIC] to assess the respective overall fit of each model to the data. Second, we conducted K-fold cross validation to assess each model's internal validity to predict cases within the *prediction sample*. This method randomly allocated strata in the *prediction sample* into *K* subsets. Each model was then re-estimated on

K-1 subsets (the *training data*) to predict expected counts of cases in the K^{th} subset (the *test data*). This was repeated over *K* trials, such that each stratum in the dataset appeared exactly once as the *test data*. At the end of this process, we derived Lin's concordance correlation coefficient [CCC] and 95% confidence intervals [95%CI] to estimate the correlation between predicted and observed counts of cases across all strata in the *prediction sample*. Finally, we estimated the root mean squared error [RMSE] to determine the average error between fitted and observed values from each model, where lower RMSE scores indicated smaller prediction error. The RMSE is derived as

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}$$

where y_i and $\hat{y}_i$ are the observed and predicted count of cases in the i^{th} stratum, respectively, and n is the number of strata.

We repeated K-fold cross-validation *h* times, generating *K* new random divisions of the data each time. We retained model fit diagnostics across *Kh* iterations, and reported the mean of Lin's CCC and RMSE to provide summary cross-validation statistics for each model. We specified *K=10* and *h=20*, as recommended for cross-validation to obtain precise model fit diagnostics.[21]

External model prediction & validation

We retained parameter coefficients from each model (using the full *prediction sample* data) and applied these to the corresponding population at-risk in the *validation sample* dataset. This gave out-of-sample prediction estimates for the expected count of cases in each stratum of the *validation sample*, given the model. We summed expected counts across relevant strata to estimate the (i) total predicted count of cases in the SEPEA region, (ii) predicted counts in each EIS, and (iii) predicted counts by LAD. These counts were further stratified by broad age group (16-35, 36-64 and 16-64 years). Because census (denominator) data was unavailable for 35 year olds alone (needed to estimate their contribution to predicted counts in the age range for EIS, 16-35 years) we assumed the risk coefficient was the same across all ages within the 35-39 year old age group. We apportioned predicted counts on a 1:4 ratio (35 years: 36-39 years) to their respective broad age groups.

To determine how well the MH-PIG[5] figure of 15 new cases per 100,000 people per year for EIS performed as a predictive tool, we also estimated the predicted count of cases in the *validation sample* under this scenario, which we termed "Model 7".

We derived prediction intervals [95% PIs] for all summary predictions from first principles for each negative binomial regression model, since their derivation is not straightforward, nor routinely implemented by statistical software. We developed a bootstrap-like approach to obtain prediction intervals from each model by simulating 1000 model-based realisations of the quantities we wished to predict, where we took the parameters to be the maximum likelihood estimates. We obtained the lower and upper bounds of the prediction intervals as the corresponding quantiles of the simulated realisations (see Appendix for full details).

To assess each model's external predictive capabilities, we derived five markers of predictive accuracy. We compared the number of times the observed count of cases in the SEPEA study fell within the prediction intervals estimated from each model for (i) the SEPEA region, (ii) at EIS level, and (iii) at LAD level. We also derived EIS- and LAD-level RMSE scores to estimate prediction error from each model in our *validation sample*. We ranked model performance (1: best, 7: worst) on these five measures, and estimated an overall mean rank to determine the overall predictive validity of each model.

Observational data on first episode psychosis in our *validation sample* were not available for the age range 36-64 years, so external validation was restricted to the 16-35 year old group. For completeness, however, we also reported overall predicted count of cases for this age group from each model.

Extrapolation to the United Kingdom

Guided by our validation procedures, we identified which model had the greatest overall predictive validity, and proposed this as a candidate for FEP incidence prediction in England and Wales. We repeated out-of-sample prediction on the sociodemographic and socioenvironmental population characteristics of each LAD in England and Wales to obtain national and LAD-level predictions. Denominator data was obtained from the ONS 2009 mid-term estimates and stratified as previously described. Overall counts were derived for three broad age groups (16-35, 36-64 and 16-64 years), and for each of these, by sex and ethnicity. 95% PIs were estimated as before. We visualised this data on maps and in tables to provide healthcare planners and commissioners with an easy-to-use tool to

forecast the expected incidence of psychosis in England and Wales. We have made this available as a free, open-use prediction tool, known as PsyMaptic (version 0.3) (Psychiatric Mapping Translating Innovations into Care; www.psymaptic.org).

Software

All negative binomial regression models, out-of-sample prediction and estimation of 95% PI were conducted in R (version 2.15.1). Internal cross-validation and model-fit diagnostics were conducted in Stata (version 11). Prediction maps for England and Wales were created using StatPlanet Plus (version 3.0) visualisation software.[22]

Results

Prediction sample

Our prediction models contained data on 1,037 persons with a first episode psychosis in the ÆSOP (n=553; 53.3%) and ELFEP (n=484; 46.7%) studies, ascertained from over 2.4m person-years at-risk. Twelve participants were excluded from the original ÆSOP sample because they were of no fixed abode and could not be geocoded to an LAD.[14]

The population at-risk in the *prediction sample* came from LAD with higher median levels of multiple and employment deprivation, extent of deprivation and population density than the population at-risk in the *validation sample*, though there were no statistically significant differences in median income deprivation between the two samples (Supplemental Table 1).

<Supplemental Table 1 about here>

Parameter coefficients obtained from the full prediction sample following negative binomial regression are shown in Table 1. As previously reported from these data,[15 23] incidence rates were generally raised in ethnic minority groups compared with the white British population. Models 2-6 included a measure of LAD deprivation (Models 2-5) or population density (Model 6), which were all associated with a significant increase in the incidence of psychotic disorder, after control for individual-level confounders. Each of these models produced a lower AIC score, indicating better fit, than a model fitted solely with individual-level covariates (Model 1). Internal cross-validation suggested all models achieved good CCC

agreement between predicted and observed cases, with low RMSE values (Table 1). Models 2-5 performed marginally better than Model 6 on these cross-validation diagnostics.

<Table 1 about here>

Validation sample

Observed participants

We identified 572 participants over the first 30 months of the SEPEA study, aged 16-35 years old, who met acceptance criteria for EIS in East Anglia. We excluded 44 participants (8.0%) who did not meet clinical criteria for ICD-10 psychotic disorder. This left an incidence sample of 528 participants from nearly 1.4m person-years at risk (37.8 per 100,000 person-years; 95%CI: 34.7, 41.2). A further 2.3m person-years at-risk accrued in the same region for people aged 36-64 years over this period. Median levels of multiple, income and employment deprivation in the region did not differ significantly from the remainder of England, although median population density and extent of deprivation in East Anglia were lower than elsewhere in England (Supplemental Table 1).

<Table 2 about here>

External model prediction & validation

The overall observed count of cases, aged 16-35 years, in the *validation sample* (n=528) fell within 95% prediction intervals in only two of seven tested models (Models 4 and 6, Table 2). Of these, the observed count was closest to the point estimate for Model 6 (508.5; 95% PI: 449.0, 559.0), fitted with age group, sex, their interaction, ethnic group and LAD population density. The observed count of cases also fell within prediction intervals from this model in five of six EIS in the study region, and 19 of 21 LADs, the most of any model (Table 3). Overall, Model 6 was ranked highest across all external model fit diagnostics (Table 3). All models outperformed the Department of Health's uniform figure of 15 cases per 100,000 people per year (Model 7), which consistently underestimated the expected count of cases observed in the *validation sample* (overall prediction: 210.5 cases; 95% PI: 183.0, 239.0).

We also reported predicted cases aged 36-64 years old from our models (Table 3), although we could not test these in our external *validation sample*. Model 6 predicted an additional 262.9 cases aged 36-64 years over a 2.5 year period in East Anglia (95% PI: 233.0, 297.0).

<Table 3 about here>

Extrapolation to England and Wales

We selected Model 6 to predict the expected count and incidence of first episode psychosis per annum in each LAD in England and Wales, and visualised this data in maps and tables freely available at www.psymaptic.org. Many maps can be visualised (for example, Supplemental Figure 1), including overall predicted incidence counts and rates for each broad age group at LAD level, by sex and ethnic group, as well as a variety of population and socioenvironmental data. According to our model, the annual number of new FEP cases in England and Wales would be 8745 (95% PI: 8558, 8933), of which our model predicted 67.9% (N=5939; 95% PI: 5785, 6102) would be seen through EIS. Only 176 (95% PI: 151, 203) cases aged 16-64 years were forecast in Wales per annum. Assuming our prediction model is accurate, it indicated that a median of 63.4% of new service users seen by EIS as predicted by our model would not have been anticipated under the current gold standard for commissioning EIS (model 7), although this varied between LAD (10^{th}-90^{th} percentile: 51.3% - 67.6%; Supplemental Figure 2).

<Supplemental Figures 2 & 3 about here>

Discussion

Principal findings

We have developed and tested several epidemiological prediction models to forecast FEP incidence in England and Wales, having taken into account regional differences in the sociodemographic and socioenvironmental profile of different populations. Inspection of our data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the greatest external predictive validity when compared with the observed caseload ascertained through EIS in our *validation sample*. This model also had good internal validity across the entire age range (16-64 years). All prediction models performed significantly better than the Department of Health's current gold standard for EIS commissioning,[5] based on a low uniform anticipated incidence rate.

Limitations & future development

We estimated prediction intervals from first principles [DJ] since there derivation is an area of statistical development.[24] We used a bootstrap-like methodology to produce 95% PI accounting for natural variation in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in

prediction models, which we assumed to be the true coefficients of risk in the population. Our approach therefore naturally led to slightly artificially narrow 95% PIs. Ideally, prediction intervals should take into account both these sources of variation, although we note that parameter uncertainty is usually small compared to the natural variation of the quantities of interest. Furthermore, ignoring this uncertainty was not necessarily undesirable for the purpose of model validation and the precise prediction of expected counts because we wished to apply stringent criterion. Here, the addition of more empirical data in the *prediction sample* would not lead to narrower PIs, though would tend to move the point estimate of risk for each coefficient closer to the true value in the population. We do not believe we have mis-estimated point estimates of risk across major sociodemographic groups, since our results accord with the wider English and International literature.[16 17 25] We sought independent confirmation that our development of 95% PI were correct (personal communication with Prof Ian White, MRC Biostatistics Unit). We recommend that all prediction point estimates from our PsyMaptic model are considered with their 95% PIs, which provide information about the natural variance in expected rates in the population.

We could not externally validate prediction models for people aged 36-64 years because comparable observed incidence data was not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models was ascertained from the same two large, well-conducted studies of first episode psychosis in England as data for the younger age group,[14 23 26] and published findings from these studies are consistent with the wider epidemiological literature for psychosis from England and internationally.[16 25 27] It will be important to ascertain the predictive capability of our model(s) in this age range, and we will seek to identify suitable samples to do so in future versions of PsyMaptic.

All prediction models had reasonable internal validity, although our proposed model performed slightly worse (most noticeably for AIC) than models which included deprivation (i.e. models 2-4) instead of population density. Our decision to use model 6 as our proposed candidate for the prediction tool was, however, supported by the fact that it produced the most accurate external forecasts of any model, despite considerable socioenvironmental differences between regions in our *prediction* and *validation* samples. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards (N~6000), or to other parts of the UK, because appropriate denominator data was not published as mid-term census estimates. The 2011 census will provide small

area and national data for the whole of the UK and will be released by ONS in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. Small area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development.

We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16-35 years old. EIS were the only mental health service for people aged 14-35 years experiencing a first episode of psychosis in East Anglia, minimising the potential for under-ascertainment in the population at-risk when derived from careful epidemiological design.[12] We are confident that our *validation sample* also contained few false positive cases for any clinically-relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS or who did not receive a clinical diagnosis of psychotic disorder during the first six months from initial referral. Future versions of PsyMaptic will include forecasts for specific psychotic disorders as standardised research-based diagnoses (using OPCRIT[28]) are currently being collected in the ongoing SEPEA study.

Meaning of the findings

If commissioners are to meet the Department of Health's vision to orientate health services around local need,[1 2 5] differences in demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data is combined with accurate population at-risk estimates this can be realised. As such, our modelling approach could have utility in many other settings and for many disorders. Our translational approach demonstrated good internal and external validity to predict the expected incidence of first episode psychosis, particularly through EIS, where 76% and 63% of all male and female adult-onset FEP cases, respectively, will typically present.[14] Since their inception in 2002, EIS in England and Wales have reported higher caseloads than they were originally envisioned to manage in the MH-PIG.[5] Empirical epidemiological data from such services supports this[10-12]; with incepted rates at least three times greater than expected based on a uniform rate of 15 per 100,000 people per year.[5] While the MH-PIG acknowledged that "…[a]n understanding of local epidemiology is needed as the size of population covered will depend on a

number of different factors" (p.55),[5] no further elaboration on how to achieve this was provided for commissioners. We believe PsyMaptic provides a possible exemplar to overcome this challenge.

Our models are not the first to be used to forecast mental illness needs in England and Wales,[29] though we believe this is the first attempt to forecast incidence rather than prevalence in the community. We recommend that our prediction methodology is used in conjunction with the wide range of public health observatory data available.[30] To this end, PsyMaptic has been included with other indicators in the Joint Commissioning Panel for Mental Health's forthcoming guidance for commissioning of public mental health services.[31]

We are not the first to express concerns over the suitability of the MH-PIG for EIS implementation.[32 33] The epidemiological literature conducted before and after its publication does not support adoption of such a low rate of first episode psychosis as a realistic basis for psychosis service planning for young people,[16 25 34-39] when incidence rates are at their highest. Our heat maps (see Supplemental Figure 2 and online) illuminate the magnitude of the discrepancy between MH-PIG forecasts and those from our prediction model in different regions of England and Wales; our data suggest the MH-PIG underestimated anticipated EIS caseload per annum by almost 50% anywhere in England and Wales. This figure exceeded 80% in some urban areas. Given the significant downstream economic savings associated with spending on EIS,[8] PsyMaptic can also be used to highlight regions where with sufficient EIS investment the greatest economic gains could be realised in terms of mental healthcare expenditure (assuming sustained intervention also leads to improved social and clinical benefit for patients[6 7]). We note that our heat maps broadly correlate with advocacy expressed for EIS by healthcare professionals in England and Wales.[40] Though by no means universal, proponents of EIS tend to be located in major conurbations – such as London,[41] Birmingham[42] or Manchester[7 43] – where demand for EIS will be highest, while those more critical of such services tend to work in more rural communities,[33 40] where but a handful of young people would be expected to come to the attention of EIS each year. Underestimating need by 50% may not produce major difficulties in a region where only two cases per year present to services, but will have great impact on service care and delivery in an EIS seeing 250 new cases per year.

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Box 1: Description of included socioenvironmental variables [1 2]	
Variable	**Classification & description**
Multiple deprivation	Weighted data from routine national sources across 7 domains: income, employment, education, health, barriers to housing & services, living environment, crime. Continuous, z-standardised scores for analysis.
Extent of deprivation	Proportion of LAD population living in 20% most deprived SOA in England (%)
Income deprivation	Proportion of all people in LAD classified as income deprived (%)
Employment deprivation	Proportion of adults of working age in LAD classified as employment deprived (%)
Population density	Population density at LAD level (people per hectare).

IMD: Index of Multiple Deprivation; LAD: Local authority district; SOA: super output area; IQR: inter-quartile range

[1]*Prediction sample* sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000)

[2]*Validation sample* sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

Table 1: Prediction models, covariates and fit: all clinically relevant psychoses (F10-39)						
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**
Variable	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**
Age group*sex interaction[1]	p=0.07	p=0.06	p=0.06	p=0.06	p=0.06	p=0.06
Ethnicity						
White British	1	1	1	1	1	1
Non-British white	2.0 (1.5, 2.5)	1.7 (1.4, 2.2)	1.7 (1.3, 2.2)	1.7 (1.3, 2.2)	1.8 (1.4, 2.3)	1.7 (1.3, 2.2)
Black Caribbean	6.0 (4.9, 7.3)	5.3 (4.3, 6.5)	5.2 (4.3, 6.4)	5.2 (4.3, 6.4)	5.4 (4.5, 6.6)	5.1 (4.2, 6.3)
Black African	4.1 (3.3, 5.1)	3.6 (2.9, 4.5)	3.5 (2.8, 4.4)	3.5 (2.8, 4.4)	3.7 (3.0, 4.6)	3.5 (2.8, 4.3)
Indian	1.7 (1.2, 2.5)	1.5 (1.1, 2.2)	1.5 (1.0, 2.2)	1.5 (1.0, 2.1)	1.6 (1.1, 2.3)	1.6 (1.1, 2.2)
Pakistani	1.8 (1.2, 2.5)	1.6 (1.0, 2.5)	1.6 (1.0, 2.4)	1.6 (1.0, 2.4)	1.6 (1.1, 2.5)	1.8 (1.3, 2.7)
Bangladeshi	2.1 (1.5, 2.8)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.2, 2.2)	1.8 (1.3, 2.5)	1.8 (1.4, 2.4)
Mixed white & black Caribbean	4.3 (2.8, 6.7)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	4.0 (2.6, 6.1)	3.9 (2.5, 6.1)
Mixed, other	1.3 (0.8, 2.3)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Other	2.2 (1.6, 3.0)	1.9 (1.4, 2.7)	1.9 (1.4, 2.6)	1.9 (1.4, 2.6)	2.0 (1.4, 2.7)	1.9 (1.4, 2.7)
Socioenvironmental variables						
IMD (z-score)	-	1.184 (1.101, 1.274)	-	-	-	-
Extent of deprivation (%)	-	-	1.008 (1.004, 1.011)	-	-	-
Income deprivation (%)	-	-	-	1.025 (1.015, 1.035)	-	-
Employment deprivation (%)	-	-	-	-	1.062 (1.032, 1.093)	-
Population density (pph)	-	-	-	-	-	1.005 (1.003, 1.007)
Internal model fit diagnostics						
AIC[2]	2571.8	2552.4	2551.3	2549.6	2556.4	2556.3
Lin's CCC (95%CI)[3]	0.75 (0.74, 0.77)	0.77 (0.75, 0.78)	0.77 (0.75, 0.79)	0.77 (0.75, 0.78)	0.77 (0.75, 0.78)	0.76 (0.74, 0.77)
RMSE (s.d.)[4]	0.75 (0.11)	0.74 (0.11)	0.74 (0.10)	0.74 (0.10)	0.74 (0.11)	0.76 (0.13)

[1]All models fitted with age group by sex interaction given *a priori* evidence for effect modification.[14 44] Likelihood ratio test p-values reported between models with and without an interaction term fitted between age group and sex. Specific IRR not been reported for clarity, but available on request

[2]AIC: Akaike's Information Criterion – lower scores denote improved model fit

[3]CCC: Lin's correlation concordance coefficient. Higher scores indicate greater correlation between observed & predicted count of cases in the *prediction sample.* Mean CCC and 95%CI reported following *h*=20 trials during cross-validation.

[4]RMSE: Root mean squared error. Lower scores indicate lower prediction error. Mean RMSE and standard deviation (s.d.) reported following *h*=20 repeats of *k*-fold cross-validation, where *k*=10.

Table 2: Observed versus predicted cases in SEPEA study for all clinically relevant psychoses, 16-35 years[1]

EIS	Observed	Model 1 Predicted (95% PI)	Model 2 Predicted (95% PI)	Model 3 Predicted (95% PI)	Model 4 Predicted (95% PI)
Overall total, 16-35 years	***528***	**641.2 (586.0, 696.1)**	**468.5 (422.0, 518.0)**	**474.7 (429.0, 522.0)**	**487.5 (441.0, 535.0)**
Cameo North	*55*	84.7 (66.0, 106.0)	68.5 (52.0, 87.0)	67.8 (51.0, 86.0)	70.2 (53.0, 90.0)
Cameo South	*137*	163.6 (135.0, 192.0)	105.5 (84.0, 129.0)	111.7 (89.0, 134.0)	110.9 (90.0, 132.0)
West Norfolk	*25*	29.2 (18.0, 41.0)	23.0 (13.0, 35.0)	22.0 (12.0, 32.0)	23.4 (14.0, 34.0)
Central Norfolk	*121*	162.6 (136.0, 191.0)	122.6 (99.0, 148.0)	123.0 (100.0, 149.0)	128.3 (104.0, 152.0)
Great Yarmouth & Waveney	*60*	49.1 (34.0, 65.0)	41.6 (28.0, 55.0)	39.9 (27.0, 53.0)	42.9 (30.0, 57.0)
Suffolk	*130*	151.9 (126.0, 178.0)	107.4 (85.0, 128.0)	110.3 (88.0, 133.0)	111.7 (90.0, 136.0)
Overall total, 36-64 years	-	332.2 (292.0, 373.0)	244.0 (213.0, 276.0)	248.6 (216.0, 280.0)	256.3 (228.0, 291.0)

EIS	Observed	Model 5 Predicted (95% PI)	Model 6 Predicted (95% PI)	Model 7 Predicted (95% PI)
Overall total, 16-35 years	***528***	**477.1 (428.0, 523.0)**	**508.5 (459.0, 559.0)**	**210.5 (183.0, 239.0)**
Cameo North	*55*	69.1 (52.0, 88.0)	64.5 (48.0, 82.0)	27.1 (17.0, 38.0)
Cameo South	*137*	100.7 (79.0, 123.0)	131.1 (108.0, 157.0)	49.7 (36.0, 64.0)
West Norfolk	*25*	24.7 (16.0, 35.0)	22.3 (13.0, 33.0)	10.5 (5.0, 17.0)
Central Norfolk	*121*	128.2 (105.0, 153.0)	132.5 (108.0, 157.0)	55.2 (41.0, 70.0)
Great Yarmouth & Waveney	*60*	47.7 (35.0, 63.0)	38.0 (26.0, 51.0)	17.4 10.0, 26.0)
Suffolk	*130*	106.6 (86.0, 128.0)	120.0 (96.0, 143.0)	50.6 (37.0, 65.0)
Overall total, 36-64 years	-	249.7 (221.0, 284.0)	262.9 (233.0, 297.0)	345.7 (310.0, 383.0)

[1]Numbers in green denote where observed count fell within 95% prediction interval [95% PI] for people aged 16-35 years. Observed data for people aged 36-64 years in the *validation sample* was not available.

Model 1: Age group, sex, their interaction and ethnicity
Model 2: Model 1 + IMD
Model 3: Model 1 + extent of deprivation
Model 4: Model 1 + income deprivation
Model 5: Model 1 + employment deprivation
Model 6: Model 1 + population density
Model 7: Department of Health uniform figure for EIS of 15 new cases per 100,000 people per year.

Table 3: External model validation diagnostics[1]

Model	Overall correct prediction? [rank]	EIS (N=6)		LAD (N=21)		Mean ranking [rank of mean ranking]
		Number correct [rank]	RMSE [rank]	Number correct [rank]	RMSE [rank]	
Model 1	No [3]	4 [2]	25.6 [6]	18 [2]	8.13 [6]	3.8 [4]
Model 2	No [3]	3 [6]	18.4 [4]	17 [5]	6.87 [4]	4.4 [6]
Model 3	No [3]	4 [2]	16.4 [3]	18 [2]	6.51 [3]	2.6 [3]
Model 4	Yes [1]	4 [2]	16.3 [2]	18 [2]	6.40 [2]	1.8 [2]
Model 5	No [3]	4 [2]	19.4 [5]	16 [6]	7.11 [5]	4.2 [5]
Model 6	Yes [1]	5 [1]	11.9 [1]	19 [1]	5.93 [1]	1.0 [1]
Model 7	No [3]	0 [7]	59.4 [7]	5 [7]	18.32 [7]	6.2 [7]

[1]For each diagnostic, models are placed in rank order [1=best model, 7=worst model] with ties given the same ranking. The mean ranking and rank provide an estimate of the overall performance of various models.

RMSE: Root mean squared error (lower scores indicate lower error); EIS: Early Intervention in Psychosis Service; LAD: Local Authority District

Article Summary

Article Focus

- Commissioners require precise information on the health needs of their local populations to effectively plan health services
- A failure to arm mental health commissioners with precise epidemiological data led to an underestimate of actual activity in early intervention in psychosis services [EIS]
- We sought to develop a prediction tool for the incidence of first episode psychosis [FEP], by applying precise estimates of epidemiological risk in various sociodemographic groups to the structure of the population at-risk in a second region, where the observed incidence had been concurrently ascertained

Key Messages

- A model of psychosis incidence which included age, sex, ethnicity and population density yielded precise FEP predictions in our second region, out-performing the Department of Health in England's current gold standard for EIS commissioning.
- We have translated this model into a freely available prediction tool (www.psymaptic.org) to facilitate evidence-based healthcare commissioning
- Our tool could be extended to many international settings and other disorders to inform healthcare commissioning, when epidemiological risk can be well-characterised and the structure of the underlying population at-risk is known

Strengths and limitations

- Our modelling approach used robust epidemiological data from two large studies of first episode psychosis in England to provide estimates of incidence in a third study region, producing accurate forecasts
- Due to data availability it was not possible to validate our prediction tool in settings outside of England and Wales, or for specific psychotic disorders. As data become available we will extend the capability of our prediction tool.

Supplemental Table 1: Socioenvironmental variables at local authority district [LAD] level considered in epidemiological prediction models

Variable		England[1]	Prediction sample[2]	Validation sample[1]	Mann-Whitney test[3]: Z; p-value	
					Prediction vs. Validation	Validation vs. England
Number of LAD	-	326	14	20 (+1 partial)	-	-
Multiple deprivation (z-standardised)	Median (IQR): Min/Max:	0 (1)[4] -1.7 / 2.9	1.0 (-0.5, 2.4) -1.1 / 2.9	-0.7 (-1.0, 0.3) -1.4 / 1.0	2.4; p=0.02	1.5; p=0.12
Extent of deprivation (%)	Median (IQR): Min/Max:	9.0 (1.3, 23.9) 0.0 / 83.6	28.0 (4.0, 63.0) 0.0 / 83.0	1.4 (.4, 12.8) 0.0 / 29.7	2.4; p=0.02	2.2; p=0.03
Income deprivation (%)	Median (IQR): Min/Max:	11.7 (8.6, 16.1) 3.9 / 32.8	15.5 (8.2, 24.7) 5.9 / 34.4	9.0 (8.2, 14.9) 6.0 / 19.1	1.5; p=0.14	1.3; p=0.19
Employment deprivation (%)	Median (IQR): Min/Max:	8.0 (5.8, 10.8) 2.1 / 18.8	11.6 (6.1, 14.1) 6.1 / 14.1	6.4 (5.4, 10.1) 3.9 / 13.9	2.5; p=0.01	1.4; p=0.17
Population density (people per hectare)	Median (IQR): Min/Max:	5.1 (1.8, 17.4) 0.2 / 137.1	19.4 (9.3, 81.9) 2.6 / 106.4	1.5 (1.2, 3.1) 0.9 / 30.0	3.7; p<0.001	3.4; p=0.001

IQR: inter-quartile range; LAD: Local Authority District

[1]Sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

[2]Sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000).

[3]Mann-Whitney test performs test that the median LAD socioenvironmental scores for the prediction & validation data come from the same population distribution; p<0.05 indicates evidence that the median scores are significantly different

[4]For England we displayed the mean and s.d. of the z-score of deprivation (as shown, underlined), instead of the median and IQR.

Appendix (supplementary): Development of 95% prediction intervals for negative binomial regression models

To obtain 95% prediction intervals from each model, we took all parameter estimates from the fitted negative binomial regression, including the over-dispersion parameter θ, as the true values when constructing prediction intervals. We then used a Monte Carlo procedure, where we simulated realisations using the Gamma-Poisson representation of the negative binomial distribution. For each iteration, we first simulated the random components of the linear predictors from Gamma(θ,θ), which were multiplied by the point predictions (or equivalently e^{υ}, where υ is the non-random component of the linear predictor) to give the Poisson rates for the counts that comprised the predictions. We then simulated Poisson counts using these rates and summed them to provide one realisation of the quantity we wished to predict. By repeating this process many (n=1000) times the distribution of the quantity to be predicted was obtained, from which 95% prediction intervals were obtained using the 2.5% and 97.5% quantiles.

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Data sharing statement

Extra data is available at our prediction website, PsyMaptic: www.psymaptic.org. We have made a large array of prediction data freely available to interested users, who can visualise prediction data in maps and tables for a range of psychotic disorder predictions by major sociodemographic subgroup and by LAD. Future versions of PsyMaptic will release data for other regions and at other geographical levels. Users can also download LAD-specific and national summaries of prediction data from our models in tabular form. Finally, additional explanatory material about how to use the data and the PsyMaptic website is also available at www.psymaptic.org. Bespoke data not provided freely on our website may be requested from the authors at the cost of data extraction. The empirical data underlying the prediction models (ÆSOP and ELFEP) or the validation sample (SEPEA) is not freely available as the studies are ongoing, but papers detailing the main findings from these studies have previously been published elsewhere.

Competing interests statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (i) JBK has support from the Wellcome Trust for the submitted work (grant number WT085540) and PBJ has support from the NIHR (grant RP-PG-0606-1335); (ii) DJ, JP, FW, DF, JC, RMM have no relationships with any company that might have an interest in the submitted work in the previous 3 years; (iii) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (iv) no author holds non-financial interests that may be relevant to the submitted work.

Role of funders

The funders were not involved in the design, collection, analysis, interpretation of the data, writing the report or the decision to submit the article for publication. All authors were independent from the funders in contributing to this work.

Ethical approval

Ethical approval to conduct the original ÆSOP and East London First Episode Psychosis studies was granted from local research ethics committees in their respective centres prior to the original date of onset of the study. We were granted ethical approval to conduct the work related to the present manuscript, including use of data from the SEPEA study, from the Cambridgeshire 3 REC (09/H0306/39).

Guarantorship

JBK takes full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

Contributorship

JBK was responsible for concept, design, analysis, data extrapolation, interpretation of the data, drafting the report and developing the content for the websites www.psymaptic.org, www.psymaptic.com and www.psymaptic.co.uk. JBK was also the chief investigator of the SEPEA study, where the *validation sample* data was obtained. He gave final approval of this version of the manuscript to be published.

DJ was responsible for developing and initially implementing the statistical approach with regard to prediction intervals from count-based regression. He also contributed to drafting and editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JP is principal collaborator on the SEPEA study in the CAMEO early intervention in psychosis services. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

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JC is chief investigator of the ELFEP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

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PBJ is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He contributed to the development of the prediction methodology and edited the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

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STROBE statement

Our STROBE statement is provided as a supplementary file.

Supplemental Figure 1: Screenshot of web-based PsyMaptic prediction tool

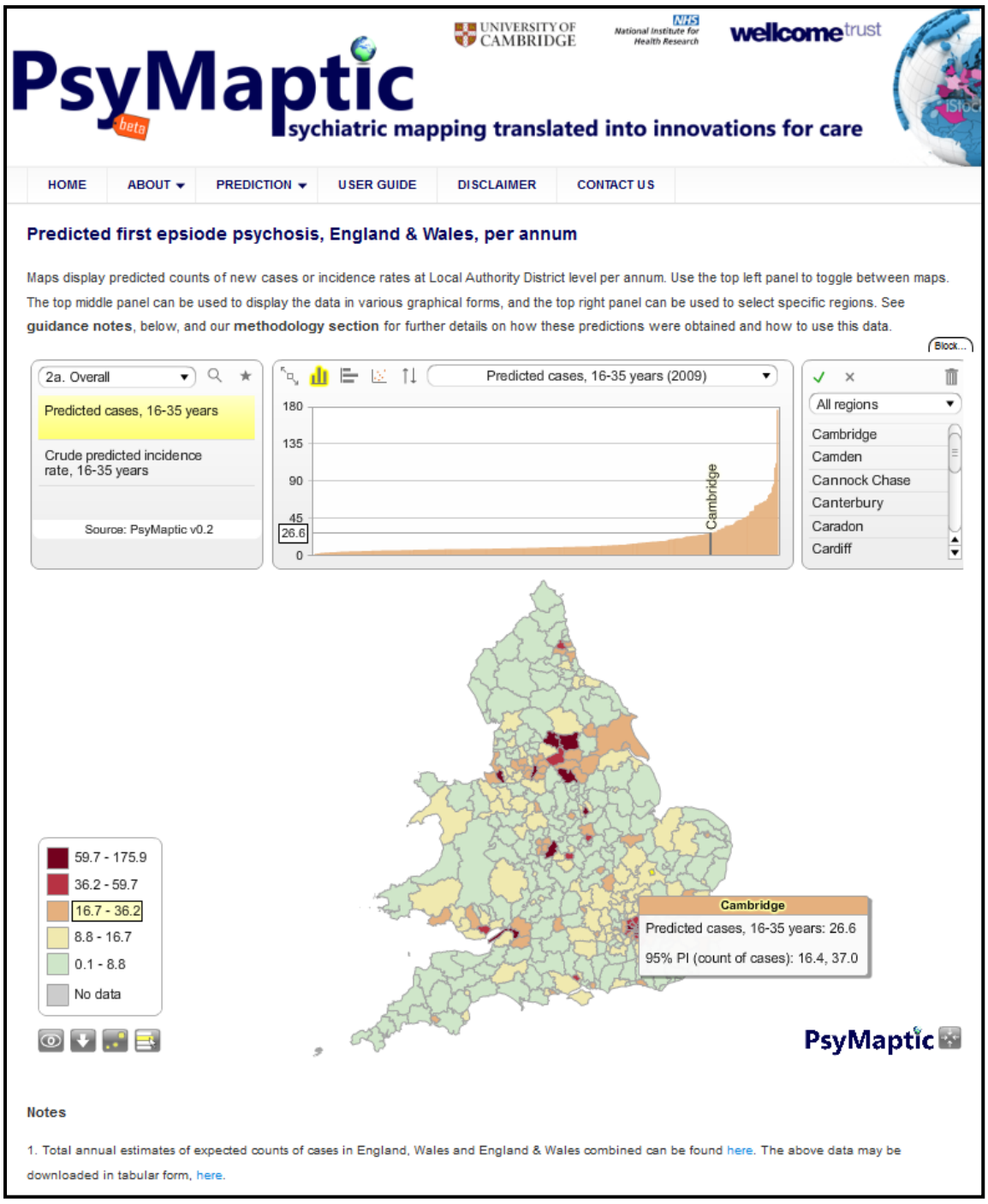

Figure legend: Screenshot shows the PsyMaptic prediction tool made freely available at www.psymaptic.org. This example shows a prediction map of the annual expected count of new cases of psychotic disorder for people aged 16-35 years across 376 Local Authority Districts [LAD] in England & Wales from our candidate prediction model (Model 6). Each prediction is presented with corresponding 95% prediction intervals. Count data are categorised into the following percentiles: green: 0-50% of LAD; yellow: 50.1-75%; orange: 75.1-90%; red: 90.1-95%; dark red: 95.1-100%. Our PsyMaptic prediction maps are provided with additional graphical utility (histograms, scatterplots, region selection) and are freely available at www.psymaptic.org

Supplemental Figure 2: Proportional difference in expected counts of incident FEP cases per year, 16-35 years, between our prediction model and the Department of Health's uniform rate upon which EIS commissioning was based in England & Wales

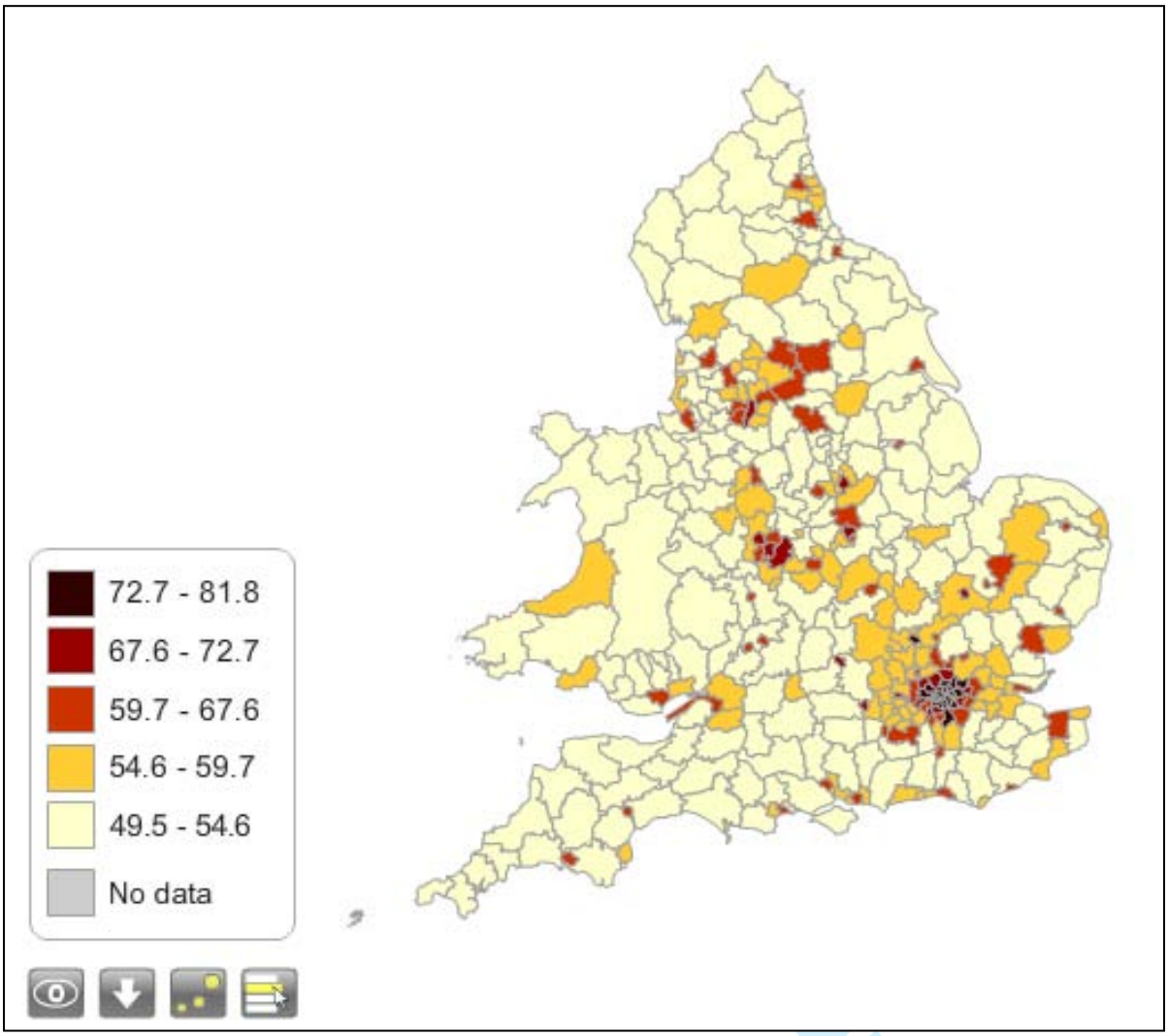

Figure legend: Annual difference in predicted counts of psychotic disorder between our proposed prediction model (Model 6) and the Department of Health's uniform rate of 15 new cases per 100,000 people per year, upon which EIS were based, expressed as a proportion. It can be interpreted as the proportion of expected cases, aged 16-35 years old, from our models which the Department of Health's uniform rate would not have predicted to have occurred in each LAD. See www.psymaptic.org for interactive maps.

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A population-level prediction tool for the incidence of first episode psychosis: translational epidemiology based on cross-sectional data

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A population-level prediction tool for the incidence of first episode psychosis: translational epidemiology based on cross-sectional data

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Word count: 5,478

Access to online data: Part of the development of this manuscript includes the visualisation of prediction data in map and tabular format on a website created for this project: www.psymaptic.org. We have password-protected relevant prediction data on these pages so only editors and peer reviewers can access this data until the peer review process is complete. We invite you to access these pages by visiting www.psymaptic.org and navigating to "*prediction>for peer reviewers*" on the top menu bar. From here, you can access the data as *prediction maps*, *national summary tables* or *downloadable data*. Please enter the password **pr2012** when prompted.

Abstract

Objectives: Specialist early intervention services [EIS] for people aged 14-35 years with first episodes of psychosis [FEP] have been commissioned throughout England since 2001. A single estimate of population need was used everywhere, but true incidence varies enormously according to sociodemographic factors. We sought to develop a realistically-complex, population-based prediction tool for FEP, based on precise estimates of epidemiological risk.

Design & participants: Data from 1037 participants in two cross-sectional population-based FEP studies were fitted to several negative binomial regression models to estimate risk coefficients across combinations of different sociodemographic and socioenvironmental factors. We applied these coefficients to the population at-risk of a third, socioeconomically different region to predict expected caseload over 2.5 years, where observed rates of ICD-10 F10-39 FEP had been concurrently ascertained via EIS.

Setting: Empirical data from London, Nottingham and Bristol predicted counts in the population at-risk in the East Anglia region of England.

Main outcome measures: Observed counts compared with predicted counts (with 95% prediction intervals) at regional, EIS and local authority district [LAD] levels in East Anglia to establish predictive validity of each model.

Results: A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in EIS in East Anglia (95%PI: 459, 559), compared with 528 observed participants . This model predicted correctly in 5/6 EIS and 19/21 LAD. All models performed better than the current gold standard for EIS commissioning in England (716 cases; 95%PI: 664-769).

Conclusions: We have developed a prediction tool for incidence of psychotic disorders in England and Wales, made freely available online (www.psymaptic.org) to provide healthcare commissioners with accurate forecasts of FEP based on robust epidemiology and anticipated local population need. Initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.

Background

Commissioners of health and social care require precise information on the health needs of their local populations[1], especially if parity of mental and physical health is to be realised.[2] Mental health disorders alone represent the leading disease burden in the UK (22.8%).[3] They contribute substantially to healthcare expenditure and societal costs even before physical ill health is taken into account. The Centre for Mental Health estimated total costs of mental health to British health services and society at £105 billion in 2009/10,[4] a figure expected to double over the next 20 years.[2] These are serious challenges compounded by a paucity of information on which to commission appropriate services. Early intervention in psychosis services [EIS] for people aged 14-35 years with a first episode of psychosis [FEP] offer a useful example of failure to map services to local need.

EIS are a major evidence-based innovation, systematically commissioned throughout England and Wales over the past decade.[5] When EIS intervention is sustained there is evidence that people with psychosis achieve better functional and social outcomes.[6-7] Such services are also highly cost-effective.[4 8-9] However, EIS were originally commissioned on an anticipated rate of 150 new cases of any psychotic disorder per 1,000,000 of the total population per year in the Department of Health's Mental Health Policy Implementation Guide [MH-PIG].[5] In 2001 in England and Wales, 29.3% of the population were aged 14-35 years old, meaning that the MH-PIG commissioned incidence rate was approximately 51 cases per 100,000 person-years in the age range covered by EIS. Following their deployment, anecdotal reports began to emerge from EIS in different regions to suggest that a uniform figure for commissioning was simultaneously under-[10] and over-estimating[11] actual observed need in urban and rural populations, respectively. Recent epidemiological evidence of FEP incidence in rural communities in England has suggested that rates are somewhat lower than the uniform figure upon which services were commissioned, [12-13] confirming previous calls that a "one-size-fits-all" prescription for EIS implementation is unlikely to lead to the efficient allocation of finite mental health resources.[14-15]

Using rich epidemiological data on variation in the incidence of first episode psychosis according to major sociodemographic risk factors,[16-19] we describe the development and validation of a population-level prediction tool capable of accurately estimating the expected incidence of psychiatric disorder, based on the sociodemographic structure of the population in a given region. Applied to FEP as proof-of-concept, we show it is possible to closely predict expected incidence in a given population, where the observed count of cases was within the prediction intervals forecast by our models. We applied our

most precise prediction model to the population of England and Wales to provide health commissioners with a translational epidemiological prediction tool to underpin information-based service planning.

Methods

Our prediction models were based on epidemiological data from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [ÆSOP] and the East London First Episode Psychoses [ELFEP] studies,[18 20] two methodologically-similar population-based FEP studies. We fitted various count-based regression models with different combinations of sociodemographic and socioenvironmental factors, well-established in the literature to be associated with the incidence of psychotic disorder.[21-22] We first established the relative *internal validity* of each model by estimating internal model fit diagnostics to assess how well each model fitted the empirical data (henceforth, the *prediction sample*). We next sought to estimate the *external validity* of each model by applying model-based parameter coefficients to the population structure of a purposefully different region of England, East Anglia (henceforth, the *validation sample*). This out-of-sample prediction technique allowed us to obtain the expected incidence of disorder in this region forecast by each model, which we compared with observed rates simultaneously ascertained in this region via the ongoing Social Epidemiology of Psychoses in East Anglia [SEPEA] study.[13] We performed various model fit diagnostics to identify which, if any, model demonstrated utilisable predictive capability.

Empirical data underlying prediction models (*prediction sample*)

Case ascertainment (numerator)

The designs of the ÆSOP and ELFEP studies have been described in detail elsewhere,[18 20] with features relevant to the present paper summarised here. Case ascertainment took place over two years in ELFEP (Newham: 1996-8; Tower Hamlets & Hackney: 1998-2000) and the Southeast London and Nottingham centres of the ÆSOP study (1997-9), and over the first 9 months of 1997 in Bristol (ÆSOP). All service bases were screened regularly for potential new contacts aged 16-64 years (18-64 in ELFEP) resident within these catchment areas. Leakage studies were conducted to identify participants missed by this initial screen, but meeting inclusion criteria for FEP.[18 20] All participants who received an ICD-10 F10-39 diagnosis for psychotic disorder following assessment via the Schedules for Clinical Assessment in Neuropsychiatry were included in the incident sample, except those with an organic medical basis to their disorder or profound learning difficulty. Data on age-at-contact, sex and ethnicity were collected on included participants. We geocoded participants' residential postcode at first contact to their

corresponding local authority district [LAD] to allow us to model possible neighbourhood effects associated with the incidence of psychotic disorder, such as population density or socioeconomic deprivation.

Population at-risk

We estimated the population at-risk using the 2001 Census of Great Britain, adjusted for study duration, and stratified by age group (16-17, 18-19, then 5-year age bands), sex and ethnicity. Ethnicity was based on self-ascription according to one of ten categories derived from the census: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white & black Caribbean, other mixed ethnic backgrounds and all other ethnicities.

Socioenvironmental variable estimation

We estimated LAD -level deprivation using the 2004 Index of Multiple Deprivation [IMD] in England, which estimated domains of deprivation using measures predominantly collected close to the time of our case ascertainment periods (see Box 1).[23] We z-standardised English LAD IMD scores to have a mean of zero and standard deviation of one, and extracted IMD z-scores for the 14 LADs in the ÆSOP and ELFEP studies. To inspect whether any particular deprivation domain was a better predictor of psychosis incidence than IMD, we also considered LAD-level income deprivation, employment deprivation and the extent of deprivation in our models (Box 1). We estimated population density by dividing LAD usual resident population by its area (in hectares), using ArcGIS 9.3 software.

<Box 1 about here>

Observed data for external validation of prediction models (*validation sample*)

Observed participants and population at-risk data for our *validation sample* was obtained from the SEPEA study, an ongoing study of the incidence of psychotic disorders incepted over three years (2009-12) through one of six EIS covering 20 LAD and a subsection of one LAD (the town of Royston, Hertfordshire) in Norfolk (three EIS: West, Central and Great Yarmouth & Waveney), Suffolk (one EIS) and Cambridgeshire, Royston & Peterborough (CAMEO North and South EIS).[13]

Case ascertainment

To establish the incepted incidence of first episode psychosis as seen through EIS, entry criteria for the SEPEA study were:

- Referral to an EIS in East Anglia for suspected first episode of psychosis
- Aged 16-35 years old at first referral to EIS (17-35 years in CAMEO services)
- Resident within the catchment area at first referral
- First referral during case ascertainment period (2009-12)

At six months after EIS acceptance, or discharge from the service, whichever was sooner, we asked the clinician responsible for care to provide an ICD-10 F10-39 psychiatric diagnosis using all information available. We excluded participants without a clinical FEP diagnosis, or participants presenting with an organic basis to their disorder or profound learning disability. For remaining participants, basic sociodemographic and postcode information was recorded and classified in the same way as in the *prediction sample*. We included participants presenting to EIS during the first 2.5 years of the ongoing SEPEA study.

Population at-risk

We estimated the population at-risk of East Anglia using 2009 mid-year census estimates published by the Office for National Statistics [ONS] at LAD-level, by age group, sex and ethnicity.[24] These estimates used the 2001 census base, adjusted for immigration, births and deaths each year. It was not possible to obtain 2009 mid-year estimates for the town of Royston, because data were only published at LAD level. Here, we thus used denominator data from the 2001 census data, in order to estimate the population at-risk in Royston. We do not believe this would have substantially invalidated our results as this town represented 0.6% of the overall population at-risk (n=9,555) in the SEPEA study. Denominator data were multiplied by 2.5 to account for person-years of exposure in the *validation sample*.

Socioenvironmental variable estimation

For each LAD in the SEPEA study we obtained corresponding socioenvironmental variables to those included in our *prediction sample,* using updated data collected as close to the SEPEA case ascertainment period as possible. Population density was estimated using 2009 mid-term population estimates. Our measures of deprivation were derived from the IMD 2010,[25] which was estimated in an analogous way to 2004 data, but collected from sources obtained immediately prior to the SEPEA study.

Statistical techniques

Dataset generation

We constructed a dataset for the regression analysis of count data by pooling data from the ÆSOP & ELFEP studies (the *prediction sample*). Data were stratified by age group, sex, ethnicity and LAD, such that each stratum represented the total count of FEP cases in a unique sociodemographic group for a given LAD, with a corresponding estimate of the population at-risk, treated as an offset in our models. Our socioenvironmental measures (population density, deprivation) were adjoined to the dataset for each LAD.

Population at-risk data from the *validation sample* were stratified in the same way and retained in a separate database. The count of cases was entered as a variable with missing values, which we could predict into, given the model coefficients and population at-risk.

Prediction models

We used the *prediction sample* data to fit negative binomial regression models to obtain parameter coefficients of incidence for the sociodemographic and socioenvironmental factors included in each model. We considered the internal and external predictive capabilities of six models, all of which contained age group, sex, an age-sex interaction term and ethnicity. Model 1 contained no further covariates. Model 2 also included IMD. We replaced IMD with either income, employment or the extent of deprivation, respectively, in models 3-5. Model 6 included population density. Initial exploration of the *prediction sample* data indicated the presence of possible over-dispersion (variance (δ^2=1.37) exceeded mean (μ=0.4) count of cases) so negative binomial regression was preferred to Poisson regression since it explicitly models any over-dispersion with an extra dispersion parameter.

Internal model cross-validation & prediction

We assessed internal model validity in three ways. First we used Akaike's Information Criterion [AIC] to assess the respective overall fit of each model to the data. Second, we conducted K-fold cross validation to assess each model's internal validity to predict cases within the *prediction sample*. This method randomly allocated strata in the *prediction sample* into *K* subsets. Each model was then re-estimated on *K-1* subsets (the *training data*) to predict expected counts of cases in the K^{th} subset (the *test data*). This was repeated over *K* trials, such that each stratum in the dataset appeared exactly once as the *test data*.

At the end of this process, we derived Lin's concordance correlation coefficient [CCC] and 95% confidence intervals [95%CI] to estimate the correlation between predicted and observed counts of cases across all strata in the *prediction sample*. Finally, we estimated the root mean squared error [RMSE] to determine the average error between fitted and observed values from each model, where lower RMSE scores indicated smaller prediction error. The RMSE is derived as

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}$$

where y_i and $\hat{y}_i$ are the observed and predicted count of cases in the i^{th} stratum, respectively, and n is the number of strata.

We repeated K-fold cross-validation *h* times, generating *K* new random divisions of the data each time. We retained model fit diagnostics across *Kh* iterations, and reported the mean of Lin's CCC and RMSE to provide summary cross-validation statistics for each model. We specified *K=10* and *h=20*, as recommended for cross-validation to obtain precise model fit diagnostics.[26]

External model prediction & validation

We retained parameter coefficients from each model (using the full *prediction sample* data) and applied these to the corresponding population at-risk in the *validation sample* dataset. This gave out-of-sample prediction estimates for the expected count of cases in each stratum of the *validation sample*, given the model. We summed expected counts across relevant strata to estimate the (i) total predicted count of cases in the SEPEA region, (ii) predicted counts in each EIS, and (iii) predicted counts by LAD. These counts were further stratified by broad age group (16-35, 36-64 and 16-64 years). Because census (denominator) data was unavailable for 35 year olds alone (needed to estimate their contribution to predicted counts in the age range for EIS, 16-35 years) we assumed the risk coefficient was the same across all ages within the 35-39 year old age group. We apportioned predicted counts on a 1:4 ratio (35 years: 36-39 years) to their respective broad age groups.

To determine how well the MH-PIG[5] figure of 51 new cases per 100,000 people per year for EIS performed as a predictive tool, we also estimated the predicted count of cases in the *validation sample* under this scenario, which we termed "Model 7".

We derived prediction intervals [95% PIs] for all summary predictions from first principles for each negative binomial regression model, since their derivation is not straightforward, nor routinely implemented by statistical software. Prediction intervals are similar to confidence intervals, but account for standard errors introduced in both the *prediction* and *validation* samples. We developed a bootstrap-like approach to obtain prediction intervals from each model by simulating 1000 model-based realisations of the quantities we wished to predict, where we took the parameters to be the maximum likelihood estimates. We obtained the lower and upper bounds of the prediction intervals as the corresponding quantiles of the simulated realisations (see Appendix for full details).

To assess each model's external predictive capabilities, we considered five markers of predictive accuracy. We compared the number of times the observed count of cases in the SEPEA study fell within the prediction intervals estimated from each model for (i) the SEPEA region, (ii) at EIS level, and (iii) at LAD level. We also derived EIS- and LAD-level RMSE scores to estimate prediction error from each model in our *validation sample*. We ranked model performance (1: best, 7: worst) on these five measures, and estimated an overall mean rank to determine the overall predictive validity of each model.

Observational data on first episode psychosis in our *validation sample* were not available for the age range 36-64 years, so external validation was restricted to the 16-35 year old group. For completeness, however, we also reported overall predicted count of cases for this age group from each model.

Extrapolation to the United Kingdom

Guided by our validation procedures, we identified which model had the greatest overall predictive validity, and proposed this as a candidate for FEP incidence prediction in England and Wales. We repeated out-of-sample prediction on the sociodemographic and socioenvironmental population characteristics of each LAD in England and Wales to obtain national and LAD-level predictions. Denominator data was obtained from the ONS 2009 mid-term estimates and stratified as previously described. Overall counts were derived for three broad age groups (16-35, 36-64 and 16-64 years), and for each of these, by sex and ethnicity. 95% PIs were estimated as before. We visualised this data on maps and in tables to provide healthcare planners and commissioners with an easy-to-use tool to forecast the expected incidence of psychosis in England and Wales. We have made this available as a free, open-use prediction tool, known as PsyMaptic (version 0.4) (Psychiatric Mapping Translating

Innovations into Care; www.psymaptic.org). Counts of cases predicted by our model were compared with those obtained under the Department of Health's uniform rate in each LAD. We expressed these comparisons as ratios with 95% CIs derived using the same method as for standardised morbidity ratios [SMR]. This approach was conservative because here we substituted the usual numerator in an SMR, the observed, O, for a predicted count. Unlike an observed count, no sampling variation is present for the predicted count, only uncertainty due to the model from which the prediction was estimated. Since variance in the prediction is therefore much smaller than the variance normally present for the numerator (O) this led to conservative estimates of 95% CI. Ratios in LAD where 95% CI did not span unity could therefore be interpreted as regions where there was strong evidence that the predictions from our model differed significantly from those predicted by the Department of Health's uniform rate.

Software

All negative binomial regression models, out-of-sample prediction and estimation of 95% PI were conducted in R (version 2.15.1). Internal cross-validation and model-fit diagnostics were conducted in Stata (version 11). Prediction maps for England and Wales were created using StatPlanet Plus (version 3.0) visualisation software.[27]

Results

Prediction sample

Our prediction models contained data on 1,037 persons with a first episode psychosis in the ÆSOP (n=553; 53.3%) and ELFEP (n=484; 46.7%) studies, ascertained from over 2.4m person-years at-risk. Twelve participants were excluded from the original ÆSOP sample because they were of no fixed abode and could not be geocoded to an LAD.[18]

The population at-risk in the *prediction sample* came from LAD with higher median levels of multiple and employment deprivation, extent of deprivation and population density than the population at-risk in the *validation sample*, though there were no statistically significant differences in median income deprivation between the two samples (Supplemental Table 1).

<Supplemental Table 1 about here>

Parameter coefficients obtained from the full prediction sample following negative binomial regression are shown in Table 1. As previously reported from these data,[20 28] incidence rates were generally raised in ethnic minority groups compared with the white British population. Models 2-6 included a measure of LAD deprivation (Models 2-5) or population density (Model 6), which were all significantly associated with increased incidence of psychotic disorder, after control for individual-level confounders. Each of these models produced a lower AIC score than a model fitted solely with individual-level covariates (Model 1), indicating better internal fit. Internal cross-validation suggested all models achieved good CCC agreement between predicted and observed cases, with low RMSE values (Table 1).

<Table 1 about here>

Validation sample

Observed participants

We identified 572 participants over the first 30 months of the SEPEA study, aged 16-35 years old, who met acceptance criteria for EIS in East Anglia. We excluded 44 participants (8.0%) who did not meet clinical criteria for ICD-10 psychotic disorder. This left an incidence sample of 528 participants from nearly 1.4m person-years at risk (37.8 per 100,000 person-years; 95%CI: 34.7, 41.2). A further 2.3m person-years at-risk accrued in the same region for people aged 36-64 years over this period. Median levels of multiple, income and employment deprivation in the region did not differ significantly from the remainder of England, although median population density and extent of deprivation in East Anglia were lower than elsewhere in England (Supplemental Table 1).

<Table 2 about here>

External model prediction & validation

The overall observed count of cases, aged 16-35 years, in the *validation sample* (n=528) fell within 95% prediction intervals in only two of seven tested models (Models 4 and 6, Table 2). Of these, the observed count was closest to the point estimate for Model 6 (508.5; 95% PI: 449.0, 559.0), fitted with age group, sex, their interaction, ethnic group and LAD population density. The observed count of cases also fell within prediction intervals from this model in five of six EIS in the study region, and 19 of 21 LADs, the most of any model (Table 3). This model had the lowest error scores at EIS (RMSE=11.9) and LAD (RMSE=5.9) levels of any model. Overall, Model 6 was ranked highest across all external model fit

diagnostics (Table 3). All models outperformed the Department of Health's uniform figure of 51 cases per 100,000 people per year (Model 7), which generally overestimated cases in the *validation sample* (overall prediction: 715.7 cases; 95% PI: 664.0, 769.0).

We also reported predicted cases aged 36-64 years old from our models (Table 3), although we could not test these in the *validation sample*. Model 6 predicted an additional 262.9 cases aged 36-64 years over a 2.5 year period in East Anglia (95% PI: 233.0, 297.0).

<Table 3 about here>

Extrapolation to England and Wales

We predicted the expected count and incidence of first episode psychosis per annum in each LAD in England and Wales based on Model 6, and visualised this data in maps and tables freely available at www.psymaptic.org. Many maps can be visualised (for example, Supplemental Figure 1), including overall predicted incidence counts and rates for each broad age group at LAD level, by sex and ethnic group, as well as a variety of population and socioenvironmental data. According to our model, the annual number of new FEP cases in England and Wales would be 8745 (95% PI: 8558, 8933), of which our model predicted 67.9% (N=5939; 95% PI: 5785, 6102) would be seen through EIS. Only 176 (95% PI: 151, 203) cases aged 16-64 years were forecast in Wales per annum. Assuming our prediction model is accurate, it indicated that the Department of Health's current uniform rate of 51 per 100,000 person-years was higher than the predicted point estimates for rates forecast by our PsyMaptic model in 351 LAD (93%) in England and Wales, but was lower than predicted by our model in Birmingham and several London boroughs (Supplemental Figure 2, left hand map). Under a conservative approach, these differences achieved statistical significance in parts of London (where the Department of Health's model underestimated need as predicted by PsyMaptic), and in some more rural parts of England and Wales (where the Department of Health's model over-estimated need) (Supplemental Figure 2, right hand map).

<Supplemental Figures 1 & 2 about here>

Discussion

Principal findings

We have developed and tested several epidemiological prediction models to forecast FEP incidence in England and Wales, having taken into account regional differences in the sociodemographic and socioenvironmental profile of different populations. Inspection of our data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the greatest external predictive validity when compared with the observed FEP caseload ascertained through EIS in our *validation sample*. This model also had good internal validity across the entire age range (16-64 years). All models performed significantly better in predicting the incidence of clinically relevant first episode psychosis than the Department of Health's current gold standard for EIS commissioning,[5] based on a uniform incidence rate. Our data suggested the figure used to commission EIS over-estimated the likely true incidence rates of FEP in rural areas and under-estimated them in urban settings, although we acknowledge that commissioning decisions will need to be based on several additional factors, including the level of pre-clinical or non-psychotic psychopathology requiring assessment at initial referral to EIS, and variation in service organisation, remit and delivery.

Limitations & future development

Our prediction models were based on epidemiological data obtained from large, robust population-based FEP studies for people aged 16-64 years.[18-19] Our best-fitting model had good internal validity over this age range, and good external validity over the age range 16-35 years. While this covered the majority of adult onset psychosis cases seen in mental health services, including EIS, we recognise that some EIS teams incept people from 14 years old. We were unable to extrapolate our models to this age range, given the current absence of incidence data for this group in England. Data from Scandinavia suggest that the incidence of such "early onset" psychoses is absolutely low,[29] although the rate may have been increasing in the last few decades, probably as a result of movement towards earlier detection. We were also unable to externally validate prediction models for people aged 36-64 years, because comparable observed incidence data was not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models was ascertained from the same two large, well-conducted studies as for data on the younger age group.[18-19 28] Furthermore, published findings from these studies are consistent with the wider epidemiological literature for psychosis in England and internationally.[17 21 30] It will be important to validate the predictive capability of our model(s) in this age range, and we will seek to identify suitable samples to do so in future versions of PsyMaptic.

All prediction models had reasonable internal validity, although our proposed model performed slightly worse (most noticeably for AIC) than models which included deprivation (i.e. models 2-4) instead of population density. Our decision to use model 6 as our proposed candidate for the prediction tool was supported by the fact that it produced the most accurate external forecasts of any model, despite considerable socioenvironmental differences between regions in our *prediction* and *validation* samples. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards (N~6000), or to other parts of the UK, because appropriate denominator data was not published as mid-term census estimates. The 2011 census will provide small area and national data for the whole of the UK, scheduled for release by ONS in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. We will then be able to develop models to explore cross-level interactions, such as the association between individual ethnicity and neighbourhood-level ethnic density. Small area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development.

We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16-35 years old. EIS were the only mental health service for people aged 14-35 years experiencing a first episode of psychosis in East Anglia, minimising the potential for under-ascertainment in the population at-risk when derived from careful epidemiological design.[13] We are confident that our *validation sample* also contained few false positive cases for any clinically-relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS or who did not receive a clinical diagnosis of psychotic disorder during the first six months from initial referral. It is important to recognise that while our prediction models are based on diagnosed clinically relevant psychotic disorders, service commissioning will also need to account for additional pre-clinical or non-psychotic psychiatric morbidity presenting to EIS, particularly in services which operate early detection models or implement "watch-and-wait" briefs. The SEPEA data used to validate our models do not predict (1) the number of "false positive" subjects who may require psychiatric triage and assessment even though they are not accepted by EIS, or (2) the number of "true positive" subjects accepted by services, but who did not meet epidemiological criteria for inclusion in the *validation sample* of the SEPEA study (those living outside the catchment area at first contact, or those transferred

from other services); these people will consume varying degrees of service resources which needs to be considered in service planning.

We also note that pathways to care may affect the level of incidence observed in EIS, since many filters are likely to operate before subjects come to the attention of EIS. These will include local level service organisation and the relationship between Community Mental Health Teams [CMHTs], Child and Adolescent Mental Health [CAMHs] and EIS. Furthermore, acceptance criteria for entry to EIS vary, which will have a downstream effect on the number of new cases of clinically relevant psychoses received in each team. Future versions of PsyMaptic will include forecasts for specific psychotic disorders, as standardised research-based diagnoses (using OPCRIT[31]) are currently being collected in the ongoing SEPEA study in order to provide more detailed forecasts. Acceptance rates to EIS may also be influenced by local community awareness of such services. While our prediction models outperformed the current gold standard for EIS commissioning in England when restricted to clinically relevant caseloads, we recommend that our models are best interpreted as forecasts of the expected burden of first episode psychosis in given populations, and not the expected burden which will necessarily be seen through EIS given these issues.

We estimated prediction intervals from first principles [DJ] since there derivation is an area of statistical development.[32] We used a bootstrap-like methodology to produce 95% PI accounting for natural variation in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in prediction models, which we assumed to be the true coefficients of risk in the population. Our approach therefore naturally led to slightly artificially narrow 95% PIs. This was not necessarily undesirable for the purpose of model validation and the precise prediction of expected counts because we wished to apply stringent criteria. Ideally, prediction intervals should take into account both these sources of variation, although we note that parameter uncertainty is usually small compared to the natural variation of the quantities of interest. The addition of more empirical data in the *prediction sample* would not lead to narrower PIs, though would tend to move the point estimate of risk for each coefficient closer to the true value in the population. We do not believe we have mis-estimated point estimates of risk across major sociodemographic groups, since our results accord with the wider literature.[17 21-22] We sought independent confirmation that our development of 95% PI were correct (personal communication with Prof Ian White, MRC Biostatistics Unit). We recommend that all prediction point estimates from our

PsyMaptic model are considered with their 95% PIs, which provide information about the natural variance in expected rates in the population.

Meaning of the findings

If commissioners are to meet the Department of Health's vision to orientate health services around local need,[1-2 5] differences in demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data is combined with accurate population at-risk estimates this can be realised. As such, our modelling approach could have utility in many other settings and for many disorders. Our translational approach demonstrated good internal and external validity to predict the expected incidence of first episode psychosis, particularly through EIS, where 76% and 63% of all male and female adult-onset FEP cases, respectively, will typically present.[18] Since their inception in 2002, EIS in England and Wales have reported both lower[11] and higher[10] caseloads than they were originally envisioned to manage,[5] with shortfalls or excesses in anticipated demand for services aligned to the degree of urbanisation in the underlying catchment area. Others have noted that EIS provision in rural areas may be difficult to implement effectively,[14-15] and while the MH-PIG acknowledged that "…[a]n understanding of local epidemiology is needed as the size of population covered will depend on a number of different factors" (p.55),[5] no further elaboration on how to achieve this was provided. We believe PsyMaptic provides a possible tool to overcome this challenge, improving the description and prediction of local population need beyond the MH-PIG and including individual- and neighbourhood-level indicators of local need.[17] From an aetiological perspective, we acknowledge that variables such as ethnicity or population density are likely to be markers for a suite of more complex, interactive social, genetic and environmental determinants of psychosis.[33]

Our models are not the first to be used to forecast mental illness needs in England and Wales,[34] though we believe this is the first attempt to forecast incidence rather than prevalence in the community. We recommend that our prediction methodology is used in conjunction with the wide range of public health observatory data available,[35] as well as the caveats presented above. PsyMaptic has been included with other indicators in the Joint Commissioning Panel for Mental Health's forthcoming guidance for commissioning of public mental health services.[36] Ongoing monitoring and audit of EIS will be vital to ensure services meet the fidelity criteria upon which they were originally commissioned,[11 37] including

ensuring that service capacity matches local need as closely as possible. As part of this process, we will need to externally validate our models in a wider range of settings, refining them based on empirical observation.

We note that advocacy expressed for EIS by healthcare professionals in England and Wales broadly correlates with demand for services as predicted by PsyMaptic.[38] Though by no means universal, proponents of EIS tend to be located in major conurbations – such as London,[39] Birmingham[40] or Manchester[7 41] – where demand for EIS will be highest, while those who suggest EIS resources could be used more effectively elsewhere tend to work in more rural communities,[15 38] where but a handful of young people would be expected to come to the attention of EIS each year. It is possible that both sides are correct and that more resources are required to help with the tide of psychotic illness in inner cities. Resources might be used more effectively in other ways, elsewhere, so long as the needs of the small number of young people who suffer a FEP each year are met; a dedicated specialist EIS may not be the most effective approach when anticipated demand will be very low.

Given the significant downstream economic savings associated with spending on EIS as estimated in an urban setting,[8] PsyMaptic could be used to highlight regions where sufficient investment to appropriate mental health services would lead to greatest economic gains in terms of mental healthcare expenditure (assuming sustained intervention also leads to improved social and clinical benefit for patients[6-7]). PsyMaptic can also be used to highlight regional variation in demand according to age, sex and ethnic group, allowing service planners to tailor provision around the socio-cultural characteristics of their local populations. Our prediction tool for first episode psychosis, which translates robust empirical epidemiological data on psychosis risk to the population structure of different regions, offers a methodology for improving the allocation of finite mental health resources based around local need.

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Box 1: Description of included socioenvironmental variables [1 2]	
Variable	**Classification & description**
Multiple deprivation	Weighted data from routine national sources across 7 domains: income, employment, education, health, barriers to housing & services, living environment, crime. Continuous, z-standardised scores for analysis.
Extent of deprivation	Proportion of LAD population living in 20% most deprived SOA in England (%)
Income deprivation	Proportion of all people in LAD classified as income deprived (%)
Employment deprivation	Proportion of adults of working age in LAD classified as employment deprived (%)
Population density	Population density at LAD level (people per hectare).

IMD: Index of Multiple Deprivation; LAD: Local authority district; SOA: super output area; IQR: inter-quartile range

[1]*Prediction sample* sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000)

[2]*Validation sample* sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

Table 1: Prediction models, covariates and fit: all clinically relevant psychoses (F10-39)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Variable	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**
Age group*sex interaction[1]	p=0.07	p=0.06	p=0.06	p=0.06	p=0.06	p=0.06
Ethnicity						
White British	1	1	1	1	1	1
Non-British white	2.0 (1.5, 2.5)	1.7 (1.4, 2.2)	1.7 (1.3, 2.2)	1.7 (1.3, 2.2)	1.8 (1.4, 2.3)	1.7 (1.3, 2.2)
Black Caribbean	6.0 (4.9, 7.3)	5.3 (4.3, 6.5)	5.2 (4.3, 6.4)	5.2 (4.3, 6.4)	5.4 (4.5, 6.6)	5.1 (4.2, 6.3)
Black African	4.1 (3.3, 5.1)	3.6 (2.9, 4.5)	3.5 (2.8, 4.4)	3.5 (2.8, 4.4)	3.7 (3.0, 4.6)	3.5 (2.8, 4.3)
Indian	1.7 (1.2, 2.5)	1.5 (1.1, 2.2)	1.5 (1.0, 2.2)	1.5 (1.0, 2.1)	1.6 (1.1, 2.3)	1.6 (1.1, 2.2)
Pakistani	1.8 (1.2, 2.5)	1.6 (1.0, 2.5)	1.6 (1.0, 2.4)	1.6 (1.0, 2.4)	1.6 (1.1, 2.5)	1.8 (1.3, 2.7)
Bangladeshi	2.1 (1.5, 2.8)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.2, 2.2)	1.8 (1.3, 2.5)	1.8 (1.4, 2.4)
Mixed white & black Caribbean	4.3 (2.8, 6.7)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	4.0 (2.6, 6.1)	3.9 (2.5, 6.1)
Mixed, other	1.3 (0.8, 2.3)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Other	2.2 (1.6, 3.0)	1.9 (1.4, 2.7)	1.9 (1.4, 2.6)	1.9 (1.4, 2.6)	2.0 (1.4, 2.7)	1.9 (1.4, 2.7)
Socioenvironmental variables						
IMD (z-score)	-	1.184 (1.101, 1.274)	-	-	-	-
Extent of deprivation (%)	-	-	1.008 (1.004, 1.011)	-	-	-
Income deprivation (%)	-	-	-	1.025 (1.015, 1.035)	-	-
Employment deprivation (%)	-	-	-	-	1.062 (1.032, 1.093)	-
Population density (pph)	-	-	-	-	-	1.005 (1.003, 1.007)
Internal model fit diagnostics						
AIC[2]	2571.8	2552.4	2551.3	2549.6	2556.4	2556.3
Mean Lin's CCC (95%CI)[3]	0.75 (0.74, 0.77)	0.77 (0.75, 0.78)	0.77 (0.75, 0.79)	0.77 (0.75, 0.78)	0.77 (0.75, 0.78)	0.76 (0.74, 0.77)
Mean RMSE (s.d.)[4]	0.75 (0.11)	0.74 (0.11)	0.74 (0.10)	0.74 (0.10)	0.74 (0.11)	0.76 (0.13)

[1]All models fitted with age group by sex interaction given *a priori* evidence for effect modification.[18 42] Likelihood ratio test p-values reported between models with and without an interaction term fitted between age group and sex. Specific IRR not been reported for clarity, but available on request

[2]AIC: Akaike's Information Criterion – lower scores denote improved model fit

[3]CCC: Lin's correlation concordance coefficient. Higher scores indicate greater correlation between observed & predicted count of cases in the *prediction sample.* Mean CCC and 95%CI reported following *h*=20 trials during cross-validation.

[4]RMSE: Root mean squared error. Lower scores indicate lower prediction error. Mean RMSE and standard deviation (s.d.) reported following *h*=20 repeats of *k*-fold cross-validation, where *k*=10.

Table 2: Observed versus predicted cases in SEPEA study for all clinically relevant psychoses, 16-35 years[1]

EIS	Observed	Model 1 Predicted (95% PI)	Model 2 Predicted (95% PI)	Model 3 Predicted (95% PI)	Model 4 Predicted (95% PI)
Overall total, 16-35 years	***528***	**641.2 (586.0, 696.1)**	**468.5 (422.0, 518.0)**	**474.7 (429.0, 522.0)**	**487.5 (441.0, 535.0)**
Cameo North	*55*	84.7 (66.0, 106.0)	68.5 (52.0, 87.0)	67.8 (51.0, 86.0)	70.2 (53.0, 90.0)
Cameo South	*137*	163.6 (135.0, 192.0)	105.5 (84.0, 129.0)	111.7 (89.0, 134.0)	110.9 (90.0, 132.0)
West Norfolk	*25*	29.2 (18.0, 41.0)	23.0 (13.0, 35.0)	22.0 (12.0, 32.0)	23.4 (14.0, 34.0)
Central Norfolk	*121*	162.6 (136.0, 191.0)	122.6 (99.0, 148.0)	123.0 (100.0, 149.0)	128.3 (104.0, 152.0)
Great Yarmouth & Waveney	*60*	49.1 (34.0, 65.0)	41.6 (28.0, 55.0)	39.9 (27.0, 53.0)	42.9 (30.0, 57.0)
Suffolk	*130*	151.9 (126.0, 178.0)	107.4 (85.0, 128.0)	110.3 (88.0, 133.0)	111.7 (90.0, 136.0)
Overall total, 36-64 years	-	332.2 (292.0, 373.0)	244.0 (213.0, 276.0)	248.6 (216.0, 280.0)	256.3 (228.0, 291.0)

EIS	Observed	Model 5 Predicted (95% PI)	Model 6 Predicted (95% PI)	Model 7 Predicted (95% PI)
Overall total, 16-35 years	***528***	**477.1 (428.0, 523.0)**	**508.5 (459.0, 559.0)**	**715.6 (664.0, 769.0)**
Cameo North	*55*	69.1 (52.0, 88.0)	64.5 (48.0, 82.0)	92.1 (74.0, 111.0)
Cameo South	*137*	100.7 (79.0, 123.0)	131.1 (108.0, 157.0)	169.0 (144.0, 195.0)
West Norfolk	*25*	24.7 (16.0, 35.0)	22.3 (13.0, 33.0)	35.8 (25.0, 48.0)
Central Norfolk	*121*	128.2 (105.0, 153.0)	132.5 (108.0, 157.0)	187.7 (161.0, 215.0)
Great Yarmouth & Waveney	*60*	47.7 (35.0, 63.0)	38.0 (26.0, 51.0)	59.1 (44.0, 74.0)
Suffolk	*130*	106.6 (86.0, 128.0)	120.0 (96.0, 143.0)	172.1 (147.0, 198.0)
Overall total, 36-64 years	-	249.7 (221.0, 284.0)	262.9 (233.0, 297.0)	1175.4 (1109.0, 1243.0)

[1]Numbers in green denote where observed count fell within 95% prediction interval [95% PI] for people aged 16-35 years. Observed data for people aged 36-64 years in the *validation sample* was not available.

Model 1: Age group, sex, their interaction and ethnicity
Model 2: Model 1 + IMD
Model 3: Model 1 + extent of deprivation
Model 4: Model 1 + income deprivation
Model 5: Model 1 + employment deprivation
Model 6: Model 1 + population density
Model 7: Department of Health uniform figure for EIS of 15 new cases per 100,000 people per year.

Table 3: External model validation diagnostics[1]

Model	Overall correct prediction? [rank]	EIS (N=6)		LAD (N=21)		Mean ranking [rank of mean ranking]
		Number correct [rank]	RMSE [rank]	Number correct [rank]	RMSE [rank]	
Model 1	No [3]	4 [2]	25.6 [6]	18 [2]	8.1 [6]	3.8 [4]
Model 2	No [3]	3 [6]	18.4 [4]	17 [5]	6.9 [4]	4.4 [6]
Model 3	No [3]	4 [2]	16.4 [3]	18 [2]	6.5 [3]	2.6 [3]
Model 4	Yes [1]	4 [2]	16.3 [2]	18 [2]	6.4 [2]	1.8 [2]
Model 5	No [3]	4 [2]	19.4 [5]	16 [6]	7.1 [5]	4.2 [5]
Model 6	Yes [1]	5 [1]	11.9 [1]	19 [1]	5.9 [1]	1.0 [1]
Model 7	No [3]	1 [7]	38.1 [7]	13 [7]	11.0 [7]	6.2 [7]

[1]For each diagnostic, models are placed in rank order [1=best model, 7=worst model] with ties given the same ranking. The mean ranking and rank provide an estimate of the overall performance of various models.

RMSE: Root mean squared error (lower scores indicate lower error); EIS: Early Intervention in Psychosis Service; LAD: Local Authority District

Article Summary

Article Focus

- Commissioners require precise information on the health needs of their local populations to effectively plan health services
- A failure to arm mental health commissioners with precise epidemiological data led to mis-estimation of actual activity in early intervention in psychosis services [EIS]
- We sought to develop a prediction tool for the incidence of first episode psychosis [FEP], by applying precise estimates of epidemiological risk in various sociodemographic groups to the structure of the population at-risk in a second region, where the observed incidence had been concurrently ascertained

Key Messages

- A model of psychosis incidence which included age, sex, ethnicity and population density yielded precise FEP predictions in our second region, out-performing the Department of Health in England's current gold standard for EIS commissioning.
- We have translated this model into a freely available prediction tool (www.psymaptic.org) to facilitate evidence-based healthcare commissioning of socioculturally relevant services according to local need
- Our tool could be extended to many international settings and other disorders to inform healthcare commissioning, when epidemiological risk can be well-characterised and the structure of the underlying population at-risk is known

Strengths and limitations

- Our modelling approach used robust epidemiological data from two large studies of first episode psychosis in England to provide estimates of incidence in a third study region, producing accurate FEP forecasts
- While our models provide estimates of the expected clinical burden of FEP in the community, services may see a broader range of psychopathology consuming resources, or incepted rates may be influenced by supply-side organisational factors
- Due to data availability it was not possible to validate our prediction tool in settings outside of England and Wales, or for specific psychotic disorders. As data become available we will extend the capability of our prediction tool.

Supplemental Table 1: Socioenvironmental variables at local authority district [LAD] level considered in epidemiological prediction models						
Variable		**England[1]**	**Prediction sample[2]**	**Validation sample[1]**	**Mann-Whitney test[3]: Z; p-value**	
					Prediction vs. Validation	**Validation vs. England**
Number of LAD	-	326	14	20 (+1 partial)	-	-
Multiple deprivation (z-standardised)	Median (IQR): Min/Max:	0 (1)[4] -1.7 / 2.9	1.0 (-0.5, 2.4) -1.1 / 2.9	-0.7 (-1.0, 0.3) -1.4 / 1.0	2.4; p=0.02	1.5; p=0.12
Extent of deprivation (%)	Median (IQR): Min/Max:	9.0 (1.3, 23.9) 0.0 / 83.6	28.0 (4.0, 63.0) 0.0 / 83.0	1.4 (.4, 12.8) 0.0 / 29.7	2.4; p=0.02	2.2; p=0.03
Income deprivation (%)	Median (IQR): Min/Max:	11.7 (8.6, 16.1) 3.9 / 32.8	15.5 (8.2, 24.7) 5.9 / 34.4	9.0 (8.2, 14.9) 6.0 / 19.1	1.5; p=0.14	1.3; p=0.19
Employment deprivation (%)	Median (IQR): Min/Max:	8.0 (5.8, 10.8) 2.1 / 18.8	11.6 (6.1, 14.1) 6.1 / 14.1	6.4 (5.4, 10.1) 3.9 / 13.9	2.5; p=0.01	1.4; p=0.17
Population density (people per hectare)	Median (IQR): Min/Max:	5.1 (1.8, 17.4) 0.2 / 137.1	19.4 (9.3, 81.9) 2.6 / 106.4	1.5 (1.2, 3.1) 0.9 / 30.0	3.7; p<0.001	3.4; p=0.001

IQR: inter-quartile range; LAD: Local Authority District

[1]Sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

[2]Sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000).

[3]Mann-Whitney test performs test that the median LAD socioenvironmental scores for the prediction & validation data come from the same population distribution; p<0.05 indicates evidence that the median scores are significantly different

[4]For England we displayed the mean and s.d. of the z-score of deprivation (as shown, underlined), instead of the median and IQR.

Appendix (supplementary): Development of 95% prediction intervals for negative binomial regression models

To obtain 95% prediction intervals from each model, we took all parameter estimates from the fitted negative binomial regression, including the over-dispersion parameter θ, as the true values when constructing prediction intervals. We then used a Monte Carlo procedure, where we simulated realisations using the Gamma-Poisson representation of the negative binomial distribution. For each iteration, we first simulated the random components of the linear predictors from Gamma(θ,θ), which were multiplied by the point predictions (or equivalently e^{υ}, where υ is the non-random component of the linear predictor) to give the Poisson rates for the counts that comprised the predictions. We then simulated Poisson counts using these rates and summed them to provide one realisation of the quantity we wished to predict. By repeating this process many (n=1000) times the distribution of the quantity to be predicted was obtained, from which 95% prediction intervals were obtained using the 2.5% and 97.5% quantiles.

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Data sharing statement

Extra data is available at our prediction website, PsyMaptic: www.psymaptic.org. We have made a large array of prediction data freely available to interested users, who can visualise prediction data in maps and tables for a range of psychotic disorder predictions by major sociodemographic subgroup and by LAD. Future versions of PsyMaptic will release data for other regions and at other geographical levels. Users can also download LAD-specific and national summaries of prediction data from our models in tabular form. Finally, additional explanatory material about how to use the data and the PsyMaptic website is also available at www.psymaptic.org. Bespoke data not provided freely on our website may be requested from the authors at the cost of data extraction. The empirical data underlying the prediction models (ÆSOP and ELFEP) or the validation sample (SEPEA) is not freely available as the studies are ongoing, but papers detailing the main findings from these studies have previously been published elsewhere.

Competing interests statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (i) JBK has support from the Wellcome Trust for the submitted work (grant number WT085540) and PBJ has support from the NIHR (grant RP-PG-0606-1335); (ii) DJ, JP, FW, DF, JC, RMM have no relationships with any company that might have an interest in the submitted work in the previous 3 years; (iii) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (iv) no author holds non-financial interests that may be relevant to the submitted work.

Role of funders

The funders were not involved in the design, collection, analysis, interpretation of the data, writing the report or the decision to submit the article for publication. All authors were independent from the funders in contributing to this work.

Ethical approval

Ethical approval to conduct the original ÆSOP and East London First Episode Psychosis studies was granted from local research ethics committees in their respective centres prior to the original date of onset of the study. We were granted ethical approval to conduct the work related to the present manuscript, including use of data from the SEPEA study, from the Cambridgeshire 3 REC (09/H0306/39).

Guarantorship

JBK takes full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

Contributorship

JBK was responsible for concept, design, analysis, data extrapolation, interpretation of the data, drafting the report and developing the content for the websites www.psymaptic.org, www.psymaptic.com and www.psymaptic.co.uk. JBK was also the chief investigator of the SEPEA study, where the *validation sample* data was obtained. He gave final approval of this version of the manuscript to be published.

DJ was responsible for developing and initially implementing the statistical approach with regard to prediction intervals from count-based regression. He also contributed to drafting and editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JP is principal collaborator on the SEPEA study in the CAMEO early intervention in psychosis services. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

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FW is co-principal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JC is chief investigator of the ELFEP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

RMM is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

PBJ is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He contributed to the development of the prediction methodology and edited the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

Licences and granting of rights

STROBE statement

Our STROBE statement is provided as a supplementary file.

A population-level prediction tool for the incidence of first episode psychosis: translational epidemiology based on cross-sectional data

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Word count: 5,478~~586~~

Access to online data: Part of the development of this manuscript includes the visualisation of prediction data in map and tabular format on a website created for this project: www.psymaptic.org. We have password-protected relevant prediction data on these pages so only editors and peer reviewers can access this data until the peer review process is complete. We invite you to access these pages by visiting www.psymaptic.org and navigating to "*prediction>for peer reviewers*" on the top menu bar. From here, you can access the data as *prediction maps*, *national summary tables* or *downloadable data*. Please enter the password **pr2012** when prompted.

Abstract

Objectives: Specialist early intervention services [EIS] for people aged 14-35 years with first episodes of psychosis [FEP] have been commissioned throughout England since 2001. A single estimate of population need was used everywhere, but true incidence ~~Mental health commissioners require precise information on local populations needs; these vary~~ varies enormously according to soci~~oal and~~ demographic factors. We sought to develop a realistically-complex, population-based prediction tool for FEP, based on precise estimates of epidemiological risk.

Design & participants: Data from ~~over~~ 103~~700~~ ~~FEP~~ participants ~~from~~ in two cross-sectional population-based FEP ~~epidemiological~~ studies were fitted to several ~~different~~ negative binomial regression models to estimate risk coefficients across combinations of different sociodemographic and socioenvironmental factors. We applied these coefficients to the population at-risk of a third, socioeconomically different region to predict expected caseload over ~~a~~ 2.5 years ~~period~~, where observed rates of ICD-10 F10-39 FEP had been concurrently ascertained via EIS.

Setting: Empirical data from London, Nottingham and Bristol predicted~~ing~~ counts in the population at-risk in the East Anglia region of England.

Main outcome measures: ~~We compared o~~Observed counts compared with predicted counts (with 95% prediction intervals) at regional, EIS and local authority district [LAD] levels in East Anglia to establish ~~the~~ predictive validity of each model.

Results: A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in EIS in East Anglia (95%PI: 459, 559), compared with 528 ~~FEP~~ observed participants ~~observed over the same period~~. This model predicted correctly in 5/6 EIS and 19/21 LAD. All models performed better than the current gold standard for EIS ~~early intervention in psychosis service~~ commissioning in England (~~210~~716 cases; 95%PI: 664~~183~~-769~~239~~).

Conclusions: We have developed a prediction tool for ~~the~~ incidence of psychotic disorders in England and Wales, ~~and~~ made ~~this~~ freely available ~~as a free~~ online ~~tool~~ (www.psymaptic.org) to provide ~~mental~~ healthcare commissioners with accurate forecasts of FEP based on ~~a~~ robust epidemiology and anticipated local population need. ~~Our approach could potentially be applied to several other settings and disorders.~~ Initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.

Background

Commissioners of health and social care require precise information on the health needs of their local populations[1], especially if parity of mental and physical health is to be realised. Recent policy promotes the importance of mental health care alongside physical health, recognising the intimate relationship between the two.[2] Many people with severe mental health disorders have dire physical health[2]; they suffer an average of 15-20 life-years lost, with premature deaths predominately attributable to cardiovascular disease.

Mental health disorders alone represent the leading disease burden in the UK (22.8%).[3] They contribute substantially to healthcare expenditure and societal costs even before physical ill health is taken into account. The Centre for Mental Health estimated total costs of mental health to British health services and society at £105 billion in 2009/10,[4] a figure expected to double over the next 20 years.[2] These are serious challenges compounded by a paucity of information on which to commission appropriate services. Early intervention in psychosis services [EIS] for people aged 14-35 years with a first episode of psychosis [FEP] offer a useful example of failure to arm commissioners with adequate information to map services to local need.

EIS are a major evidence-based innovation, systematically commissioned throughout England and Wales over the past decade.[5] When EIS intervention is sustained there is evidence that people with psychosis achieve better functional and social outcomes.[6-7] Such services are also highly cost-effective.[4 8-9]

However, EIS were originally commissioned on an anticipated rate of 150 new cases of any psychotic disorder per 1,000,000 of the total population people per year in the Department of Health's Mental Health Policy Implementation Guide [MH-PIG].[5] In 2001 in England and Wales, 29.3% of the population were aged 14-35 years old, meaning that the MH-PIG commissioned incidence rate was approximately 51 cases per 100,000 person-years in the age range covered by EIS. Following their deployment, anecdotal reports began to emerge from EIS in different regions to suggest that a uniform figure for commissioning was simultaneously under-[10] and over-estimating[11] actual observed need in urban and rural populations, respectively. Recent epidemiological evidence of FEP incidence in rural communities

in England has suggested that rates are somewhat lower than the uniform figure upon which services were commissioned, [12-13] confirming previous calls that a "one-size-fits-all" prescription for EIS implementation is unlikely to lead to the efficient allocation of finite mental health resources.[14-15]

Using rich epidemiological data on variation in the incidence of first episode psychosis according to major sociodemographic risk factors,[16-19] ~~a figure at least three times lower than reported thereafter. The error came from confusing schizophrenia, a particular constellation of psychotic symptoms with chronicity built into its definition, with all psychotic disorders requiring care. This was compounded by the fact that recent evidence concerning the rich epidemiological profile of first episode psychosis [FEP] was not translated into commissioning guidance.~~

~~W~~we describe the development and validation of a population-level prediction tool capable of accurately estimating the expected incidence of psychiatric disorder, based on the sociodemographic structure of the population in a given region~~in a given population, underpinned by well-characterised epidemiological models~~. Applied to FEP as proof-of-concept, we show it is possible to ~~precisely~~ closely predict expected incidence in a given population, where the observed count of cases was within the prediction intervals forecast by our models. We applied our most precise prediction model to the population of England and Wales to provide health commissioners with a translational epidemiological prediction tool to underpin information-based service planning.

Methods

Our prediction models were based on epidemiological data from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [ÆSOP] and the East London First Episode Psychoses [ELFEP] studies,[18 20] two ~~recent,~~ methodologically-similar population-based FEP studies. We fitted various count-based regression models with different combinations of sociodemographic and socioenvironmental factors, well-established in the literature to be associated with the incidence of psychotic disorder.[21-22] We first established the relative *internal validity* of each model by estimating internal model fit diagnostics to assess how well each model fitted the empirical data (henceforth, ~~referred to as~~ the *prediction sample*). We next sought to estimate the *external validity* of each model by applying model-based parameter coefficients to the population structure of a purposefully ~~deliberately~~ different region of England, East Anglia (henceforth, ~~referred to as~~ the *validation sample*). This out-of-sample prediction technique allowed us to obtain the expected incidence of disorder in this region forecast by each model,

which we compared with observed rates simultaneously ascertained in this region via the ongoing Social Epidemiology of Psychoses in East Anglia [SEPEA] study.[13] We performed various model fit diagnostics to identify which, if any, model demonstrated utilisable predictive capability.

Empirical data underlying prediction models (*prediction sample*)

Case ascertainment (numerator)

The designs of the ÆSOP and ELFEP studies have been described in detail elsewhere,[18 20] with features relevant to the present paper summarised here. Case ascertainment took place over two years in ELFEP (Newham: 1996-8; Tower Hamlets & Hackney: 1998-2000) and the Southeast London and Nottingham centres of the ÆSOP study (1997-9), and over the first 9 months of 1997 in Bristol (ÆSOP). All service bases were screened regularly for potential new contacts aged 16-64 years (18-64 in ELFEP) resident within these catchment areas. Leakage studies were conducted to identify participants missed by this initial screen, but meeting inclusion criteria for FEP.[18 20] All participants who received an ICD-10 F10-39 diagnosis for psychotic disorder following assessment via the Schedules for Clinical Assessment in Neuropsychiatry were included in the incident sample, except those with an organic medical basis to their disorder or profound learning difficulty. Data on age-at-contact, sex and ethnicity were collected on included participants. We geocoded participants' residential postcode at first contact to their corresponding local authority district [LAD] to allow us to model possible neighbourhood effects associated with the incidence of psychotic disorder, such as population density or socioeconomic deprivation.

Population at-risk

We estimated the population at-risk ~~from which participants originated~~ using the 2001 Census of Great Britain, adjusted for study duration, and stratified by age group (16-17, 18-19, then 5-year age bands), sex and ethnicity. Ethnicity was based on self-ascription according to one of ten categories derived from the census: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white & black Caribbean, other mixed ethnic backgrounds and all other ethnicities.

Socioenvironmental variable estimation

We estimated LAD -level deprivation using the 2004 Index of Multiple Deprivation [IMD] in England, which estimated domains of deprivation using measures predominantly collected close to the time of our case ascertainment periods (see Box 1).[23] We z-standardised English LAD IMD scores to have a mean

of zero and standard deviation of one, and extracted IMD z-scores for the 14 LADs in the ÆSOP and ELFEP studies. To inspect whether any particular deprivation domain was a better predictor of psychosis incidence than IMD, we also considered LAD-level income deprivation, employment deprivation and the extent of deprivation in our models (Box 1). We ~~also~~ estimated population density~~,~~ by dividing LAD usual resident population by its area (in hectares), using ArcGIS 9.3 software.

<Box 1 about here>

Observed data for external validation of prediction models (*validation sample*)

~~The~~ Oobserved ~~numerator (~~participant~~s)~~ and ~~denominator (~~population at-risk~~)~~ data for our *validation sample* was obtained from the SEPEA study, an ongoing study of the incidence of psychotic disorders incepted over three years (2009-12) through one of six EIS covering 20 LAD and a subsection of one LAD (the town of Royston, Hertfordshire) in Norfolk (three EIS: West, Central and Great Yarmouth & Waveney), Suffolk (one EIS) and Cambridgeshire, Royston & Peterborough (CAMEO North and South EIS).[13]

Case ascertainment

To establish the incepted incidence of first episode psychosis as seen through EIS, entry criteria for the SEPEA study were:

- Referral to an EIS in East Anglia for suspected first episode of psychosis
- Aged 16-35 years old at first referral to EIS (17-35 years in CAMEO services)
- Resident within the catchment area at first referral
- First referral during case ascertainment period (2009-12)

At six months after EIS acceptance~~referral~~, or discharge from the service, whichever was sooner, we asked the clinician responsible for ~~the~~ care ~~of the participant~~ to provide an ICD-10 F10-39 psychiatric diagnosis using all information available. We excluded participants without a clinical FEP diagnosis, or participants presenting with an organic basis to their disorder or profound learning disability. For remaining participants, basic sociodemographic and postcode information was recorded and classified in the same way as in the *prediction sample*. We included participants presenting to EIS during the first 2.5 years of the ongoing SEPEA study.

Population at-risk

We estimated the population at-risk of East Anglia using ~~the latest (~~2009~~)~~ mid-year census estimates published by the Office for National Statistics [ONS] at LAD-level, by age group, sex and ethnicity.[24] These estimates used the 2001 census base, adjusted for immigration, births and deaths each year. It was not possible to obtain 2009 mid-year estimates for the town of Royston, because data were only published at ~~the~~ LAD~~-~~ level~~, not by town~~. Here, we thus used denominator data from the 2001 census data, ~~published for Royston~~ in order to estimate the population at-risk in Royston. We do not believe this would have substantially invalidated our results as this town represented 0.6% of the overall population at-risk (n=9,555) in the SEPEA study. Denominator data were multiplied by 2.5 to account for person-years of exposure in the *validation sample*.

Socioenvironmental variable estimation

For each LAD in the SEPEA study we obtained corresponding socioenvironmental variables to those included in our *prediction sample,* using updated data collected as close to the SEPEA ~~study~~ case ascertainment period as possible. Population density was estimated using 2009 mid-term population estimates. Our measures of deprivation were derived from the IMD 2010,[25] which was estimated in an analogous way to 2004 data, but collected from ~~data~~ sources obtained immediately prior to the SEPEA study.

Statistical techniques

Dataset generation

We constructed a dataset for the regression analysis of count data by pooling ~~numerator and denominator~~ data from the ÆSOP & ELFEP studies (the *prediction sample*). Data were stratified by age group, sex, ethnicity and LAD, such that each stratum represented the total count of FEP cases in a unique sociodemographic group for a given LAD, with a corresponding estimate of the population at-risk, treated as an offset in our models. Our socioenvironmental measures (population density, deprivation) were adjoined to the dataset for each LAD.

Population at-risk data from the *validation sample* were stratified in the same way and retained in a separate database. The ~~C~~count of cases was ~~were~~ entered as a variable with missing values, which we could ~~wished to~~ predict into, given the model coefficients and population at-risk.

Prediction models

We used the *prediction sample* data to fit negative binomial regression models to obtain parameter coefficients of incidence for the sociodemographic and socioenvironmental factors included in each model. We considered the internal and external predictive capabilities of six models, all of which contained age group, sex, an age-sex interaction term and ethnicity. Model 1 contained no further covariates. Model 2 also included IMD. We replaced IMD with either income, employment or the extent of deprivation, respectively, in models 3-5. Model 6 included population density. Initial exploration of the *prediction sample* data indicated the presence of possible over-dispersion (variance (δ^2=1.37) exceeded mean (μ=0.4) count of cases) so negative binomial regression was preferred to Poisson regression since it explicitly models any over-dispersion with an extra dispersion parameter.

Internal model cross-validation & prediction

We assessed internal model validity in three ways. First we used Akaike's Information Criterion [AIC] to assess the respective overall fit of each model to the data. Second, we conducted K-fold cross validation to assess each model's internal validity to predict cases within the *prediction sample*. This method randomly allocated strata in the *prediction sample* into *K* subsets. Each model was then re-estimated on *K-1* subsets (the *training data*) to predict expected counts of cases in the K^{th} subset (the *test data*). This was repeated over *K* trials, such that each stratum in the dataset appeared exactly once as the *test data*. At the end of this process, we derived Lin's concordance correlation coefficient [CCC] and 95% confidence intervals [95%CI] to estimate the correlation between predicted and observed counts of cases across all strata in the *prediction sample*. Finally, we estimated the root mean squared error [RMSE] to determine the average error between fitted and observed values from each model, where lower RMSE scores indicated smaller prediction error. The RMSE is derived as

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}$$

where y_i and $\hat{y}_i$ are the observed and predicted count of cases in the i^{th} stratum, respectively, and n is the number of strata.

We repeated K-fold cross-validation *h* times, generating *K* new random divisions of the data each time. We retained model fit diagnostics across *Kh* iterations, and reported the mean of Lin's CCC and RMSE to provide summary cross-validation statistics for each model. We specified *K=10* and *h=20*, as recommended for cross-validation to obtain precise model fit diagnostics.[26]

External model prediction & validation

We retained parameter coefficients from each model (using the full *prediction sample* data) and applied these to the corresponding population at-risk in the *validation sample* dataset. This gave out-of-sample prediction estimates for the expected count of cases in each stratum of the *validation sample*, given the model. We summed expected counts across relevant strata to estimate the (i) total predicted count of cases in the SEPEA region, (ii) predicted counts in each EIS, and (iii) predicted counts by LAD. These counts were further stratified by broad age group (16-35, 36-64 and 16-64 years). Because census (denominator) data was unavailable for 35 year olds alone (needed to estimate their contribution to predicted counts in the age range for EIS, 16-35 years) we assumed the risk coefficient was the same across all ages within the 35-39 year old age group. We apportioned predicted counts on a 1:4 ratio (35 years: 36-39 years) to their respective broad age groups.

To determine how well the MH-PIG[5] figure of ~~1~~51 new cases per 100,000 people per year for EIS performed as a predictive tool, we also estimated the predicted count of cases in the *validation sample* under this scenario, which we termed "Model 7".

We derived prediction intervals [95% PIs] for all summary predictions from first principles for each negative binomial regression model, since their derivation is not straightforward, nor routinely implemented by statistical software. Prediction intervals are similar to confidence intervals, but account for standard errors introduced in both the *prediction* and *validation* samples. We developed a bootstrap-like approach to obtain prediction intervals from each model by simulating 1000 model-based realisations of the quantities we wished to predict, where we took the parameters to be the maximum likelihood estimates. We obtained the lower and upper bounds of the prediction intervals as the corresponding quantiles of the simulated realisations (see Appendix for full details).

To assess each model's external predictive capabilities, we ~~derived~~ considered five markers of predictive accuracy. We compared the number of times the observed count of cases in the SEPEA study fell within

the prediction intervals estimated from each model for (i) the SEPEA region, (ii) at EIS level, and (iii) at LAD level. We also derived EIS- and LAD-level RMSE scores to estimate prediction error from each model in our *validation sample*. We ranked model performance (1: best, 7: worst) on these five measures, and estimated an overall mean rank to determine the overall predictive validity of each model.

Observational data on first episode psychosis in our *validation sample* were not available for the age range 36-64 years, so external validation was restricted to the 16-35 year old group. For completeness, however, we also reported overall predicted count of cases for this age group from each model.

Extrapolation to the United Kingdom

Guided by our validation procedures, we identified which model had the greatest overall predictive validity, and proposed this as a candidate for FEP incidence prediction in England and Wales. We repeated out-of-sample prediction on the sociodemographic and socioenvironmental population characteristics of each LAD in England and Wales to obtain national and LAD-level predictions. Denominator data was obtained from the ONS 2009 mid-term estimates and stratified as previously described. Overall counts were derived for three broad age groups (16-35, 36-64 and 16-64 years), and for each of these, by sex and ethnicity. 95% PIs were estimated as before. We visualised this data on maps and in tables to provide healthcare planners and commissioners with an easy-to-use tool to forecast the expected incidence of psychosis in England and Wales. We have made this available as a free, open-use prediction tool, known as PsyMaptic (version 0.43) (Psychiatric Mapping Translating Innovations into Care; www.psymaptic.org). Counts of cases predicted by our model were compared with those obtained under the Department of Health's uniform rate in each LAD. We expressed these comparisons as ratios with 95% CIs derived using the same method as for standardised morbidity ratios [SMR]. This approach was conservative because here we substituted the usual numerator in an SMR, the observed, O, for a predicted count. Unlike an observed count, no sampling variation is present for the predicted count, only uncertainty due to the model from which the prediction was estimated. Since variance in the prediction is therefore much smaller than the variance normally present for the numerator (O) this led to conservative estimates of 95% CI. Ratios in LAD where 95% CI did not span unity could therefore be interpreted as regions where there was strong evidence that the predictions from our model differed significantly from those predicted by the Department of Health's uniform rate.

Software

All negative binomial regression models, out-of-sample prediction and estimation of 95% PI were conducted in R (version 2.15.1). Internal cross-validation and model-fit diagnostics were conducted in Stata (version 11). Prediction maps for England and Wales were created using StatPlanet Plus (version 3.0) visualisation software.[27]

Results

Prediction sample

Our prediction models contained data on 1,037 persons with a first episode psychosis in the ÆSOP (n=553; 53.3%) and ELFEP (n=484; 46.7%) studies, ascertained from over 2.4m person-years at-risk. Twelve participants were excluded from the original ÆSOP sample because they were of no fixed abode and could not be geocoded to an LAD.[18]

The population at-risk in the *prediction sample* came from LAD with higher median levels of multiple and employment deprivation, extent of deprivation and population density than the population at-risk in the *validation sample*, though there were no statistically significant differences in median income deprivation between the two samples (Supplemental Table 1).

<Supplemental Table 1 about here>

Parameter coefficients obtained from the full prediction sample following negative binomial regression are shown in Table 1. As previously reported from these data,[20 28] incidence rates were generally raised in ethnic minority groups compared with the white British population. Models 2-6 included a measure of LAD deprivation (Models 2-5) or population density (Model 6), which were all significantly associated with ~~a significant~~ increased ~~in the~~ incidence of psychotic disorder, after control for individual-level confounders. Each of these models produced a lower AIC score~~, indicating better fit,~~ than a model fitted solely with individual-level covariates (Model 1), indicating better internal fit. Internal cross-validation suggested all models achieved good CCC agreement between predicted and observed cases, with low RMSE values (Table 1). ~~Models 2-5 performed marginally better than Model 6 on these cross-validation diagnostics.~~

<Table 1 about here>

Validation sample

Observed participants

We identified 572 participants over the first 30 months of the SEPEA study, aged 16-35 years old, who met acceptance criteria for EIS in East Anglia. We excluded 44 participants (8.0%) who did not meet clinical criteria for ICD-10 psychotic disorder. This left an incidence sample of 528 participants from nearly 1.4m person-years at risk (37.8 per 100,000 person-years; 95%CI: 34.7, 41.2). A further 2.3m person-years at-risk accrued in the same region for people aged 36-64 years over this period. Median levels of multiple, income and employment deprivation in the region did not differ significantly from the remainder of England, although median population density and extent of deprivation in East Anglia were lower than elsewhere in England (Supplemental Table 1).

<Table 2 about here>

External model prediction & validation

The overall observed count of cases, aged 16-35 years, in the *validation sample* (n=528) fell within 95% prediction intervals in only two of seven tested models (Models 4 and 6, Table 2). Of these, the observed count was closest to the point estimate for Model 6 (508.5; 95% PI: 449.0, 559.0), fitted with age group, sex, their interaction, ethnic group and LAD population density. The observed count of cases also fell within prediction intervals from this model in five of six EIS in the study region, and 19 of 21 LADs, the most of any model (Table 3). This model had the lowest error scores at EIS (RMSE=11.9) and LAD (RMSE=5.9) levels of any model. Overall, Model 6 was ranked highest across all external model fit diagnostics (Table 3). All models outperformed the Department of Health's uniform figure of ~~1~~51 cases per 100,000 people per year (Model 7), which ~~consistently~~ generally over~~under~~estimated ~~the expected count of~~ cases ~~observed~~ in the *validation sample* (overall prediction: 715.7~~210.5~~ cases; 95% PI: 664~~183~~.0, 769~~239~~.0).

We also reported predicted cases aged 36-64 years old from our models (Table 3), although we could not test these in ~~our external~~ the *validation sample*. Model 6 predicted an additional 262.9 cases aged 36-64 years over a 2.5 year period in East Anglia (95% PI: 233.0, 297.0).

<Table 3 about here>

Extrapolation to England and Wales

We ~~selected Model 6 to~~ predicted the expected count and incidence of first episode psychosis per annum in each LAD in England and Wales based on Model 6, and visualised this data in maps and tables freely available at www.psymaptic.org. Many maps can be visualised (for example, Supplemental Figure 1), including overall predicted incidence counts and rates for each broad age group at LAD level, by sex and ethnic group, as well as a variety of population and socioenvironmental data. According to our model, the annual number of new FEP cases in England and Wales would be 8745 (95% PI: 8558, 8933), of which our model predicted 67.9% (N=5939; 95% PI: 5785, 6102) would be seen through EIS. Only 176 (95% PI: 151, 203) cases aged 16-64 years were forecast in Wales per annum. Assuming our prediction model is accurate, it indicated that the Department of Health's current uniform rate of 51 per 100,000 person-years was higher than the predicted point estimates for rates forecast by our PsyMaptic model in 351 LAD (93%) in England and Wales, but was lower than predicted by our model in Birmingham and several London boroughs (Supplemental Figure 2, left hand map). Under a conservative approach, these differences achieved statistical significance in parts of London (where the Department of Health's model underestimated need as predicted by PsyMaptic), and in some more rural parts of England and Wales (where the Department of Health's model over-estimated need) (Supplemental Figure 2, right hand map).~~a median of 63.4% of new service users seen by EIS as predicted by our model would not have been anticipated under the current gold standard for commissioning EIS (model 7), although this varied between LAD (10th-90th percentile: 51.3% - 67.6%; Supplemental Figure 2).~~

<Supplemental Figures 1~~2~~ & 2~~3~~ about here>

Discussion

Principal findings

We have developed and tested several epidemiological prediction models to forecast FEP incidence in England and Wales, having taken into account regional differences in the sociodemographic and socioenvironmental profile of different populations. Inspection of our data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the greatest external predictive validity when compared with the observed FEP caseload ascertained through EIS in our *validation sample*. This model also had good internal validity across the entire age range (16-64 years). All ~~prediction~~ models performed significantly better in predicting the incidence of

clinically relevant first episode psychosis than the Department of Health's current gold standard for EIS commissioning,[5] based on a ~~low~~ uniform ~~anticipated~~ incidence rate. Our data suggested the figure used to commission EIS over-estimated the likely true incidence rates of FEP in rural areas and under-estimated them in urban settings, although we acknowledge that commissioning decisions will need to be based on several additional factors, including the level of pre-clinical or non-psychotic psychopathology requiring assessment at initial referral to EIS, and variation in service organisation, remit and delivery.

Limitations & future development

Our prediction models were based on epidemiological data obtained from large, robust population-based FEP studies for people aged 16-64 years.[18-19] Our best-fitting model had good internal validity over this age range, and good external validity over the age range 16-35 years. While this covered the majority of adult onset psychosis cases seen in mental health services, including EIS, we recognise that some EIS teams incept people from 14 years old. We were unable to extrapolate our models to this age range, given the current absence of incidence data for this group in England. Data from Scandinavia suggest that the incidence of such "early onset" psychoses is absolutely low,[29] although the rate may have been increasing in the last few decades, probably as a result of movement towards earlier detection. We were also unable to ~~could not~~ externally validate prediction models for people aged 36-64 years, because comparable observed incidence data was not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models was ascertained from the same two large, well-conducted studies ~~of first episode psychosis in England~~ as for data on ~~for~~ the younger age group.~~,~~[18-19 28] Furthermore, ~~and~~ published findings from these studies are consistent with the wider epidemiological literature for psychosis in ~~from~~ England and internationally.[17 21 30] It will be important to ~~ascertain~~ validate the predictive capability of our model(s) in this age range, and we will seek to identify suitable samples to do so in future versions of PsyMaptic.

All prediction models had reasonable internal validity, although our proposed model performed slightly worse (most noticeably for AIC) than models which included deprivation (i.e. models 2-4) instead of population density. Our decision to use model 6 as our proposed candidate for the prediction tool was ~~,~~ ~~however,~~ supported by the fact that it produced the most accurate external forecasts of any model, despite considerable socioenvironmental differences between regions in our *prediction* and *validation*

samples. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards (N~6000), or to other parts of the UK, because appropriate denominator data was not published as mid-term census estimates. The 2011 census will provide small area and national data for the whole of the UK, scheduled for ~~and will be~~ release~~d~~ by ONS in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. We will then be able to develop models to explore cross-level interactions, such as the association between individual ethnicity and neighbourhood-level ethnic density. Small area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development.

We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16-35 years old. EIS were the only mental health service for people aged 14-35 years experiencing a first episode of psychosis in East Anglia, minimising the potential for under-ascertainment in the population at-risk when derived from careful epidemiological design.[13] We are confident that our *validation sample* also contained few false positive cases for any clinically-relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS or who did not receive a clinical diagnosis of psychotic disorder during the first six months from initial referral. It is important to recognise that while our prediction models are based on diagnosed clinically relevant psychotic disorders, service commissioning will also need to account for additional pre-clinical or non-psychotic psychiatric morbidity presenting to EIS, particularly in services which operate early detection models or implement "watch-and-wait" briefs. The SEPEA data used to validate our models do not predict (1) the number of "false positive" subjects who may require psychiatric triage and assessment even though they are not accepted by EIS, or (2) the number of "true positive" subjects accepted by services, but who did not meet epidemiological criteria for inclusion in the *validation sample* of the SEPEA study (those living outside the catchment area at first contact, or those transferred from other services); these people will consume varying degrees of service resources which needs to be considered in service planning.

We also note that pathways to care may affect the level of incidence observed in EIS, since many filters are likely to operate before subjects come to the attention of EIS. These will include local level service organisation and the relationship between Community Mental Health Teams [CMHTs], Child and

Adolescent Mental Health [CAMHs] and EIS. Furthermore, acceptance criteria for entry to EIS vary, which will have a downstream effect on the number of new cases of clinically relevant psychoses received in each team. -Future versions of PsyMaptic will include forecasts for specific psychotic disorders, as standardised research-based diagnoses (using OPCRIT[31]) are currently being collected in the ongoing SEPEA study in order to provide more detailed forecasts. Acceptance rates to EIS may also be influenced by local community awareness of such services. While our prediction models outperformed the current gold standard for EIS commissioning in England when restricted to clinically relevant caseloads, we recommend that our models are best interpreted as forecasts of the expected burden of first episode psychosis in given populations, and not the expected burden which will necessarily be seen through EIS given these issues.

We estimated prediction intervals from first principles [DJ] since there derivation is an area of statistical development.[32] We used a bootstrap-like methodology to produce 95% PI accounting for natural variation in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in prediction models, which we assumed to be the true coefficients of risk in the population. Our approach therefore naturally led to slightly artificially narrow 95% PIs. This was not necessarily undesirable for the purpose of model validation and the precise prediction of expected counts because we wished to apply stringent criteria. Ideally, prediction intervals should take into account both these sources of variation, although we note that parameter uncertainty is usually small compared to the natural variation of the quantities of interest. ~~Furthermore, ignoring this uncertainty was not necessarily undesirable for the purpose of model validation and the precise prediction of expected counts because we wished to apply stringent criterion. Here, t~~The addition of more empirical data in the *prediction sample* would not lead to narrower PIs, though would tend to move the point estimate of risk for each coefficient closer to the true value in the population. We do not believe we have mis-estimated point estimates of risk across major sociodemographic groups, since our results accord with the wider ~~English and International~~ literature.[17 21-22] We sought independent confirmation that our development of 95% PI were correct (personal communication with Prof Ian White, MRC Biostatistics Unit). We recommend that all prediction point estimates from our PsyMaptic model are considered with their 95% PIs, which provide information about the natural variance in expected rates in the population.

Meaning of the findings

If commissioners are to meet the Department of Health's vision to orientate health services around local need,[1-2 5] differences in demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data is combined with accurate population at-risk estimates this can be realised. As such, our modelling approach could have utility in many other settings and for many disorders. Our translational approach demonstrated good internal and external validity to predict the expected incidence of first episode psychosis, particularly through EIS, where 76% and 63% of all male and female adult-onset FEP cases, respectively, will typically present.[18] Since their inception in 2002, EIS in England and Wales have reported both lower[11] and higher[10] caseloads than they were originally envisioned to manage ~~in the MH-PIG,~~.[5] with shortfalls or excesses in anticipated demand for services aligned to the degree of urbanisation in the underlying catchment area. Others have noted that EIS provision in rural areas may be difficult to implement effectively,[14-15] ~~Empirical epidemiological data from such services supports this; with incepted rates at least three times greater than expected based on a uniform rate of 15 per 100,000 people per year.~~ and~~W~~ while the MH-PIG acknowledged that "…[a]n understanding of local epidemiology is needed as the size of population covered will depend on a number of different factors" (p.55),[5] no further elaboration on how to achieve this was provided ~~for commissioners~~. We believe PsyMaptic provides a possible ~~exemplar~~ tool to overcome this challenge, improving the description and prediction of local population need beyond the MH-PIG and including individual- and neighbourhood-level indicators of local need.[17] From an aetiological perspective, we acknowledge that variables such as ethnicity or population density are likely to be markers for a suite of more complex, interactive social, genetic and environmental determinants of psychosis.[33]

Our models are not the first to be used to forecast mental illness needs in England and Wales,[34] though we believe this is the first attempt to forecast incidence rather than prevalence in the community. We recommend that our prediction methodology is used in conjunction with the wide range of public health observatory data available,[35] as well as the caveats presented above. ~~To this end,~~ PsyMaptic has been included with other indicators in the Joint Commissioning Panel for Mental Health's forthcoming guidance for commissioning of public mental health services.[36] Ongoing monitoring and audit of EIS will be vital to ensure services meet the fidelity criteria upon which they were originally commissioned,[11 37] including ensuring that service capacity matches local need as closely as possible. As part of this process,

we will need to externally validate our models in a wider range of settings, refining them based on empirical observation.

We note that ~~our heat maps broadly correlate with~~ advocacy expressed for EIS by healthcare professionals in England and Wales broadly correlates with demand for services as predicted by PsyMaptic.[38] Though by no means universal, proponents of EIS tend to be located in major conurbations – such as London,[39] Birmingham[40] or Manchester[7 41] – where demand for EIS will be highest, while those who suggest EIS resources could be used more effectively elsewhere ~~more critical of such services~~ tend to work in more rural communities,[15 38] where but a handful of young people would be expected to come to the attention of EIS each year. It is possible that both sides are correct and that more resources are required to help with the tide of psychotic illness in inner cities. Resources might be used more effectively in other ways, elsewhere, so long as the needs of the small number of young people who suffer a FEP each year are met; a dedicated specialist EIS may not be the most effective approach when anticipated demand will be very low.

~~We are not the first to express concerns over the suitability of the MH-PIG for EIS implementation.[14 15] The epidemiological literature conducted before and after its publication does not support adoption of such a low rate of first episode psychosis as a realistic basis for psychosis service planning for young people, when incidence rates are at their highest. Our heat maps (see Supplemental Figure 2 and online) illuminate the magnitude of the discrepancy between MH-PIG forecasts and those from our prediction model in different regions of England and Wales; our data suggest the MH-PIG underestimated anticipated EIS caseload per annum by almost 50% anywhere in England and Wales. This figure exceeded 80% in some urban areas.~~ Given the significant downstream economic savings associated with spending on EIS as estimated in an urban setting,[8] PsyMaptic could~~an also~~ be used to highlight regions where ~~with~~ sufficient ~~EIS~~ investment to appropriate mental health services would lead to ~~the~~ greatest economic gains ~~could be realised~~ in terms of mental healthcare expenditure (assuming sustained intervention also leads to improved social and clinical benefit for patients[6-7]). ~~If valid,~~ PsyMaptic can also be used to highlight regional variation in demand according to age, sex and ethnic group, allowing service planners to tailor provision around the socio-cultural characteristics of their local populations. Our prediction tool for first episode psychosis, which translates robust empirical epidemiological data on psychosis risk to the population structure of different regions, offers a methodology for improving the allocation of finite mental health resources based around local need. ~~Underestimating need by 50% may~~

~~not produce major difficulties in a region where only two cases per year present to services, but will have great impact on service care and delivery in an EIS seeing 250 new cases per year.~~

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Box 1: Description of included socioenvironmental variables [1 2]	
Variable	**Classification & description**
Multiple deprivation	Weighted data from routine national sources across 7 domains: income, employment, education, health, barriers to housing & services, living environment, crime. Continuous, z-standardised scores for analysis.
Extent of deprivation	Proportion of LAD population living in 20% most deprived SOA in England (%)
Income deprivation	Proportion of all people in LAD classified as income deprived (%)
Employment deprivation	Proportion of adults of working age in LAD classified as employment deprived (%)
Population density	Population density at LAD level (people per hectare).

IMD: Index of Multiple Deprivation; LAD: Local authority district; SOA: super output area; IQR: inter-quartile range

[1]*Prediction sample* sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000)

[2]*Validation sample* sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

Table 1: Prediction models, covariates and fit: all clinically relevant psychoses (F10-39)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Variable	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**
Age group*sex interaction[1]	p=0.07	p=0.06	p=0.06	p=0.06	p=0.06	p=0.06
Ethnicity						
White British	1	1	1	1	1	1
Non-British white	2.0 (1.5, 2.5)	1.7 (1.4, 2.2)	1.7 (1.3, 2.2)	1.7 (1.3, 2.2)	1.8 (1.4, 2.3)	1.7 (1.3, 2.2)
Black Caribbean	6.0 (4.9, 7.3)	5.3 (4.3, 6.5)	5.2 (4.3, 6.4)	5.2 (4.3, 6.4)	5.4 (4.5, 6.6)	5.1 (4.2, 6.3)
Black African	4.1 (3.3, 5.1)	3.6 (2.9, 4.5)	3.5 (2.8, 4.4)	3.5 (2.8, 4.4)	3.7 (3.0, 4.6)	3.5 (2.8, 4.3)
Indian	1.7 (1.2, 2.5)	1.5 (1.1, 2.2)	1.5 (1.0, 2.2)	1.5 (1.0, 2.1)	1.6 (1.1, 2.3)	1.6 (1.1, 2.2)
Pakistani	1.8 (1.2, 2.5)	1.6 (1.0, 2.5)	1.6 (1.0, 2.4)	1.6 (1.0, 2.4)	1.6 (1.1, 2.5)	1.8 (1.3, 2.7)
Bangladeshi	2.1 (1.5, 2.8)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.2, 2.2)	1.8 (1.3, 2.5)	1.8 (1.4, 2.4)
Mixed white & black Caribbean	4.3 (2.8, 6.7)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	4.0 (2.6, 6.1)	3.9 (2.5, 6.1)
Mixed, other	1.3 (0.8, 2.3)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Other	2.2 (1.6, 3.0)	1.9 (1.4, 2.7)	1.9 (1.4, 2.6)	1.9 (1.4, 2.6)	2.0 (1.4, 2.7)	1.9 (1.4, 2.7)
Socioenvironmental variables						
IMD (z-score)	-	1.184 (1.101, 1.274)	-	-	-	-
Extent of deprivation (%)	-	-	1.008 (1.004, 1.011)	-	-	-
Income deprivation (%)	-	-	-	1.025 (1.015, 1.035)	-	-
Employment deprivation (%)	-	-	-	-	1.062 (1.032, 1.093)	-
Population density (pph)	-	-	-	-	-	1.005 (1.003, 1.007)
Internal model fit diagnostics						
AIC[2]	2571.8	2552.4	2551.3	2549.6	2556.4	2556.3
Mean Lin's CCC (95%CI)[3]	0.75 (0.74, 0.77)	0.77 (0.75, 0.78)	0.77 (0.75, 0.79)	0.77 (0.75, 0.78)	0.77 (0.75, 0.78)	0.76 (0.74, 0.77)
Mean RMSE (s.d.)[4]	0.75 (0.11)	0.74 (0.11)	0.74 (0.10)	0.74 (0.10)	0.74 (0.11)	0.76 (0.13)

[1]All models fitted with age group by sex interaction given *a priori* evidence for effect modification.[18 42] Likelihood ratio test p-values reported between models with and without an interaction term fitted between age group and sex. Specific IRR not been reported for clarity, but available on request

[2]AIC: Akaike's Information Criterion – lower scores denote improved model fit

[3]CCC: Lin's correlation concordance coefficient. Higher scores indicate greater correlation between observed & predicted count of cases in the *prediction sample.* Mean CCC and 95%CI reported following *h*=20 trials during cross-validation.

[4]RMSE: Root mean squared error. Lower scores indicate lower prediction error. Mean RMSE and standard deviation (s.d.) reported following *h*=20 repeats of *k*-fold cross-validation, where *k*=10.

Table 2: Observed versus predicted cases in SEPEA study for all clinically relevant psychoses, 16-35 years[1]

EIS	Observed	Model 1 Predicted (95% PI)	Model 2 Predicted (95% PI)	Model 3 Predicted (95% PI)	Model 4 Predicted (95% PI)
Overall total, 16-35 years	***528***	**641.2 (586.0, 696.1)**	**468.5 (422.0, 518.0)**	**474.7 (429.0, 522.0)**	**487.5 (441.0, 535.0)**
Cameo North	*55*	84.7 (66.0, 106.0)	68.5 (52.0, 87.0)	67.8 (51.0, 86.0)	70.2 (53.0, 90.0)
Cameo South	*137*	163.6 (135.0, 192.0)	105.5 (84.0, 129.0)	111.7 (89.0, 134.0)	110.9 (90.0, 132.0)
West Norfolk	*25*	29.2 (18.0, 41.0)	23.0 (13.0, 35.0)	22.0 (12.0, 32.0)	23.4 (14.0, 34.0)
Central Norfolk	*121*	162.6 (136.0, 191.0)	122.6 (99.0, 148.0)	123.0 (100.0, 149.0)	128.3 (104.0, 152.0)
Great Yarmouth & Waveney	*60*	49.1 (34.0, 65.0)	41.6 (28.0, 55.0)	39.9 (27.0, 53.0)	42.9 (30.0, 57.0)
Suffolk	*130*	151.9 (126.0, 178.0)	107.4 (85.0, 128.0)	110.3 (88.0, 133.0)	111.7 (90.0, 136.0)
Overall total, 36-64 years	-	332.2 (292.0, 373.0)	244.0 (213.0, 276.0)	248.6 (216.0, 280.0)	256.3 (228.0, 291.0)

EIS	Observed	Model 5 Predicted (95% PI)	Model 6 Predicted (95% PI)	Model 7 Predicted (95% PI)
Overall total, 16-35 years	***528***	**477.1 (428.0, 523.0)**	**508.5 (459.0, 559.0)**	**715~~210~~.65 (664~~183~~.0, 769~~239~~.0)**
Cameo North	*55*	69.1 (52.0, 88.0)	64.5 (48.0, 82.0)	92~~27~~.1~~1~~ (74~~17~~.0, 111~~38~~.0)
Cameo South	*137*	100.7 (79.0, 123.0)	131.1 (108.0, 157.0)	169.0~~49.7~~ (~~36~~144.0, 195~~64~~.0)
West Norfolk	*25*	24.7 (16.0, 35.0)	22.3 (13.0, 33.0)	35.8~~10.5~~ (25.0, ~~17~~48.0)
Central Norfolk	*121*	128.2 (105.0, 153.0)	132.5 (108.0, 157.0)	187~~55~~.72 (~~41~~161.0, 215~~70~~.0)
Great Yarmouth & Waveney	*60*	47.7 (35.0, 63.0)	38.0 (26.0, 51.0)	59.1~~7.4~~ ~~10~~(44.0, ~~26~~74.0)
Suffolk	*130*	106.6 (86.0, 128.0)	120.0 (96.0, 143.0)	172~~50~~.16~~6~~ (143~~7~~.0, ~~65~~198.0)
Overall total, 36-64 years	-	249.7 (221.0, 284.0)	262.9 (233.0, 297.0)	~~345~~1175.4~~7~~ (1109~~310~~.0, 1243~~383~~.0)

[1]Numbers in green denote where observed count fell within 95% prediction interval [95% PI] for people aged 16-35 years. Observed data for people aged 36-64 years in the *validation sample* was not available.

Model 1: Age group, sex, their interaction and ethnicity
Model 2: Model 1 + IMD
Model 3: Model 1 + extent of deprivation
Model 5: Model 1 + employment deprivation
Model 6: Model 1 + population density
Model 7: Department of Health uniform figure for EIS of 15 new cases per

Model 4: Model 1 + income deprivation	100,000 people per year.

Table 3: External model validation diagnostics[1]

Model	Overall correct prediction? [rank]	EIS (N=6)		LAD (N=21)		Mean ranking [rank of mean ranking]
		Number correct [rank]	RMSE [rank]	Number correct [rank]	RMSE [rank]	
Model 1	No [3]	4 [2]	25.6 [6]	18 [2]	8.13 [6]	3.8 [4]
Model 2	No [3]	3 [6]	18.4 [4]	17 [5]	6.987 [4]	4.4 [6]
Model 3	No [3]	4 [2]	16.4 [3]	18 [2]	6.51 [3]	2.6 [3]
Model 4	Yes [1]	4 [2]	16.3 [2]	18 [2]	6.40 [2]	1.8 [2]
Model 5	No [3]	4 [2]	19.4 [5]	16 [6]	7.11 [5]	4.2 [5]
Model 6	Yes [1]	5 [1]	11.9 [1]	19 [1]	5.93 [1]	1.0 [1]
Model 7	No [3]	01 [7]	38.159.4 [7]	135 [7]	181.032 [7]	6.2 [7]

[1]For each diagnostic, models are placed in rank order [1=best model, 7=worst model] with ties given the same ranking. The mean ranking and rank provide an estimate of the overall performance of various models.

RMSE: Root mean squared error (lower scores indicate lower error); EIS: Early Intervention in Psychosis Service; LAD: Local Authority District

Article Summary

Article Focus

- Commissioners require precise information on the health needs of their local populations to effectively plan health services
- A failure to arm mental health commissioners with precise epidemiological data led to mis-estimation ~~an underestimate~~ of actual activity in early intervention in psychosis services [EIS]
- We sought to develop a prediction tool for the incidence of first episode psychosis [FEP], by applying precise estimates of epidemiological risk in various sociodemographic groups to the structure of the population at-risk in a second region, where the observed incidence had been concurrently ascertained

Key Messages

- A model of psychosis incidence which included age, sex, ethnicity and population density yielded precise FEP predictions in our second region, out-performing the Department of Health in England's current gold standard for EIS commissioning.
- We have translated this model into a freely available prediction tool (www.psymaptic.org) to facilitate evidence-based healthcare commissioning of socioculturally relevant services according to local need
- Our tool could be extended to many international settings and other disorders to inform healthcare commissioning, when epidemiological risk can be well-characterised and the structure of the underlying population at-risk is known

Strengths and limitations

- Our modelling approach used robust epidemiological data from two large studies of first episode psychosis in England to provide estimates of incidence in a third study region, producing accurate FEP forecasts
- While our models provide estimates of the expected clinical burden of FEP in the community, services may see a broader range of psychopathology consuming resources, or incepted rates may be influenced by supply-side organisational factors
- Due to data availability it was not possible to validate our prediction tool in settings outside of England and Wales, or for specific psychotic disorders. As data become available we will extend the capability of our prediction tool.

Supplemental Table 1: Socioenvironmental variables at local authority district [LAD] level considered in epidemiological prediction models						
Variable		**England[1]**	**Prediction sample[2]**	**Validation sample[1]**	**Mann-Whitney test[3]: Z; p-value**	
					Prediction vs. Validation	**Validation vs. England**
Number of LAD	-	326	14	20 (+1 partial)	-	-
Multiple deprivation (z-standardised)	Median (IQR): Min/Max:	0 (1)[4] -1.7 / 2.9	1.0 (-0.5, 2.4) -1.1 / 2.9	-0.7 (-1.0, 0.3) -1.4 / 1.0	2.4; p=0.02	1.5; p=0.12
Extent of deprivation (%)	Median (IQR): Min/Max:	9.0 (1.3, 23.9) 0.0 / 83.6	28.0 (4.0, 63.0) 0.0 / 83.0	1.4 (.4, 12.8) 0.0 / 29.7	2.4; p=0.02	2.2; p=0.03
Income deprivation (%)	Median (IQR): Min/Max:	11.7 (8.6, 16.1) 3.9 / 32.8	15.5 (8.2, 24.7) 5.9 / 34.4	9.0 (8.2, 14.9) 6.0 / 19.1	1.5; p=0.14	1.3; p=0.19
Employment deprivation (%)	Median (IQR): Min/Max:	8.0 (5.8, 10.8) 2.1 / 18.8	11.6 (6.1, 14.1) 6.1 / 14.1	6.4 (5.4, 10.1) 3.9 / 13.9	2.5; p=0.01	1.4; p=0.17
Population density (people per hectare)	Median (IQR): Min/Max:	5.1 (1.8, 17.4) 0.2 / 137.1	19.4 (9.3, 81.9) 2.6 / 106.4	1.5 (1.2, 3.1) 0.9 / 30.0	3.7; p<0.001	3.4; p=0.001

IQR: inter-quartile range; LAD: Local Authority District

[1]Sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

[2]Sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000).

[3]Mann-Whitney test performs test that the median LAD socioenvironmental scores for the prediction & validation data come from the same population distribution; p<0.05 indicates evidence that the median scores are significantly different

[4]For England we displayed the mean and s.d. of the z-score of deprivation (as shown, underlined), instead of the median and IQR.

Appendix (supplementary): Development of 95% prediction intervals for negative binomial regression models

To obtain 95% prediction intervals from each model, we took all parameter estimates from the fitted negative binomial regression, including the over-dispersion parameter θ, as the true values when constructing prediction intervals. We then used a Monte Carlo procedure, where we simulated realisations using the Gamma-Poisson representation of the negative binomial distribution. For each iteration, we first simulated the random components of the linear predictors from Gamma(θ,θ), which were multiplied by the point predictions (or equivalently e^{υ}, where υ is the non-random component of the linear predictor) to give the Poisson rates for the counts that comprised the predictions. We then simulated Poisson counts using these rates and summed them to provide one realisation of the quantity we wished to predict. By repeating this process many (n=1000) times the distribution of the quantity to be predicted was obtained, from which 95% prediction intervals were obtained using the 2.5% and 97.5% quantiles.

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Data sharing statement

Extra data is available at our prediction website, PsyMaptic: www.psymaptic.org. We have made a large array of prediction data freely available to interested users, who can visualise prediction data in maps and tables for a range of psychotic disorder predictions by major sociodemographic subgroup and by LAD. Future versions of PsyMaptic will release data for other regions and at other geographical levels. Users can also download LAD-specific and national summaries of prediction data from our models in tabular form. Finally, additional explanatory material about how to use the data and the PsyMaptic website is also available at www.psymaptic.org. Bespoke data not provided freely on our website may be requested from the authors at the cost of data extraction. The empirical data underlying the prediction models (ÆSOP and ELFEP) or the validation sample (SEPEA) is not freely available as the studies are ongoing, but papers detailing the main findings from these studies have previously been published elsewhere.

Competing interests statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (i) JBK has support from the Wellcome Trust for the submitted work (grant number WT085540) and PBJ has support from the NIHR (grant RP-PG-0606-1335); (ii) DJ, JP, FW, DF, JC, RMM have no relationships with any company that might have an interest in the submitted work in the previous 3 years; (iii) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (iv) no author holds non-financial interests that may be relevant to the submitted work.

Role of funders

The funders were not involved in the design, collection, analysis, interpretation of the data, writing the report or the decision to submit the article for publication. All authors were independent from the funders in contributing to this work.

Ethical approval

Ethical approval to conduct the original ÆSOP and East London First Episode Psychosis studies was granted from local research ethics committees in their respective centres prior to the original date of onset of the study. We were granted ethical approval to conduct the work related to the present manuscript, including use of data from the SEPEA study, from the Cambridgeshire 3 REC (09/H0306/39).

Guarantorship

JBK takes full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

Contributorship

JBK was responsible for concept, design, analysis, data extrapolation, interpretation of the data, drafting the report and developing the content for the websites www.psymaptic.org, www.psymaptic.com and www.psymaptic.co.uk. JBK was also the chief investigator of the SEPEA study, where the *validation sample* data was obtained. He gave final approval of this version of the manuscript to be published.

DJ was responsible for developing and initially implementing the statistical approach with regard to prediction intervals from count-based regression. He also contributed to drafting and editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JP is principal collaborator on the SEPEA study in the CAMEO early intervention in psychosis services. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

DF is co-principal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

FW is co-principal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JC is chief investigator of the ELFEP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

RMM is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

PBJ is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He contributed to the development of the prediction methodology and edited the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

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STROBE statement

Our STROBE statement is provided as a supplementary file.

Supplemental Figure 1: Screenshot of web-based PsyMaptic prediction tool

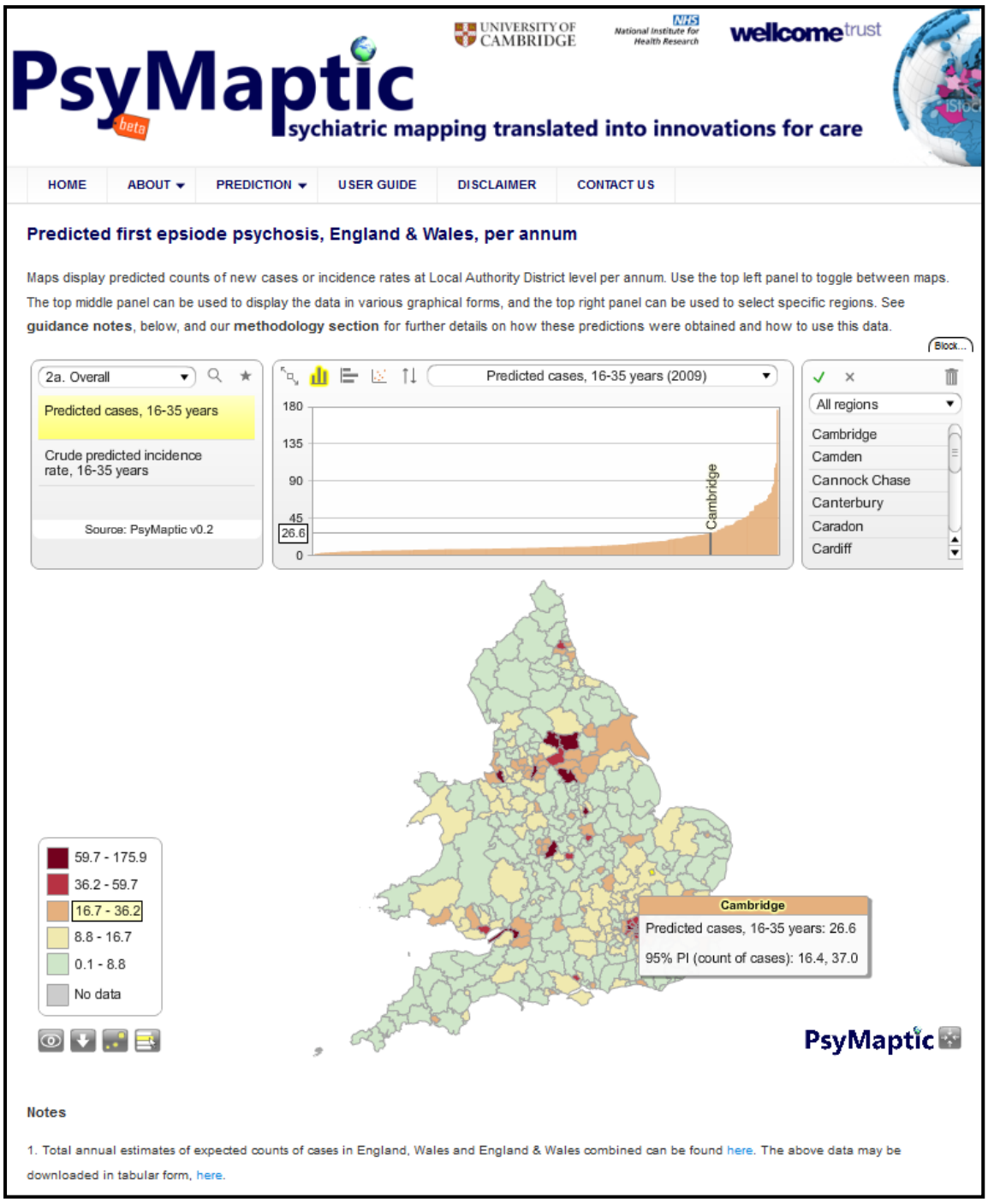

Figure legend: Screenshot shows the PsyMaptic prediction tool made freely available at www.psymaptic.org. This example shows a prediction map of the annual expected count of new cases of psychotic disorder for people aged 16-35 years across 376 Local Authority Districts [LAD] in England & Wales from our candidate prediction model (Model 6). Each prediction is presented with corresponding 95% prediction intervals. Count data are categorised into the following percentiles: green: 0-50% of LAD; yellow: 50.1-75%; orange: 75.1-90%; red: 90.1-95%; dark red: 95.1-100%. Our PsyMaptic prediction maps are provided with additional graphical utility (histograms, scatterplots, region selection) and are freely available at www.psymaptic.org

Supplemental Figure 2: PsyMaptic predicted incidence rate of psychotic disorder in England and Wales, aged 16-35 years old, compared with Department of Health uniform rate for EIS commissioning

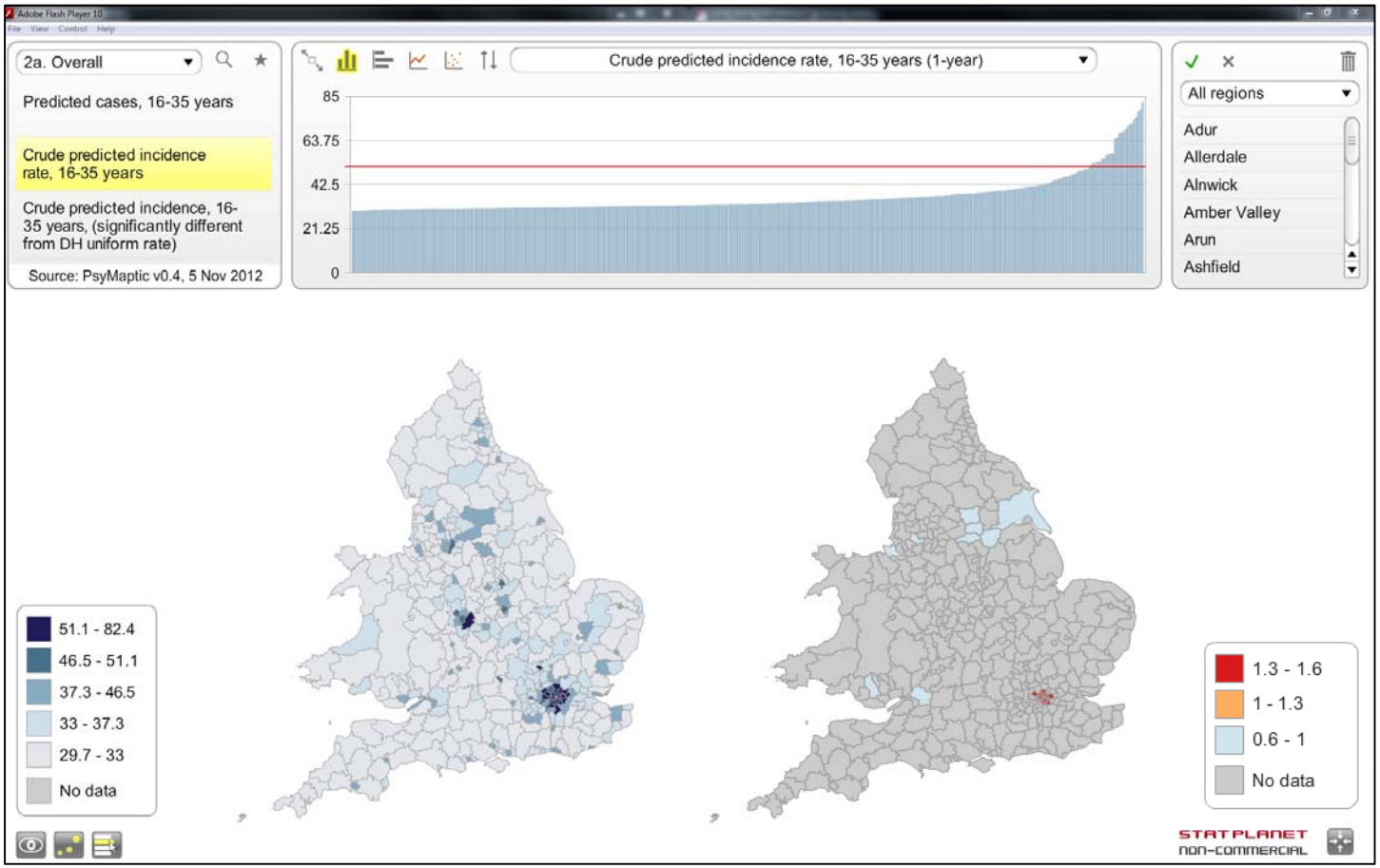

Figure legend: The graph (top) plots all LADs according to predicted incidence rates in people aged 16-35 years (per 100,000 person-years) using PsyMaptic (model 6). The red line is the uniform rate (51 cases per 100kpy), used to commission EIS. Our predicted rates fall below this in 93% of LAD in England & Wales (n=351), indicating that the Department of Health's [DH] uniform rate may have over-estimated incidence in these regions. Predicted incidence rates are plotted geographically on the left hand map, The darkest shading indicates LAD (in London and Birmingham) where the point estimate of incidence exceeded the DH uniform rate. The right hand map plots the ratio between predicted cases from PsyMaptic & the DH uniform rate. Ratios significantly exceeding unity (in orange & red) show regions where the DH rate under-estimated incidence; ratios significantly less than unity (in blue) show regions where the DH rate over-estimated incidence. This method is conservative (see methodology).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract We entitled our paper **A population-level prediction tool for first episode psychosis: development and validation**. While our paper uses cross-section data to base prediction models on, the central study design is in reference to prediction modelling using epidemiological data, which we have duly referred to.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Our abstract was written in the structured style required by the British Medical Journal for publication and included information on *background, objectives, design, setting, main outcome measures, results* and *conclusions.*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Health care planners and commissioners require accurate data on the incidence of psychotic disorder to anticipate the burdens faced by different populations in different regions. Only by using precise predictions, which take into account local need, will it be possible for health care funders and commissioners to allocate finite resources where they are most needed. There is evidence that Early Intervention in Psychosis services [EIS] were commissioned on an erroneously low uniform rate, and that commissioners were unable to satisfactorily take into local population need based on established sociodemographic and environmental risk factors for disorder. This led to misestimation of demand for EIS services in many parts of the UK. We sought to improve the information available for health care commissioners in psychosis, and particularly EIS, by developing an epidemiological prediction tool for disorder.
Objectives	3	State specific objectives, including any prespecified hypotheses To develop a population-based epidemiological prediction tool for first episode psychosis [FEP]. Our hypothesis was that our best prediction model, using informed empirical epidemiological data, should be more valid than the current gold standard for EIS planning, based on the Department of Health's Mental Health Policy Implementation Guide figure of 51 new cases per year per 100,000 people.
Methods		
Study design	4	Present key elements of study design early in the paper Pooled data from two large epidemiological studies of First Episode Psychosis [FEP] conducted with similar methodologies (the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [AESOP] study, and the East London First Episode Psychosis [ELFEP] study) were used to generate risk coefficients from six negative binomial regression models, which tested different combinations of sociodemographic (i.e. age, sex, ethnicity) and socioenvironmental factors (deprivation, population density at local authority district [LAD] level) associated with psychosis incidence. Coefficients were applied to the population at-risk of a third, markedly different region, to predict expected FEP counts over a 2.5 year period, where the observed incidence had also been ascertained.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Empirical data from the AESOP (1997-9) and ELFEP (1996-8 & 1998-2000) studies

		in London, Nottingham and Bristol was used in regression models to estimated out-of-sample predictions for the expected count of new FEP cases in the population at-risk of East Anglia over a 2.5 year period (2009-2012), where the observed count of cases incepted through EIS has also been ascertained through a third study, the Social Epidemiology of Psychoses in East Anglia [SEPEA] study.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants All participants in the AESOP and ELFEP studies, aged 16-64 years old at referral, were identified using the same study design based on the principles of the World Health Organisation Ten-Country study. Any participant presenting to services in each study's defined catchment areas with a suspected first episode of psychotic disorder over the case ascertainment period were screened. Participants were included if they were diagnosed by consensus with an ICD-10 F10-39 first episode of psychotic disorder, using standardised diagnostic data from the Schedule for the Clinical Assessment of Neuropsychiatry [SCAN] presented to a panel of clinicians blind to the ethnicity of the subject. A leakage study was conducted to identified participants missed by the initial screen. Participants in the SEPEA study, aged 16-35 years old, were identified if they were referred to one of six EIS in East Anglia for the first time with a suspected first episode of psychosis in the defined catchment area of these services over a 2.5 year period. Participants were excluded if they did not meet clinical criteria for acceptance into EIS or if, at six months after referral, a clinical diagnosis of ICD-10 F10-39 psychosis had not been observed. Observational data in people aged 36-64 years old could not be obtained as this was not part of the SEPEA study objective and no routine surveillance of this group was in place. Participants from any study were excluded if they were found to have a profound learning disability or an organic basis to their psychotic episode. The denominator populations for AESOP and ELFEP were estimated from the 2001 Census of Great Britain, while the latest mid-term census estimates (2009) stratified by age, sex and ethnicity were obtained for the denominator population in the SEPEA study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable All clinically relevant psychotic disorders as per ICD-10 F10-39 psychotic disorders were included as the main outcome variable. We included age group (16-19, then 5 year age groups until 60-64 years), sex and ethnic group (ten categories based on the 2001 census 16-category variable to include: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white & black Caribbean, other mixed ethnicities and all other ethnicities). Given evidence of effect modification of the risk of psychotic disorder over age by sex, we considered an *a priori* interaction between these variables. All individual level variables are known to be associated with the incidence of psychotic disorder and were therefore considered important predictors in our models. Additionally, for some prediction models (see

		below), we also included various socioenvironmental measures at the Local Authority District [LAD] level, such as socioeconomic deprivation or population density, since there is evidence that the incidence of psychotic disorder varies by urbanicity and deprivation. Population density was measured by dividing total population size (2001 or 2009) by LAD area. The Indices of Deprivation (2004/2010) were used to include the potential effects of four domains of deprivation relevant to psychosis incidence – multiple deprivation, the extent of deprivation in the LAD (i.e. an inequality-like measure), income deprivation and employment deprivation. These domains were obtained from the 2004 and 2010 indices of deprivation for the AESOP/ELFEP and SEPEA studies, respectively, with the source data originating from national surveys and other data sources predominantly collected close to the case ascertainment periods of each study.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group For numerator participants: Age was based on age at first referral for suspected psychotic disorder. Ethnicity and sex were assigned by self-ascription. Neighbourhood-level socioenvironmental factors were assigned to participants based on their residential address at first referral to services. For denominator (census) participants: Age was defined as age at the time of the census or mid-term census estimate. Sex and ethnicity were defined through self-ascription. LAD population density was based on the total census/mid-term population in each LAD, divided by each LAD's area (in hectares) estimated using ArcGIS software. Deprivation domains were assessed by the 2004/2010 indices of deprivation, which use a comparable methodology to assess changes in deprivation over time, integrating data from a range of nationally-collected routine data sources.
Bias	9	Describe any efforts to address potential sources of bias To minimise the risk of missing incidence participants from the AESOP and ELFEP studies leakage studies were conducted to identify all subjects with a potential FEP, not picked up by the initial screen. This was achieved by close contact with other services where FEP subjects may present, including prisons, the judicial systems, homeless shelters and so forth. In the SEPEA study, EIS provide the only service base for people experiencing FEP up to 35 years old. No leakage study was possible in SEPEA, but all services engaged in active outreach to ensure missing participants were minimised in their communities. One potential source of bias in the SEPEA study is the over-estimation of incidence rates given that EIS do not tend to diagnose participants at referral to avoid stigmatisation and to allow the full course of symptoms to emerge. We minimised the possibility of over-inclusion here by excluding all participants who did not meet clinical criteria for entry to EIS (clear evidence of psychotic symptoms, no previous referral, no previous antipsychotic treatments) and by restricting the sample only to those participants who were given a clinician-rate ICD-10 F10-39 diagnosis of psychotic disorder at first episode.

Study size	10	Explain how the study size was arrived at Studies of incidence rates have a sample size equivalent to the ability of the study to identify all true instances of first episode psychosis in a defined catchment area and population over a given time period. Thus, the sample size for all studies here is a function of these factors. We included data from the SEPEA study for 2.5 years of the 3 year study, since it was presently ongoing at the time of these analyses. We included 14 LADs in our empirical prediction data (AESOP/ELFEP) and 21 LADs in our SEPEA study region.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Variable groupings for individual level variables have been described in Section 7. For LAD-level variables, population density was entered as a continuous variable. Multiple deprivation and the extent of deprivation were entered as continuous z-standardised variables (across variation in these scores over England) to have a mean of zero and standard deviation of one. Income and employment deprivation were classified as the proportion of people in a given LAD classed as income or employment deprived.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding A summary of our statistical methodology is provided here. Full details are provided at www.psymaptic.org or in the accompanying paper to this checklist: [i] Six negative binomial regression models were fitted to the empirical data (AESOP/ELFEP). Model 1 was fitted with age group, sex, their interaction and ethnic group. Models 2-5 included the variables in Model 1 plus a single LAD deprivation measure (multiple deprivation, extent of deprivation, income and employment deprivation, respectively). Model 6 included the variables in Model 1 plus LAD population density. [ii] Internal predictive error for the whole sample, aged 16-64 years, was estimated using repeat k-fold validation to obtain estimates of the Residual Mean Squared Error and Lin's Correlation Concordance Coefficient (correlation between model predictions and the observed count of cases in the data). For each full [iii] Regression coefficients from each model obtained in [i] were applied to the population structure of the population at-risk, aged 16-35 years old, in the SEPEA study to obtain out-of-sample predictions of the expected count of cases in East Anglia over 2.5 years as seen in the age range for EIS. Predicted counts for each model were obtained for the (1) overall predicted count (2) EIS-specific counts and (3) LAD-specific counts in East Anglia. For every prediction, 95% prediction intervals were estimated, using a bootstrap-like method developed from first principles to take into account prediction error in both the prediction data and the out-of-sample dataset. [iv] We obtained similar predictions to [iii] based on a "model" (Model 7) which fitted the Department of Health's current gold standard incidence rate for EIS commissioning (51 per 100000 per year) to the SEPEA data and obtained predictions [iii](1-3) as before.

[v] The predicted counts from each model obtained in [iii] (1-3) were compared with the observed counts of cases for each grouping. We considered the number of times the observed count fell within the 95% prediction intervals from the model prediction to indicate satisfactory model fit. RMSE estimates of model fit between the predicted and observed counts at the EIS- and LAD-levels were obtained for external model validation and comparison. For each of the five diagnostics (overall fit to the observed data, number of times fitted correctly to six EIS, number of times fitted correctly to the 21 LAD, EIS-level RMSE, LAD-level RMSE) we ranked models in terms of performance (1: best, 7: worst). Ranks were averaged across these 5 diagnostics to give an overall ranking for the model which had the greatest predictive power.

[vi] Using the best model obtained in [v] we extrapolated our findings to the population structure (2009 mid-term estimates) of every LAD in England and Wales to produce a freely available prediction tool for commissioners, which forecasts (with 95% Prediction Intervals) the expected incidence of psychotic disorder in every LAD, across all major sociodemographic groups, based on empirical risk coefficients and applied to each LAD's unique population structure. This prediction data was visualised using software known as StatPlanet and uploaded to our website www.psymaptic.org to provide Psychiatric Mapping Translated into Innovations for Care [PsyMaptic], a free, online commissioning tool for health care planners, providers and commissioners.

(*b*) Describe any methods used to examine subgroups and interactions

We used the full empirical dataset aged 16-64 years to predict the expected count of cases in our validation sample (SEPEA), where the observed caseload had been restricted to the ages 16-35 years old, consistent with the age range covered by EIS. SEPEA did not identify an incidence sample in this region for people aged 36-64 years old and so we could not externally validate our models in this age range. However internal validity of our models across the entire age range, 16-64 years old, was good, and we have no reasons to believe our empirical data in the older age range would be any less valid for prediction than at younger age ranges given it was obtained from the same two studies (AESOP/ELFEP).

Interactions between age group and sex were entered into our regression models as a multiplicative statistical interaction.

(*c*) Explain how missing data were addressed

There were no missing data in this dataset

(*d*) If applicable, describe analytical methods taking account of sampling strategy

N/A

(*e*) Describe any sensitivity analyses

95% prediction intervals were developed for negative binomial regression prediction and reported for all predicted counts and incidence rates of FEP. These intervals give a measure of the confidence we have in our prediction estimates.

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 1037 participants with a first episode psychosis were included in the prediction sample of an initial sample of 1049, where 12 participants were of no fixed abode at time of entry to the study. For the SEPEA study 528 cases were observed over the study period who met entry criteria for the study from an initial sample of 572. Those excluded did not meet clinical criteria for FEP.
		(b) Give reasons for non-participation at each stage See above
		(c) Consider use of a flow diagram Not necessary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. See previously published papers on the AESOP, ELFEP and SEPEA studies as this is not directly relevant here. Of more relevance are the risk coefficients for psychosis incidence across sociodemographic and socioenvironmental groups, as reported in Table 1 of the paper accompanying to this Strobe statement includes. This table confirms the typical risk coefficients seen across these variables.
		(b) Indicate number of participants with missing data for each variable of interest 12 participants were excluded because of no fixed abode in the AESOP. These subjects were more likely to be men, but otherwise did not differ from the remainder of the sample.
Outcome data	15*	Report numbers of outcome events or summary measures N/A – see below for full results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. A model with age, sex, ethnicity and population density performed strongest overall, predicting 508 FEP participants in EIS in East Anglia (95%PI: 459, 559) compared with an observed count of 528 over the same period. This model predicted correctly in 5 of 6 EIS (83.3%) and 19 of 21 LAD (90.5%). This model achieved the highest ranking on all external diagnostic measures of any model, and reasonable internal RMSE (0.76; s.d.: 0.13) and CCC (0.76; 95% CI: 0.74, 0.77) estimates across the entire age range. All models performed better than the current gold standard for EIS service commissioning (716 cases; 95%PI: 664-769).
		(*b*) Report category boundaries when continuous variables were categorized Age groups – see above
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives

		We have developed several epidemiological prediction models to forecast expected incidence of first episode psychosis in England and Wales, and assessed their relative internal and external validity, taking into account regional differences in the sociodemographic and socioenvironmental profile of different populations. Inspection of the data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the best external predictive capabilities compared with the observed caseload ascertained through EIS in our *validation sample*. This model also had good internal validity across the entire age range considered here (16-64 years). All prediction models performed significantly better than the Department of Health's current gold standard for EIS resource allocation, based on a low uniform anticipated incidence rate.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Our predictions are based upon the assumed true rate of disorder in the population aged 16-64, 16-35 or 36-64 years old. This may differ from the caseloads observed by services, due to supply-side and demand-side issues. For example, services may see a broader range of referrals who are not psychotic or in the prodromal stage of disorder. Additional resources for false positive caseloads need to be considered in any commissioning decisions. Furthermore, demand for services may differ from the true underlying rate of FEP in the community if people are not aware of the relevant mental health services available to them. Services vary considerably in organisation, remit and structure and such factors may also affect the incepted (versus true) rate of disorder seen in EIS and other mental health services. Prediction intervals for count-based regression models are not computationally-straightforward to derive. We estimated prediction intervals from first principles [DJ], using a bootstrap-like methodology to produce 95%PI accounting for uncertainty in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in prediction models, which were assumed to be the true coefficients of risk in the population. This approach naturally leads to narrow 95%PIs given ignorance of parameter uncertainty, and is therefore desirable for model validation and the precise prediction of expected counts. The addition of more empirical data to the prediction model would thus not lead to narrower PIs, though might move the point estimate of risk for each coefficient closer to the true value in the population. We sought independent confirmation that our formula was correct (Prof Ian White, MRC Biostatistics Unit) and full details of our methodology are made available in the Appendix. We recommend that all prediction point estimates made available in our PsyMaptic model are considered with their 95%PIs, which provide information about the natural variance in expected rates in the population. We could not externally validate our prediction models for people aged 36-64 years because comparable observed incidence data was not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models was ascertained from the same two large, well-conducted studies of first episode psychosis in England as the data for the younger age group, and published findings from these studies are

		consistent with the wider epidemiological literature for psychosis from England and internationally. It will be important to ascertain the predictive capability of our model(s) where we could not externally validate our model, and we will seek to identify suitable samples to do so in future versions of PsyMaptic. All prediction models had reasonable internal validity, although our proposed model had slightly poorer internal validity (most noticeably in terms of AIC) than models which included deprivation instead of population density (i.e. Models 2-4). Model 4 (including income deprivation) had marginally greater internal validity than our candidate prediction model, but performed worse during *external validation* (Table 4), which we considered more important for the development of a prediction tool. This decision was supported by the fact that despite considerable socioenvironmental differences between regions in our *prediction* and *validation samples,* our prediction model produced accurate forecasts in a markedly different population. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards (N~6000), or to other parts of the UK, because the appropriate denominator data was not published as mid-term census estimates. The 2011 census will provide small area and national data for the whole of the UK and will be released by ONS in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. Small area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development. We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16-35 years old. EIS are the only mental health service for people aged 14-35 years experiencing a first episode of psychosis, minimising the potential for under-ascertainment in the population at-risk when derived from a careful epidemiological design. We are confident that our *validation sample* also contained few false positive cases for any clinically-relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS or who did not receive a clinical diagnosis of psychotic disorder at six months after referral. Future versions of PsyMaptic will include forecasts for specific psychotic disorders, but these are unavailable at present because standardised research-based diagnostic data (using OPCRIT) needed to obtain specific reliable diagnoses are currently being collected in the ongoing SEPEA study.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence If commissioners are to meet the Department of Health's vision to orientate health services around local need, differences in demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data is combined with accurate population at-risk estimates this can be realised. Our translational approach demonstrated good internal and external validity to predict the expected incidence of first episode psychosis, particularly through EIS where 76% and 63% of all male and female adult-onset FEP cases, respectively, would typically present. Since their

		inception in 2002, EIS in England and Wales have reported both lower and higher caseloads than they were originally typically commissioned to manage, usually depending on the urbanicity of the population. Rural communities saw much lower demand for EIS than urban services. The Mental Health-Policy Implementation Guide [MH-PIG] anticipated a uniform rate of 51 per 100,000 people per year. While the MH-PIG also acknowledged that "…[a]n understanding of local epidemiology is needed as the size of population covered will depend on a number of different factors" (p.55), no further elaboration on how to achieve this was provided for commissioners. We believe PsyMaptic provides one possible exemplar to overcome this challenge.
Generalisability	21	Discuss the generalisability (external validity) of the study results We believe our results are generalisable to the populations of England and Wales. The empirical data we used is consistent with the wider international and national literature regarding the pattern of incidence rates across different sociodemographic and socioenvironmental subgroups. Our model had good external validity in the age range 16-35 years, and we have no reason to doubt its validity for the entire adult age range for psychosis, 16-64 years old given the reasonable internal validity demonstrated. That our prediction data was based on a very different environment (urban London, Nottingham and Bristol) but still produced valid forecasts in a markedly more diverse, rural and less deprived region overall (East Anglia), suggests our model will have good validity in England and Wales. This will make our prediction model a valuable tool for mental health service planning and commissioning, based on local need and translational epidemiology, when the prediction intervals we produce here are also taken into account. Service commissioners must also provide allowances for differing structure of services and the extra (false positive) referrals that may consume service resources but do not meet clinical criteria for FEP.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 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. Peter Jones directs the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for Cambridgeshire & Peterborough and is supported by NIHR grant RP-PG-0606-1335. The SEPEA study has been adopted by the Mental Health Research Network [MHRN]. The authors are grateful to the clinical services and staff participating in the SEPEA study, and the MHRN for their support. We are grateful to Professor Ian White of the MRC Biostatistics Unit (University of Cambridge) for his guidance on developing our prediction interval methodology for negative binomial regression.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A population-level prediction tool for the incidence of first episode psychosis: translational epidemiology based on cross-sectional data

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A population-level prediction tool for the incidence of first episode psychosis: translational epidemiology based on cross-sectional data

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Article Summary

Article Focus

- Commissioners require precise information on the health needs of their local populations to effectively plan health services
- A failure to arm mental health commissioners with precise epidemiological data led to mis-estimation of actual activity in early intervention in psychosis services [EIS]
- We sought to develop a prediction tool for the incidence of first episode psychosis [FEP], by applying precise estimates of epidemiological risk in various sociodemographic groups to the structure of the population at-risk in a second region, where the observed incidence had been concurrently ascertained

Key Messages

- A model of psychosis incidence which included age, sex, ethnicity and population density yielded precise FEP predictions in our second region, out-performing the Department of Health in England's current gold standard for EIS commissioning.
- While our model provides forecasts of the burden of FEP in different populations, initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.
- We have translated this model into a freely available prediction tool (www.psymaptic.org) to facilitate evidence-based healthcare commissioning of socioculturally relevant services according to local need
-

Strengths and limitations

- Our modelling approach used robust epidemiological data from two large studies of first episode psychosis in England to provide estimates of incidence in a third study region, producing accurate FEP forecasts
- While our models provide estimates of the expected clinical burden of FEP in the community, services may see a broader range of psychopathology consuming resources, or incepted rates may be influenced by supply-side organisational factors
- Due to data availability it was not possible to validate our prediction tool in settings outside of England and Wales, or for specific psychotic disorders. As data become available we will extend the capability of our prediction tool, including into other settings and disorders.

Abstract

Objectives: Specialist early intervention services [EIS] for people aged 14-35 years with first episodes of psychosis [FEP] have been commissioned throughout England since 2001. A single estimate of population need was used everywhere, but true incidence varies enormously according to sociodemographic factors. We sought to develop a realistically-complex, population-based prediction tool for FEP, based on precise estimates of epidemiological risk.

Design & participants: Data from 1037 participants in two cross-sectional population-based FEP studies were fitted to several negative binomial regression models to estimate risk coefficients across combinations of different sociodemographic and socioenvironmental factors. We applied these coefficients to the population at-risk of a third, socioeconomically different region to predict expected caseload over 2.5 years, where observed rates of ICD-10 F10-39 FEP had been concurrently ascertained via EIS.

Setting: Empirical data from London, Nottingham and Bristol predicted counts in the population at-risk in the East Anglia region of England.

Main outcome measures: Observed counts compared with predicted counts (with 95% prediction intervals) at regional, EIS and local authority district [LAD] levels in East Anglia to establish predictive validity of each model.

Results: A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in EIS in East Anglia (95%PI: 459, 559), compared with 521 observed participants. This model predicted correctly in 5/6 EIS and 19/21 LAD. All models performed better than the current gold standard for EIS commissioning in England (716 cases; 95%PI: 664-769).

Conclusions: We have developed a prediction tool for incidence of psychotic disorders in England and Wales, made freely available online (www.psymaptic.org) to provide healthcare commissioners with accurate forecasts of FEP based on robust epidemiology and anticipated local population need. Initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.

Background

Commissioners of health and social care require precise information on the health needs of their local populations[1], especially if parity of mental and physical health is to be realised.[2] Mental health disorders alone represent the leading disease burden in the UK (22.8%).[3] They contribute substantially to healthcare expenditure and societal costs even before physical ill health is taken into account. The Centre for Mental Health estimated total costs of mental health to British health services and society at £105 billion in 2009/10,[4] a figure expected to double over the next 20 years.[2] These are serious challenges compounded by a paucity of information on which to commission appropriate services. Early intervention in psychosis services [EIS] for people aged 14-35 years with a first episode of psychosis [FEP] offer a useful example of failure to map services to local need.

EIS are a major evidence-based innovation, systematically commissioned throughout England and Wales over the past decade.[5] When EIS intervention is sustained there is evidence that people with psychosis achieve better functional and social outcomes.[6, 7] Such services are also highly cost-effective.[4, 8, 9] However, EIS were originally commissioned on an anticipated rate of 150 new cases of any psychotic disorder per 1,000,000 of the total population per year in the Department of Health's Mental Health Policy Implementation Guide [MH-PIG].[5] In 2001 in England and Wales, 29.3% of the population were aged 14-35 years old, meaning that the MH-PIG commissioned incidence rate was approximately 51 cases per 100,000 person-years in the age range covered by EIS. Following their deployment, anecdotal reports began to emerge from EIS in different regions to suggest that a uniform figure for commissioning was simultaneously under-[10] and over-estimating[11] actual observed need in urban and rural populations, respectively. Recent epidemiological evidence of FEP incidence in rural communities in England has suggested that rates are somewhat lower than the uniform figure upon which services were commissioned, [12, 13] confirming previous calls that a "one-size-fits-all" prescription for EIS implementation is unlikely to lead to the efficient allocation of finite mental health resources.[14, 15]

Using rich epidemiological data on variation in the incidence of first episode psychosis according to major sociodemographic risk factors,[16-19] we describe the development and validation of a population-level prediction tool capable of accurately estimating the expected incidence of psychiatric disorder, based on the sociodemographic structure of the population in a given region. Applied to FEP as proof-of-concept, we show it is possible to closely predict expected incidence in a given population, where the observed count of cases was within the prediction intervals forecast by our models. We applied our

most precise prediction model to the population of England and Wales to provide health commissioners with a translational epidemiological prediction tool to underpin information-based service planning.

Methods

Our prediction models were based on epidemiological data from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [ÆSOP] and the East London First Episode Psychoses [ELFEP] studies,[18, 20] two methodologically-similar population-based FEP studies. We fitted various count-based regression models with different combinations of sociodemographic and socioenvironmental factors, well-established in the literature to be associated with the incidence of psychotic disorder.[21, 22] We first established the relative *apparent validity* of each model by estimating model fit diagnostics to assess how well each model fitted the empirical data (henceforth, the *prediction sample*). We next sought to estimate the *external validity* of each model by applying model-based parameter coefficients to the population structure of a purposefully different region of England, East Anglia (henceforth, the *validation sample*). This out-of-sample prediction technique allowed us to obtain the expected incidence of disorder in this region forecast by each model, which we compared with observed rates simultaneously ascertained in this region via the ongoing Social Epidemiology of Psychoses in East Anglia [SEPEA] study.[13] We performed various model fit diagnostics to identify which, if any, model demonstrated utilisable predictive capability.

Empirical data underlying prediction models (*prediction sample*)

Case ascertainment (numerator)

The designs of the ÆSOP and ELFEP studies have been described in detail elsewhere,[18, 20] with features relevant to the present paper summarised here. Case ascertainment took place over two years in ELFEP (Newham: 1996-8; Tower Hamlets & Hackney: 1998-2000) and the Southeast London and Nottingham centres of the ÆSOP study (1997-9), and over the first 9 months of 1997 in Bristol (ÆSOP). All service bases were screened regularly for potential new contacts aged 16-64 years (18-64 in ELFEP) resident within these catchment areas. Leakage studies were conducted to identify participants missed by this initial screen, but meeting inclusion criteria for FEP.[18, 20] All participants who received an ICD-10 F10-39 diagnosis for psychotic disorder following assessment via the Schedules for Clinical Assessment in Neuropsychiatry were included in the incident sample, except those with an organic medical basis to their disorder or profound learning difficulty. Data on age-at-contact, sex and ethnicity were collected on included participants. We geocoded participants' residential postcode at first contact to their

corresponding local authority district [LAD] to allow us to model possible neighbourhood effects associated with the incidence of psychotic disorder, such as population density or socioeconomic deprivation.

Population at-risk

We estimated the population at-risk using the 2001 Census of Great Britain, adjusted for study duration, and stratified by age group (16-17, 18-19, then 5-year age bands), sex and ethnicity. Ethnicity was based on self-ascription according to one of ten categories derived from the census: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white & black Caribbean, other mixed ethnic backgrounds and all other ethnicities.

Socioenvironmental variable estimation

We estimated LAD -level deprivation using the 2004 Index of Multiple Deprivation [IMD] in England, which estimated domains of deprivation using measures predominantly collected close to the time of our case ascertainment periods (see Box 1).[23] We z-standardised English LAD IMD scores to have a mean of zero and standard deviation of one, and extracted IMD z-scores for the 14 LADs in the ÆSOP and ELFEP studies. To inspect whether any particular deprivation domain was a better predictor of psychosis incidence than IMD, we also considered LAD-level income deprivation, employment deprivation and the extent of deprivation in our models (Box 1). We estimated population density by dividing LAD usual resident population by its area (in hectares), using ArcGIS 9.3 software.

<Box 1 about here>

Observed data for external validation of prediction models (*validation sample*)

Observed participants and population at-risk data for our *validation sample* was obtained from the SEPEA study, an ongoing study of the incidence of psychotic disorders incepted over three years (2009-12) through one of six EIS covering 20 LAD and a subsection of one LAD (the town of Royston, Hertfordshire) in Norfolk (three EIS: West, Central and Great Yarmouth & Waveney), Suffolk (one EIS) and Cambridgeshire, Royston & Peterborough (CAMEO North and South EIS).[13]

Case ascertainment

To establish the incepted incidence of first episode psychosis as seen through EIS, entry criteria for the SEPEA study were:

- Referral to an EIS in East Anglia for suspected first episode of psychosis
- Aged 16-35 years old at first referral to EIS (17-35 years in CAMEO services)
- Resident within the catchment area at first referral
- First referral during case ascertainment period (2009-12)

At six months after EIS acceptance, or discharge from the service, whichever was sooner, we asked the clinician responsible for care to provide an ICD-10 F10-39 psychiatric diagnosis using all information available. We excluded participants without a clinical FEP diagnosis, or participants presenting with an organic basis to their disorder or profound learning disability. For remaining participants, basic sociodemographic and postcode information was recorded and classified in the same way as in the *prediction sample*. We included participants presenting to EIS during the first 2.5 years of the ongoing SEPEA study.

Population at-risk

We estimated the population at-risk of East Anglia using 2009 mid-year census estimates published by the Office for National Statistics [ONS] at LAD-level, by age group, sex and ethnicity.[24] These estimates used the 2001 census base, adjusted for immigration, births and deaths each year. It was not possible to obtain 2009 mid-year estimates for the town of Royston, because data were only published at LAD level. Here, we thus used denominator data from the 2001 census data, in order to estimate the population at-risk in Royston. We do not believe this would have substantially invalidated our results as this town represented 0.6% of the overall population at-risk (n=9,555) in the SEPEA study. Denominator data were multiplied by 2.5 to account for person-years of exposure in the *validation sample*.

Socioenvironmental variable estimation

For each LAD in the SEPEA study we obtained corresponding socioenvironmental variables to those included in our *prediction sample,* using updated data collected as close to the SEPEA case ascertainment period as possible. Population density was estimated using 2009 mid-term population estimates. Our measures of deprivation were derived from the IMD 2010,[25] which was estimated in an analogous way to 2004 data, but collected from sources obtained immediately prior to the SEPEA study.

Statistical techniques

Dataset generation

We constructed a dataset for the regression analysis of count data by pooling data from the ÆSOP & ELFEP studies (the *prediction sample*). Data were stratified by age group, sex, ethnicity and LAD, such that each stratum (N=2,536) represented the total count of FEP cases in a unique sociodemographic group for a given LAD, with a corresponding estimate of the population at-risk, treated as an offset in our models. Our socioenvironmental measures (population density, deprivation) were adjoined to the dataset for each LAD. Population at-risk data from the *validation sample* were stratified in the same way and retained in a separate database. Here, the count of cases, which we wished to predict, was entered as a vector of missing data which would be populated with predicted case estimates following prediction modelling.

Prediction models

We used the *prediction sample* data to fit negative binomial regression models to obtain parameter coefficients of incidence for the sociodemographic and socioenvironmental factors included in each model. We considered the internal and external predictive capabilities of six models, all of which contained age group, sex, an age-sex interaction term and ethnicity. Model 1 contained no further covariates. Model 2 also included IMD. We replaced IMD with either income, employment or the extent of deprivation, respectively, in models 3-5. Model 6 included population density. Initial exploration of the *prediction sample* data indicated the presence of possible over-dispersion (variance (δ^2=1.37) exceeded mean (μ=0.4) count of cases) so negative binomial regression was preferred to Poisson regression since it explicitly models any over-dispersion with an extra dispersion parameter.

Internal model cross-validation & prediction

We assessed apparent model validity in three ways. First we used Akaike's Information Criterion [AIC] to assess the respective overall fit of each model to the data. Second, we conducted K-fold cross-validation to assess each model's apparent validity to predict cases within the *prediction sample*. This method randomly allocated strata in the *prediction sample* into *K* subsets. Each model was then re-estimated on *K-1* subsets (the *training data*) to predict expected counts of cases in the K^{th} subset (the *test data*). This was repeated over *K* trials, such that each stratum in the dataset appeared exactly once as the *test data*. At the end of this process, we derived Lin's concordance correlation coefficient [CCC] and 95%

confidence intervals [95%CI] to estimate the correlation between predicted and observed counts of cases across all strata in the *prediction sample*. Finally, we estimated the root mean squared error [RMSE] to determine the average error between fitted and observed values from each model, where lower RMSE scores indicated smaller prediction error. The RMSE is derived as

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}$$

where y_i and $\hat{y}_i$ are the observed and predicted count of cases in the i^{th} stratum, respectively, and n is the number of strata.

We repeated K-fold cross-validation *h* times, generating *K* new random divisions of the data each time. We retained model fit diagnostics across *Kh* iterations, and reported the mean of Lin's CCC and RMSE to provide summary cross-validation statistics for each model. We specified *K=10* and *h=20*, as recommended for cross-validation to obtain precise model fit diagnostics.[26]

External model prediction & validation

We retained parameter coefficients from each model (using the full *prediction sample* data) and applied these to the corresponding population at-risk in the *validation sample* dataset. This gave out-of-sample prediction estimates for the expected count of cases in each stratum of the *validation sample*, given the model. We summed expected counts across relevant strata to estimate the (i) total predicted count of cases in the SEPEA region, (ii) predicted counts in each EIS, and (iii) predicted counts by LAD. These counts were further stratified by broad age group (16-35, 36-64 and 16-64 years). Because census (denominator) data was unavailable for 35 year olds alone (needed to estimate their contribution to predicted counts in the age range for EIS, 16-35 years) we assumed the risk coefficient was the same across all ages within the 35-39 year old age group. We apportioned predicted counts on a 1:4 ratio (35 years: 36-39 years) to their respective broad age groups.

To determine how well the MH-PIG[5] figure of 51 new cases per 100,000 people per year for EIS performed as a predictive tool, we also estimated the predicted count of cases in the *validation sample* under this scenario, which we termed "Model 7".

We derived prediction intervals [95% PIs] for all summary predictions from first principles for each negative binomial regression model, since their derivation is not straightforward, nor routinely implemented by statistical software. Prediction intervals are similar to confidence intervals, but account for standard errors introduced in both the *prediction* and *validation* samples. We developed a bootstrap-like approach to obtain prediction intervals from each model by simulating 1000 model-based realisations of the quantities we wished to predict, where we took the parameters to be the maximum likelihood estimates. We obtained the lower and upper bounds of the prediction intervals as the corresponding quantiles of the simulated realisations (see Appendix for full details).

To assess each model's external predictive capabilities, we considered five markers of predictive accuracy. We compared the number of times the observed count of cases in the SEPEA study fell within the prediction intervals estimated from each model for (i) the SEPEA region, (ii) at EIS level, and (iii) at LAD level. We also derived EIS- and LAD-level RMSE scores to estimate prediction error from each model in our *validation sample*. We ranked model performance (1: best, 7: worst) on these five measures, and estimated an overall mean rank to determine the overall predictive validity of each model.

Observational data on first episode psychosis in our *validation sample* were not available for the age range 36-64 years, so external validation was restricted to the 16-35 year old group. For completeness, however, we also reported overall predicted count of cases for this age group from each model.

Extrapolation to the United Kingdom

Guided by our validation procedures, we identified which model had the greatest overall predictive validity, and proposed this as a candidate for FEP incidence prediction in England and Wales. We repeated out-of-sample prediction on the sociodemographic and socioenvironmental population characteristics of each LAD in England and Wales to obtain national and LAD-level predictions. Denominator data was obtained from the ONS 2009 mid-term estimates and stratified as previously described. Overall counts were derived for three broad age groups (16-35, 36-64 and 16-64 years), and for each of these, by sex and ethnicity. 95% PIs were estimated as before. We visualised this data on maps and in tables to provide healthcare planners and commissioners with an easy-to-use tool to forecast the expected incidence of psychosis in England and Wales. We have made this available as a free, open-use prediction tool, known as PsyMaptic (version 0.5) (Psychiatric Mapping Translating Innovations into Care; www.psymaptic.org). Counts of cases predicted by our model were compared

with those obtained under the Department of Health's uniform rate in each LAD. We expressed these comparisons as ratios with 95% CIs derived using the same method as for standardised morbidity ratios [SMR]. This approach was conservative because here we substituted the usual numerator in an SMR, the observed, O, for a predicted count. Unlike an observed count, no sampling variation is present for the predicted count, only uncertainty due to the model from which the prediction was estimated. Since variance in the prediction is therefore much smaller than the variance normally present for the numerator (O) this led to conservative estimates of 95% CI. Ratios in LAD where 95% CI did not span unity could therefore be interpreted as regions where there was strong evidence that the predictions from our model differed significantly from those predicted by the Department of Health's uniform rate.

Software

All negative binomial regression models, out-of-sample prediction and estimation of 95% PI were conducted in R (version 2.15.1). Cross-validation and model-fit diagnostics were conducted in Stata (version 11). Prediction maps for England and Wales were created using StatPlanet Plus (version 3.0) visualisation software.[27]

Results

Prediction sample

Our prediction models contained data on 1,037 persons with a first episode psychosis in the ÆSOP (n=553; 53.3%) and ELFEP (n=484; 46.7%) studies, ascertained from over 2.4m person-years at-risk. Twelve participants were excluded from the original ÆSOP sample because they were of no fixed abode and could not be geocoded to an LAD.[18]

The population at-risk in the *prediction sample* came from LAD with higher median levels of multiple and employment deprivation, extent of deprivation and population density than the population at-risk in the *validation sample*, though there were no statistically significant differences in median income deprivation between the two samples (Supplemental Table 1).

<Supplemental Table 1 about here>

Parameter coefficients obtained from the full prediction sample following negative binomial regression are shown in Table 1. As previously reported from these data,[20, 28] incidence rates were generally raised

in ethnic minority groups compared with the white British population. Models 2-6 included a measure of LAD deprivation (Models 2-5) or population density (Model 6), which were all significantly associated with increased incidence of psychotic disorder, after control for individual-level confounders. Each of these models produced a lower AIC score than a model fitted solely with individual-level covariates (Model 1), indicating better fit. Cross-validation suggested all models achieved good CCC agreement between predicted and observed cases, with low RMSE values (Table 1).

<Table 1 about here>

Validation sample

Observed participants

We identified 572 participants over the first 30 months of the SEPEA study, aged 16-35 years old, who met acceptance criteria for EIS in East Anglia. We excluded 51 participants (8.9%) who did not meet clinical criteria for ICD-10 psychotic disorder. This left an incidence sample of 521 participants from nearly 1.4m person-years at risk (37.3 per 100,000 person-years; 95%CI: 34.2, 40.6). A further 2.3m person-years at-risk accrued in the same region for people aged 36-64 years over this period. Median levels of multiple, income and employment deprivation in the region did not differ significantly from the remainder of England, although median population density and extent of deprivation in East Anglia were lower than elsewhere in England (Supplemental Table 1).

<Table 2 about here>

External model prediction & validation

The overall observed count of cases, aged 16-35 years, in the *validation sample* (n=528) fell within 95% prediction intervals in four of seven models (Models 3 -6, Table 2). Of these, the observed count (N=521) was closest to the point estimate for Model 6 (508.5; 95% PI: 449.0, 559.0), fitted with age group, sex, their interaction, ethnic group and LAD population density. The observed count of cases also fell within prediction intervals from this model in five of six EIS in the study region, and 19 of 21 LADs, the most of any model (Table 3). This model had the lowest error scores at EIS (RMSE=11.5) and LAD (RMSE=6.0) levels of any model. Overall, Model 6 was ranked highest across all external model fit diagnostics (Table 3). All models outperformed the Department of Health's uniform figure of 51 cases per 100,000 people

per year (Model 7), which generally overestimated cases in the *validation sample* (overall prediction: 715.7 cases; 95% PI: 664.0, 769.0).

<Table 3 about here>

We also reported predicted cases aged 36-64 years old from our models (Table 3), although we could not test these in the *validation sample*. Model 6 predicted an additional 262.9 cases aged 36-64 years over a 2.5 year period in East Anglia (95% PI: 233.0, 297.0).

We also inspected the stratum-specific external validity of our best-fitting model (Model 6, Supplementary Table 2), which performed accurately for sex-specific predictions, but less well in age- and ethnicity-specific strata. Thus, our model tended to under-predict observed cases in people aged 16-19 years, but over-predicted cases observed in people over 25 years old. With respect to ethnicity, model predictions were consistent with observed FEP cases for people of non-British white, black African, Bangladeshi and mixed ethnicities. However, our model under-predicted observed rates in the white British group, and over-predicted rates in black Caribbean, Indian and Pakistani populations.

<Supplemental Table 2 about here>

Extrapolation to England and Wales

We predicted the expected count and incidence of first episode psychosis per annum in each LAD in England and Wales based on Model 6, and visualised this data in maps and tables freely available at www.psymaptic.org. Many maps can be visualised (for example, Supplemental Figure 1), including overall predicted incidence counts and rates for each broad age group at LAD level, and by sex. We will make PsyMaptic data available by ethnic group when we can improve the validity of future versions of these models for these strata. According to our model, the annual number of new FEP cases in England and Wales would be 8745 (95% PI: 8558, 8933), of which our model predicted 67.9% (N=5939; 95% PI: 5785, 6102) would be seen through EIS. Only 176 (95% PI: 151, 203) cases aged 16-64 years were forecast in Wales per annum. Assuming our prediction model is accurate, it indicated that the Department of Health's current uniform rate of 51 per 100,000 person-years was higher than the predicted point estimates for rates forecast by our PsyMaptic model in 351 LAD (93%) in England and Wales, but was lower than predicted by our model in Birmingham and several London boroughs

(Supplemental Figure 2, left hand map). Under a conservative approach, these differences achieved statistical significance in parts of London (where the Department of Health's model underestimated need as predicted by PsyMaptic), and in some more rural parts of England and Wales (where the Department of Health's model over-estimated need) (Supplemental Figure 2, right hand map).

<Supplemental Figures 1 & 2 about here>

Discussion

Principal findings

We have developed and tested several epidemiological prediction models to forecast FEP incidence in England and Wales, having taken into account regional differences in the sociodemographic and socioenvironmental profile of different populations. Inspection of our data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the greatest external predictive validity when compared with the observed FEP caseload ascertained through EIS in our *validation sample*. This model also had good apparent validity across the entire age range (16-64 years). All models performed significantly better in predicting the incidence of clinically relevant first episode psychosis than the Department of Health's current gold standard for EIS commissioning,[5] based on a uniform incidence rate. Our data suggested the figure used to commission EIS over-estimated the likely true incidence rates of FEP in rural areas, and under-estimated them in urban settings, although we acknowledge that commissioning decisions will need to be based on several additional factors, including the level of pre-clinical or non-psychotic psychopathology requiring assessment at initial referral to EIS, and variation in service organisation, remit and delivery.

Limitations & future development

Our prediction models were based on epidemiological data obtained from large, robust population-based FEP studies for people aged 16-64 years.[18, 19] The best-fitting model, overall, had good apparent validity over this age range, and good external validity over the age range 16-35 years. While this covered the majority of adult onset psychosis cases seen in mental health services, including EIS, we recognise that some EIS teams incept people from 14 years old. We were unable to extrapolate our models to this age range, given the current absence of incidence data for this group in England. Data from Scandinavia suggest that the incidence of such "early onset" psychoses is absolutely low,[29] although the rate may have been increasing in the last few decades, probably as a result of movement

towards earlier detection. We were also unable to externally validate prediction models for people aged 36-64 years, because comparable observed incidence data was not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models was ascertained from the same two large, well-conducted studies as for data on the younger age group.[18, 19, 28] Furthermore, published findings from these studies are consistent with the wider epidemiological literature for psychosis in England and internationally.[17, 21, 30] It will be important to validate the predictive capability of our model(s) in this age range, and we will seek to identify suitable samples to do so in future versions of PsyMaptic.

Our best-fitting overall model demonstrated excellent external validity for predicting sex-specific FEP cases in our *validation* region (i.e. SEPEA). It performed less well across age- and ethnic-specific stratum in this region. With respect to age, this discrepancy is most likely to be a function of EIS provision itself, which seeks to intervene as early as possible in the onset of psychosis. The effect of this will reduce median age at onset in comparison to studies conducted prior to the introduction of EIS, such as the ÆSOP and ELFEP studies, upon which our models are based. Future versions of PsyMaptic will incorporate empirical data from post-EIS studies to improve age-specific predictions. The validity of our model in some ethnic groups also requires further refinement. Much of the prediction data underlying our models came from urban environments with large proportions of ethnic minority groups. The sociodemographic profile and sociocultural experiences of these groups may be very different to those of their counterparts in other, less urban, parts of England, thus altering risk of psychosis according to ethnicity. In our observed data, a larger proportion of cases were white British than predicted by our model. If ethnicity is a partial proxy for exposure to deleterious socio-environmental experiences, such as the combined effect of social inequality, fragmentation, deprivation and population density,[31] then simultaneously incorporating such factors into our models may improve their predictive validity by ethnicity. Alternatively, risk by ethnic group may be conditional upon (i.e. interact with) environmental factors in urban areas (as with the ethnic density effect[32, 33]), but whether such interactions exist in less urban regions is not known. Forthcoming SEPEA and PsyMaptic data will explore such possibilities as 2011 census data become available.

All prediction models had reasonable apparent validity, although our proposed model performed slightly worse (most noticeably for AIC) than models which included deprivation (i.e. models 2-4) instead of population density. Our decision to use model 6 as our proposed candidate for the prediction tool was

supported by the fact that it produced the most accurate external forecasts of any model, despite considerable socioenvironmental differences between regions in our *prediction* and *validation* samples. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards (N~6000), or to other parts of the UK, because appropriate denominator data was not published as mid-term census estimates. The 2011 census will provide small area and national data for the whole of the UK, scheduled for release by ONS in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. We will then be able to develop models to explore cross-level interactions, such as the association between individual ethnicity and neighbourhood-level ethnic density. Small area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development.

We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16-35 years old. EIS were the only mental health service for people aged 14-35 years experiencing a first episode of psychosis in East Anglia, minimising the potential for under-ascertainment in the population at-risk when derived from careful epidemiological design.[13] We are confident that our *validation sample* also contained few false positive cases for any clinically-relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS or who did not receive a clinical diagnosis of psychotic disorder during the first six months from initial referral. It is important to recognise that while our prediction models are based on diagnosed clinically relevant psychotic disorders, service commissioning will also need to account for additional pre-clinical or non-psychotic psychiatric morbidity presenting to EIS, particularly in services which operate early detection models or implement “watch-and-wait” briefs. The SEPEA data used to validate our models do not predict (1) the number of “false positive” subjects who may require psychiatric triage and assessment even though they are not accepted by EIS, or (2) the number of “true positive” subjects accepted by services, but who did not meet epidemiological criteria for inclusion in the *validation sample* of the SEPEA study (those living outside the catchment area at first contact, or those transferred from other services); these people will consume varying degrees of service resources which needs to be considered in service planning.

We also note that pathways to care may affect the level of incidence observed in EIS, since many filters are likely to operate before subjects come to the attention of EIS. These will include local level service organisation and the relationship between Community Mental Health Teams [CMHTs], Child and Adolescent Mental Health [CAMHs] and EIS. Furthermore, acceptance criteria for entry to EIS vary, which will have a downstream effect on the number of new cases of clinically relevant psychoses received in each team. Future versions of PsyMaptic will include forecasts for specific psychotic disorders, as standardised research-based diagnoses (using OPCRIT[34]) are currently being collected in the ongoing SEPEA study in order to provide more detailed forecasts. Acceptance rates to EIS may also be influenced by local community awareness of such services. While our prediction models outperformed the current gold standard for EIS commissioning in England when restricted to clinically relevant caseloads, we recommend that our models are best interpreted as forecasts of the expected burden of first episode psychosis in given populations, and not the expected burden which will necessarily be seen through EIS given these issues.

We estimated prediction intervals from first principles [DJ] since there derivation is an area of statistical development.[35] We used a bootstrap-like methodology to produce 95% PI accounting for natural variation in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in prediction models, which we assumed to be the true coefficients of risk in the population. Our approach therefore naturally led to slightly artificially narrow 95% PIs. This was not necessarily undesirable for the purpose of model validation and the precise prediction of expected counts because we wished to apply stringent criteria. Ideally, prediction intervals should take into account both these sources of variation, although we note that parameter uncertainty is usually small compared to the natural variation of the quantities of interest. The addition of more empirical data in the *prediction sample* would not lead to narrower PIs, though would tend to move the point estimate of risk for each coefficient closer to the true value in the population. We do not believe we have mis-estimated point estimates of risk across major sociodemographic groups, since our results accord with the wider literature.[17, 21, 22] We sought independent confirmation that our development of 95% PI were correct (personal communication with Prof Ian White, MRC Biostatistics Unit). We recommend that all prediction point estimates from our PsyMaptic model are considered with their 95% PIs, which provide information about the natural variance in expected rates in the population.

Meaning of the findings

If commissioners are to meet the Department of Health's vision to orientate health services around local need,[1, 2, 5] differences in demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data is combined with accurate population at-risk estimates this can be realised. As such, our modelling approach could have utility in many other settings and for many disorders. Our translational approach demonstrated good validity to predict the expected incidence of first episode psychosis, particularly through EIS, where 76% and 63% of all male and female adult-onset FEP cases, respectively, will typically present.[18] Since their inception in 2002, EIS in England and Wales have reported both lower[11] and higher[10] caseloads than they were originally envisioned to manage,[5] with shortfalls or excesses in anticipated demand for services aligned to the degree of urbanisation in the underlying catchment area. Others have noted that EIS provision in rural areas may be difficult to implement effectively,[14, 15] and while the MH-PIG acknowledged that "…[a]n understanding of local epidemiology is needed as the size of population covered will depend on a number of different factors" (p.55),[5] no further elaboration on how to achieve this was provided. We believe PsyMaptic provides a possible tool to overcome this challenge, improving the description and prediction of local population need beyond the MH-PIG and including individual- and neighbourhood-level indicators of local need.[17] From an aetiological perspective, we acknowledge that variables such as ethnicity or population density are likely to be markers for a suite of more complex, interactive social, genetic and environmental determinants of psychosis.[36]

Our models are not the first to be used to forecast mental illness needs in England and Wales,[37] though we believe this is the first attempt to forecast incidence rather than prevalence in the community. We recommend that our prediction methodology is used in conjunction with the wide range of public health observatory data available,[38] as well as the caveats presented above. PsyMaptic has been included with other indicators in the Joint Commissioning Panel for Mental Health's forthcoming guidance for commissioning of public mental health services.[39] Ongoing monitoring and audit of EIS will be vital to ensure services meet the fidelity criteria upon which they were originally commissioned,[11, 40] including ensuring that service capacity matches local need as closely as possible. As part of this process, we will need to externally validate our models in a wider range of settings, refining them based on empirical observation.

We note that advocacy expressed for EIS by healthcare professionals in England and Wales broadly correlates with demand for services as predicted by PsyMaptic.[41] Though by no means universal, proponents of EIS tend to be located in major conurbations – such as London,[42] Birmingham[43] or Manchester[7, 44] – where demand for EIS will be highest, while those who suggest EIS resources could be used more effectively elsewhere tend to work in more rural communities,[15, 41] where but a handful of young people would be expected to come to the attention of EIS each year. It is possible that both sides are correct and that more resources are required to help with the tide of psychotic illness in inner cities. Resources might be used more effectively in other ways, elsewhere, so long as the needs of the small number of young people who suffer a FEP each year are met; a dedicated specialist EIS may not be the most effective approach when anticipated demand will be very low.

Given the significant downstream economic savings associated with spending on EIS as estimated in an urban setting,[8] PsyMaptic could be used to highlight regions where sufficient investment to appropriate mental health services would lead to greatest economic gains in terms of mental healthcare expenditure (assuming sustained intervention also leads to improved social and clinical benefit for patients[6, 7]). PsyMaptic can also be used to highlight regional variation in demand according to age and sex and, in future versions, by ethnicity. This will allow service planners to tailor provision around the socio-cultural characteristics of their local populations. Our prediction tool for first episode psychosis, which translates robust empirical epidemiological data on psychosis risk to the population structure of different regions, offers a methodology for improving the allocation of finite mental health resources based around local need.

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Box 1: Description of included socioenvironmental variables [1 2]	
Variable	**Classification & description**
Multiple deprivation	Weighted data from routine national sources across 7 domains: income, employment, education, health, barriers to housing & services, living environment, crime. Continuous, z-standardised scores for analysis.
Extent of deprivation	Proportion of LAD population living in 20% most deprived SOA in England (%)
Income deprivation	Proportion of all people in LAD classified as income deprived (%)
Employment deprivation	Proportion of adults of working age in LAD classified as employment deprived (%)
Population density	Population density at LAD level (people per hectare).

IMD: Index of Multiple Deprivation; LAD: Local authority district; SOA: super output area; IQR: inter-quartile range

[1]*Prediction sample* sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000)

[2]*Validation sample* sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

Table 1: Prediction models, covariates and fit: all clinically relevant psychoses (F10-39)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Variable	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**
Age group*sex interaction[1]	p=0.07	p=0.06	p=0.06	p=0.06	p=0.06	p=0.06
Ethnicity						
White British	1	1	1	1	1	1
Non-British white	2.0 (1.5, 2.5)	1.7 (1.4, 2.2)	1.7 (1.3, 2.2)	1.7 (1.3, 2.2)	1.8 (1.4, 2.3)	1.7 (1.3, 2.2)
Black Caribbean	6.0 (4.9, 7.3)	5.3 (4.3, 6.5)	5.2 (4.3, 6.4)	5.2 (4.3, 6.4)	5.4 (4.5, 6.6)	5.1 (4.2, 6.3)
Black African	4.1 (3.3, 5.1)	3.6 (2.9, 4.5)	3.5 (2.8, 4.4)	3.5 (2.8, 4.4)	3.7 (3.0, 4.6)	3.5 (2.8, 4.3)
Indian	1.7 (1.2, 2.5)	1.5 (1.1, 2.2)	1.5 (1.0, 2.2)	1.5 (1.0, 2.1)	1.6 (1.1, 2.3)	1.6 (1.1, 2.2)
Pakistani	1.8 (1.2, 2.5)	1.6 (1.0, 2.5)	1.6 (1.0, 2.4)	1.6 (1.0, 2.4)	1.6 (1.1, 2.5)	1.8 (1.3, 2.7)
Bangladeshi	2.1 (1.5, 2.8)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.2, 2.2)	1.8 (1.3, 2.5)	1.8 (1.4, 2.4)
Mixed white & black Caribbean	4.3 (2.8, 6.7)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	4.0 (2.6, 6.1)	3.9 (2.5, 6.1)
Mixed, other ethnicities	1.3 (0.8, 2.3)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Other ethnicities	2.2 (1.6, 3.0)	1.9 (1.4, 2.7)	1.9 (1.4, 2.6)	1.9 (1.4, 2.6)	2.0 (1.4, 2.7)	1.9 (1.4, 2.7)
Socioenvironmental variables						
IMD (z-score)	-	1.184 (1.101, 1.274)	-	-	-	-
Extent of deprivation (%)	-	-	1.008 (1.004, 1.011)	-	-	-
Income deprivation (%)	-	-	-	1.025 (1.015, 1.035)	-	-
Employment deprivation (%)	-	-	-	-	1.062 (1.032, 1.093)	-
Population density (pph)	-	-	-	-	-	1.005 (1.003, 1.007)
Model fit diagnostics						
AIC[2]	2571.8	2552.4	2551.3	2549.6	2556.4	2556.3
Mean Lin's CCC (95%CI)[3]	0.75 (0.74, 0.77)	0.77 (0.75, 0.78)	0.77 (0.75, 0.79)	0.77 (0.75, 0.78)	0.77 (0.75, 0.78)	0.76 (0.74, 0.77)
Mean RMSE (s.d.)[4]	0.75 (0.11)	0.74 (0.11)	0.74 (0.10)	0.74 (0.10)	0.74 (0.11)	0.76 (0.13)

IRR: Incidence rate ratio; AIC: Akaike's Information Criterion; CCC: Lin's correlation concordance coefficient; RMSE: Root mean squared error.

[1]All models fitted with age group by sex interaction given *a priori* evidence for effect modification.[18, 45] Likelihood ratio test p-values reported between models with and without an interaction term fitted between age group and sex. Specific IRR not been reported for clarity, but available on request

[2]– lower scores denote improved model fit

[3]Higher scores indicate greater correlation between observed & predicted count of cases in the *prediction sample.* Mean CCC and 95%CI reported following *h*=20 trials during cross-validation.

[4]Lower scores indicate lower prediction error. Mean RMSE and standard deviation (s.d.) reported following *h*=20 repeats of *k*-fold cross-validation, where *k*=10.

Table 2: Observed versus predicted cases in SEPEA study for all clinically relevant psychoses, 16-35 years[1]

EIS	Observed	Model 1 Predicted (95% PI)	Model 2 Predicted (95% PI)	Model 3 Predicted (95% PI)	Model 4 Predicted (95% PI)
Overall total, 16-35 years	***521***	**641.2 (586.0, 696.1)**	**468.5 (422.0, 518.0)**	**474.7 (429.0, 522.0)**	**487.5 (441.0, 535.0)**
Cameo North	*55*	84.7 (66.0, 106.0)	68.5 (52.0, 87.0)	67.8 (51.0, 86.0)	70.2 (53.0, 90.0)
Cameo South	*134*	163.6 (135.0, 192.0)	105.5 (84.0, 129.0)	111.7 (89.0, 134.0)	110.9 (90.0, 132.0)
West Norfolk	*26*	29.2 (18.0, 41.0)	23.0 (13.0, 35.0)	22.0 (12.0, 32.0)	23.4 (14.0, 34.0)
Central Norfolk	*120*	162.6 (136.0, 191.0)	122.6 (99.0, 148.0)	123.0 (100.0, 149.0)	128.3 (104.0, 152.0)
Great Yarmouth & Waveney	*60*	49.1 (34.0, 65.0)	41.6 (28.0, 55.0)	39.9 (27.0, 53.0)	42.9 (30.0, 57.0)
Suffolk	*126*	151.9 (126.0, 178.0)	107.4 (85.0, 128.0)	110.3 (88.0, 133.0)	111.7 (90.0, 136.0)
Overall total, 36-64 years	-	332.2 (292.0, 373.0)	244.0 (213.0, 276.0)	248.6 (216.0, 280.0)	256.3 (228.0, 291.0)

EIS	Observed	Model 5 Predicted (95% PI)	Model 6 Predicted (95% PI)	Model 7 Predicted (95% PI)
Overall total, 16-35 years	***521***	**477.1 (428.0, 523.0)**	**508.5 (459.0, 559.0)**	**715.6 (664.0, 769.0)**
Cameo North	*55*	69.1 (52.0, 88.0)	64.5 (48.0, 82.0)	92.1 (74.0, 111.0)
Cameo South	*134*	100.7 (79.0, 123.0)	131.1 (108.0, 157.0)	169.0 (144.0, 195.0)
West Norfolk	*26*	24.7 (16.0, 35.0)	22.3 (13.0, 33.0)	35.8 (25.0, 48.0)
Central Norfolk	*120*	128.2 (105.0, 153.0)	132.5 (108.0, 157.0)	187.7 (161.0, 215.0)
Great Yarmouth & Waveney	*60*	47.7 (35.0, 63.0)	38.0 (26.0, 51.0)	59.1 (44.0, 74.0)
Suffolk	*126*	106.6 (86.0, 128.0)	120.0 (96.0, 143.0)	172.1 (147.0, 198.0)
Overall total, 36-64 years	-	249.7 (221.0, 284.0)	262.9 (233.0, 297.0)	1175.4 (1109.0, 1243.0)

[1]Numbers in green denote where observed count fell within 95% prediction interval [95% PI] for people aged 16-35 years. Observed data for people aged 36-64 years in the *validation sample* was not available.

Model 1: Age group, sex, their interaction and ethnicity
Model 2: Model 1 + IMD
Model 3: Model 1 + extent of deprivation
Model 4: Model 1 + income deprivation
Model 5: Model 1 + employment deprivation
Model 6: Model 1 + population density
Model 7: Department of Health uniform figure for EIS of 15 new cases per 100,000 people per year.

Table 3: External model validation diagnostics[1]

Model	Observed case count within SEPEA overall prediction intervals? [rank]	EIS (N=6)		LAD (N=21)		Mean ranking [rank of mean ranking]
		Number correct [rank]	RMSE [rank]	Number correct [rank]	RMSE [rank]	
Model 1	No [5]	3 [6]	27.0 [6]	18 [2]	8.9 [6]	5.0 [6]
Model 2	No [5]	4 [4]	16.8 [4]	18 [2]	6.4 [4]	4.8 [5]
Model 3	Yes [1]	5 [1]	14.9 [2]	17 [5]	6.1 [2]	2.2 [2]
Model 4	Yes [1]	4 [4]	14.9 [2]	17 [5]	6.1 [2]	2.8 [3]
Model 5	Yes [1]	5 [1]	17.8 [5]	18 [2]	6.7 [5]	2.8 [3]
Model 6	Yes [1]	5 [1]	11.5 [1]	19 [1]	6.0 [1]	1.0 [1]
Model 7	No [5]	2 [7]	39.6 [7]	13 [7]	11.7 [7]	6.6 [7]

[1]For each diagnostic, models are placed in rank order [1=best model, 7=worst model] with ties given the same ranking. The mean ranking and rank provide an estimate of the overall performance of various models.

RMSE: Root mean squared error (lower scores indicate lower error); EIS: Early Intervention in Psychosis Service; LAD: Local Authority District

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Data sharing statement

Extra data is available at our prediction website, PsyMaptic: www.psymaptic.org. We have made a large array of prediction data freely available to interested users, who can visualise prediction data in maps and tables for a range of psychotic disorder predictions by major sociodemographic subgroup and by LAD. Future versions of PsyMaptic will release data for other regions and at other geographical levels. Users can also download LAD-specific and national summaries of prediction data from our models in tabular form. Finally, additional explanatory material about how to use the data and the PsyMaptic website is also available at www.psymaptic.org. Bespoke data not provided freely on our website may be requested from the authors at the cost of data extraction. The empirical data underlying the prediction models (ÆSOP and ELFEP) or the validation sample (SEPEA) is not freely available as the studies are ongoing, but papers detailing the main findings from these studies have previously been published elsewhere.

Competing interests statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (i) JBK has support from the Wellcome Trust for the submitted work (grant number WT085540) and PBJ has support from the NIHR (grant RP-PG-0606-1335); (ii) DJ, JP, FW, DF, JC, RMM have no relationships with any company that might have an interest in the submitted work in the previous 3 years; (iii) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (iv) no author holds non-financial interests that may be relevant to the submitted work.

Role of funders

The funders were not involved in the design, collection, analysis, interpretation of the data, writing the report or the decision to submit the article for publication. All authors were independent from the funders in contributing to this work.

Ethical approval

Ethical approval to conduct the original ÆSOP and East London First Episode Psychosis studies was granted from local research ethics committees in their respective centres prior to the original date of onset of the study. We were granted ethical approval to conduct the work related to the present manuscript, including use of data from the SEPEA study, from the Cambridgeshire 3 REC (09/H0306/39).

Guarantorship

JBK takes full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

Contributorship

JBK was responsible for concept, design, analysis, data extrapolation, interpretation of the data, drafting the report and developing the content for the websites www.psymaptic.org, www.psymaptic.com and www.psymaptic.co.uk. JBK was also the chief investigator of the SEPEA study, where the *validation sample* data was obtained. He gave final approval of this version of the manuscript to be published.

DJ was responsible for developing and initially implementing the statistical approach with regard to prediction intervals from count-based regression. He also contributed to drafting and editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JP is principal collaborator on the SEPEA study in the CAMEO early intervention in psychosis services. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

DF is co-principal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

FW is co-principal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JC is chief investigator of the ELFEP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

RMM is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

PBJ is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He contributed to the development of the prediction methodology and edited the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

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STROBE statement

Our STROBE statement is provided as a supplementary file.

A population-level prediction tool for the incidence of first episode psychosis: translational epidemiology based on cross-sectional data

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Word count: ~~65~~,052~~478~~

~~**Access to online data:** Part of the development of this manuscript includes the visualisation of prediction data in map and tabular format on a website created for this project: www.psymaptic.org. We have password protected relevant prediction data on these pages so only editors and peer reviewers can access this data until the peer review process is complete. We invite you to access these pages by visiting www.psymaptic.org and navigating to *"prediction>for peer reviewers"* on the top menu bar. From here, you can access the data as *prediction maps, national summary tables* or *downloadable data*. Please enter the password **pr2012** when prompted.~~

Comment [JK1]: To be deleted before final publication

Abstract

Objectives: Specialist early intervention services [EIS] for people aged 14-35 years with first episodes of psychosis [FEP] have been commissioned throughout England since 2001. A single estimate of population need was used everywhere, but true incidence varies enormously according to sociodemographic factors. We sought to develop a realistically-complex, population-based prediction tool for FEP, based on precise estimates of epidemiological risk.

Design & participants: Data from 1037 participants in two cross-sectional population-based FEP studies were fitted to several negative binomial regression models to estimate risk coefficients across combinations of different sociodemographic and socioenvironmental factors. We applied these coefficients to the population at-risk of a third, socioeconomically different region to predict expected caseload over 2.5 years, where observed rates of ICD-10 F10-39 FEP had been concurrently ascertained via EIS.

Setting: Empirical data from London, Nottingham and Bristol predicted counts in the population at-risk in the East Anglia region of England.

Main outcome measures: Observed counts compared with predicted counts (with 95% prediction intervals) at regional, EIS and local authority district [LAD] levels in East Anglia to establish predictive validity of each model.

Results: A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in EIS in East Anglia (95%PI: 459, 559), compared with 5218 observed participants. This model predicted correctly in 5/6 EIS and 19/21 LAD. All models performed better than the current gold standard for EIS commissioning in England (716 cases; 95%PI: 664-769).

Conclusions: We have developed a prediction tool for incidence of psychotic disorders in England and Wales, made freely available online (www.psymaptic.org) to provide healthcare commissioners with accurate forecasts of FEP based on robust epidemiology and anticipated local population need. Initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.

Background

Commissioners of health and social care require precise information on the health needs of their local populations[1], especially if parity of mental and physical health is to be realised.[2] Mental health disorders alone represent the leading disease burden in the UK (22.8%).[3] They contribute substantially to healthcare expenditure and societal costs even before physical ill health is taken into account. The Centre for Mental Health estimated total costs of mental health to British health services and society at £105 billion in 2009/10,[4] a figure expected to double over the next 20 years.[2] These are serious challenges compounded by a paucity of information on which to commission appropriate services. Early intervention in psychosis services [EIS] for people aged 14-35 years with a first episode of psychosis [FEP] offer a useful example of failure to map services to local need.

EIS are a major evidence-based innovation, systematically commissioned throughout England and Wales over the past decade.[5] When EIS intervention is sustained there is evidence that people with psychosis achieve better functional and social outcomes.[6, 7] Such services are also highly cost-effective.[4, 8, 9] However, EIS were originally commissioned on an anticipated rate of 150 new cases of any psychotic disorder per 1,000,000 of the total population per year in the Department of Health's Mental Health Policy Implementation Guide [MH-PIG].[5] In 2001 in England and Wales, 29.3% of the population were aged 14-35 years old, meaning that the MH-PIG commissioned incidence rate was approximately 51 cases per 100,000 person-years in the age range covered by EIS. Following their deployment, anecdotal reports began to emerge from EIS in different regions to suggest that a uniform figure for commissioning was simultaneously under-[10] and over-estimating[11] actual observed need in urban and rural populations, respectively. Recent epidemiological evidence of FEP incidence in rural communities in England has suggested that rates are somewhat lower than the uniform figure upon which services were commissioned, [12, 13] confirming previous calls that a "one-size-fits-all" prescription for EIS implementation is unlikely to lead to the efficient allocation of finite mental health resources.[14, 15]

Using rich epidemiological data on variation in the incidence of first episode psychosis according to major sociodemographic risk factors,[16-19] we describe the development and validation of a population-level prediction tool capable of accurately estimating the expected incidence of psychiatric disorder, based on the sociodemographic structure of the population in a given region. Applied to FEP as proof-of-concept, we show it is possible to closely predict expected incidence in a given population, where the observed count of cases was within the prediction intervals forecast by our models. We applied our

most precise prediction model to the population of England and Wales to provide health commissioners with a translational epidemiological prediction tool to underpin information-based service planning.

Methods

Our prediction models were based on epidemiological data from the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [ÆSOP] and the East London First Episode Psychoses [ELFEP] studies,[18, 20] two methodologically-similar population-based FEP studies. We fitted various count-based regression models with different combinations of sociodemographic and socioenvironmental factors, well-established in the literature to be associated with the incidence of psychotic disorder.[21, 22] We first established the relative ~~*internal*~~*apparent validity* of each model by estimating ~~internal~~ model fit diagnostics to assess how well each model fitted the empirical data (henceforth, the *prediction sample*). We next sought to estimate the *external validity* of each model by applying model-based parameter coefficients to the population structure of a purposefully different region of England, East Anglia (henceforth, the *validation sample*). This out-of-sample prediction technique allowed us to obtain the expected incidence of disorder in this region forecast by each model, which we compared with observed rates simultaneously ascertained in this region via the ongoing Social Epidemiology of Psychoses in East Anglia [SEPEA] study.[13] We performed various model fit diagnostics to identify which, if any, model demonstrated utilisable predictive capability.

Empirical data underlying prediction models (*prediction sample*)

Case ascertainment (numerator)

The designs of the ÆSOP and ELFEP studies have been described in detail elsewhere,[18, 20] with features relevant to the present paper summarised here. Case ascertainment took place over two years in ELFEP (Newham: 1996-8; Tower Hamlets & Hackney: 1998-2000) and the Southeast London and Nottingham centres of the ÆSOP study (1997-9), and over the first 9 months of 1997 in Bristol (ÆSOP). All service bases were screened regularly for potential new contacts aged 16-64 years (18-64 in ELFEP) resident within these catchment areas. Leakage studies were conducted to identify participants missed by this initial screen, but meeting inclusion criteria for FEP.[18, 20] All participants who received an ICD-10 F10-39 diagnosis for psychotic disorder following assessment via the Schedules for Clinical Assessment in Neuropsychiatry were included in the incident sample, except those with an organic medical basis to their disorder or profound learning difficulty. Data on age-at-contact, sex and ethnicity were collected on included participants. We geocoded participants' residential postcode at first contact to their

corresponding local authority district [LAD] to allow us to model possible neighbourhood effects associated with the incidence of psychotic disorder, such as population density or socioeconomic deprivation.

Population at-risk

We estimated the population at-risk using the 2001 Census of Great Britain, adjusted for study duration, and stratified by age group (16-17, 18-19, then 5-year age bands), sex and ethnicity. Ethnicity was based on self-ascription according to one of ten categories derived from the census: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white & black Caribbean, other mixed ethnic backgrounds and all other ethnicities.

Socioenvironmental variable estimation

We estimated LAD -level deprivation using the 2004 Index of Multiple Deprivation [IMD] in England, which estimated domains of deprivation using measures predominantly collected close to the time of our case ascertainment periods (see Box 1).[23] We z-standardised English LAD IMD scores to have a mean of zero and standard deviation of one, and extracted IMD z-scores for the 14 LADs in the ÆSOP and ELFEP studies. To inspect whether any particular deprivation domain was a better predictor of psychosis incidence than IMD, we also considered LAD-level income deprivation, employment deprivation and the extent of deprivation in our models (Box 1). We estimated population density by dividing LAD usual resident population by its area (in hectares), using ArcGIS 9.3 software.

<Box 1 about here>

Observed data for external validation of prediction models (*validation sample*)

Observed participants and population at-risk data for our *validation sample* was obtained from the SEPEA study, an ongoing study of the incidence of psychotic disorders incepted over three years (2009-12) through one of six EIS covering 20 LAD and a subsection of one LAD (the town of Royston, Hertfordshire) in Norfolk (three EIS: West, Central and Great Yarmouth & Waveney), Suffolk (one EIS) and Cambridgeshire, Royston & Peterborough (CAMEO North and South EIS).[13]

Case ascertainment

To establish the incepted incidence of first episode psychosis as seen through EIS, entry criteria for the SEPEA study were:

- Referral to an EIS in East Anglia for suspected first episode of psychosis
- Aged 16-35 years old at first referral to EIS (17-35 years in CAMEO services)
- Resident within the catchment area at first referral
- First referral during case ascertainment period (2009-12)

At six months after EIS acceptance, or discharge from the service, whichever was sooner, we asked the clinician responsible for care to provide an ICD-10 F10-39 psychiatric diagnosis using all information available. We excluded participants without a clinical FEP diagnosis, or participants presenting with an organic basis to their disorder or profound learning disability. For remaining participants, basic sociodemographic and postcode information was recorded and classified in the same way as in the *prediction sample*. We included participants presenting to EIS during the first 2.5 years of the ongoing SEPEA study.

Population at-risk

We estimated the population at-risk of East Anglia using 2009 mid-year census estimates published by the Office for National Statistics [ONS] at LAD-level, by age group, sex and ethnicity.[24] These estimates used the 2001 census base, adjusted for immigration, births and deaths each year. It was not possible to obtain 2009 mid-year estimates for the town of Royston, because data were only published at LAD level. Here, we thus used denominator data from the 2001 census data, in order to estimate the population at-risk in Royston. We do not believe this would have substantially invalidated our results as this town represented 0.6% of the overall population at-risk (n=9,555) in the SEPEA study. Denominator data were multiplied by 2.5 to account for person-years of exposure in the *validation sample*.

Socioenvironmental variable estimation

For each LAD in the SEPEA study we obtained corresponding socioenvironmental variables to those included in our *prediction sample,* using updated data collected as close to the SEPEA case ascertainment period as possible. Population density was estimated using 2009 mid-term population estimates. Our measures of deprivation were derived from the IMD 2010,[25] which was estimated in an analogous way to 2004 data, but collected from sources obtained immediately prior to the SEPEA study.

Statistical techniques

Dataset generation

We constructed a dataset for the regression analysis of count data by pooling data from the ÆSOP & ELFEP studies (the *prediction sample*). Data were stratified by age group, sex, ethnicity and LAD, such that each stratum (N=2,536) represented the total count of FEP cases in a unique sociodemographic group for a given LAD, with a corresponding estimate of the population at-risk, treated as an offset in our models. Our socioenvironmental measures (population density, deprivation) were adjoined to the dataset for each LAD.

Population at-risk data from the *validation sample* were stratified in the same way and retained in a separate database. Here, ~~T~~the count of cases, which we wished to predict, was ~~-~~entered as a vector of ~~variable with~~ missing data ~~values,~~ which would be populated with predicted case estimates following prediction modelling~~we could predict into, given the model coefficients and population at risk~~.

Prediction models

We used the *prediction sample* data to fit negative binomial regression models to obtain parameter coefficients of incidence for the sociodemographic and socioenvironmental factors included in each model. We considered the internal and external predictive capabilities of six models, all of which contained age group, sex, an age-sex interaction term and ethnicity. Model 1 contained no further covariates. Model 2 also included IMD. We replaced IMD with either income, employment or the extent of deprivation, respectively, in models 3-5. Model 6 included population density. Initial exploration of the *prediction sample* data indicated the presence of possible over-dispersion (variance (δ^2=1.37) exceeded mean (μ=0.4) count of cases) so negative binomial regression was preferred to Poisson regression since it explicitly models any over-dispersion with an extra dispersion parameter.

Internal model cross-validation & prediction

We assessed ~~internal~~apparent model validity in three ways. First we used Akaike's Information Criterion [AIC] to assess the respective overall fit of each model to the data. Second, we conducted K-fold cross-validation to assess each model's ~~internal~~apparent validity to predict cases within the *prediction sample*. This method randomly allocated strata in the *prediction sample* into *K* subsets. Each model was then re-estimated on *K-1* subsets (the *training data*) to predict expected counts of cases in the K^{th} subset (the

test data). This was repeated over *K* trials, such that each stratum in the dataset appeared exactly once as the *test data*. At the end of this process, we derived Lin's concordance correlation coefficient [CCC] and 95% confidence intervals [95%CI] to estimate the correlation between predicted and observed counts of cases across all strata in the *prediction sample*. Finally, we estimated the root mean squared error [RMSE] to determine the average error between fitted and observed values from each model, where lower RMSE scores indicated smaller prediction error. The RMSE is derived as

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}}$$

where y_i and $\hat{y}_i$ are the observed and predicted count of cases in the i^{th} stratum, respectively, and n is the number of strata.

We repeated K-fold cross-validation *h* times, generating *K* new random divisions of the data each time. We retained model fit diagnostics across *Kh* iterations, and reported the mean of Lin's CCC and RMSE to provide summary cross-validation statistics for each model. We specified *K=10* and *h=20*, as recommended for cross-validation to obtain precise model fit diagnostics.[26]

External model prediction & validation

We retained parameter coefficients from each model (using the full *prediction sample* data) and applied these to the corresponding population at-risk in the *validation sample* dataset. This gave out-of-sample prediction estimates for the expected count of cases in each stratum of the *validation sample*, given the model. We summed expected counts across relevant strata to estimate the (i) total predicted count of cases in the SEPEA region, (ii) predicted counts in each EIS, and (iii) predicted counts by LAD. These counts were further stratified by broad age group (16-35, 36-64 and 16-64 years). Because census (denominator) data was unavailable for 35 year olds alone (needed to estimate their contribution to predicted counts in the age range for EIS, 16-35 years) we assumed the risk coefficient was the same across all ages within the 35-39 year old age group. We apportioned predicted counts on a 1:4 ratio (35 years: 36-39 years) to their respective broad age groups.

To determine how well the MH-PIG[5] figure of 51 new cases per 100,000 people per year for EIS performed as a predictive tool, we also estimated the predicted count of cases in the *validation sample* under this scenario, which we termed "Model 7".

We derived prediction intervals [95% PIs] for all summary predictions from first principles for each negative binomial regression model, since their derivation is not straightforward, nor routinely implemented by statistical software. Prediction intervals are similar to confidence intervals, but account for standard errors introduced in both the *prediction* and *validation* samples. We developed a bootstrap-like approach to obtain prediction intervals from each model by simulating 1000 model-based realisations of the quantities we wished to predict, where we took the parameters to be the maximum likelihood estimates. We obtained the lower and upper bounds of the prediction intervals as the corresponding quantiles of the simulated realisations (see Appendix for full details).

To assess each model's external predictive capabilities, we considered five markers of predictive accuracy. We compared the number of times the observed count of cases in the SEPEA study fell within the prediction intervals estimated from each model for (i) the SEPEA region, (ii) at EIS level, and (iii) at LAD level. We also derived EIS- and LAD-level RMSE scores to estimate prediction error from each model in our *validation sample*. We ranked model performance (1: best, 7: worst) on these five measures, and estimated an overall mean rank to determine the overall predictive validity of each model.

Observational data on first episode psychosis in our *validation sample* were not available for the age range 36-64 years, so external validation was restricted to the 16-35 year old group. For completeness, however, we also reported overall predicted count of cases for this age group from each model.

Extrapolation to the United Kingdom

Guided by our validation procedures, we identified which model had the greatest overall predictive validity, and proposed this as a candidate for FEP incidence prediction in England and Wales. We repeated out-of-sample prediction on the sociodemographic and socioenvironmental population characteristics of each LAD in England and Wales to obtain national and LAD-level predictions. Denominator data was obtained from the ONS 2009 mid-term estimates and stratified as previously described. Overall counts were derived for three broad age groups (16-35, 36-64 and 16-64 years), and for each of these, by sex and ethnicity. 95% PIs were estimated as before. We visualised this data on

maps and in tables to provide healthcare planners and commissioners with an easy-to-use tool to forecast the expected incidence of psychosis in England and Wales. We have made this available as a free, open-use prediction tool, known as PsyMaptic (version 0.54) (Psychiatric Mapping Translating Innovations into Care; www.psymaptic.org). Counts of cases predicted by our model were compared with those obtained under the Department of Health's uniform rate in each LAD. We expressed these comparisons as ratios with 95% CIs derived using the same method as for standardised morbidity ratios [SMR]. This approach was conservative because here we substituted the usual numerator in an SMR, the observed, O, for a predicted count. Unlike an observed count, no sampling variation is present for the predicted count, only uncertainty due to the model from which the prediction was estimated. Since variance in the prediction is therefore much smaller than the variance normally present for the numerator (O) this led to conservative estimates of 95% CI. Ratios in LAD where 95% CI did not span unity could therefore be interpreted as regions where there was strong evidence that the predictions from our model differed significantly from those predicted by the Department of Health's uniform rate.

Software

All negative binomial regression models, out-of-sample prediction and estimation of 95% PI were conducted in R (version 2.15.1). ~~Internal C~~cross-validation and model-fit diagnostics were conducted in Stata (version 11). Prediction maps for England and Wales were created using StatPlanet Plus (version 3.0) visualisation software.[27]

Results

Prediction sample

Our prediction models contained data on 1,037 persons with a first episode psychosis in the ÆSOP (n=553; 53.3%) and ELFEP (n=484; 46.7%) studies, ascertained from over 2.4m person-years at-risk. Twelve participants were excluded from the original ÆSOP sample because they were of no fixed abode and could not be geocoded to an LAD.[18]

The population at-risk in the *prediction sample* came from LAD with higher median levels of multiple and employment deprivation, extent of deprivation and population density than the population at-risk in the *validation sample*, though there were no statistically significant differences in median income deprivation between the two samples (Supplemental Table 1).

<Supplemental Table 1 about here>

Parameter coefficients obtained from the full prediction sample following negative binomial regression are shown in Table 1. As previously reported from these data,[20, 28] incidence rates were generally raised in ethnic minority groups compared with the white British population. Models 2-6 included a measure of LAD deprivation (Models 2-5) or population density (Model 6), which were all significantly associated with increased incidence of psychotic disorder, after control for individual-level confounders. Each of these models produced a lower AIC score than a model fitted solely with individual-level covariates (Model 1), indicating better ~~internal~~ fit. ~~Internal c~~Cross-validation suggested all models achieved good CCC agreement between predicted and observed cases, with low RMSE values (Table 1).

<Table 1 about here>

Validation sample

Observed participants

We identified 572 participants over the first 30 months of the SEPEA study, aged 16-35 years old, who met acceptance criteria for EIS in East Anglia. We excluded 5144 participants (8.90%) who did not meet clinical criteria for ICD-10 psychotic disorder. This left an incidence sample of 5218 participants from nearly 1.4m person-years at risk (37.38 per 100,000 person-years; 95%CI: 34.72, 40.61.2). A further 2.3m person-years at-risk accrued in the same region for people aged 36-64 years over this period. Median levels of multiple, income and employment deprivation in the region did not differ significantly from the remainder of England, although median population density and extent of deprivation in East Anglia were lower than elsewhere in England (Supplemental Table 1).

<Table 2 about here>

External model prediction & validation

The overall observed count of cases, aged 16-35 years, in the *validation sample* (n=528) fell within 95% prediction intervals in four~~only two~~ of seven ~~tested~~ models (Models 34 ~~and~~ 6, Table 2). Of these, the observed count (N=521) was closest to the point estimate for Model 6 (508.5; 95% PI: 449.0, 559.0), fitted with age group, sex, their interaction, ethnic group and LAD population density. The observed count of cases also fell within prediction intervals from this model in five of six EIS in the study region,

and 19 of 21 LADs, the most of any model (Table 3). This model had the lowest error scores at EIS (RMSE=11.59) and LAD (RMSE=6.05.9) levels of any model. Overall, Model 6 was ranked highest across all external model fit diagnostics (Table 3). All models outperformed the Department of Health's uniform figure of 51 cases per 100,000 people per year (Model 7), which generally overestimated cases in the *validation sample* (overall prediction: 715.7 cases; 95% PI: 664.0, 769.0).

<Table 3 about here>

We also reported predicted cases aged 36-64 years old from our models (Table 3), although we could not test these in the *validation sample*. Model 6 predicted an additional 262.9 cases aged 36-64 years over a 2.5 year period in East Anglia (95% PI: 233.0, 297.0).

We also inspected the stratum-specific external validity of our best-fitting model (Model 6, Supplementary Table 2), which performed accurately for sex-specific predictions, but less well in age- and ethnicity-specific strata. Thus, our model tended to under-predict observed cases in people aged 16-19 years, but over-predicted cases observed in people over 25 years old. With respect to ethnicity, model predictions were consistent with observed FEP cases for people of non-British white, black African, Bangladeshi and mixed ethnicities. However, our model under-predicted observed rates in the white British group, and over-predicted rates in black Caribbean, Indian and Pakistani populations.

<Supplemental Table 2 about here>

Extrapolation to England and Wales

We predicted the expected count and incidence of first episode psychosis per annum in each LAD in England and Wales based on Model 6, and visualised this data in maps and tables freely available at www.psymaptic.org. Many maps can be visualised (for example, Supplemental Figure 1), including overall predicted incidence counts and rates for each broad age group at LAD level, and -by sex. We will make PsyMaptic data -available by ~~and~~ ethnic group when we can improve the validity of future versions of these models for these strata~~, as well as a variety of population and socioenvironmental data~~.

According to our model, the annual number of new FEP cases in England and Wales would be 8745 (95% PI: 8558, 8933), of which our model predicted 67.9% (N=5939; 95% PI: 5785, 6102) would be seen through EIS. Only 176 (95% PI: 151, 203) cases aged 16-64 years were forecast in Wales per annum.

Assuming our prediction model is accurate, it indicated that the Department of Health's current uniform rate of 51 per 100,000 person-years was higher than the predicted point estimates for rates forecast by our PsyMaptic model in 351 LAD (93%) in England and Wales, but was lower than predicted by our model in Birmingham and several London boroughs (Supplemental Figure 2, left hand map). Under a conservative approach, these differences achieved statistical significance in parts of London (where the Department of Health's model underestimated need as predicted by PsyMaptic), and in some more rural parts of England and Wales (where the Department of Health's model over-estimated need) (Supplemental Figure 2, right hand map).

<Supplemental Figures 1 & 2 about here>

Discussion

Principal findings

We have developed and tested several epidemiological prediction models to forecast FEP incidence in England and Wales, having taken into account regional differences in the sociodemographic and socioenvironmental profile of different populations. Inspection of our data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the greatest external predictive validity when compared with the observed FEP caseload ascertained through EIS in our *validation sample*. This model also had good ~~internal~~apparent validity across the entire age range (16-64 years). All models performed significantly better in predicting the incidence of clinically relevant first episode psychosis than the Department of Health's current gold standard for EIS commissioning,[5] based on a uniform incidence rate. Our data suggested the figure used to commission EIS over-estimated the likely true incidence rates of FEP in rural areas, and under-estimated them in urban settings, although we acknowledge that commissioning decisions will need to be based on several additional factors, including the level of pre-clinical or non-psychotic psychopathology requiring assessment at initial referral to EIS, and variation in service organisation, remit and delivery.

Limitations & future development

Our prediction models were based on epidemiological data obtained from large, robust population-based FEP studies for people aged 16-64 years.[18, 19] The~~Our~~ best-fitting model, overall, had good ~~internal~~apparent validity over this age range, and good external validity over the age range 16-35 years. While this covered the majority of adult onset psychosis cases seen in mental health services, including

EIS, we recognise that some EIS teams incept people from 14 years old. We were unable to extrapolate our models to this age range, given the current absence of incidence data for this group in England. Data from Scandinavia suggest that the incidence of such "early onset" psychoses is absolutely low,[29] although the rate may have been increasing in the last few decades, probably as a result of movement towards earlier detection. We were also unable to externally validate prediction models for people aged 36-64 years, because comparable observed incidence data was not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models was ascertained from the same two large, well-conducted studies as for data on the younger age group.[18, 19, 28] Furthermore, -published findings from these studies are consistent with the wider epidemiological literature for psychosis in England and internationally.[17, 21, 30] It will be important to validate the predictive capability of our model(s) in this age range, and we will seek to identify suitable samples to do so in future versions of PsyMaptic.

Our best-fitting overall model demonstrated excellent external validity for predicting sex-specific FEP cases in our *validation* region (i.e. SEPEA). It performed less well across age- and ethnic-specific stratum in this region. With respect to age, this discrepancy is most likely to be a function of EIS provision itself, which seeks to intervene as early as possible in the onset of psychosis. The effect of this will reduce median age at onset in comparison to studies conducted prior to the introduction of EIS, such as the ÆSOP and ELFEP studies, upon which our models are based. Future versions of PsyMaptic will incorporate empirical data from post-EIS studies to improve age-specific predictions. The validity of our model in some ethnic groups also requires further refinement. Much of the prediction data underlying our models came from urban environments with large proportions of ethnic minority groups. The sociodemographic profile and sociocultural experiences of these groups may be very different to those of their counterparts in other, less urban, parts of England, thus altering risk of psychosis according to ethnicity. In our observed data, a larger proportion of cases were white British than predicted by our model. If ethnicity is a partial proxy for exposure to deleterious socio-environmental experiences, such as the combined effect of social inequality, fragmentation, deprivation and population density,[31] then simultaneously incorporating such factors into our models may improve their predictive validity by ethnicity. Alternatively, risk by ethnic group may be conditional upon (i.e. interact with) environmental factors in urban areas (as with the ethnic density effect[32, 33]), but whether such interactions exist in less urban regions is not known. Forthcoming SEPEA and PsyMaptic data will explore such possibilities as 2011 census data become available.

All prediction models had reasonable ~~internal~~apparent validity, although our proposed model performed slightly worse (most noticeably for AIC) than models which included deprivation (i.e. models 2-4) instead of population density. Our decision to use model 6 as our proposed candidate for the prediction tool was supported by the fact that it produced the most accurate external forecasts of any model, despite considerable socioenvironmental differences between regions in our *prediction* and *validation* samples. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards (N~6000), or to other parts of the UK, because appropriate denominator data was not published as mid-term census estimates. The 2011 census will provide small area and national data for the whole of the UK, scheduled for release by ONS in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. We will then be able to develop models to explore cross-level interactions, such as the association between individual ethnicity and neighbourhood-level ethnic density. Small area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development.

We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16-35 years old. EIS were the only mental health service for people aged 14-35 years experiencing a first episode of psychosis in East Anglia, minimising the potential for under-ascertainment in the population at-risk when derived from careful epidemiological design.[13] We are confident that our *validation sample* also contained few false positive cases for any clinically-relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS or who did not receive a clinical diagnosis of psychotic disorder during the first six months from initial referral. It is important to recognise that while our prediction models are based on diagnosed clinically relevant psychotic disorders, service commissioning will also need to account for additional pre-clinical or non-psychotic psychiatric morbidity presenting to EIS, particularly in services which operate early detection models or implement "watch-and-wait" briefs. The SEPEA data used to validate our models do not predict (1) the number of "false positive" subjects who may require psychiatric triage and assessment even though they are not accepted by EIS, or (2) the number of "true positive" subjects accepted by services, but who did not meet epidemiological criteria for inclusion in the *validation sample* of the SEPEA study (those living outside the catchment area at first contact, or those transferred

from other services); these people will consume varying degrees of service resources which needs to be considered in service planning.

We also note that pathways to care may affect the level of incidence observed in EIS, since many filters are likely to operate before subjects come to the attention of EIS. These will include local level service organisation and the relationship between Community Mental Health Teams [CMHTs], Child and Adolescent Mental Health [CAMHs] and EIS. Furthermore, acceptance criteria for entry to EIS vary, which will have a downstream effect on the number of new cases of clinically relevant psychoses received in each team. Future versions of PsyMaptic will include forecasts for specific psychotic disorders, as standardised research-based diagnoses (using OPCRIT[34]) are currently being collected in the ongoing SEPEA study in order to provide more detailed forecasts. Acceptance rates to EIS may also be influenced by local community awareness of such services. While our prediction models outperformed the current gold standard for EIS commissioning in England when restricted to clinically relevant caseloads, we recommend that our models are best interpreted as forecasts of the expected burden of first episode psychosis in given populations, and not the expected burden which will necessarily be seen through EIS given these issues.

We estimated prediction intervals from first principles [DJ] since there derivation is an area of statistical development.[35] We used a bootstrap-like methodology to produce 95% PI accounting for natural variation in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in prediction models, which we assumed to be the true coefficients of risk in the population. Our approach therefore naturally led to slightly artificially narrow 95% PIs. This was not necessarily undesirable for the purpose of model validation and the precise prediction of expected counts because we wished to apply stringent criteria. Ideally, prediction intervals should take into account both these sources of variation, although we note that parameter uncertainty is usually small compared to the natural variation of the quantities of interest. The addition of more empirical data in the *prediction sample* would not lead to narrower PIs, though would tend to move the point estimate of risk for each coefficient closer to the true value in the population. We do not believe we have mis-estimated point estimates of risk across major sociodemographic groups, since our results accord with the wider literature.[17, 21, 22] We sought independent confirmation that our development of 95% PI were correct (personal communication with Prof Ian White, MRC Biostatistics Unit). We recommend that all prediction point estimates from our

PsyMaptic model are considered with their 95% PIs, which provide information about the natural variance in expected rates in the population.

Meaning of the findings

If commissioners are to meet the Department of Health's vision to orientate health services around local need,[1, 2, 5] differences in demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data is combined with accurate population at-risk estimates this can be realised. As such, our modelling approach could have utility in many other settings and for many disorders. Our translational approach demonstrated good ~~internal and external~~ validity to predict the expected incidence of first episode psychosis, particularly through EIS, where 76% and 63% of all male and female adult-onset FEP cases, respectively, will typically present.[18] Since their inception in 2002, EIS in England and Wales have reported both lower[11] and higher[10] caseloads than they were originally envisioned to manage,[5] with shortfalls or excesses in anticipated demand for services aligned to the degree of urbanisation in the underlying catchment area. Others have noted that EIS provision in rural areas may be difficult to implement effectively,[14, 15] and while the MH-PIG acknowledged that "…[a]n understanding of local epidemiology is needed as the size of population covered will depend on a number of different factors" (p.55),[5] no further elaboration on how to achieve this was provided. We believe PsyMaptic provides a possible tool to overcome this challenge, improving the description and prediction of local population need beyond the MH-PIG and including individual- and neighbourhood-level indicators of local need.[17] From an aetiological perspective, we acknowledge that variables such as ethnicity or population density are likely to be markers for a suite of more complex, interactive social, genetic and environmental determinants of psychosis.[36]

Our models are not the first to be used to forecast mental illness needs in England and Wales,[37] though we believe this is the first attempt to forecast incidence rather than prevalence in the community. We recommend that our prediction methodology is used in conjunction with the wide range of public health observatory data available,[38] as well as the caveats presented above. PsyMaptic has been included with other indicators in the Joint Commissioning Panel for Mental Health's forthcoming guidance for commissioning of public mental health services.[39] Ongoing monitoring and audit of EIS will be vital to ensure services meet the fidelity criteria upon which they were originally commissioned,[11, 40] including

ensuring that service capacity matches local need as closely as possible. As part of this process, we will need to externally validate our models in a wider range of settings, refining them based on empirical observation.

We note that advocacy expressed for EIS by healthcare professionals in England and Wales broadly correlates with demand for services as predicted by PsyMaptic.[41] Though by no means universal, proponents of EIS tend to be located in major conurbations – such as London,[42] Birmingham[43] or Manchester[7, 44] – where demand for EIS will be highest, while those who suggest EIS resources could be used more effectively elsewhere tend to work in more rural communities,[15, 41] where but a handful of young people would be expected to come to the attention of EIS each year. It is possible that both sides are correct and that more resources are required to help with the tide of psychotic illness in inner cities. Resources might be used more effectively in other ways, elsewhere, so long as the needs of the small number of young people who suffer a FEP each year are met; a dedicated specialist EIS may not be the most effective approach when anticipated demand will be very low.

Given the significant downstream economic savings associated with spending on EIS as estimated in an urban setting,[8] PsyMaptic could be used to highlight regions where sufficient investment to appropriate mental health services would lead to greatest economic gains in terms of mental healthcare expenditure (assuming sustained intervention also leads to improved social and clinical benefit for patients[6, 7]). PsyMaptic can also be used to highlight regional variation in demand according to age and ~~,~~ sex and, in future versions, by ethnicity ~~group~~. This will~~,~~ allow~~ing~~ service planners to tailor provision around the socio-cultural characteristics of their local populations. Our prediction tool for first episode psychosis, which translates robust empirical epidemiological data on psychosis risk to the population structure of different regions, offers a methodology for improving the allocation of finite mental health resources based around local need.

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Box 1: Description of included socioenvironmental variables [1 2]	
Variable	**Classification & description**
Multiple deprivation	Weighted data from routine national sources across 7 domains: income, employment, education, health, barriers to housing & services, living environment, crime. Continuous, z-standardised scores for analysis.
Extent of deprivation	Proportion of LAD population living in 20% most deprived SOA in England (%)
Income deprivation	Proportion of all people in LAD classified as income deprived (%)
Employment deprivation	Proportion of adults of working age in LAD classified as employment deprived (%)
Population density	Population density at LAD level (people per hectare).

IMD: Index of Multiple Deprivation; LAD: Local authority district; SOA: super output area; IQR: inter-quartile range

[1]*Prediction sample* sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000)

[2]*Validation sample* sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

Table 1: Prediction models, covariates and fit: all clinically relevant psychoses (F10-39)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Variable	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**	**IRR (95%CI)**
Age group*sex interaction[1]	p=0.07	p=0.06	p=0.06	p=0.06	p=0.06	p=0.06
Ethnicity						
White British	1	1	1	1	1	1
Non-British white	2.0 (1.5, 2.5)	1.7 (1.4, 2.2)	1.7 (1.3, 2.2)	1.7 (1.3, 2.2)	1.8 (1.4, 2.3)	1.7 (1.3, 2.2)
Black Caribbean	6.0 (4.9, 7.3)	5.3 (4.3, 6.5)	5.2 (4.3, 6.4)	5.2 (4.3, 6.4)	5.4 (4.5, 6.6)	5.1 (4.2, 6.3)
Black African	4.1 (3.3, 5.1)	3.6 (2.9, 4.5)	3.5 (2.8, 4.4)	3.5 (2.8, 4.4)	3.7 (3.0, 4.6)	3.5 (2.8, 4.3)
Indian	1.7 (1.2, 2.5)	1.5 (1.1, 2.2)	1.5 (1.0, 2.2)	1.5 (1.0, 2.1)	1.6 (1.1, 2.3)	1.6 (1.1, 2.2)
Pakistani	1.8 (1.2, 2.5)	1.6 (1.0, 2.5)	1.6 (1.0, 2.4)	1.6 (1.0, 2.4)	1.6 (1.1, 2.5)	1.8 (1.3, 2.7)
Bangladeshi	2.1 (1.5, 2.8)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.2, 2.2)	1.8 (1.3, 2.5)	1.8 (1.4, 2.4)
Mixed white & black Caribbean	4.3 (2.8, 6.7)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	3.9 (2.5, 6.0)	4.0 (2.6, 6.1)	3.9 (2.5, 6.1)
Mixed, other ethnicities	1.3 (0.8, 2.3)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)	1.2 (0.7, 2.1)
Other ethnicities	2.2 (1.6, 3.0)	1.9 (1.4, 2.7)	1.9 (1.4, 2.6)	1.9 (1.4, 2.6)	2.0 (1.4, 2.7)	1.9 (1.4, 2.7)
Socioenvironmental variables						
IMD (z-score)	-	1.184 (1.101, 1.274)	-	-	-	-
Extent of deprivation (%)	-	-	1.008 (1.004, 1.011)	-	-	-
Income deprivation (%)	-	-	-	1.025 (1.015, 1.035)	-	-
Employment deprivation (%)	-	-	-	-	1.062 (1.032, 1.093)	-
Population density (pph)	-	-	-	-	-	1.005 (1.003, 1.007)
~~*Internal m*~~*Model fit diagnostics*						
AIC[2]	2571.8	2552.4	2551.3	2549.6	2556.4	2556.3
Mean Lin's CCC (95%CI)[3]	0.75 (0.74, 0.77)	0.77 (0.75, 0.78)	0.77 (0.75, 0.79)	0.77 (0.75, 0.78)	0.77 (0.75, 0.78)	0.76 (0.74, 0.77)
Mean RMSE (s.d.)[4]	0.75 (0.11)	0.74 (0.11)	0.74 (0.10)	0.74 (0.10)	0.74 (0.11)	0.76 (0.13)

IRR: Incidence rate ratio; AIC: Akaike's Information Criterion; CCC: Lin's correlation concordance coefficient; RMSE: Root mean squared error.

[1]All models fitted with age group by sex interaction given *a priori* evidence for effect modification.[18, 45] Likelihood ratio test p-values reported between models with and without an interaction term fitted between age group and sex. Specific IRR not been reported for clarity, but available on request

[2]~~AIC: Akaike's Information Criterion –~~ lower scores denote improved model fit

[3]~~CCC: Lin's correlation concordance coefficient.~~ Higher scores indicate greater correlation between observed & predicted count of cases in the *prediction sample.* Mean CCC and 95%CI reported following *h*=20 trials during cross-validation.

[4]~~RMSE: Root mean squared error.~~ Lower scores indicate lower prediction error. Mean RMSE and standard deviation (s.d.) reported following *h*=20 repeats of *k*-fold cross-validation, where *k*=10.

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Table 2: Observed versus predicted cases in SEPEA study for all clinically relevant psychoses, 16-35 years[1]

		Model 1	Model 2	Model 3	Model 4
EIS	**Observed**	**Predicted (95% PI)**	**Predicted (95% PI)**	**Predicted (95% PI)**	**Predicted (95% PI)**
Overall total, 16-35 years	~~52~~18	**641.2 (586.0, 696.1)**	**468.5 (422.0, 518.0)**	**474.7 (429.0, 522.0)**	**487.5 (441.0, 535.0)**
Cameo North	55	84.7 (66.0, 106.0)	68.5 (52.0, 87.0)	67.8 (51.0, 86.0)	70.2 (53.0, 90.0)
Cameo South	13~~47~~	163.6 (135.0, 192.0)	105.5 (84.0, 129.0)	111.7 (89.0, 134.0)	110.9 (90.0, 132.0)
West Norfolk	2~~65~~	29.2 (18.0, 41.0)	23.0 (13.0, 35.0)	22.0 (12.0, 32.0)	23.4 (14.0, 34.0)
Central Norfolk	12~~10~~	162.6 (136.0, 191.0)	122.6 (99.0, 148.0)	123.0 (100.0, 149.0)	128.3 (104.0, 152.0)
Great Yarmouth & Waveney	60	49.1 (34.0, 65.0)	41.6 (28.0, 55.0)	39.9 (27.0, 53.0)	42.9 (30.0, 57.0)
Suffolk	12~~630~~	151.9 (126.0, 178.0)	107.4 (85.0, 128.0)	110.3 (88.0, 133.0)	111.7 (90.0, 136.0)
Overall total, 36-64 years	-	332.2 (292.0, 373.0)	244.0 (213.0, 276.0)	248.6 (216.0, 280.0)	256.3 (228.0, 291.0)

		Model 5	Model 6	Model 7
EIS	**Observed**	**Predicted (95% PI)**	**Predicted (95% PI)**	**Predicted (95% PI)**
Overall total, 16-35 years	~~52~~18	**477.1 (428.0, 523.0)**	**508.5 (459.0, 559.0)**	**715.6 (664.0, 769.0)**
Cameo North	55	69.1 (52.0, 88.0)	64.5 (48.0, 82.0)	92.1 (74.0, 111.0)
Cameo South	13~~47~~	100.7 (79.0, 123.0)	131.1 (108.0, 157.0)	169.0 (144.0, 195.0)
West Norfolk	2~~65~~	24.7 (16.0, 35.0)	22.3 (13.0, 33.0)	35.8 (25.0, 48.0)
Central Norfolk	12~~10~~	128.2 (105.0, 153.0)	132.5 (108.0, 157.0)	187.7 (161.0, 215.0)
Great Yarmouth & Waveney	60	47.7 (35.0, 63.0)	38.0 (26.0, 51.0)	59.1 (44.0, 74.0)
Suffolk	12~~630~~	106.6 (86.0, 128.0)	120.0 (96.0, 143.0)	172.1 (147.0, 198.0)
Overall total, 36-64 years	-	249.7 (221.0, 284.0)	262.9 (233.0, 297.0)	1175.4 (1109.0, 1243.0)

[1]Numbers in green denote where observed count fell within 95% prediction interval [95% PI] for people aged 16-35 years. Observed data for people aged 36-64 years in the *validation sample* was not available.

Model 1: Age group, sex, their interaction and ethnicity
Model 2: Model 1 + IMD
Model 3: Model 1 + extent of deprivation
Model 4: Model 1 + income deprivation
Model 5: Model 1 + employment deprivation
Model 6: Model 1 + population density
Model 7: Department of Health uniform figure for EIS of 15 new cases per 100,000 people per year.

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Table 3: External model validation diagnostics[1]

Model	Observed case count within OSEPEA overall correct prediction intervals? [rank]	EIS (N=6)		LAD (N=21)		Mean ranking [rank of mean ranking]
		Number correct [rank]	RMSE [rank]	Number correct [rank]	RMSE [rank]	
Model 1	No [53]	34 [62]	27.05.6 [6]	18 [2]	8.91 [6]	5.03.8 [64]
Model 2	No [53]	43 [64]	168.84 [4]	18 [25]	6.49 [4]	43.48 [56]
Model 3	YesNo [13]	54 [21]	146.94 [32]	178 [25]	6.135 [32]	23.602 [32]
Model 4	Yes [1]	4 [42]	14.96.3 [2]	187 [25]	6.14 [2]	21.868 [23]
Model 5	YesNo [31]	54 [12]	179.48 [5]	186 [62]	6.7.1 [5]	24.82 [53]
Model 6	Yes [1]	5 [1]	11.59 [1]	19 [1]	65.90 [1]	1.0 [1]
Model 7	No [53]	12 [7]	398.16 [7]	13 [7]	11.70 [7]	6.62 [7]

[1]For each diagnostic, models are placed in rank order [1=best model, 7=worst model] with ties given the same ranking. The mean ranking and rank provide an estimate of the overall performance of various models.

RMSE: Root mean squared error (lower scores indicate lower error); EIS: Early Intervention in Psychosis Service; LAD: Local Authority District

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Article Summary

Article Focus

- Commissioners require precise information on the health needs of their local populations to effectively plan health services
- A failure to arm mental health commissioners with precise epidemiological data led to mis-estimation of actual activity in early intervention in psychosis services [EIS]
- We sought to develop a prediction tool for the incidence of first episode psychosis [FEP], by applying precise estimates of epidemiological risk in various sociodemographic groups to the structure of the population at-risk in a second region, where the observed incidence had been concurrently ascertained

Key Messages

- A model of psychosis incidence which included age, sex, ethnicity and population density yielded precise FEP predictions in our second region, out-performing the Department of Health in England's current gold standard for EIS commissioning.
- While our model provides forecasts of the burden of FEP in different populations, initial assessment of some people who do not require subsequent EIS care means additional service resources, not addressed here, will be required.
- We have translated this model into a freely available prediction tool (www.psymaptic.org) to facilitate evidence-based healthcare commissioning of socioculturally relevant services according to local need
- ~~Our tool could be extended to many international settings and other disorders to inform healthcare commissioning, when epidemiological risk can be well-characterised and the structure of the underlying population at-risk is known~~

Strengths and limitations

- Our modelling approach used robust epidemiological data from two large studies of first episode psychosis in England to provide estimates of incidence in a third study region, producing accurate FEP forecasts
- While our models provide estimates of the expected clinical burden of FEP in the community, services may see a broader range of psychopathology consuming resources, or incepted rates may be influenced by supply-side organisational factors
- Due to data availability it was not possible to validate our prediction tool in settings outside of England and Wales, or for specific psychotic disorders. As data become available we will extend the capability of our prediction tool, including into other settings and disorders.

Supplemental Table 1: Socioenvironmental variables at local authority district [LAD] level considered in epidemiological prediction models

Variable		England[1]	Prediction sample[2]	Validation sample[1]	Mann-Whitney test[3]: Z; p-value	
					Prediction vs. Validation	Validation vs. England
Number of LAD	-	326	14	20 (+1 partial)	-	-
Multiple deprivation (z-standardised)	Median (IQR): Min/Max:	0 (1)[4] -1.7 / 2.9	1.0 (-0.5, 2.4) -1.1 / 2.9	-0.7 (-1.0, 0.3) -1.4 / 1.0	2.4; p=0.02	1.5; p=0.12
Extent of deprivation (%)	Median (IQR): Min/Max:	9.0 (1.3, 23.9) 0.0 / 83.6	28.0 (4.0, 63.0) 0.0 / 83.0	1.4 (.4, 12.8) 0.0 / 29.7	2.4; p=0.02	2.2; p=0.03
Income deprivation (%)	Median (IQR): Min/Max:	11.7 (8.6, 16.1) 3.9 / 32.8	15.5 (8.2, 24.7) 5.9 / 34.4	9.0 (8.2, 14.9) 6.0 / 19.1	1.5; p=0.14	1.3; p=0.19
Employment deprivation (%)	Median (IQR): Min/Max:	8.0 (5.8, 10.8) 2.1 / 18.8	11.6 (6.1, 14.1) 6.1 / 14.1	6.4 (5.4, 10.1) 3.9 / 13.9	2.5; p=0.01	1.4; p=0.17
Population density (people per hectare)	Median (IQR): Min/Max:	5.1 (1.8, 17.4) 0.2 / 137.1	19.4 (9.3, 81.9) 2.6 / 106.4	1.5 (1.2, 3.1) 0.9 / 30.0	3.7; p<0.001	3.4; p=0.001

IQR: inter-quartile range; LAD: Local Authority District

[1]Sources: Population density – 2009 mid-year census estimates; Deprivation variables: 2010 Indices of Deprivation, predominantly collected from data sources just prior to SEPEA case ascertainment period (2008)

[2]Sources: Population density – 2001 census estimates; Deprivation variables: 2004 Indices of Deprivation, predominantly collected from data sources close to ÆSOP & ELFEP case ascertainment periods (i.e. 1997-2000).

[3]Mann-Whitney test performs test that the median LAD socioenvironmental scores for the prediction & validation data come from the same population distribution; p<0.05 indicates evidence that the median scores are significantly different

[4]For England we displayed the mean and s.d. of the z-score of deprivation (as shown, underlined), instead of the median and IQR.

Supplementary Table 2: Stratum-specific external validity of our PsyMaptic prediction model in people aged 16-35 years old (Model 7)

	Observed N[1] (SEPEA)	Predicted N[2] (Model 7)	95% PI[3]	Observed N within 95% PI?[4]
Sex				
Men	345	338.9	(299.0, 382.0)	**Yes**
Women	176	169.5	(144.0, 196.0)	**Yes**
Age group				
16-17	66	24.8	(15.0, 36.0)	No
18-19	95	72.1	(55.0, 90.0)	No
20-24	183	159.8	(131.0, 189.0)	**Yes**
25-29	107	152.4	(128.0, 179.0)	No
30-34	65	85.3	(66.0, 105.0)	No
35	5	14.2	(7.0, 22.0)	No
Ethnicity				
White British	410	335.2	(299.0, 375.0)	No
Non-British white	44	43.7	(31.0, 57.0)	**Yes**
Black Caribbean	5	18.3	(10.0, 27.0)	No
Black African	14	20.3	(12.0, 31.0)	**Yes**
Indian	1	20.9	(13.0, 31.0)	No
Pakistani	6	13.8	(7.0, 22.0)	No
Bangladeshi	6	3.8	(0.0, 8.0)	**Yes**
Mixed, white & black Caribbean	5	10.6	(5.0, 18.0)	**Yes**
Mixed, other ethnicities	12	7.5	(3.0, 13.0)	**Yes**
Other ethnicities	18	34.5	(23.0, 46.0)	No

[1]Observed number of cases meeting SEPEA criteria for FEP over 2.5 years (n=521).

[2]Predicted caseloads over 2.5 years based on model estimates from ÆSOP & ELFEP data extrapolated to the population at-risk, aged 16-35 years, in the SEPEA study

[3]95% prediction intervals

[4]Reports whether the observed number of cases falls within the prediction intervals given by the model

Appendix (supplementary): Development of 95% prediction intervals for negative binomial regression models

To obtain 95% prediction intervals from each model, we took all parameter estimates from the fitted negative binomial regression, including the over-dispersion parameter θ, as the true values when constructing prediction intervals. We then used a Monte Carlo procedure, where we simulated realisations using the Gamma-Poisson representation of the negative binomial distribution. For each iteration, we first simulated the random components of the linear predictors from Gamma(θ,θ), which were multiplied by the point predictions (or equivalently e^{υ}, where υ is the non-random component of the linear predictor) to give the Poisson rates for the counts that comprised the predictions. We then simulated Poisson counts using these rates and summed them to provide one realisation of the quantity we wished to predict. By repeating this process many (n=1000) times the distribution of the quantity to be predicted was obtained, from which 95% prediction intervals were obtained using the 2.5% and 97.5% quantiles.

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Data sharing statement

Extra data is available at our prediction website, PsyMaptic: www.psymaptic.org. We have made a large array of prediction data freely available to interested users, who can visualise prediction data in maps and tables for a range of psychotic disorder predictions by major sociodemographic subgroup and by LAD. Future versions of PsyMaptic will release data for other regions and at other geographical levels. Users can also download LAD-specific and national summaries of prediction data from our models in tabular form. Finally, additional explanatory material about how to use the data and the PsyMaptic website is also available at www.psymaptic.org. Bespoke data not provided freely on our website may be requested from the authors at the cost of data extraction. The empirical data underlying the prediction models (ÆSOP and ELFEP) or the validation sample (SEPEA) is not freely available as the studies are ongoing, but papers detailing the main findings from these studies have previously been published elsewhere.

Competing interests statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (i) JBK has support from the Wellcome Trust for the submitted work (grant number WT085540) and PBJ has support from the NIHR (grant RP-PG-0606-1335); (ii) DJ, JP, FW, DF, JC, RMM have no relationships with any company that might have an interest in the submitted work in the previous 3 years; (iii) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (iv) no author holds non-financial interests that may be relevant to the submitted work.

Role of funders

The funders were not involved in the design, collection, analysis, interpretation of the data, writing the report or the decision to submit the article for publication. All authors were independent from the funders in contributing to this work.

Ethical approval

Ethical approval to conduct the original ÆSOP and East London First Episode Psychosis studies was granted from local research ethics committees in their respective centres prior to the original date of onset of the study. We were granted ethical approval to conduct the work related to the present manuscript, including use of data from the SEPEA study, from the Cambridgeshire 3 REC (09/H0306/39).

Guarantorship

JBK takes full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

Contributorship

JBK was responsible for concept, design, analysis, data extrapolation, interpretation of the data, drafting the report and developing the content for the websites www.psymaptic.org, www.psymaptic.com and www.psymaptic.co.uk. JBK was also the chief investigator of the SEPEA study, where the *validation sample* data was obtained. He gave final approval of this version of the manuscript to be published.

DJ was responsible for developing and initially implementing the statistical approach with regard to prediction intervals from count-based regression. He also contributed to drafting and editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JP is principal collaborator on the SEPEA study in the CAMEO early intervention in psychosis services. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

DF is co-principal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

FW is co-principal collaborator on the SEPEA study in the Norfolk and Suffolk Foundation Trust. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

JC is chief investigator of the ELFEP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

RMM is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He also contributed to editing the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

PBJ is co-chief investigator of the ÆSOP study and provided part of the empirical dataset underlying the prediction model for use in this project. He contributed to the development of the prediction methodology and edited the final version of this manuscript. He gave final approval of this version of the manuscript to be published.

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STROBE statement

Our STROBE statement is provided as a supplementary file.

Supplemental Figure 1: Screenshot of web-based PsyMaptic prediction tool

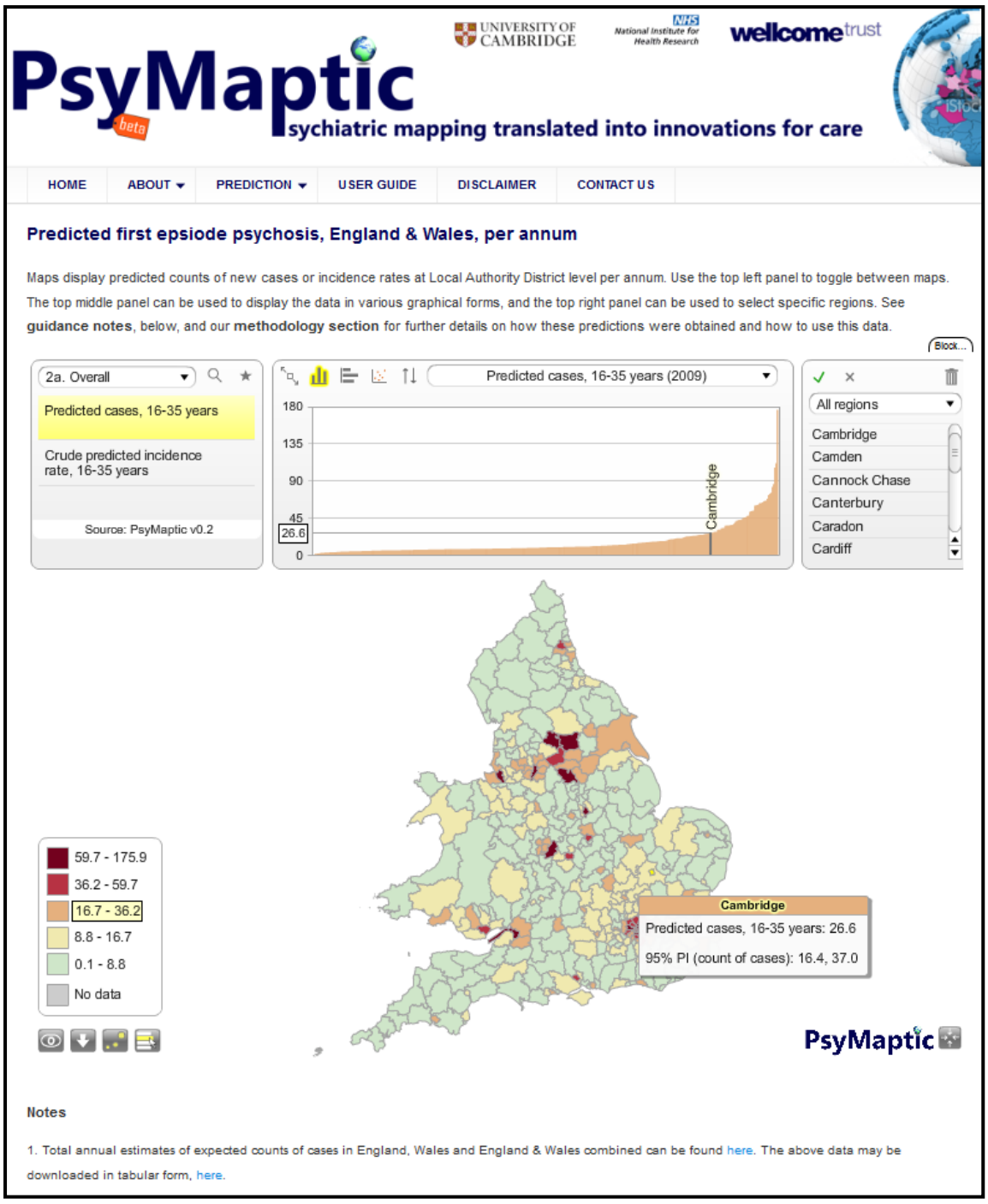

Figure legend: Screenshot shows the PsyMaptic prediction tool made freely available at www.psymaptic.org. This example shows a prediction map of the annual expected count of new cases of psychotic disorder for people aged 16-35 years across 376 Local Authority Districts [LAD] in England & Wales from our candidate prediction model (Model 6). Each prediction is presented with corresponding 95% prediction intervals. Count data are categorised into the following percentiles: green: 0-50% of LAD; yellow: 50.1-75%; orange: 75.1-90%; red: 90.1-95%; dark red: 95.1-100%. Our PsyMaptic prediction maps are provided with additional graphical utility (histograms, scatterplots, region selection) and are freely available at www.psymaptic.org

Supplemental Figure 2: PsyMaptic predicted incidence rate of psychotic disorder in England and Wales, aged 16-35 years old, compared with Department of Health uniform rate for EIS commissioning

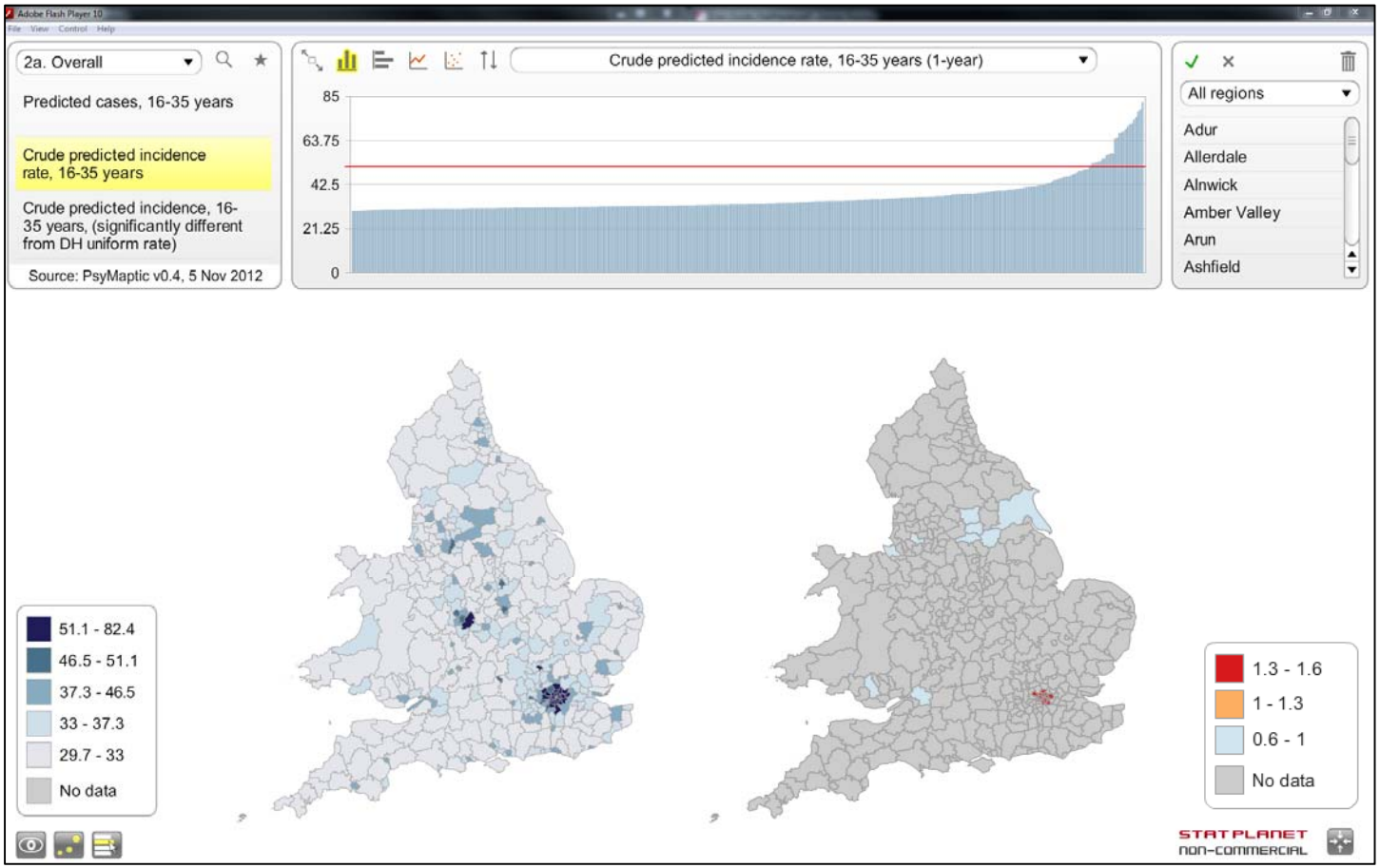

Figure legend: The graph (top) plots all LADs according to predicted incidence rates in people aged 16-35 years (per 100,000 person-years) using PsyMaptic (model 6). The red line is the uniform rate (51 cases per 100kpy), used to commission EIS. Our predicted rates fall below this in 93% of LAD in England & Wales (n=351), indicating that the Department of Health's [DH] uniform rate may have over-estimated incidence in these regions. Predicted incidence rates are plotted geographically on the left hand map, The darkest shading indicates LAD (in London and Birmingham) where the point estimate of incidence exceeded the DH uniform rate. The right hand map plots the ratio between predicted cases from PsyMaptic & the DH uniform rate. Ratios significantly exceeding unity (in orange & red) show regions where the DH rate under-estimated incidence; ratios significantly less than unity (in blue) show regions where the DH rate over-estimated incidence. This method is conservative (see methodology).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract We entitled our paper **A population-level prediction tool for first episode psychosis: development and validation**. While our paper uses cross-section data to base prediction models on, the central study design is in reference to prediction modelling using epidemiological data, which we have duly referred to.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Our abstract was written in the structured style required by the British Medical Journal for publication and included information on *background, objectives, design, setting, main outcome measures, results* and *conclusions.*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Health care planners and commissioners require accurate data on the incidence of psychotic disorder to anticipate the burdens faced by different populations in different regions. Only by using precise predictions, which take into account local need, will it be possible for health care funders and commissioners to allocate finite resources where they are most needed. There is evidence that Early Intervention in Psychosis services [EIS] were commissioned on an erroneously low uniform rate, and that commissioners were unable to satisfactorily take into local population need based on established sociodemographic and environmental risk factors for disorder. This led to misestimation of demand for EIS services in many parts of the UK. We sought to improve the information available for health care commissioners in psychosis, and particularly EIS, by developing an epidemiological prediction tool for disorder.
Objectives	3	State specific objectives, including any prespecified hypotheses To develop a population-based epidemiological prediction tool for first episode psychosis [FEP]. Our hypothesis was that our best prediction model, using informed empirical epidemiological data, should be more valid than the current gold standard for EIS planning, based on the Department of Health's Mental Health Policy Implementation Guide figure of 51 new cases per year per 100,000 people.
Methods		
Study design	4	Present key elements of study design early in the paper Pooled data from two large epidemiological studies of First Episode Psychosis [FEP] conducted with similar methodologies (the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [AESOP] study, and the East London First Episode Psychosis [ELFEP] study) were used to generate risk coefficients from six negative binomial regression models, which tested different combinations of sociodemographic (i.e. age, sex, ethnicity) and socioenvironmental factors (deprivation, population density at local authority district [LAD] level) associated with psychosis incidence. Coefficients were applied to the population at-risk of a third, markedly different region, to predict expected FEP counts over a 2.5 year period, where the observed incidence had also been ascertained.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Empirical data from the AESOP (1997-9) and ELFEP (1996-8 & 1998-2000) studies

		in London, Nottingham and Bristol was used in regression models to estimated out-of-sample predictions for the expected count of new FEP cases in the population at-risk of East Anglia over a 2.5 year period (2009-2012), where the observed count of cases incepted through EIS has also been ascertained through a third study, the Social Epidemiology of Psychoses in East Anglia [SEPEA] study.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants All participants in the AESOP and ELFEP studies, aged 16-64 years old at referral, were identified using the same study design based on the principles of the World Health Organisation Ten-Country study. Any participant presenting to services in each study's defined catchment areas with a suspected first episode of psychotic disorder over the case ascertainment period were screened. Participants were included if they were diagnosed by consensus with an ICD-10 F10-39 first episode of psychotic disorder, using standardised diagnostic data from the Schedule for the Clinical Assessment of Neuropsychiatry [SCAN] presented to a panel of clinicians blind to the ethnicity of the subject. A leakage study was conducted to identified participants missed by the initial screen. Participants in the SEPEA study, aged 16-35 years old, were identified if they were referred to one of six EIS in East Anglia for the first time with a suspected first episode of psychosis in the defined catchment area of these services over a 2.5 year period. Participants were excluded if they did not meet clinical criteria for acceptance into EIS or if, at six months after referral, a clinical diagnosis of ICD-10 F10-39 psychosis had not been observed. Observational data in people aged 36-64 years old could not be obtained as this was not part of the SEPEA study objective and no routine surveillance of this group was in place. Participants from any study were excluded if they were found to have a profound learning disability or an organic basis to their psychotic episode. The denominator populations for AESOP and ELFEP were estimated from the 2001 Census of Great Britain, while the latest mid-term census estimates (2009) stratified by age, sex and ethnicity were obtained for the denominator population in the SEPEA study.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable All clinically relevant psychotic disorders as per ICD-10 F10-39 psychotic disorders were included as the main outcome variable. We included age group (16-19, then 5 year age groups until 60-64 years), sex and ethnic group (ten categories based on the 2001 census 16-category variable to include: white British, non-British white, black Caribbean, black African, Indian, Pakistani, Bangladeshi, mixed white & black Caribbean, other mixed ethnicities and all other ethnicities). Given evidence of effect modification of the risk of psychotic disorder over age by sex, we considered an *a priori* interaction between these variables. All individual level variables are known to be associated with the incidence of psychotic disorder and were therefore considered important predictors in our models. Additionally, for some prediction models (see

		below), we also included various socioenvironmental measures at the Local Authority District [LAD] level, such as socioeconomic deprivation or population density, since there is evidence that the incidence of psychotic disorder varies by urbanicity and deprivation. Population density was measured by dividing total population size (2001 or 2009) by LAD area. The Indices of Deprivation (2004/2010) were used to include the potential effects of four domains of deprivation relevant to psychosis incidence – multiple deprivation, the extent of deprivation in the LAD (i.e. an inequality-like measure), income deprivation and employment deprivation. These domains were obtained from the 2004 and 2010 indices of deprivation for the AESOP/ELFEP and SEPEA studies, respectively, with the source data originating from national surveys and other data sources predominantly collected close to the case ascertainment periods of each study.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group For numerator participants: Age was based on age at first referral for suspected psychotic disorder. Ethnicity and sex were assigned by self-ascription. Neighbourhood-level socioenvironmental factors were assigned to participants based on their residential address at first referral to services. For denominator (census) participants: Age was defined as age at the time of the census or mid-term census estimate. Sex and ethnicity were defined through self-ascription. LAD population density was based on the total census/mid-term population in each LAD, divided by each LAD's area (in hectares) estimated using ArcGIS software. Deprivation domains were assessed by the 2004/2010 indices of deprivation, which use a comparable methodology to assess changes in deprivation over time, integrating data from a range of nationally-collected routine data sources.
Bias	9	Describe any efforts to address potential sources of bias To minimise the risk of missing incidence participants from the AESOP and ELFEP studies leakage studies were conducted to identify all subjects with a potential FEP, not picked up by the initial screen. This was achieved by close contact with other services where FEP subjects may present, including prisons, the judicial systems, homeless shelters and so forth. In the SEPEA study, EIS provide the only service base for people experiencing FEP up to 35 years old. No leakage study was possible in SEPEA, but all services engaged in active outreach to ensure missing participants were minimised in their communities. One potential source of bias in the SEPEA study is the over-estimation of incidence rates given that EIS do not tend to diagnose participants at referral to avoid stigmatisation and to allow the full course of symptoms to emerge. We minimised the possibility of over-inclusion here by excluding all participants who did not meet clinical criteria for entry to EIS (clear evidence of psychotic symptoms, no previous referral, no previous antipsychotic treatments) and by restricting the sample only to those participants who were given a clinician-rate ICD-10 F10-39 diagnosis of psychotic disorder at first episode.

Study size	10	Explain how the study size was arrived at Studies of incidence rates have a sample size equivalent to the ability of the study to identify all true instances of first episode psychosis in a defined catchment area and population over a given time period. Thus, the sample size for all studies here is a function of these factors. We included data from the SEPEA study for 2.5 years of the 3 year study, since it was presently ongoing at the time of these analyses. We included 14 LADs in our empirical prediction data (AESOP/ELFEP) and 21 LADs in our SEPEA study region.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Variable groupings for individual level variables have been described in Section 7. For LAD-level variables, population density was entered as a continuous variable. Multiple deprivation and the extent of deprivation were entered as continuous z-standardised variables (across variation in these scores over England) to have a mean of zero and standard deviation of one. Income and employment deprivation were classified as the proportion of people in a given LAD classed as income or employment deprived.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding A summary of our statistical methodology is provided here. Full details are provided at www.psymaptic.org or in the accompanying paper to this checklist: [i] Six negative binomial regression models were fitted to the empirical data (AESOP/ELFEP). Model 1 was fitted with age group, sex, their interaction and ethnic group. Models 2-5 included the variables in Model 1 plus a single LAD deprivation measure (multiple deprivation, extent of deprivation, income and employment deprivation, respectively). Model 6 included the variables in Model 1 plus LAD population density. [ii] Apparent predictive error for the whole sample, aged 16-64 years, was estimated using repeat k-fold validation to obtain estimates of the Residual Mean Squared Error and Lin's Correlation Concordance Coefficient (correlation between model predictions and the observed count of cases in the data). For each full [iii] Regression coefficients from each model obtained in [i] were applied to the population structure of the population at-risk, aged 16-35 years old, in the SEPEA study to obtain out-of-sample predictions of the expected count of cases in East Anglia over 2.5 years as seen in the age range for EIS. Predicted counts for each model were obtained for the (1) overall predicted count (2) EIS-specific counts and (3) LAD-specific counts in East Anglia. For every prediction, 95% prediction intervals were estimated, using a bootstrap-like method developed from first principles to take into account prediction error in both the prediction data and the out-of-sample dataset. [iv] We obtained similar predictions to [iii] based on a "model" (Model 7) which fitted the Department of Health's current gold standard incidence rate for EIS commissioning (51 per 100000 per year) to the SEPEA data and obtained predictions [iii](1-3) as before.

[v] The predicted counts from each model obtained in [iii] (1-3) were compared with the observed counts of cases for each grouping. We considered the number of times the observed count fell within the 95% prediction intervals from the model prediction to indicate satisfactory model fit. RMSE estimates of model fit between the predicted and observed counts at the EIS- and LAD-levels were obtained for external model validation and comparison. For each of the five diagnostics (overall fit to the observed data, number of times fitted correctly to six EIS, number of times fitted correctly to the 21 LAD, EIS-level RMSE, LAD-level RMSE) we ranked models in terms of performance (1: best, 7: worst). Ranks were averaged across these 5 diagnostics to give an overall ranking for the model which had the greatest predictive power.

[vi] Using the best model obtained in [v] we extrapolated our findings to the population structure (2009 mid-term estimates) of every LAD in England and Wales to produce a freely available prediction tool for commissioners, which forecasts (with 95% Prediction Intervals) the expected incidence of psychotic disorder in every LAD, across all major sociodemographic groups, based on empirical risk coefficients and applied to each LAD's unique population structure. This prediction data was visualised using software known as StatPlanet and uploaded to our website www.psymaptic.org to provide Psychiatric Mapping Translated into Innovations for Care [PsyMaptic], a free, online commissioning tool for health care planners, providers and commissioners.

(*b*) Describe any methods used to examine subgroups and interactions

We used the full empirical dataset aged 16-64 years to predict the expected count of cases in our validation sample (SEPEA), where the observed caseload had been restricted to the ages 16-35 years old, consistent with the age range covered by EIS. SEPEA did not identify an incidence sample in this region for people aged 36-64 years old and so we could not externally validate our models in this age range. However apparent validity of our models across the entire age range, 16-64 years old, was good, and we have no reasons to believe our empirical data in the older age range would be any less valid for prediction than at younger age ranges given it was obtained from the same two studies (AESOP/ELFEP).

Interactions between age group and sex were entered into our regression models as a multiplicative statistical interaction.

(*c*) Explain how missing data were addressed

There were no missing data in this dataset

(*d*) If applicable, describe analytical methods taking account of sampling strategy

N/A

(*e*) Describe any sensitivity analyses

95% prediction intervals were developed for negative binomial regression prediction and reported for all predicted counts and incidence rates of FEP. These intervals give a measure of the confidence we have in our prediction estimates.

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 1037 participants with a first episode psychosis were included in the prediction sample of an initial sample of 1049, where 12 participants were of no fixed abode at time of entry to the study. For the SEPEA study 521 cases were observed over the study period who met entry criteria for the study from an initial sample of 572. Those excluded did not meet clinical criteria for FEP.
		(b) Give reasons for non-participation at each stage See above
		(c) Consider use of a flow diagram Not necessary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. See previously published papers on the AESOP, ELFEP and SEPEA studies as this is not directly relevant here. Of more relevance are the risk coefficients for psychosis incidence across sociodemographic and socioenvironmental groups, as reported in Table 1 of the paper accompanying to this Strobe statement includes. This table confirms the typical risk coefficients seen across these variables.
		(b) Indicate number of participants with missing data for each variable of interest 12 participants were excluded because of no fixed abode in the AESOP. These subjects were more likely to be men, but otherwise did not differ from the remainder of the sample.
Outcome data	15*	Report numbers of outcome events or summary measures N/A – see below for full results
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. A model with age, sex, ethnicity and population density performed strongest overall, predicting 508 FEP participants in EIS in East Anglia (95%PI: 459, 559) compared with an observed count of 521 over the same period. This model predicted correctly in 5 of 6 EIS (83.3%) and 19 of 21 LAD (90.5%). This model achieved the highest ranking on all external diagnostic measures of any model, and reasonable apparent RMSE (0.76; s.d.: 0.13) and CCC (0.76; 95% CI: 0.74, 0.77) estimates across the entire age range. All models performed better than the current gold standard for EIS service commissioning (716 cases; 95%PI: 664-769). Inspection of stratum-specific predictions of our best model in the SEPEA region suggested results were accurate by sex. For age, our models tended to underpredict caseloads at younger ages, but over predict caseloads at older ages (up to 35 years old). This was probably due to the nature of EIS themselves, which alter i.e. lower the median age at onset. Our prediction data was based on pre-EIS epidemiological data, so future versions of PsyMaptic need to incorporate new EIS data. Results by ethnicity were mixed with accurate predictions in some, but not all ethnic groups. This will continue to be refined.

		(*b*) Report category boundaries when continuous variables were categorized Age groups – see above
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives We have developed several epidemiological prediction models to forecast expected incidence of first episode psychosis in England and Wales, and assessed their relative apparent and external validity, taking into account regional differences in the sociodemographic and socioenvironmental profile of different populations. Inspection of the data suggested that a model fitted with age group, sex, their interaction, ethnic group and LAD-level population density provided the best external predictive capabilities compared with the observed caseload ascertained through EIS in our *validation sample*. This model also had good apparent validity across the entire age range considered here (16-64 years). All prediction models performed significantly better than the Department of Health's current gold standard for EIS resource allocation, based on a low uniform anticipated incidence rate.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Our predictions are based upon the assumed true rate of disorder in the population aged 16-64, 16-35 or 36-64 years old. This may differ from the caseloads observed by services, due to supply-side and demand-side issues. For example, services may see a broader range of referrals who are not psychotic or in the prodromal stage of disorder. Additional resources for false positive caseloads need to be considered in any commissioning decisions. Furthermore, demand for services may differ from the true underlying rate of FEP in the community if people are not aware of the relevant mental health services available to them. Services vary considerably in organisation, remit and structure and such factors may also affect the incepted (versus true) rate of disorder seen in EIS and other mental health services. Prediction intervals for count-based regression models are not computationally-straightforward to derive. We estimated prediction intervals from first principles [DJ], using a bootstrap-like methodology to produce 95%PI accounting for uncertainty in the *validation sample*, but ignoring parameter uncertainty in the coefficients included in prediction models, which were assumed to be the true coefficients of risk in the population. This approach naturally leads to narrow 95%PIs given ignorance of parameter uncertainty, and is therefore desirable for model validation and the precise prediction of expected counts. The addition of more empirical data to the prediction model would thus not lead to narrower PIs, though might move the point estimate of risk for each coefficient closer to the true value in the population. We sought independent confirmation that our formula was correct (Prof Ian White, MRC Biostatistics Unit) and full details of our methodology are made available in the

Appendix. We recommend that all prediction point estimates made available in our PsyMaptic model are considered with their 95%PIs, which provide information about the natural variance in expected rates in the population.

We could not externally validate our prediction models for people aged 36-64 years because comparable observed incidence data was not available in our *validation sample*. We have no reason to believe our predictions will be invalid for this group, however, since the empirical data which underpinned our models was ascertained from the same two large, well-conducted studies of first episode psychosis in England as the data for the younger age group, and published findings from these studies are consistent with the wider epidemiological literature for psychosis from England and internationally. It will be important to ascertain the predictive capability of our model(s) where we could not externally validate our model, and we will seek to identify suitable samples to do so in future versions of PsyMaptic.

All prediction models had reasonable apparent validity, although our proposed model had slightly poorer apparent validity (most noticeably in terms of AIC) than models which included deprivation instead of population density (i.e. Models 2-4). Model 4 (including income deprivation) had marginally greater apparent validity than our candidate prediction model, but performed worse during *external validation* (Table 4), which we considered more important for the development of a prediction tool. This decision was supported by the fact that despite considerable socioenvironmental differences between regions in our *prediction* and *validation samples,* our prediction model produced accurate forecasts in a markedly different population. We were unable to predict the expected incidence of psychotic disorder in geographical areas smaller than LADs, such as electoral wards (N~6000), or to other parts of the UK, because the appropriate denominator data was not published as mid-term census estimates. The 2011 census will provide small area and national data for the whole of the UK and will be released by ONS in mid-2013. This will allow us to update our tool to the latest population estimates for the UK, and refine our PsyMaptic tool at a smaller geographical level for fine-grained healthcare commissioning. Small area prediction models will require a multilevel approach, not attempted here, because obtaining predictions from multilevel random effects models is not straightforward and requires active statistical development.

We believe case ascertainment in our *validation sample* led to a reliable estimate of the incidence of psychotic disorder for people aged 16-35 years old. EIS are the only mental health service for people aged 14-35 years experiencing a first episode of psychosis, minimising the potential for under-ascertainment in the population at-risk when derived from a careful epidemiological design. We are confident that our *validation sample* also contained few false positive cases for any clinically-relevant psychoses, since participants were excluded who failed to meet acceptance criteria for EIS or who did not receive a clinical diagnosis of psychotic disorder at six months after referral. Future versions of PsyMaptic will include forecasts for specific psychotic disorders, but these are unavailable at present because standardised research-based diagnostic data (using OPCRIT) needed to obtain specific reliable diagnoses are currently being collected in the ongoing SEPEA study.

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,

		multiplicity of analyses, results from similar studies, and other relevant evidence If commissioners are to meet the Department of Health's vision to orientate health services around local need, differences in demand for EIS and other mental and physical health services will need to be taken into account to allocate finite resources where they are most needed. The PsyMaptic prediction model provides proof-of-concept that when robust empirical epidemiological data is combined with accurate population at-risk estimates this can be realised. Our translational approach demonstrated good apparent and external validity to predict the expected incidence of first episode psychosis, particularly through EIS where 76% and 63% of all male and female adult-onset FEP cases, respectively, would typically present. Since their inception in 2002, EIS in England and Wales have reported both lower and higher caseloads than they were originally typically commissioned to manage, usually depending on the urbanicity of the population. Rural communities saw much lower demand for EIS than urban services. The Mental Health-Policy Implementation Guide [MH-PIG] anticipated a uniform rate of 51 per 100,000 people per year. While the MH-PIG also acknowledged that "…[a]n understanding of local epidemiology is needed as the size of population covered will depend on a number of different factors" (p.55), no further elaboration on how to achieve this was provided for commissioners. We believe PsyMaptic provides one possible exemplar to overcome this challenge.
Generalisability	21	Discuss the generalisability (external validity) of the study results We believe our results are generalisable to the populations of England and Wales. The empirical data we used is consistent with the wider international and national literature regarding the pattern of incidence rates across different sociodemographic and socioenvironmental subgroups. Our model had good external validity in the age range 16-35 years, and we have no reason to doubt its validity for the entire adult age range for psychosis, 16-64 years old given the reasonable apparent validity demonstrated. That our prediction data was based on a very different environment (urban London, Nottingham and Bristol) but still produced valid forecasts in a markedly more diverse, rural and less deprived region overall (East Anglia), suggests our model will have good validity in England and Wales. This will make our prediction model a valuable tool for mental health service planning and commissioning, based on local need and translational epidemiology, when the prediction intervals we produce here are also taken into account. Service commissioners must also provide allowances for differing structure of services and the extra (false positive) referrals that may consume service resources but do not meet clinical criteria for FEP.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 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. Peter Jones directs the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for Cambridgeshire & Peterborough and is supported by NIHR grant RP-PG-0606-1335. The SEPEA study has been adopted by the Mental Health Research Network [MHRN]. The authors are grateful to the clinical services and staff participating in the SEPEA study, and the MHRN for their support. We are grateful to Professor Ian White of the MRC

Biostatistics Unit (University of Cambridge) for his guidance on developing our prediction interval methodology for negative binomial regression.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.