Synopsis no.: S2.2.

Preliminary title: Variation in the Incidence of schizophrenia and other psychotic disorders across Europe: findings from the multi-centre EU-GEI study

Contact info for the person(s) proposing the synopsis

Name: James Kirkbride

Partner no: P23 /CMSUC

e-mail address: j.kirkbride@ucl.ac.uk

Publication category: 2

Working and writing group: J Kirkbride*, A Szoke*, P Jones, A Mule#, J-P Selten, I Tarricone, J Bobes, L de Haan, E Velthorst, J van Os, B Rutten, M Ruggeri, D Berardi, C Morgan, R Murray, A Lasalvia#, P Menezes, L. Sideli, D La Barbera

***Senior authors, # first authors**

Work Packages involved: WP2

Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: South London, Amsterdam, Paris, Creteil, Verona, Sao Paolo, Barcelona, Madrid, Valencia
Rural: Cambridgeshire, Leiden, Clermont-Ferrand, Palermo, Oviedo, Santiago, Cuenca, Bologna

Co-authors as above. Others TBC but list should be near-complete

Objectives (scientific background, hypothesis, methods, and expected results):

Background:

Previous studies have that the incidence of certain psychotic disorders, particularly schizophrenia and other non-affective psychoses, is raised in urban compared with rural environments. The reasons for this remain poorly understood, though associations between the degree of urbanisation of birth place, duration of exposure to urban environments and later psychosis risk suggest at least a partially causal role for putative environmental factors in urban environments. Affective psychotic disorders do not show such a strong gradient. It is unclear whether these phenomenon occur in all settings. International comparisons are difficult, given varying methodological approaches to estimating the incidence of psychotic disorders in different settings. Furthermore, the majority of the literature on this topic has been informed by studies in northern and western Europe; predominantly in the UK, the Netherlands, Sweden and Denmark. It is not known whether urban-rural gradients in the incidence of non-affective psychoses are also present in other settings, including Southern Europe and Latin America. An absence of such gradients, or significant differences in their magnitude in these countries may point to differing patterns of exposure to underlying social and economic determinants of psychosis.

The EU-GEI study provided us with the unique opportunity to accurately estimate the incidence of psychotic disorders using a homogeneous methodological approach in sixteen heterogeneous settings across five countries, incorporating urban, suburban and rural catchment areas. As such data from this study will enable us to examine the variation of incidence rates across different national contexts and to assess the role of the urban-rural characteristics and north-south gradient in the differences in incidence observed.

Aims

1. To compare incidence rates of psychotic disorders across 16 centres located in 5 European countries [France (Creteil, Paris, Clermont-Ferrand), Netherlands (Amsterdam, Leiden), Italy (Bologna, Palermo, Verona), Spain (Barcelona,

Cuenca, Madrid, Oviedo, Santiago, Valencia) and UK (Cambridge, London)].

2. To detect urban-rural differences in the incidence of schizophrenia and other psychotic disorders in 16 partner sites in the EU-GEI study.
3. To determine whether these differences are present for both non-affective and affective psychotic disorders, separately
4. To determine whether the incidence of psychotic disorders exhibited a broad, north-south gradient across European countries

Hypotheses:

1. After indirect standardisation for age, sex and migration* the incidence of schizophrenia and other non-affective psychotic disorders would be greater in more urban settings than more rural settings
2. After indirect standardisation for age, sex and migration* the incidence of affective psychotic disorders would not show urban-rural variation
3. Variation between settings in the incidence of non-affective psychosis, after standardisation, would be independently associated with specific measures of urbanicity, including overall population density and socioeconomic deprivation.
4. Using a standardised methodological approach to estimate the incidence of psychotic disorders in different European settings a North-South gradient would be present in the incidence of psychotic disorders.

*where available, or equivalent

Methods

All cases presenting to one of sixteen participating centres in WP2 of the EUGEI study with a suspected first episode of psychosis [FEP] were potentially eligible for inclusion in the study. Participants had to meet the following criteria:

Inclusion Criteria

- Age 18 to 64 at first presentation
- Resident within a clearly defined catchment (study) area
- Presence of an untreated first episode of psychosis (even if long-standing) (ICD-10: F20-29; F30-33 [DSM equivalents: 295.xx to 298.xx]) during the study period

Exclusion Criteria

- Treatment (broadly defined as contact with mental health services) for an episode of psychosis outside of the study period
- Evidence of psychotic symptoms precipitated by an organic cause
- Transient psychotic symptoms resulting from acute intoxication as defined by ICD-10

Case ascertainment

The case ascertainment period lasted for three years in most of the centres. The earliest start date was 1 May 2010 (London) and the last start date was 1 June 2012 (Paris). Eleven of 16 centres had begun case ascertainment by the end of 2010, four centres began recruitment in 2011 and one centre began recruitment in 2012 (Paris). Participants had to pass a clinical screen to confirm an ICD-10 diagnosis of first episode psychosis [F20-33]. Basic demographic and clinical data, including operationalised research-based diagnoses using the OPCRIT system, were available.

Basic demographic data were collected on all clients according to Section 1 of a specifically designed sociodemographic schedule for use in the EU-GEI study, the Schedules for the Assessment of Social Contexts and Experiences [SASCE]. For incidence cases, who did not also take part in the full EU-GEI study, as much data as possible were collected from Section 1 of the SASCE, including date of birth, sex, ethnicity, country of birth, parental country of birth, first language, employment history and social class.

Denominator data

Corresponding denominator data for each of the sixteen centres was estimated from routine statistics collated by local or national governments in each setting, in order to estimate the population at-risk. Denominator data was stratified by age group, sex and either ethnicity or country of birth, depending on the local availability of published data. For example, routinely available population statistics in the UK and Netherlands are published according to ethnicity, but in other countries i.e. France and Italy, the concept of ethnicity is not a routinely accepted cultural division, reflecting local, historical differences in migration and ethnicity. Instead, in such countries, population data are estimated according to country of birth. Analyses will be undertaken on datasets from different areas which meet sufficient quality standards (on required denominator, exposure and outcome data) for each analysis. Inclusion of centres (or not) in contributing to the results may vary depending on the exact analysis.

Exposures of interest

Urban-rural exposure status will be defined in three ways. The first definition was based on study setting, as originally identified for the purpose of the EU-GEI study. Centres were purposefully selected for the EU-GEI study based on their rural or urban location. Thus, the South London catchment, Amsterdam, Barcelona, Madrid, Verona, Paris and Creteil all covered exclusively urban populations in major conurbations. Remaining centres included regional capitals or large towns, but also included predominantly rural populations. Second, we ascertained the total population density of each study region by estimating the total population size of each setting and dividing it by the total area (in hectares) of that region. A GIS was established, using ArcGIS, for case ascertainment purposes, estimation of study size areas and other analytical studies. Third, each study setting was defined according to the level of overall deprivation in each region, as defined by the proportion of people unemployed in the population, median income levels and education. To inspect possible variance in latitude gradients, the mid-point in each centre will be estimated and entered into models as a continuous exposure.

Analyses

Crude incidence rates were estimated in each study centre. These rates were indirectly standardised to the age-sex stratum-specific rates for the overall (i.e. total) rates for all participating centres in the EU-GEI study. Total stratum-specific rates were applied to the corresponding population stratum in each setting to produce the expected number of cases in each strata. By comparing the expected number to the observed number we can obtain the standardized incidence ratio in each setting, which compares whether the observed number of cases in a given setting exceeded the expected rate in the EU-GEI study. This allowed us to inspect broad geographical variation in rates, by study centre, having standardized for the effects of age group and sex. This modelling process was then repeated, but with additional standardization for country of birth/ethnicity. Modelling was conducted separately for all psychotic disorders, as well as non-affective and affective psychotic disorders separately.

To inspect variation according to our three, broad measures of urbanicity we conducted Poisson regression. Each stratum represented a unique demographic stratum (as available from the data) with a corresponding count of observed number of cases and the population at-risk. Age group, sex, ethnicity/country of birth, where available, were all entered into the Poisson model as *a priori* confounders, with an interaction term fitted between age group and sex. Each urbanicity variable was then entered into the model to obtain incidence rate ratios according to urban-rural status, population density and deprivation. Models will be checked for departures from assumptions for Poisson processes (i.e. variance exceeding the mean) and methods to overcome these introduced where necessary i.e. negative binomial regression, zero-inflated models. To inspect variation according to the north-south gradient the mid latitude point of each study area will be entered as a covariate in the analyses, having controlled for measures of urbanicity.

Expected results

See hypotheses

Data needed for the study: All incidence cases in each centre, their age, sex, ethnicity or country of birth and diagnosis (non-affective, affective). Corresponding data for the denominator data in each centre. Total population (all ages) in each setting and area (in hectares) will also need collecting to assess population density. A measure of area level deprivation may also be estimated, but this needs to be comparable internationally. We will develop methods for this. Dr Kirkbride will establish a GIS for delineation of the catchment area of each study centre and estimates of longitude and latitude

Plan for statistical analysis (overall strategy): Indirect standardisation and Poisson regression. ArcGIS to estimate area of each catchment area.

Other analyses/methods:

Involvement of external Parties (non EU-GEI): We will need to obtain denominator data (population data) from the regional or national government agency responsible for the collection of census statistics in each region/country.

IPR check:

Timeframe: Data to be provided to the analysis team by end 2014. Analyses to begin late 2014 early 2015, circulation of manuscript to authors spring 2015, publication by summer 2015.

Additional comments: EUGEI wide consensus (and possible statistical advice) will be required on how to deal with international differences in the availability of population data by ethnicity or country of birth. From a statistical perspective, a fundamental question is "do the strata in each study centre have to be the same, or can you have different strata in different settings and still analyse the data in a meaningful way" i.e. in the UK we might stratify by white British, black Caribbean and Asian, but in the Netherlands we might stratify by white Dutch, black Caribbean Moroccan and Turkish" – where there is no, or little, overlap, can we enter zeroes for the strata, and is this still meaningful/valid analytically? The problem becomes more complex when data from France or Italy are introduced, where data are not stratified by ethnicity, but by country of origin (Africa, Caribbean etc)…

Note: while ethnicity/country of birth is not the focus of this synopsis, it is not really viable to publish differential rates by rural-urban status without controlling for ethnicity in some way. For example, we know that part of the reason why rates of disorder are higher in London than Cambridge is simply due to the greater proportion of ethnic minority groups who would confound any associations between urbanicity and psychosis.