Policy Research Programme
PRP Incidence of Schizophrenia

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Reference Number PR-SC-0908-10009

Date submitted

1. Application

Project Title*:	Systematic review of the incidence, prevalence and aetiology of schizophrenia and other psychoses in England		
Project Duration *: (months)	9.0	Total funding requested: (£'s)	£72,991.00
		Proposed Start Date *:	01 February 2009

2. Lead Applicant's Details

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Role in project*:	Principal Investigator

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* field is mandatory (see Guidance notes)

App Ref No: PR-SC-0908-10009

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Where did you hear about the programme*: (drop down)	NIHR website

4. Co-applicant details

Co-applicant 1

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Co-applicant 2

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Co-applicant 3

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Co-applicant 6

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Role in project:	Member of steering committee. To provide expertise on linking social environmental correlates of psychosis to neurobiology at interpretation phase

5. Scientific Summary*

Background **(400-800 characters)**:

Schizophrenia & other psychotic disorders are associated with considerable social disability, stigma and family burden. In the UK, recent estimates put the total societal costs of schizophrenia at £6.7 billion. Our understanding of the epidemiology of these disorders has changed radically in recent years as studies have shown that incidence varies by gender & place. In particular, there is emerging evidence that the environment (both social and physical) increases risk over the life course. Prevalence has been studied less, but for public policy and service planning purposes it is clearly important. Thus, a systematic review of the incidence, prevalence and environmental correlates of schizophrenia & other psychoses will inform public policy and may reveal clues about aetiology.

Aims **(400-800 characters)**:

To determine:

1. Whether the incidence & prevalence of schizophrenia & other psychoses are increasing (or decreasing) over time in England?
2. Whether geographical, ethnic & gender differences in incidence & prevalence are becoming more (or less) marked over time in England?
3. Whether incidence rates are higher when established through early intervention services than other observational research?
4. What are the candidate environmental factors (social & physical) that may account for: a) variation in incidence & prevalence by geographical area, ethnicity & gender; and b) trends in rates over time?
5. What are the economic cost implications, for health services & society, of variation & trends in incidence & prevalence: a) by geographical area, ethnicity & gender; and b) over time?

Plan of Investigation **(400-800 characters)**:

To conduct a systematic review of all published & unpublished literature from 1952 to 2008 on the incidence & prevalence of schizophrenia & other psychoses in England. Psychotic disorders with an organic basis will be excluded. A systematic search of the literature through bibliographic databases will be devised in consultation with an expert advisory group. Citation & reference searches and contact with study investigators will identify other published & unpublished studies. Abstracts will be screened and data on methodological quality and incidence/prevalence/aetiology extracted from papers that meet inclusion criteria. Analyses will be conducted to meet aims above, using meta-analyses & meta-regressions if appropriate. The expert group will discuss the importance of findings.

Potential Impact **(400-800 characters)**:

A better understanding of the incidence & prevalence of schizophrenia and other psychoses, and their environmental correlates, will allow policy makers to better plan modern mental health services and prioritise need in England. Our findings, strengthened by consultation with our expert group, will clearly highlight where variation exists in the incidence & prevalence of schizophrenia and other psychoses (i.e. by age, gender, ethnicity, social groups, place, methodological design) so that research can be translated into policy recommendations to deliver services where need is greatest. Our expert group & economic advisor (McCrone) will translate our findings into policy recommendations concerning how best to deliver services where they are needed most.

6. Lay / Plain English Summary*

(600-2000 characters)

Psychotic symptoms (e.g. hallucinations, delusions, strange behaviour) characterise the most serious mental disorders, in particular schizophrenia and, less commonly, mania and severe depression. These conditions are often associated with considerable social disability, stigma, and family burden. In the UK, recent estimates put the total societal costs of schizophrenia at £6.7 billion. Much of these costs arose from lost productivity and informal care and private expenditures borne by families. If we can better understand the distribution of these disorders in England, and what factors may cause them, we can provide valuable information for healthcare planners to provide better services to the people who need them most and reduce the burden placed on sufferers and the people who have to care for them.

We will conduct a comprehensive review of all available published and unpublished literature on the incidence (new cases) and prevalence (new cases and existing cases combined) of schizophrenia and other psychotic disorders in England from 1952-2008. We will extract, evaluate and combine all available data on serious mental illness rates to determine whether there are differences in incidence and prevalence over time and by age, gender, ethnic group membership and geographical area/place. We will also consider whether any differences can be explained in the way that different studies were conducted. We will also systematically review the literature on what factors in the social and physical environment might influence the rates of these disorders. We will consult a panel of experts in the field and share decision making and findings with service users at all stages of the proposal to improve the meaningfulness of the project, and to ensure the widest possible dissemination of our results.

7. Relevance of the proposed research to Policy Research Programme research brief*:

Please indicate the policy relevance of your research and how you can help facilitate the use of your findings for applied purposes **(Maximum 5000 characters).**

Our proposed project, and its component parts, has been designed to meet the aims and objectives of the PRP research brief in full. We will undertake systematic reviews of the incidence and prevalence of schizophrenia and other psychoses and examine available data on potential factors influencing these rates. The reviews will be undertaken by an expert systematic reviewer recruited to the project, working with a part time research assistant and a part time funded biostatistics PhD student (see Annex 4). The project team will be guided by our steering group, who have a broad and detailed understanding of the psychiatric epidemiology literature on schizophrenia and other psychotic disorders (Jones, Murray, Morgan, Kirkbride, Boydell, David, Croudace), and experience of systematic review methodology (Croudace & Jones have been part of previous PRP reviews).

We believe our research proposal fulfils the PRP brief for the following specific reasons:

1. Research team: We have established a research team which includes a broad range of skills, expertise and experience. The Principal Investigators are amongst the leading psychiatric researchers in the country and both have experience of conducing large-scale epidemiological studies, and in the design and dissemination of systematic reviews [1-3]. The steering committee incorporates expertise in clinical psychiatry, epidemiology, public health, health services research, methodology and population-based neuroscience. This combination ensures methodological rigour and the capacity to interpret the complex patterning of epidemiological data by various sociodemographic dimensions in England. We have a wealth of expertise on the potential clinical and neuroscientific validity of the epidemiological findings and sufficient linkages to policy matters in order to translate our findings into public health and health services utility. Input from our methodological advisors will ensure the quality of our systematic review methodology, and the appropriate use of statistics in any meta-analyses or meta-regressions.

2. Research history: Our group has been active in conducting epidemiological studies of the incidence and prevalence of schizophrenia and other psychotic disorders in England for more than two decades. The published outputs from members of our project team have contributed substantially to the national and international understanding of the environmental correlates of psychoses (for example, see findings from the ÆSOP study [4-11]), predominantly through studies in the United Kingdom. We are also involved in the ongoing collection of data addressing the incidence and prevalence of schizophrenia and other psychotic disorders in England and allied risk factors. We are therefore ideally placed to systematically review the With regard to future data, members of the team founder members of (Jones, Murray), or researchers on (Kirkbride, Croudace) the MRC e-science Psygrid project that is currently collecting prospective incidence data on first episode psychoses in 8 English cities.

3. Research environment: We propose to conduct the research in two 5* rated psychiatry research facilities in England at the previous Research Assessment Exercise [RAE] (2001), the University of Cambridge Department of Psychiatry and the Institute of Psychiatry [IoP], London. Our researchers in both these settings have considerable experience in administering and conducting research, including systematic reviews [1-3, 12-15] and are well-connected with national mental health research networks and service-user initiatives. Both centres have extensive experience of population-based and clinical epidemiology of schizophrenia and other

psychoses, as well as researching health service developments for early detection of psychotic cases.

4. Study design: We believe our project components and review design (detailed below) will address the aims and objectives of the PRP brief in an innovative way. We have provided a robust methodology for each aim to systematically review available data on the incidence and prevalence of schizophrenia and other psychotic disorders, and several key risk factors. We have identified key contemporary methodological and subgroups where research questions should be directed (see aims). Although the intention is to provide quantitative results, it is important to recognise that some of the conclusions will depend on the judgements of the expert group who will interpret the data, and consider aspects of data quality and reporting (see below). This group will be particularly useful in establishing consensus on areas of psychiatric epidemiology where methodological approaches and subsequent findings are highly heterogeneous and difficult to review systematically, such as the disparate methodologies used to investigate the role of social environments on the risk of schizophrenia and other psychoses.

8. Application of findings to help the delivery of policy and practice in health and/or social care*:

(Maximum 1,500 characters)

The methodology and findings of our systematic review will be an important resource for revealing trends in disease patterns over time, and should inform current practice and future policy in mental health services. A better understanding of the incidence and prevalence of schizophrenia and other psychoses, and the impact of several key environmental correlates, will allow policy makers to plan modern mental health services and prioritise need in England. Our findings will clearly highlight the main sources of variation in the incidence and prevalence of schizophrenia and other psychotic disorders (age, gender, ethnicity, social groups, place, methodological influences) so that this research informs policy. We expect that the review findings on past trends in incidence and prevalence will be useful in developing predictions concerning the likely future burden of serious mental illness in England. We envisage that our executive summary (part of the key study outputs) will present a clear list of recommendations, action points, priority areas. This will be strengthened by consultation with our expert group (see below), allowing epidemiological evidence to be translated into service provision.

9. Aims of the project*:

Including the research question and, where appropriate, the main hypothesis to be addressed **(Maximum 3,500 characters)**.

Our primary objective is to review all existing literature since 1952 on the incidence and prevalence of schizophrenia and other psychoses in England, and candidate environmental risk factors, in order to inform better service planning. We will identify where variations in incidence, prevalence and environmental correlates of schizophrenia and other psychoses exist across various sub-groups (i.e. age, gender, place, social geography, ethnicity, other social group(s) and methodological dimensions) and across time. This will elucidate which factors are most pertinent for planning modern mental health services.

To meet this objective, we will investigate five interrelated research questions (aims) that will inform service planning and delivery in England:

1. Whether the incidence & prevalence of schizophrenia & other psychoses are increasing (or decreasing) over time in England?
2. Whether geographical, ethnic & gender differences in incidence & prevalence are becoming more (or less) marked over time in England?
3. Whether incidence rates are higher when established through early intervention services than other observational research?
4. What are the candidate environmental factors (social & physical) that may account for: a) variation in incidence & prevalence by geographical area, ethnicity & gender; and b) trends in rates over time?
5. What are the economic cost implications, for health services & society, of variation & trends in incidence & prevalence: a) by geographical area, ethnicity & gender; and b) over time?

We will investigate these questions through a series of systematic reviews of published and unpublished data, utilising as appropriate and where possible meta-analyses.

10. Background*:

Detailing the size and nature of the problem to be addressed; including a brief literature review of previous work and relevant ongoing research, and indicating why the applicants are well placed to carry out the work. **(Maximum 5,000 characters)**.

Schizophrenia and other psychoses are associated with considerable social disability, stigma, and family burden. In the UK, recent estimates put the total societal costs of schizophrenia at £6.7 billion, largely arising from lost productivity and informal care and private expenditures borne by families [16]. Knowledge of the distribution & determinants of these disorders is essential to inform policy and service delivery.

Our understanding of the epidemiology of psychotic disorders has changed radically in recent years [17]. It had been widely assumed that incidence rates were broadly similar globally (and for men & women), following erroneous interpretation of the WHO 10-country study by those not involved in the work [18]. Recent original research & meta-analyses, including our own, have shown marked variation exists by place, gender and social group [4, 8, 19]. There is also emerging evidence that the environment (both social & physical) increases risk over the life course [20]. Prevalence has been studied less, but for the purposes of public policy and service planning, it is clearly important.

10.1 Research leading to proposal

Incidence: In the 3-centre *Æ*SOP study of first-episode psychosis, we found significantly higher rates in men, in our most urban centre (Southeast London) and for Black and Minority Ethnic [BME] groups; notably Black Caribbean (RR=6.7; 95%CI: 5.4-8.3) and Black African (RR: 4.1=95%CI: 3.2-5.3) groups [4, 8]. In a comparable study in East London, we found rates remained elevated in BME groups independent of socioeconomic status [21]. These data reflect, and extend, findings from two recent meta-analyses [19, 22].

With regard to time trends, we found a large increase in incidence of schizophrenia in Southeast London, particularly from the late 1980s onwards [23]. This was particularly marked in young people; noteworthy, as it has been suggested that newly established EI services, designed for younger people, report higher incidence rates than observational studies. In contrast, our recent analysis of data over 20 years in Nottingham suggested incidence had remained constant [6]. The wider literature is equally inconsistent [23-26]. It is unclear whether these variations reflect real trends in different areas or methodological artefacts [27].

Aetiology: There is now evidence linking the social environment (e.g. social capital, social fragmentation, ethnic density) [5, 28-31] and individual social experience over the life course (e.g. childhood adversity, adult social disadvantage, discrimination, substance use) with the onset of psychotic disorders [2, 11, 32-34]. Our recent work has added to this by suggesting that higher rates of psychosis in urban areas and BME groups may partially be a function of cumulative environmental risks over time [33]. Critically, plausible mechanisms now exist that potentially explain how social adversity over the life course impacts on gene expression, biological development, and cognitive and affective processes to increase risk of psychosis. These new insights have implications for policy and practice. Arguably, of the aetiological factors implicated, adverse environments are the most amenable to intervention, opening the door for preventive public health initiatives targeted at ameliorating the negative effects of adverse social environments and experiences.

Prevalence: Schizophrenia and other psychoses may be more common than previously

thought. In one of the most rigorous studies to date, estimates of lifetime prevalence of psychotic disorders in Finland were in excess of 3%, irrespective of data source used [35]. In contrast with the literature on incidence, a recent systematic review [36] found no variation in prevalence by area (i.e. urban/rural) or gender, though others have reported heterogeneity [37]. Schizophrenia was more prevalent in migrant groups (median RR=1.8), but this difference was lower than reported for incidence. Comparable findings for Black Caribbean groups in the UK have been reported [38]. We do not know whether methodological factors, particularly differences in the assessment of psychotic disorder, explain such discrepancies.

10.2 Importance of proposal

Recent meta-analyses of incidence & prevalence have been international in scope [19, 22, 36, 37]. Because of their global outlook, their generalisability to England is unclear. There has been no similar attempt to systematically review research on environmental risks - with the exception of our cannabis use review [2] - or time trends in incidence & prevalence. Further, we do not know whether there are time trends in estimates by service type (i.e. EIS), gender, place, social geography or indeed social group(s). We intend to focus on these questions as a basis for highlighting key areas for policy, planning, service delivery and practice.

11. Research plan and methodology*:

Including, where appropriate, the following; study design, justification of sample size, power calculation, selection and exclusion criteria of sample, method of allocation, methods of data collection (such as questionnaires), outcome measures and methods of analysis. **(Maximum 10,000 characters)**.

11.1 Search strategies

Inclusion criteria: To identify studies we will apply simple inclusion criteria, as follows: a) contains original data on i) incident cases of non-organic adult onset psychosis (16-64 years); or ii) prevalent cases of non-organic adult onset psychosis (16-64 years); or iii) one or more environmental risk factor; b) study conducted partially, or fully, in England; and c) study conducted between 1952 (before which we have found that no appropriate data were available [25]) and the end of 2008.

We will identify all studies of the incidence & prevalence of, and environmental risk factors for, schizophrenia & other psychoses, published or unpublished, meeting the above criteria by:

1. A systematic search of as wide a range of relevant bibliographic databases as possible, including (but not necessarily restricted to): Medline/PubMed (including MeSH terms); PsychINFO; EMBASE; Web of Science. We will apply a comprehensive list of search terms, building on existing review methodologies and combining terms for schizophrenia & other psychoses with (as necessary) terms for incidence, prevalence and environmental risk factors.

Specifically in relation to environmental factors, our search will be guided by expertise within the research team & expert group, to ensure all potential environmental risk factors are covered, including (but not limited to) individual level social factors (childhood abuse and adversity, socioeconomic status, life events and ongoing difficulties, indicators of adult social disadvantage and isolation, discrimination), area level social factors (social capital, social fragmentation, ethnic density), and substance use (particularly cannabis).

The combined search results will then be scrutinised by the research assistant by title and abstract to determine potential eligibility for inclusion in the review. Remaining abstracts will be reviewed by at least two members of the project team & steering committee to see if there is sufficient information to include them for review. Inconsistently rated abstracts will be reviewed by a third team member. The remaining papers will be obtained and read to confirm inclusion.

2. Scrutiny of references of all included papers to identify any papers not uncovered by electronic searching

3. Citation searches will search forward from each included study

4. Contact researchers involved in current or past epidemiological studies of schizophrenia & other psychosis enquire about relevant unpublished data

5. Consultation with experts, including a purposefully convened panel of experts (see below)

11.2 Data extraction

We will develop data extraction forms for each of our reviews of incidence, prevalence and aetiology, in order to systematically & consistently collate relevant information. We will

record information on: methodological aspects of included studies to assess methodological quality, and: data, in order to allow (where possible) inclusion in meta-analyses. The extracted data will be double entered and discrepancies checked.

Information to be extracted: Methodological aspects: operational definitions of incidence, prevalence and environmental factors (including urbanicity & ethnicity), subject recruitment, data collection, analyses (in particular, standardisation and adjustment for potential confounders); Data: Evidence of true population-base, sample size, age range, diagnostic and sociodemographic characteristics of sample, incidence (prevalence) rates [where possible, raw data], incidence (prevalence) rate ratios [where possible, raw data], proportions exposed to environmental factors [where possible, raw data], odds ratios [where possible, raw data].

11.3 Analyses

In the first instance, we will collate all information from included studies in tabular form, allowing for detailed descriptions of findings, including observations of notable variation. These initial findings will be discussed extensively by the project team & steering committee. Meta-analyses will be used if there is sufficient rational & data to do so. Pooled estimates can obscure important variation in the data [39], but meta-analysis, used appropriately, can also highlight important heterogeneity [40]. Where possible, we will estimate incidence & prevalence rates from included studies for specified time periods, and compare these over time, in order to identify trends [see 6, 23]. Following on from this, we will conduct 3 further analyses, as follows:

Methodological quality: We will agree a set of criteria to assess the methodological quality of included studies, and eventually check the sensitivity of our results against excluded studies. The criteria we will use are likely to be derived from those applied in other systematic reviews of psychiatric studies [2, 19, 36, 37, 39]. The areas to be covered will include: operational definition, and systematic assessment, of key concepts (e.g. ethnicity, urbanicity), sample size, bias (selection and information), adjustment for confounding. A rating system will be developed for each area, yielding an overall score of methodological quality.

Meta-analyses: When it is deemed possible to pool data into an empirical synthesis we will conduct meta-analyses of incidence & prevalence, and consider variations in these rates by geographical area, ethnicity, gender and time trends using meta-regression analyses. In addition, we will examine data for evidence of publication bias by using funnel plots to compare incidence & prevalence rates from published and unpublished studies. We anticipate meta-analyses will only be possible for incidence & prevalence rates, given methodological variability in the study of environmental factors. For aetiological factors we will adopt a narrative analytical approach, guided by our project team & expert group.

Using data obtained on incidence & prevalence over time we will develop model projections for future rates of schizophrenia & other psychoses. We have experience of such analysis (Kirkbride) [41]. We are also involved in an ongoing project to model the predicted incidence of psychoses in 8 MHRN centres in England using empirical models from ÆSOP & ELFEP studies [42]. We will undertake similar analyses using data from our review to provide vital information for planning modern mental health services in England.

Economic analyses: Based on findings from meta-analyses, we will model the economic costs associated with variation in the incidence & prevalence of schizophrenia & other psychoses. The Centre for the Economics of Mental Health (IoP), with whom we work closely, has conducted numerous economic evaluations relating to psychosis. From these, and work

conducted elsewhere, we will estimate the annual costs of psychosis (disaggregated by sector). Where possible, these costs will be broken down by gender & ethnicity, with adjustments made for geographical location. The costs will be attached to the data on incidence & prevalence in order to estimate annual and long-term resource implications of psychosis.

11.4 Expert group

In order to advise at each stage of the proposed study, we will establish an expert group of academics & other key stakeholders, invited to participate by the steering committee at the outset of the study. Stakeholders will come from many disciplines including psychiatry, epidemiology, public health, health services research, health economics and service user groups. Each member of the group will be invited to comment, by e-mail and/or letter, on the proposed search strategy (including search terms), identified literature (including providing information on potential studies for inclusion), data extraction forms, analyses, and interpretation of findings (following circulation of a preliminary report). At the analysis & interpretation stage, the expert group will meet. Preliminary findings will be presented & discussed, with implications for public health, service provision, and clinical practice considered in detail using a focus group format. This will allow key stakeholders to contribute their knowledge to the final report. Such an approach will be particularly useful in considering environmental correlates of schizophrenia, where despite efforts to elucidate risk factors, little empirical consensus has emerged. Such discussions will help prioritise our findings for policy makers & allied public health practitioners.

11.5 Methodological challenges

A systematic review on the incidence & prevalence of schizophrenia & other psychoses has many potential methodological challenges. Our plan of research has been designed, where possible, to address these:

• Our approach is sensitive to the issues of variation in study design, by providing for systematic assessment of methodological quality

• Our collaborative group has many leading academics within the field, many of whom who have set up original studies which will make up a large proportion of the empirical base of any systematic reviews. We are also involved in ongoing studies of incidence & prevalence and their socioenvironmental correlates. We have expertise in systematic reviews & meta-analyses

• Our systematic review is restricted to England. However, guided by the steering committee and expert group, we will incorporate evidence from the international literature into study outputs, when it supports or contradicts the findings in England. Such an approach may reveal important variations (or similarities) in incidence, prevalence and aetiology across countries & cultures; potentially important for both hypothesis generation and health services provision

11.6 Study outputs

We will produce a final report with executive summary as required. We will produce other outputs–oral presentations, posters, peer-reviewed academic publications, online media–to maximise the impact of our research and reach as many stakeholder groups as possible, including service users, tailoring outputs appropriately (see below).

12. Please provide details of public involvement in the proposed research*:

(Maximum 2,000 characters).

The extent and causes of schizophrenia and other psychoses are issues of considerable public interest, not least because of the severe stigma that attaches to those diagnosed with these disorders and the consequences for family and wider society. We will seek to ensure that key stakeholders are involved at each stage of the project. To this end, we have formally consulted the Service User Research Enterprise and the mental health charity Rethink in developing our proposal, and will continue to involve representatives from these groups in the conduct, analysis, interpretation and dissemination of findings from this project. This will primarily be achieved by these groups being represented on our expert panel. In addition, findings will be disseminated, as appropriate, through key stakeholder outlets (see dissemination below).

13. If you do not plan active public involvement in the research, please explain why not (if you do not plan to include the public please go to question 15)*:

(Maximum 1,000 characters).

Not applicable

14. Proposed level and nature of public involvement in the research*:

Please tick all relevant boxes

	Consultation	Collaboration	User led / user controlled
Development of the grant application	☒	☐	☐
Design and management of the research	☐	☒	☐
Undertaking the research	☐	☒	☐
Analysis	☐	☒	☐
Dissemination of research findings	☐	☒	☐

Consultation
Researchers consult members of the public about the research e.g. through individual contacts, one-off meetings.

Collaboration
This includes active, on-going partnerships between researchers and members of the public e.g. involvement of members of the public on the project steering group, or as research partners on a project.

User led / user controlled
Members of the public lead the research and are in control of the research. This is often, through a community or voluntary organisation led by service users.

15. Please indicate the way in which diversity is relevant to your research?*:

The Department of Health encourages those commissioning or undertaking research to consider the relevance of diversity issues (ethnicity, age, gender, disability, religion, and sexual orientation) as an integral part of planning and delivering research programmes and projects.
(Maximum 1,000 characters).

By definition our systematic review will cover the diverse groups in England likely to be at elevated risk of schizophrenia and other psychotic disorders. We have demonstrated that the incidence and prevalence of such disorders are heterogeneous and vary along key dimensions, including by age, gender, ethnicity, immigrant status, social status and place. We have made explicit provision in our aims to study these difficult to reach groups, including immigrants & young people (i.e. EIS). Further, we will include such groups as stakeholders in our expert group. Understanding this heterogeneity will highlight those communities and areas which have the highest burden of psychoses and pave the way for better public policy and health services provision where it is most needed; often in communities which have other correlated health and social inequalities, including greater morbidity and mortality on a range of outcomes [43, 44], poverty, crime, poor social cohesion and discrimination.

16. Project plan*: indicating the milestones for the project

(Maximum 3,500 characters).

Timetable: A Gantt chart is provided in Annex 3. Briefly, the timetable will be as follows, where each task number refers to the Gantt chart:

[Task 1] Orientation and devise & carry out search strategy, including consultation of expert group regarding search strategy: 1.5 months (start to 1.5 months)
[Task 2] Collate & screen abstracts: 2 months (month 1-3)
[Task 3] Obtain papers & apply exclusion criteria to papers: 2 months (month 2-4)
[Task 4] Data extraction: 3 months (month 3-6)
[Task 5] Synthesis of data & meta-analyses, including consultation with expert group on preliminary findings: 4 months (month 4-8)
[Task 6] Prepare report & other study outputs: 3 months (month 6-9)

Roles:

Principal investigators: will oversee the study design & implementation, and formulate the main research aims in collaboration with the steering committee. The PIs have considerable experience in project management and will take overall responsibility to ensure the study outputs are met on time and budget.

Steering committee: The steering committee will work in collaboration with the project team at the start of the study to devise a quasi-peer-reviewed research strategy (via additional consultation with the expert group). The steering committee will provide the clinical, psychiatric and epidemiological capacity to ensure the design of the study is capable of meeting its aims. The steering group, including PIs, will identify which aims are priorities for discussion with the expert group (i.e. Aims 1, 4-5). This will ensure that the project team can prioritise data synthesis so that the relevant preliminary findings can be disseminated to the expert group as close as possible to the start of data analysis to ensure outputs are completed on time. The steering committee will collaborate with the project team to obtain included papers during data collection. The steering committee will interpret the results of analyses and coordinate the study outputs in collaboration with the project team. The steering committee, which has thorough knowledge of the relevant international psychiatric epidemiology literature, will augment the results of the systematic review at this stage with relevant work from outside of England. The steering committee will disseminate results to the expert group and design and lead focus groups with this group (Morgan).

Project team: Will consist of a senior researcher with expertise in systematic reviews (0.8 FTE, 9 months), a research assistant [RA] (0.5 FTE, 6 months) & funded biostatistics PhD student. The senior researcher will implement the study, assisted by the RA. The senior researcher will work closely with the steering committee, methodological advisor & lead investigators (Jones & Murray). The PhD student has statistical expertise in the application of meta-analyses (see Annex 4) and will provide 2 hours statistical consultation per week. The project team will screen papers, apply exclusion criteria and extract data from included studies. They will conduct the analyses and work with the steering committee to produce study outputs.

Methodological advisor: will liaise with the senior member of the project team (see section below) to ensure that the review is systematic and that meta-analyses are used as appropriate. Advise at all stages of the project. Our methodological advisor (Croudace) is convenor of the

MHRN Methodology Research Group & methodological representative to their Advisory, Adoption & Allocation Committee.

17. Project management*:

Outlining the processes that will be put in place to ensure that the project is well managed, commenting on the management structure, identifying the project manager, meetings schedule, financial management etc. **(Maximum 1,500 characters)**.

In order to successfully deliver the aims of the project and required outputs, we will implement a structured management hierarchy. At the project team level, one researcher will be based in Cambridge, the other in London (IoP), to benefit from local expertise in the research team at each institution. The project team will have daily telephone/email contact with each other & fortnightly face-to-face progress meetings. The senior researcher will be responsible for implementing the study. The project team will have monthly meetings with at least two members of the steering committee to deal with any issues arising and to monitor progress. The steering committee will provide additional clinical, epidemiological, methodological and public health expertise and be available via email/telephone at all times. The steering committee will manage the expert group phase of the study. Principal investigators will have overall control of project management to ensure aims are met and outputs are delivered on time & budget. The project team & steering committee will have weekly email/telephone contact with PIs. All members of the research team will meet at least 3 times during the project: near the start of the study to ensure its scope & methodology are understood; prior to data synthesis to allow the project team to report interim findings, and; near the end of the project to agree on the content of study outputs. Financial management will be administered from the University of Cambridge.

18. Methods of disseminating the findings of the research*:

Please indicate your plans for disseminating the findings of this research (after it has been through the DH process of peer review to ensure that it is scientifically robust – see guidance notes). **(Maximum 2,000 characters)**.

The study outputs will be disseminated in a variety of ways to a number of different audiences to ensure all stakeholders are targeted.

Service users: included at the design stage via the expert group, appropriate methods of dissemination will be identified, including oral presentations and press releases to mental health support groups and the popular media. We have close contacts with the Service User Group for England [SURGE], the Service User Research Enterprise [SURE] at the IoP and Service User and Carer Involvement [SUI] group in Cambridge, who run frequent research groups for users and carers telling them what's going on and promoting new ideas, methods and projects. We will also approach mental health charities (i.e. Rethink) to disseminate findings.

Policy makers, health service practitioners, clinical services and NHS: To be reached through the publication of the final report; our main study output. To ensure our findings reach to researchers and policy makers in mental health in England we will work closely with the MHRN with whom we (Jones, Murray, Croudace, David) have strong links. Findings will be disseminated to their annual conference and regional meetings. Our research team has considerable clinical involvement through management of clinical services for people with psychoses. All these groups will be offered oral presentations and/or understandable reports of the findings for the target audience.

Public health specialists, health economists and clinical and academic psychiatric research communities: dissemination via a variety of academic & non-academic media, including oral conference/meeting presentations, poster presentations, publication in peer-reviewed academic literature. The research team has a proven record of publishing in high-impact journals which will maximise the impact of the findings from this study in directing policy, public health and future research agendas. We will work with the MHRN to disseminate findings.

19. Value for money*:

Justification for costs proposed. **(Maximum 2,000 characters).**

Improving our understanding of the incidence, prevalence and aetiology of schizophrenia and other psychoses in England will be important for planning modern mental health services which are sensitive to variation in service need along the aforementioned dimensions of age, gender, ethnicity, place and social group (in terms of both the wider social environment and individual social factors). Understanding where this variation exists will ensure resources for mental health services are allocated efficiently across the NHS. The opportunity to systematically review the literature from Early Intervention Services will be important in determining their clinical utility and value for money. Further, improving our understanding of time trends in the incidence and prevalence of schizophrenia and other psychotic disorders will allow us to develop model projections which will give policymakers and mental health service providers important information about the likely future burden placed on mental health services and how this might vary along sociodemographic and environmental axes. Ultimately, anticipating the future burden of psychoses will allow planners to allocate limited resources more efficiently across mental health services. Our proposal also has a second strand to it, in that a systematic review of potential environmental correlates of the incidence and prevalence of psychoses, and the discussion of the validity of these factors in respect to aetiology with an expert panel, may generate new (or consensus) hypotheses for future research, and to an extent galvanise the research community into elucidating the specific, complex aetiological processes underpinning psychoses onset. In turn, in the longer term, such research translates back into improved service provision and implementation of putative public health prevention strategies.

20. Intellectual Property

Is there likely to be any intellectual property derived from this project?: (Yes/No) Yes

21. Ethical approval

Will ethical approval be required?*: (Yes/No) No

If not, please indicate why not. **(Maximum 1,000 characters):**

The methodology of our systematic review does not require the recruitment of subjects into the study since it is reliant on secondary data from published and unpublished sources. It will not be possible to identify any individual from any obtained data included in our systematic review since it is based on secondary data, which will be obtained in cross-tabular rather than individual format. For these reasons the study will not require ethical approval.

22. Declaration concerning other applications

Previous applications*: Is the work proposed in this application under consideration by another funding body, or currently being funded by another funding body?: (Yes/No) No

If you have answered **Yes** to the above please complete the remainder of question 22*.
Title of previous application:
Lead applicant's surname:
Lead applicant's forename:
Funding body to whom it was submitted:
Outcome: Please Select...
If unsuccessful, please indicate why (Maximum 1,000 characters).

23. Other information

Sources of information:

Please indicate any other organisations that you have contacted in the course of preparing this application and describe their input. **(Maximum 2,000 characters)**.

Dr Paul McCrone, Centre for Economics of Mental Health [CEMH], Institute of Psychiatry [IoP]. We are grateful to Dr McCrone for his input in designing the economic analyses module of this application (see section 11). We will work with Dr McCrone and CEMH to undertake these analyses.

Mr Ian White, Biostatistics Institute, University of Cambridge, and his PhD student, Daniel Jackson, were contacted regarding Daniel's involvement in the project. Daniel has experience in meta-analysis techniques (CV attached in Annex 4) and will consult on the project (2 hours per week). He will work in consultation with Dr Tim Croudace. Both Ian White and Daniel Jackson saw a draft of this application.

24. Monitoring information*

Department of Health monitoring*

In order to categorise applications, the following list of research areas has been provided. Please

categorise your research using the following selection boxes. This information will be used solely for monitoring.

Main subject of the research – choose most appropriate category from the UKCRC Health Categories list AND most appropriate from UKCRC detailed list of Research Activity Codes. For guidance please see the UKCRC Health Research Analysis which can be found at http://www.ukcrc.org/

(For example: Health Category – Cardiovascular and Research Activity – 6.4 Evaluation of Treatment, surgery).

Subject Categories: (Please tick all that apply…..)

Blood	☐	Musculoskeletal	☐
Cancer	☐	Neurological	☐
Cardiovascular	☐	Oral and Gastrointestinal	☐
Congenital Disorders	☐	Renal and Urogenital	☐
Ear	☐	Reproductive Health and Childbirth	☐
Eye	☐		
Health and Social Care Workforce	☐	Respiratory	☐
Health Economics	☐	Skin	☐
Health Inequalities	☐	Social Care	☐
Health Promotion	☐		
Health Protection	☐		
Infection	☐	Specific User Issues	☐
Inflammatory and Immune System	☐		
Information and Communication Technologies in Health & Social Care	☐	Stroke	☐
Injuries and Accidents	☐	Generic Health Relevance	☐
Mental Health	☒	Other	☐
Metabolic and Endocrine	☐		

Research Activity Codes: (For each category please tick all that apply…..)

1 Underpinning Research	
1.1 Normal biological development and functioning	☐
1.2 Psychological and socioeconomic processes	☒

1.3 Chemical and physical sciences	☐
1.4 Methodologies and measurements	☒
1.5 Resources and infrastructure (underpinning)	☒
2 Aetiology	
2.1 Biological and endogenous factors	☐
2.2 Factors relating to physical environment	☒
2.3 Psychological social and economic factors	☒
2.4 Surveillance and distribution	☒
2.5 Research design and methodologies (aetiology)	☒
2.6 Resources and infrastructure (aetiology)	☒
3 Prevention of Disease and Conditions and Promotion of Well-Being	
3.1 Primary prevention interventions to modify behaviours or promote well-being	☐
3.2 Interventions to alter physical and biological environmental risks	☐
3.3 Nutrition and chemoprevention	☐
3.4 Vaccines	☐
3.5 Resources and infrastructure (prevention)	☐
4 Detection Screening and Diagnosis	
4.1 Discovery and preclinical testing of markers and technologies	☐
4.2 Evaluation of markers and technologies	☐
4.3 Influences and impact	☐
4.4 Population screening	☐
4.5 Resources and infrastructure (detection)	☐
5 Development of Treatments and Therapeutic Interventions	
5.1 Pharmaceuticals	☐
5.2 Cellular and gene therapies	☐
5.3 Medical devices	☐
5.4 Surgery	☐
5.5 Radiotherapy	☐
5.6 Psychological and behavioural	☐
5.7 Physical	☐
5.8 Complementary	☐
5.9 Resources and infrastructure (development of treatments)	☐
6 Evaluation of Treatments and Therapeutic Interventions	
6.1 Pharmaceuticals	☐
6.2 Cellular and gene therapies	☐
6.3 Medical devices	☐
6.4 Surgery	☐
6.5 Radiotherapy	☐
6.6 Psychological and behavioural	☐
6.7 Physical	☐
6.8 Complementary	☐
6.9 Resources and infrastructure (evaluation of treatments)	☐
7 Management of Diseases and Conditions	
7.1 Individual care needs	☒
7.2 End of life care	☐
7.3 Management and decision making	☒
7.4 Resources and infrastructure (disease management)	☒

8 Health and Social Care Services Research

8.1 Organisation and delivery of services	☒
8.2 Health and welfare economics	☒
8.3 Policy ethics and research governance	☐
8.4 Research design and methodologies	☐
8.5 Resources and infrastructure (health services)	☒

For <u>each</u> category below please tick all that apply

Research Team:

Academic	☒
Allied health profession	☒
Clinician - GP	☐
Clinician - hospital	☒
NHS Manager	☐
NHS Scientist	☐
Patient/User	☐
Other Profession (please specify)	☐

……

Type of research/methodology:

Clinical trial – phase I, II, III or IV	☐
Cohort study	☐
Epidemiological	☒
Meta analysis	☒
Qualitative study	☒
Retrospective review	☐
Survey	☐
Systematic review	☒
Other (please specify)	☐

……

Setting in which research will take place:

Emergency care	☐
Primary care	☐
Secondary care	☒
Specialist centre	☐
Community	☒
Interface (between any of the above)	☒

Subjects of research:

Adolescents	☐
Children	☐
Elderly	☐
Mentally ill people	☒
People with learning disabilities	☐
Physically disabled people	☐
Other (please specify)	☐

……

For each question please select a response from the drop down box below

Region in which research will take place:	East of England
Is the research multi-centre?	YES
Place of work of lead applicant:	Mental Health Trust
Profession of lead applicant:	Academic

25. Application finances*

Please provide a justification of the costs of the project **on the associated finance form***.

26. Suggestion of Peer Reviewers

Please suggest three potential peer reviewers who have the relevant expertise to provide appropriate peer review for your application. These reviewers should be independent and have no conflict of interest with respect to your application. Your suggestions will be used as only one source of peer reviewers and may not be approached to undertake this review.

Reviewer 1.

Title:	Prof
Surname:	van Os
Forename:	Jim
Department:	School for Mental Health and Neuroscience
Institution:	University of Maastricht
Telephone:	0031 43 3875443
e-mail address:	j.vanos@sp.unimaas.nl

Reviewer 2.

Title:	Prof
Surname:	McGrath
Forename:	John
Department:	Queensland Brain Institute
Institution:	University of Queensland
Telephone:	0061 7 3346 6372
e-mail address:	john_mcgrath@qcmhr.uq.edu.au

Reviewer 3.

Title:	Prof
Surname:	Bebbington
Forename:	Paul
Department:	Department of Mental Health Sciences
Institution:	University College London
Telephone:	020 7679 9465
e-mail address:	p.bebbington@ucl.ac.uk

27. Declarations and signatures*

Please print this page, have it authorised and return it by post to the address below.

In order for your application to be accepted you are required to gain approval from the relevant authorities within your institution. These approvals are required to ensure that the costs submitted are agreed by the host institution as an accurate estimate of the cost of undertaking the proposed research. These approvals must be in the form of a "wet ink" signature. Failure to submit this agreement will result in your application being rejected.

The confirmation of costs must be completed and returned by Friday 24th October 2008, 5:00PM .

Project Reference: ……

Title: ……

……

Lead applicant ……

Host Institution ……

Institutional stamp

I confirm that the information given on this form is complete and correct, that all co-applicants mentioned on this form have seen a copy of this application; and that I shall be actively engaged in this project and responsible for its overall management.

Signed: ……. Date ……..
(Lead Applicant)

I confirm that I have checked the financial details of application (PR-SC-0908-10009) and that this institution is prepared to carry out this project at the stated costs and to administer the award if made. The staff grades and salaries quoted are correct and in accordance with the normal practice of this institution.

Signed ……. Date ……..
(Finance Officer)

I confirm that I have read this application and that, if funded, the work will be accommodated and administered in this institution and that the applicants for whom we are responsible may undertake this work.

Signed ……. Date ……..
(Representative of the institution hosting the research *e.g.* clinical director, R&D manager or Chief Executive.)

IN ORDER FOR YOUR APPLICATION TO BE ACCEPTED, THE CONFIRMATION OF COSTS FORM MUST BE SIGNED BY THE RELEVANT AUTHORITIES FROM YOUR INSTITUTION AND RETURNED TO THE POSTAL ADDRESS BELOW, BY THE DEADLINE ABOVE.

NIHR-CCF
PO BOX 407
TEDDINGTON
TW11 0XX