

# Systematic Review of the Incidence and Prevalence of Schizophrenia and Other Psychoses in England

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Conducted for the  
Department of Health  
Policy Research Programme

Jan 2012

Final Corrected Version (version 1.05)

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## EXECUTIVE SUMMARY

### Background (Chapter 1)

The Department of Health commissioned this series of systematic reviews on the incidence and prevalence of schizophrenia and other psychotic disorders in England. **Incidence<sup>i</sup>** is the number of people who develop an illness for the first time, per year, in a given place; **prevalence** is the proportion of a defined community who already have or develop an illness at a particular time or during a specified period. **Psychotic disorders** are a group of mental illnesses characterised by delusions, hallucinations and other problems of thought and emotion. **Schizophrenia** is a particular type of psychotic disorder, as are **affective psychoses** that can include psychotic depression and bipolar disorder. In this summary we concentrate on all psychoses as a broad group, and on schizophrenia and affective psychoses as two main sub-types of psychotic disorders; the full report contains a more detailed breakdown.

The incidence of psychotic disorders was once thought quite similar across populations and communities but it now seems that there are big differences. It is important to understand these differences in order to meet the needs of service users and carers in early intervention services (EIS) and other mental health services. Understanding differences is also vital for prevention. Psychotic disorders can cause great disability for sufferers and burden for families. They are expensive to society due to the costs of care and treatment and to lost work opportunities for some sufferers, particularly as their onset is often in young adult life.

### Aims (Chapter 2)

1. Systematically review the existing evidence from the past 60 years regarding the incidence and prevalence of all psychotic disorders, schizophrenia and affective psychotic disorders in England
2. Identify variation in the incidence and prevalence by sociodemographic (e.g. age, sex, social class, ethnicity) and geographical factors

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<sup>i</sup> See full report Glossary for explanation and definition of all terms in **bold indigo text**

3. Understand whether rates have changed over time, particularly regarding the introduction of EIS in England from 2002 and concerns that increasing use of cannabis may lead to psychotic illness
4. Estimate the costs related to variation in incidence and prevalence of psychotic disorders

### **Methodology (Chapter 3)**

The study team comprised librarians, information scientists, statisticians, psychiatrists, psychologists, health economists, social scientists and epidemiologists. Using key search terms we identified all published and unpublished studies of the incidence or prevalence of psychotic disorders, conducted wholly or partially in England, between 1950 and 2009. Electronic databases (MEDLINE, PsychINFO, EMBASE, CINAHL, ASSIA, HMIC) were searched, as were the published papers that this search identified. We wrote to researchers to identify missed or unpublished studies. Scientists sometimes publish many reports from one study so we made sure we included any study only once. We assessed each one for quality and extracted the information on incidence and prevalence. We identified *all* the studies, assessed their precision and quality, judged whether studies give a similar message and then, where possible, pooled all equivalent information from the best and most comparable studies. This simple method answered many questions such as whether these disorders are more common in men, whether different age groups are affected and whether some ethnic groups have a greater burden of psychotic disorders. Sometimes more complex techniques were used to make the information from different studies more comparable ([regression](#)) or to use studies from different situations in order to answer an over-arching question ([meta-regression](#)). For example, we used meta-regression to find out whether schizophrenia occurred more commonly in densely populated city communities than in towns or rural areas because virtually no single study covered all types of environment; they just studied either a city or a rural area, not both. We took a similar approach to looking at changes over time because no study of rates covered the whole 60 year time period. Our review provided more information on these and other questions than had ever before been assembled for England. An international scientific group advised the process. Independent experts reviewed our work that we updated in the light of their detailed comments.

## Results (Chapter 4)

We identified 5,262 potentially important and relevant publications; 227 were from the “grey” or non-scientific literature. A further 30 (one unpublished) were identified by searching the papers and asking researchers. Our work is based on 148 individual studies that met our inclusion criteria (see main report Figure 4.1).

**All psychotic disorders (Section 4.2.1)** had an overall (pooled) annual incidence of 32 cases per 100,000 people. Incidence was higher in men than in women before age 45, but more equal, thereafter. Rates for black and minority ethnic (BME) groups were much higher than in the comparison population. This was a very consistent finding from all studies, obvious without the more complex techniques, and generally consistent for men and women (main report, Section 4.2.1.3). Several types of study found no compelling evidence of changes in incidence over time (main report, Section 4.2.1.4) or of significant urban-rural differences. None of these effects was affected by study quality.

**Schizophrenia (Section 4.2.3)** showed a pooled annual incidence of 15 per 100,000 people. There was a much higher incidence in younger men compared with women, and for BME groups compared with the majority; most of the studies supported this finding. Incidence was relatively stable over time. Any increases that were found could be explained by changes in the ethnic make-up of the relevant community. There was evidence for variation according to social disadvantage with higher rates in more disadvantaged communities and neighbourhoods. None of these effects was dependent on study quality.

**Affective psychoses (Section 4.2.4)** had a pooled annual incidence of 12 per 100,000 people. Unlike schizophrenia, men and women had a similar incidence that decreased with age. Affective psychoses were more common in BME groups but appeared not to have become more or less common since 1950. In contrast to schizophrenia, there was no evidence of any geographical or neighbourhood effects on incidence.

**Rates in early intervention services (EIS) for psychosis compared with rates from other studies** (main report, Section 8.2.1). The search identified one conference abstract and one paper studying rates in EIS. Comparing these rates with a large study undertaken before EIS were

implemented indicated that there are more (rates 75% higher) young people being treated by these EIS than were expected when they were commissioned.

### **Prevalence (Chapter 5)**

Studies of the prevalence of all psychotic disorders showed considerable variation in methodology, quality and in results so were more difficult to pool. Overall, the studies suggested that 4 people from every 1000 have, or have had an active psychotic disorder over the past year (annual prevalence). This increases with age but has not risen over the 60 years we reviewed. Most of the burden from current, rather than new psychosis (that is prevalence rather than incidence) comes from schizophrenia. However, some affective psychoses like bipolar disorder keep coming back so are a greater burden on people and more expensive than might be expected; this is considered, below.

The literature from **specialised, institutional settings (Chapter 6)** contained a mixture of methods and approaches. Prevalence of psychotic disorder was consistently much higher in these settings (i.e. judicial & custodial services, homeless shelters, residential homes) than in the general population.

**Costs for services and society (Chapter 7)** were estimated as the annual economic burden of these disorders in relation to the total UK population in 2009. We based these estimates on the prevalence data identified in Chapter 5 and recent estimates of relevant costs in the UK.

The total cost per year of a broadly defined schizophrenia (**non-affective psychoses**) was placed at £8.8bn. Service costs contributed £3.5bn (40%) to this, and informal care £1.2bn (13%). Lost employment was the single largest cost to society (£4.1bn per annum; 47%). Costs were slightly higher for men (£4.8bn; 55%) than women (£4.0bn; 45%), reflecting the prevalence of disorder. Psychiatric inpatient care represented the single largest service cost (£1.7bn). The distribution of costs for **schizophrenia** as a separate outcome was similar, with an annual estimated cost to the UK of £5.25bn.

For **affective psychosis** the total cost to UK services and society per annum was almost to the same as the cost of schizophrenia (£5.0bn), reflecting the higher per-patient costs associated

with bipolar disorder in spite of its lower prevalence. In contrast to non-affective psychoses, the majority of this figure came from NHS costs (£4.05bn; 80%). Informal care costs (£167m; 3%) and costs of lost employment (829m; 16%) were relatively low.

### **Discussion & Conclusions (Chapter 8)**

We considered more evidence about the incidence and prevalence of psychotic disorders in England than has ever before been brought together. The results are important for the NHS. These conditions more commonly arise in young adults than older people, in men, in the BME groups studied, in cities and in poorer neighbourhoods. Therefore, the needs of some communities will differ greatly from the needs of others, with variation apparent at a local level. This variation must be taken into account during service commissioning; one size does not fit all communities. Our work could be developed into a practical prediction tool for commissioners and those providing mental health services. Psychotic disorders are enormously expensive so it is important to get the services right.

The proportion of BME groups in an area has an important bearing upon incidence of psychosis in that locality. The raised rates in BME groups were consistent across studies, were not confined to schizophrenia, were demonstrated in the highest quality studies designed to investigate the issue, and did not require sophisticated statistical methods to show the effect. The review does not show *why* some BME groups are at greater risk of psychosis. Factors such as age, sex, urbanicity and socio-economic disadvantage are important in all communities, including BME groups. Psychological stressors make important contributions to the cause of psychosis and may be more common in the BME groups that have been studied. There needs to be more research into this important issue and strenuous efforts to provide the right services. We do not know what is happening in the recently migrated populations such as those from the former Soviet Union or Eastern Europe; further epidemiological research is required.

There was no evidence that the incidence of psychotic illnesses has increased over time in the way that might have been expected if increased cannabis use were having an effect. However, there have been recent increases in the strength of commonly used cannabis preparations so there needs to be continued vigilance in the years ahead.

There are few studies of prevalence, a very basic parameter. Improved NHS clinical information systems could help improve our knowledge of this area. Studies revealed fewer differences in prevalence between population groups and geographical areas than we found for incidence. Illnesses such as schizophrenia represent the main, on-going personal and economic burden but the costs of other illness such as bipolar disorder were also very high.

### **Recommendations (Chapter 8)**

1. Service commissioners and planners should take into account the detailed variation in incidence of psychotic disorders, particularly non-affective psychoses (schizophrenia) at the local population level.
2. The greatest driver of variation in incidence, once the age, sex and socio-economic structure of a population is taken into account, is the proportion of people from BME communities. This has to be acknowledged at the service planning and political level, with more research being required to understand this important phenomenon. Future changes regarding recent migrant groups need to be studied.
3. DH should commission the development of a prediction tool that integrates small-area (local) population data and the findings from the review. This would produce information about the numbers of people each year who will develop a psychotic illness (population need) in any given area. This would ensure that services can be designed to meet population need and would greatly help commissioners and service providers.
4. In addition to the prediction tool (Recommendation 3), the numbers of people being treated for first onset psychosis (administrative incidence) should be studied through EIS so as to refine prediction and to ensure that services are being planned and delivered properly. Some EIS may have much higher caseloads than were expected; others may have lower caseloads. A prediction tool and the routine monitoring of administrative incidence would reduce the likelihood of a mismatch between population need, commissioning and the services provided.
5. New NHS information systems should be routinely used to collect current and future information on the variation in (administrative) incidence and prevalence of these disorders. This will support service delivery and research into the causes of illness.

6. Social factors in the urban environment, including indicators of low community cohesion, were associated with increased incidence rates of schizophrenia. Further research into these factors may reveal prevention opportunities and help unravel the multilevel causes of psychosis. This is a public health priority.



## **ACKNOWLEDGEMENTS**

This project was funded by the Department of Health Policy Research Programme. The work reflects the views of the research team, and not necessarily those of the Department of Health. The team forms part of the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for Cambridgeshire and Peterborough and received library and search support from the East of England Evidence Adoption Centre.

The authors of this review were helped by many people. We are grateful to Professor John McGrath for his wise guidance during the planning and conduct of this review. His expertise allowed us to improve the final quality of this work. The CLAHRC and Evidence Adoption Centre played a pivotal role in providing us with expert librarians and other resources when designing and conducting the systematic search strategy; we are indebted to them. We thank Anna Capasso for making this possible, and Katerina Lagoudaki for help in drafting the report summary. Without the diligent, patient help and expertise of the librarians involved in this project, we would have been unable to develop such a comprehensive and systematic strategy to search the research literature. We therefore pass on our heartfelt thanks to Karen Rigby, Kerry Herbert and Margaret Bevan at the Education Library, Hinchingsbrooke Health Care NHS Trust, as well as to Barbara Norrey from the Mid Essex PCT for her expert guidance on the grey literature. We are grateful to Ian White, MRC Biostatistics Unit, for providing access to expertise to conduct the analyses contained within this review. We would also like to thank the following researchers for providing timely clarifications or additional data for some studies and citations included in this report: Prof. Brian Cooper, Prof. Tom Burns, Prof. Francis Creed, Prof. Thomas Barnes, Prof Peter Congdon, Prof. Philippa Garety, Prof. Joe Kai, Dr Andrew Thompson, Dr Emma Mitford, Dr Martin Frisher, Prof. Ilana Crome and Kate Beaven and Ellie Smith from the Office for National Statistics. Finally, we are grateful to Alan Roach and the PRP team for patiently guiding this review towards completion. In addition we detail below acknowledgements specific to various authors of this report.

Further details of this report, supplemental tables and files can be downloaded from [www.psychiatry.cam.ac.uk/epicentre](http://www.psychiatry.cam.ac.uk/epicentre)

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## **Chapter 1: Background**

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## **1.0 BACKGROUND**

Psychotic disorders are serious mental disorders typically characterised by experiences of delusions, hallucinations and thought disorder. These can be broadly categorised into non-affective (e.g., schizophrenia), affective (e.g., major depressive disorder with psychotic symptoms; bipolar disorder with psychotic symptoms) and substance-induced disorders. All are associated with significant personal distress, social disability, and need for care. Overall, the average age of onset is in the mid- to late- twenties, with evidence that onset tends to occur earlier for non-affective disorders and later for women. Prognosis is highly variable, with outcomes tending to be less severe and chronic in those with an affective or substance induced disorder compared with those with a non-affective disorder.

The impact extends beyond the individual, often leading to considerable burden for families and significant direct (via need for care) and indirect (via impact on capacity for economic activity) costs for society. Among those with a long-standing diagnosis of schizophrenia, for example, rates of employment tend to be extremely low, at around 10% to 20%.<sup>1</sup> This is not only a consequence of the intrinsic nature of the disorder, but also partly stems from widespread stigma and discrimination.<sup>2</sup>

The most recent estimates for schizophrenia suggest that, in the UK, total costs of service provision in 2007 were around £2.2 billion, with these projected to rise to £3.7 billion by 2026.<sup>3</sup> When costs of lost employment are added, these figures rise to £4.0 billion for 2007, with a projected rise to £6.7 billion by 2026. Similar costs have been estimated for bipolar disorder.<sup>3</sup> Understanding the distribution and determinants of these disorders is essential to inform effective public health policies and the planning and delivery of mental health care as information on any changes in rates over time, due to shifts in either causes (aetiology) or health service factors.

## **1.1 A changed epidemiological landscape**

### **1.1.1 The unravelling of equal incidence**

Our understanding of the epidemiology of psychotic disorders has changed radically in recent years as our questions have become more sophisticated. It had long been thought that the incidence of schizophrenia was broadly similar in developed and developing countries (perhaps even globally), and for men and women. This assumption was not a well-tested hypothesis, but arose empirically from results reported by the World Health Organisation 10-country study of schizophrenia,<sup>4</sup> conducted in the 1980s. This landmark study found that incidence rates for narrowly defined schizophrenia were not significantly different between those sites for which usable data was available (using the conventional statistical threshold of  $p < 0.05$ ).

The samples in each site, however, were relatively small and this finding may have been a consequence of inadequate statistical power. There was, in fact, a two-fold difference between the site with the lowest rate (7 per 100,000 in Aarhus, Denmark) and the site with the highest rate (14 per 100,000 in Nottingham, UK) and for broadly defined schizophrenia there was evidence of (statistically significant) marked variations. Further, recent original epidemiological research<sup>5, 6</sup> and meta-analyses,<sup>7-9</sup> including our own research,<sup>10-13</sup> have shown conclusively that marked variation in incidence of psychotic disorders exists by place, gender and social group. For example, a meta-analysis of 100 incidence studies found around a five-fold variation in rates, even after the bottom 10% and top 10% reported rates were excluded. This study further found evidence that rates are higher in men (rate ratio median: 1.4), urban areas and in migrant populations (rate ratio median: 4.6). Each of these latter two findings has been consistently replicated.

### **1.1.2 Understanding variation according by urbanicity**

In addition to the above meta-analysis, for example, more recent and specific studies have confirmed the finding of high rates of schizophrenia in more densely populated (urban) centres. [The evidence on affective psychosis is however less clear cut, and may be more equivocal.<sup>14, 15</sup>] In England, our own study<sup>11</sup> of the incidence of all psychoses (the Aetiology of Schizophrenia and Other Psychoses [ÆSOP]) found that rates of schizophrenia were higher in south-east London compared with less densely populated sites in the other study centres: the UK cities of

Nottingham and Bristol. In a meta-analysis of ten studies, for example, Krabbendam and van Os<sup>16</sup> report a pooled **odds ratio** of 1.72 (95% CI 1.53, 1.92), indicating on average a 70% higher incidence in urban compared with rural areas. Moreover, those studies that were able to adjust for potential confounders show that this association cannot be entirely explained by the effects of demographic characteristics such as age, gender, ethnicity (ethnic minority group), social class, or markers of genetic risk.<sup>16</sup> What is more, there is now evidence that these findings are not simply a function of individuals predisposed to develop, or in the process of developing, schizophrenia drifting into the relative (social) anonymity of more deprived city centre areas.

In a study of 1.89 million people drawn from Danish population registers, Pedersen and Mortensen<sup>17</sup> investigated the relationship between place of birth, place of residence before the age of 15 years, and risk of schizophrenia. They found (in line with Marcelis et al,<sup>18</sup> in an earlier Dutch study): 1) at each age, risk of schizophrenia increased in line with *degree of urbanisation* (a concept that we tackle later in this report); and 2) individuals living in areas with a higher degree of urbanisation than five years earlier had an increased risk for schizophrenia (**rate ratio** [RR]: 1.40; **95% confidence intervals** [95% CI]: 1.28, 1.51), while individuals living in areas with a lower degree of urbanisation than five years earlier had a decreased risk (RR: 0.82; 95% CI: 0.77, 0.88). In other words, moving to a less densely populated, urban area during upbringing reduced the risk of schizophrenia (and vice versa).

### **1.1.3 Variation in rates of psychotic disorder by ethnicity**

The evidence of high incidence rates of schizophrenia, and other psychoses, in migrant and minority ethnic groups is equally extensive and has achieved a high level consistency across studies. In a meta-analysis of population-based incidence studies of schizophrenia with a total of 50 effect sizes, Cantor-Graae and Selten found a mean weighted relative risk [RR] for schizophrenia of 2.9 for migrant groups (including first and subsequent generations) compared with host populations. The relative risk was particularly high in migrants from developing

countries (RR 3.3), in second generation migrants (RR 4.5),<sup>ii 19</sup> and in migrants from countries where the majority population is black (RR:4.8). This latter finding is largely a reflection of studies of black Caribbean populations in the UK and the Netherlands.

The most recent studies that have reported incidence rates for psychotic disorders in migrant and minority ethnic populations in the UK continue to find very high rates in the black Caribbean and now also the black African populations. For example, the *ÆSOP* study found that the incidence of all psychoses was over six times higher in Black Caribbean and over four times higher in black African populations in the UK, compared with White British.<sup>10</sup> These findings held across all three centres (south-east London, Nottingham, Bristol), for men and women, and across all age groups.<sup>10</sup> The degree of increased risk, however, is not consistent across migrant and minority ethnic groups, as hinted at in the meta-analysis conducted by Cantor-Graee and Selten.<sup>7</sup> For example, in the *ÆSOP* study, the incidence of psychosis, although increased, was raised to a much lesser extent in Asian and Other White (i.e., non-British) populations.<sup>10</sup> In a more recent study in east London, the incidence was again found to be higher in most migrant and minority ethnic groups.<sup>20</sup> However, in Pakistani and Bangladeshi populations, this appeared to be evident for women only. In the Netherlands, the incidence appears to be highest in Moroccan migrants.<sup>21</sup>

#### **1.1.4 Trends in incidence over time**

With regard to time trends, our own work demonstrated a large increase in incidence of schizophrenia in Southeast London, particularly from the late 1980s onwards.<sup>22</sup> This was particularly marked in young people; noteworthy, as it has been suggested (but not yet empirically confirmed) that newly established early intervention (or EI) services, designed for better meeting the health care needs of younger people experiencing possible signs of psychosis, or early stages of the disorder, report higher incidence rates than observational studies. In contrast, our recent analysis of data more than two decades of epidemiological data

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<sup>ii</sup> A more recent review, however, did not find evidence that rates were higher in second generation compared with first generation migrants. The mean weighted relative risks in this analysis were 2.3 for first generation and 2.1 for second generation.



(three studies spanning 20 calendar years) in Nottingham suggested incidence did not vary at all, but had largely remained constant.<sup>23</sup> The wider literature is equally inconsistent.<sup>24-26</sup> It is unclear whether these variations reflect real trends in different areas or methodological artefacts that highlight the possible weaknesses in epidemiological study designs, or failures to successfully implement fieldwork evenly across the length and breadth (and service settings) operating in local catchment areas.<sup>27</sup>

## **1.2 A note on diagnosis**

The literature to date has tended to focus on schizophrenia or, more recently, on all clinically relevant psychoses. Much less attention has been given to comparing diagnostic sub-groups in this clinical group. This is important as what research there is, points to notable variations by sub-category. As already noted above, the high incidence rate in cities appears to be specific to non-affective psychotic disorders. Data from the ÆSOP study suggest that the incidence of depressive psychosis is relatively low compared with schizophrenia and manic psychoses<sup>11</sup> and, further, that the high rates among black minority ethnic groups are most pronounced for schizophrenia and mania.<sup>10</sup> This suggests more careful attention needs to be paid to similarities and differences between diagnostic groups within the broader spectrum of clinical morbidity spanned by the collection of psychotic disorders, distinguished by core symptomatology and phenomenology.

## **1.3 Aetiology**

Understanding variations in the incidence of disorder by place and social group may shed light on aetiology, which in turn is necessary for developing effective public health initiatives and interventions. The epidemiological data on incidence rates of psychosis introduced (necessarily somewhat selectively, in advance of our systematic review!) above have contributed to renewed interest in examining the role of environmental factors in the onset of all psychoses. There is, for example, now evidence linking measures of the social environment (captured by notions such as e.g. social capital, social fragmentation, and ethnic density (a population composition measure)<sup>28-32</sup> and individual (subjective) social experiences over the life course (e.g. exposure to childhood adversity such as severe privation or abuse, adult social disadvantage, (racial) discrimination, and alcohol or substance use/abuse) with the onset of psychotic disorders.<sup>13, 32, 33</sup>

Our own and other recent work has added to this by suggesting that higher rates of psychosis in urban areas and black and minority ethnic groups may partially be a function of cumulative environmental risks over time and of the less easily measured, but still tangible, characteristics of the social as well as physical neighbourhoods in which people live.<sup>34</sup> For example, there is increasing evidence that the high rates in urban areas are linked to societal characteristics that vary with local social geography, such as social fragmentation and that the high rates in migrant and minority ethnic groups are linked to quantitative variations in population composition such as that captured by ethnic density. 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 likely have quite profound implications for health care policy, public health and health service (including clinical) 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 similar damaging (socially toxic) experiences.

The literature on the impact of environmental exposures on risk of schizophrenia and other psychoses is of course, already vast. A useful starting point in synthesising data on socio-environmental factors is to focus only (initially) on those that have been directly implicated in efforts to account for the population-level differences in incidence (e.g., social fragmentation, social capital, ethnic density), an area of growing interest with potential public health implications that has not yet, as far as we are aware, been subject to a major systematic review.

#### **1.4 Prevalence**

Prevalence has been studied less than incidence, but for the purposes of public policy and service planning, it is clearly important in providing information about the extent of ongoing need in specific areas and populations.

Beginning quite generally, and broadly, diagnoses of schizophrenia and other psychotic disorders may be more common than was previously thought. In one of the most rigorous studies to date, from a country where enumeration of prevalent cases is likely to be high, estimates of lifetime prevalence of psychotic disorders in Finland were in excess of 3%,

irrespective of data source used.<sup>35</sup> If replicated in other countries, or settings, this may indicate a greater level of need than previously assumed. In contrast with the literature on incidence, a recent systematic review<sup>9</sup> found no variation in prevalence by area (i.e. urban/rural) or gender, though others have reported more evidence for heterogeneity.<sup>36</sup> 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 (i.e. raised prevalence but to a much lower degree than incidence) have been reported.<sup>37</sup> If valid, what these discrepancies potentially point to are variations in outcome, i.e. to better outcomes in cities and in migrant and minority ethnic populations. What we do not know, however, is whether methodological factors, particularly differences in the assessment of psychotic disorder, explain such discrepancies and the evidence concerning course and outcome in the UK black Caribbean population are equivocal, with a majority of studies suggesting prognosis is similar in black Caribbean and white patients.

### **1.5 Early Intervention in Psychosis**

During the past ten years, the development of early intervention in psychosis [EIS] services for those with a psychotic disorder has become a priority in a number of countries, including the NHS in England.<sup>38, 39</sup> This has been driven by a popular initiative in psychosis research that (we would say tentatively) suggests reducing delays in help-seeking following the onset of a first episode of psychosis and intervening early can significantly improve the course and outcome of the disorder, either delaying onset or improving outcome.<sup>40-42</sup> For service planners, knowledge of the incidence of psychosis in specific areas, and trends over time, is important for determining levels of potential need; for policy makers and service providers, understanding the factors that lead to onset and the predominant characteristics and circumstances of patients can inform the interventions provided. Further, data on prevalence is not only valuable for determining overall levels of need, if available over time it can provide some indication of the population level impact of early intervention services. If early intervention does ameliorate the long-term course and outcome of psychosis, this should have a positive and detectable impact on estimated prevalence (eventually reducing the numbers with psychosis).

Another potential effect of early intervention services, particularly if these are publicised and have strong links with primary care, is greater detection of new patients with psychosis. In so far

as studies of incidence are predominantly studies of service contacts for a first episode, the provision of early intervention may reveal higher rates of disorder than previously documented, with a further knock on effect on service planning.

### **1.6 Importance of the current systematic reviews**

The recent research and meta-analyses of incidence and prevalence outlined above have been international in scope.<sup>7-9, 36</sup> Because of their global outlook, their applicability to England is unclear. As the example of early intervention services shows, more specific data are needed of direct relevance to policy, planning and development in England. There has, however, been no similar attempt to systematically review research on environmental risks - with the exception of our cannabis use review<sup>33</sup> - or time trends in incidence and prevalence estimates. 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.

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## **Chapter 2: Aims & Objectives**

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## 2.0 AIMS AND OBJECTIVES

### 2.1 Aims

The aim of the review was to systematically appraise the literature on the **incidence** and **prevalence** of schizophrenia and other psychotic disorders between 1950 and 2009, conducted wholly or partially in England. The broad aims of the review were to

- Identify any variation (or otherwise) in the incidence and prevalence of psychotic disorders by sociodemographic and geographical factors
- Determine whether rates had changed over time, particularly with regard to the introduction of Early Intervention in Psychosis Services [EIS] in England from 2002.
- Estimate the associated economic implications of any variation in incidence and prevalence of schizophrenia and other psychotic disorders

In order to investigate these aims, we structured our review of the literature across three **research streams** of research: studies pertaining to the *incidence* of psychotic disorder in the general population, studies pertaining to the *prevalence* of psychotic disorders in the general population and studies pertaining to **special population groups**. These groups included studies conducted in specialist settings, such as prisons, the judicial system, the armed forces or hostels and sheltered accommodation settings. Since variation in the rate of schizophrenia and other psychotic disorder may have differed across these research streams, we took the decision to separate out these streams of research when addressing the above aims.

### 2.2 Specific objectives

From the above aims, we identified some specific objectives that this review sought to address. In particular, we sought to determine:

- A. Whether data from studies conducted in England were consistent with the epidemiological landscape of psychotic disorders, as described
- B. Whether the incidence and prevalence of schizophrenia and other psychoses are increasing (or decreasing) over time in England?

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

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## **Chapter 3: Methodology**

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## 3.0 METHODOLOGY

### 3.1 General systematic review approach

We adhered to strict methodological principles for the systematic reviewing of data. We closely followed the guidance provided by the PRISMA statement<sup>43</sup>, and include a copy of the PRISMA checklist (Appendix VIII) and a modified version of the PRISMA flowchart (Figure 4.1) in our review. We followed the recommendations of the [Cochrane Collaboration](#) while conducting the review to ensure methodological rigour, transparency, thoroughness and replicability. In particular, we included the following over-arching features into the design and conduct of the review:

- 3.1.1 Structured review format** – to present the results in a clear, understandable way
- 3.1.2 Detailed methodology** – to ensure transparency and replicability, and allow robust conclusions and inferences to be drawn from the data
- 3.1.3 Quality assessment** – to appraise the design features of different studies so that results may be systematised and interpreted not only based on the stock of previous literature, but based also on the quality of the conducted studies (see Section 3.4.4 for more details)
- 3.1.4 Thorough and systematic search strategy** – to ensure that all possible sources of relevant material are identified which meet the scope and inclusion criteria of the review, including both published and unpublished literature (see Section 3.3 and 3.4)
- 3.1.5 Appropriate data analysis** – where data from different studies is of sufficient quality it will be possible to perform meta-analyses to estimate summary measures of the incidence and prevalence of schizophrenia and other psychotic disorders (meta-analysis). In general the rates presented in this review highly heterogeneous so we present the pooled results, using the random effects model for meta-analysis, as descriptive rather than inferential statistics and we refrain from displaying the pooled results on forest plots. The pooled results are interpreted as giving an indication of typical study rates, which are intrinsically very variable from one study to the next. Since the pooled results are used for description rather than inference, the pooling of the highly heterogeneous results is much less contentious

here but we recognise that, in general, the pooling of highly disparate research findings in this way presents genuine issues. I<sup>2</sup> statistics are used to quantify heterogeneity and these descriptive statistics are of interest in addition to the pooled rates.<sup>44</sup> An I<sup>2</sup> value between 0.75 and 1.0 (75% to 100%) indicates considerable heterogeneity.<sup>45</sup> Since the data was often extremely heterogeneous, the fit of meta-regressions (Section 3.5) cannot be expected to be good, so this statistical tool is used to explore whether there is evidence that three variables – urbanicity, study quality and time – have any predictive value in the context of this systematic review and meta-analysis. For two of these variables (urbanicity and time) we also present data from original studies, which have directly investigated the effect of these variables on incidence rates of psychosis. Meta-regressions are included to test support for these findings or to illuminate possible areas for future study, where the original data is sparse.

### **3.2 Project management and organisation**

The project was co-led by the Department of Psychiatry, University of Cambridge (CI: Professor Peter Jones), and the Department of Psychological Medicine, Institute of Psychiatry (CI: Professor Robin Murray). Both organisations have a strong, international pedigree in conducting studies investigating the psychiatric epidemiology of schizophrenia and other psychotic disorders, thus providing a strong understanding of the relevant epidemiological literature. Through both organisations we were able to utilise local expertise, available across several domains of the review, including data searches and identification of relevant material (assisted by the Evidence Adoption Centre, Cambridgeshire and Peterborough Foundation Trust), data synthesis and analysis (in conjunction with the MRC Biostatistics Unit, University of Cambridge) and health economics expertise (from the Centre for the Economics of Mental Health [CEMH], Institute of Psychiatry). More details of the management structure of the project are given below.

#### **3.2.1 Steering committee**

The steering committee was led by the principal investigators of the study (PBJ, RMM, JBK, TJC, CM) who oversaw the design, implementation, analysis and will coordinate dissemination of the project as reports, presentations and academic publications in peer-reviewed journals. The

steering group met in person three times during the project period (which lasted almost 12 months) and had regularly phone (monthly) and email (weekly) contacts in order to progress and coordinate work.

### **3.2.2 Expert groups**

#### *3.2.2.1 Expert librarian group (Evidence Adoption Centre)*

This systematic review allowed us to collaborate with the library services funded by the NHS in the East of England and with the Evidence Adoption Centre [EAC]. The latter was established in 2008 as the East of England's coordinating centre for the Adoption of Evidence-Based Practice and Innovation. It was set up to help commissioners across the east of England to make better commissioning decisions regarding the adoption of new health technologies, innovations and new ways of working (see [www.eac.cpft.nhs.uk](http://www.eac.cpft.nhs.uk)). The EAC coordinated four librarians from two NHS library services to provide the project with expertise in search strategies, database scrutiny and data retrieval. We worked closely with the librarians throughout several stages of our review, from the design and implementation of our search strategies through to data retrieval. Karen Rigby, Kerry Hebert and Margaret Bevan from the NHS Education Library at Hinchingsbrooke Hospital provided expertise in the scrutiny and retrieval of data from databases indexing published articles. Barbara Norrey at the Essex PCT library provided expertise in the scrutiny and retrieval of relevant data from unpublished sources and indexing services related to Governmental reports and other sources of grey literature. The expert librarian group were responsible for conducting the searches that we designed (see Section 3.3), obtaining citation abstracts and full versions of relevant articles where necessary, either in electronic or paper format and delivering them to the research team.

#### *3.2.2.2 Expert meta-analytical group*

We collaborated with Dr Dan Jackson at the MRC Biostatistics Unit, University of Cambridge, who provided expert advice throughout the study, from the design phase through to analysis, interpretation and dissemination. Dr Jackson is an expert in meta-analysis and meta-regression techniques and conducted the analyses relevant to Objectives A-E (see Section 2.2) of this report. In addition, there was mentoring from Senior Scientist, Ian White, at the MRC Biostatistics Unit.

### *3.2.2.3 Expert health economics group (Centre for the Economics of Mental Health)*

The Centre for the Economics of Mental Health, Institute of Psychiatry, provided expertise to meet the final objective of the project; to provide an estimate of the economic implications of the results presented in this review. The research was led by Professor Paul McCrone at the CEMH. CEMH comprises of a team of globally-renowned health economists investigating several economic aspects of mental health. Using economic methods and tools, CEMH examine policy and practice questions, primarily in the mental health field. For this review, CEMH provided economic cost implications for health services and societies given the variation in incidence and prevalence identified in this review. The methods used by the CEMH to meet this exercise are fully described in Section 3.8.6.

### *3.2.2.4 Expert academic group*

In order to advise at each stage of the study, we established an expert group of academics and other key stakeholders, invited to participate by the steering committee at the outset of the study. Stakeholders had backgrounds in many disciplines including psychiatry, epidemiology, public health, health services research, health economics and service user groups. Each member of the group was 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). Preliminary findings were presented to the expert group, with discussion centred on the implications for public health, service provision, and clinical practice considered in detail. Such an approach was particularly useful in considering environmental correlates of schizophrenia, where despite efforts to elucidate risk factors, little empirical consensus has emerged. These discussions were aimed at helping to prioritise our findings for policy makers and allied public health practitioners.

## **3.3 Identification of relevant citations and studies**

We define a **citation** as any reference to data, published or unpublished research, reports or official documents potentially relevant to the aims and objectives of this review. A citation refers to a unique piece of work, published or otherwise. A **study** is defined as a research programme from where the data and information presented in a **citation** may have originated.

A research **study** may have several citations associated with it, while some citations may have included data from two or more studies. In this review, each included citation was given two identifiers; a **citation ID**, unique to that citation, and a **study ID**, which identified the research study to which the citation belonged. Where a citation included data from two or more distinct studies, the study ID was labelled “Study1.Study2”.<sup>iii</sup> In this report, citations are referenced [C1, C2, C3...C<sub>n</sub>], while studies are referenced [S1, S2, S3...S<sub>n</sub>].

Our search strategy proceeded in three distinct phases (see below) in consultation with our expert librarian and academic groups. The search strategy covered the widest possible number of electronic databases indexing relevant published and grey literature, as well as methods to ensure all unpublished sources were also ascertained. Our search strategy was guided by the inclusion criteria we defined for the review.

### 3.3.1 Inclusion criteria

Inclusion criteria for the review were formulated by the steering group and discussed with our expert academic group. In light of this consultation phase, we expanded the temporal scope of the study from 1952-2008 to 1950-2009. Studies appropriate to the systematic review had to meet the following entry criteria:

- *Time period*: Published between 1950 – 2009
- *Extent*: Studies conducted wholly or partially in England
- *Scope*: Published or unpublished literature
- *Contains original data* on
  - **incident** cases of **non-organic** adult onset psychosis (16-64 years); or
  - **prevalent** cases of non-organic adult onset psychosis (16-64 years); or
  - one or more socioenvironmental risk factor pertaining to incidence/prevalence

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<sup>iii</sup> For example, a citation with a study ID of “6.14” would indicate that this citation contained data from two separate studies; study 6 and study 14.

**Original data** was defined as any data in the citation which presented an incidence or prevalence rate or a risk estimate for a socioenvironmental risk factor related to incidence/prevalence (for example, a rate ratio for a given risk factor such as social class, migration or deprivation). Our definition of **original data** included citations where although no incidence or prevalence rates were published, there was sufficient data present within the citation to *derive* an estimate of incidence or prevalence. All **derived incidence or prevalence rates** were reviewed by consensus agreement between PBJ, TJC and JBK.

### 3.3.2 Stage 1 – Literature search and abstract review

#### 3.3.2.1 Published literature

To identify relevant published studies, a systematic literature search was conducted using four electronic databases (**MEDLINE**, **PSycINFO**, **EMBASE**, **CINAHL** – see Box 3.1) to find titles or abstracts containing a combination of a psychiatric condition term<sup>iv</sup>, an epidemiological term<sup>v</sup> and a UK location term<sup>vii</sup>. Only studies published between January 1950 and 31 December 2009 (in **MEDLINE** and **PSycINFO**), between 1 January 1980 and 31 December 2009 (in **EMBASE**)

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<sup>iv</sup> Schizo\* OR (psychotic or psychosis or psychoses) OR bipolar adj3 disorder\* OR delusion\* adj3 disorder\* OR dementia adj (praecox or precoc) OR (((severe or serious or chronic) adj mental adj (illness\* or disorder\*)) or SMI) OR (mani\* adj3 depressi\*) OR (affective disorders, psychotic/ or bipolar disorder/ or schizoid personality disorder/ or schizotypal personality disorder/ or exp "schizophrenia and disorders with psychotic features"/ or psychoses, alcoholic/ or psychoses, substance-induced/)

<sup>v</sup> (inciden\* or prevalen\* or epidemiolog\*) OR ((first\* or 1st\* or hospital\*) adj3 (episode\* or contact\* or admission\* or admit\*)) OR (case adj3 register\*) OR case control\* OR (prospectiv\* or population\* or communit\* or survey\*)

<sup>vi</sup> An additional literature search of epidemiological-related terms (cohort\*, cross section\*, observation\* and surveillance) combined with a psychiatric condition term and a location term was conducted in MEDLINE and found to be of small interest for this study. Only 3 (0.4%) of the 847 references generated by this search in MEDLINE were found to be potentially relevant.

<sup>vii</sup> Great Britain OR (England or United Kingdom or UK or Britain or GB or British or Wales or Scotland or Ireland) OR (Bath or Birmingham or Bradford or Brighton or Hove or Bristol or Carlisle or Cambridge or Canterbury or Chester or Chichester or Coventry or Derby or Durham or Ely or Exeter or Gloucester or Hereford or Kingston upon Hull or Hull or Lancaster or Leeds or Leicester or Lichfield or Lincoln or Liverpool or London or Manchester or Newcastle upon Tyne or Norwich or Nottingham or Oxford or Peterborough or Plymouth or Portsmouth or Preston or Ripon or Salford or Salisbury or Sheffield or Southampton or st Albans or (Stoke adj2 Trent) or Sunderland or Truro or Wakefield or Wells or Westminster or Winchester or Wolverhampton or Worcester or York) OR (Reading or Dudley or Northampton or Luton or Milton Keynes or Walsall or Southend or Huddersfield or Poole or Middlesbrough or Blackpool or Bolton or Ipswich or Telford or West Bromwich or Stockport or Slough or Watford or Rotherham or Eastbourne or Sutton Coldfield or Blackburn or Colchester or Oldham or Crawley or st Helens) OR (Barking or Dagenham or Barnet or Bexley or Brent or Bromley or Camden or Croydon or Ealing or Enfield or Greenwich or Hackney or Hammersmith or Fulham or Haringey or Harrow or Havering or Hillingdon or Hounslow or Islington or Kensington or Chelsea or Kingston upon Thames or Lambeth or Lewisham or Merton or Newham or Redbridge or Richmond upon Thames or Southwark or Sutton or Tower Hamlets or Waltham Forest or Wandsworth or Westminster or Camberwell)

and between 1 January 1981 and 31 December (in [CINAHL](#)) were included in the search (see Appendix II for full search terms and strategies). Editorials, book reviews and obituaries were excluded unless they contained original data.

**Box 3.1: Overview of bibliographic databases used to identify relevant citations**

	Database	Dates covered	Scope	Website*
1.	<a href="#">MEDLINE</a>	1947-	>18m citations to journal articles in the life sciences from more than 5,400 journals	<a href="http://www.nlm.nih.gov/databases/databases_medline.html">www.nlm.nih.gov/databases/databases_medline.html</a>
2.	<a href="#">PSycINFO</a>	1800-	>2.9m citations. Systematic coverage of psychological literature, includes journals, books, and dissertation abstracts	<a href="http://www.apa.org/pubs/databases/psycinfo/">www.apa.org/pubs/databases/psycinfo/</a>
3.	<a href="#">EMBASE</a>	1947-	>20m citations from >7,000 biomedical journals, including >2000 not in MEDLINE	<a href="http://www.embase.com">www.embase.com</a>
4.	<a href="#">CINAHL</a>	1981-	Cumulative Index to Nursing and Allied Health Literature. Indexes ~3000 nursing and allied health journals	<a href="http://www.cinahl.com">www.cinahl.com</a>
5.	<a href="#">ASSIA</a>	1987-	Applied Social Science Index and Abstracts. Covers health, social services, psychology, sociology and social sciences. ~0.5m citations from 500 journals	<a href="http://www.csa.com/factsheets/assia-set-c.php">www.csa.com/factsheets/assia-set-c.php</a>
6.	<a href="#">HMIC</a>	1983-	Health Management Information Consortium database of clinical medicine and public health literature. >300k citations. Combines Department of Health Library and Information Service and King's Fund Information and Library Service. Includes journals, official reports and grey literature	<a href="http://www.ovid.com/site/catalog/DataBase/99.jsp">www.ovid.com/site/catalog/DataBase/99.jsp</a>

\*Accessed 6<sup>th</sup> July, 2010

### 3.3.2.2 Grey literature

To identify relevant studies, a systematic literature search was conducted using two electronic databases ([ASSIA](#) and [HMIC](#), see Box 3.1) to find titles or abstracts containing the same combination of a psychiatric condition term and an epidemiological term. A UK location term was not used in ASSIA as it is a relatively small database. Only studies published between 1

<sup>viii</sup> In addition, thesaurus searching was used to identify relevant psychiatric and geographic location subject headings within each database. (As PsycINFO does not include location subject headings, the location field was searched in addition to title and abstract).

January 1987 and 31 December 2009 (in ASSIA) and from 1 January 1983<sup>ix</sup> and 31 December 2009 were included (see Appendix II for full search terms).

### **3.3.2.3 Abstract review**

Two independent raters (JBK, TJC) applied inclusion criteria to the citation abstracts extracted at Stage 1. Where abstracts were not available, the full paper was obtained. The raters assigned citations to one of three possible groups “met inclusion criteria for review”, “possibly meets inclusion criteria for review” or “did not meet inclusion criteria for review”. The “possibly” category was used where there was insufficient information in the title/abstract to include or exclude the study, or where there was disagreement between the two raters. For these citations, the full paper was obtained.

At this stage, these groupings were not considered final. i.e. citations which “met inclusion criteria” or “possibly met inclusion criteria” still had to undergo review of the full text of the manuscript in order to be included in the review (see Section 3.3.2). Given the broad, comprehensive search strategy we employed, it was not practical or cost-efficient to obtain and read the full text for citations which at Stage 1 (title and abstract review) “did not meet inclusion criteria”. However, we adopted a conservative approach to excluding citations at this stage, only excluding citations where there was definite evidence to support this decision. Furthermore, we ensured safeguards were put in place in our search strategy to minimise the number “false negative” studies we may have omitted in error at this stage (for example, by conducting citation and author searches – see Section 3.3.2)

### **3.3.3 Stage 2 – Full text manuscript review**

Full manuscripts were obtained by the expert librarian group for all citations which either “met inclusion criteria” or “possibly met inclusion criteria” for the review. All manuscripts were

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<sup>ix</sup> HMIC provides a comprehensive database search from 1983 onwards, although coverage of Governmental Departmental materials dates back to 1919



reviewed by consensus between JBK and TJC, with discrepancies resolved by a third reviewer (PBJ). This list of included citations formed the basis of studies included in the review.

### **3.3.4 Stage 3 – Citation and investigator searches for missed or unpublished data**

We conducted citation searches based on the reference lists of all papers identified at the end of stage 2, as well as from known meta-analyses and reviews relevant to the review.<sup>7, 46-48</sup> This ensured that we had not missed any potentially relevant citations during stages 1 and 2. Potential citations were reviewed in the same way as at stage 1 and 2, with those meeting criteria for the review being included in the final sample of citations.

At any point during stages 1-3 where there was insufficient data to determine a citation's eligibility into this review, we contacted the senior investigating author of the study in question to ask for any further published or unpublished data they might have of relevance to the review. We established a final sample of citations meeting inclusion criteria for the study, as identified via our search strategy. From these citations, we then extracted all relevant data.

### **3.3.5 Database management and manuscript sourcing**

At Stage 1, all titles and abstracts of citations identified by the search were provided by the expert librarian group in Endnote format. Endnote (v9) is an electronic citation reference management system, which allows the user to quickly search, manage and review large citation lists. Endnote was used to manage citations and identify duplicates at all stages during the identification process. Endnote files are available on request.

All full manuscripts were provided by the expert librarian group in paper, book or electronic format, with all necessary access and use permissions granted prior to their distribution.

## **3.4 Data extraction**

### **3.4.1 Overview**

Data from the final sample of citations were extracted at the University of Cambridge by AE overseen by the local steering committee (PBJ, TJC, JBK). The expert advisory group, led by Professor John McGrath, provided guidance on creating a comprehensive data extraction list, to include **study-level variables**, **rate-level variables** and **meta-variables** (i.e. the quality of the

studies themselves). We extracted all relevant data into a Microsoft Excel spreadsheet, the final version of which is included on the enclosed memory stick and will be made available online subject to permission by the funders. The data extraction process was conducted by AE. To ensure data extraction quality, a random sample of studies (5%) was selected and cross-checked by JBK. This process confirmed a high degree of data extraction accuracy (<0.5% error was identified).

### **3.4.2 Study-level variables**

Study level variables provided information about the design of the study including authors, study title, publication source (or unpublished), year of publication, study type (incidence, prevalence, risk factor, special population – for example, prisons), study setting, study length, age range, diagnostic outcomes studied (see Section 3.4.5.3), case finding methodology, source of denominator data, linked/associated citations and other notes.

### **3.4.3 Rate-level variables**

Rate-level variables included information about the estimates of incidence and prevalence in each study, as well as other relevant numerical data, including the size of the **numerator** (people with the disorder identified by the study) and the **denominator** population (people without the disorder under study). We included all rate-level data reported in each study, by age, sex ethnicity or country of birth (as reported). In general, studies investigating the incidence and prevalence of psychotic disorder in the UK according to ethnicity used two principle ways of exploring rates by ethnicity. The studies conducted earlier in the research period of this review tended to report and estimate rates according to country of birth. This practice reflected both the way in which the denominator population (often from the census) was recorded and the contemporary history of migration in the UK; during the 1950s to 1970s the UK saw large waves of immigration from former colonial nations, taking advantage of labour market opportunities in the UK following WWII. Since, in principle, the vast majority of the immigrant population at-risk in the early psychiatric morbidity studies were born outside of the UK, country of birth could be considered an adequate proxy for first generation migrant status. This is the way we suggest data presented in this report by country of birth is interpreted. Recognising the changing population dynamics in the UK more recently, both the Census and epidemiological studies have moved towards using ethnicity (sometimes in combination with country of birth) to differentiate

between the white or white British baseline population and first generation migrants and their offspring. Thus, more recent studies of psychotic disorder in the population predominantly present incidence and prevalence rates according to ethnic group. We have preserved the structure of the original reports in this survey, but this explanatory note is of importance.

Various studies reported incidence and prevalence data along a number of other sociodemographic domains, such as by marital status or socioeconomic position. Such categorisations were diverse, and often limited to single citations. They are not the main focus of this review but the data has been extracted to permit future analysis. Indeed, given the size and scope of this systematic review, the possible permutations of variables and outcomes for data analysis are extremely large (see Section 3.4.5). Currently, the main body of this report includes results from all analyses completed to date. As these results, and this report, are shared with reviewers and dissemination audiences, it is of course highly likely that requests for, or opportunities for more data arise. With an unlimited resource, clearly a wide range of other analyses are possible.

Generally, there were too few citations which specifically addressed variation in the incidence and prevalence of psychotic disorders over time or between study settings (though for some outcomes there was sufficient data to review change in rates over time directly). Given the importance of assessing the association between rates of psychoses and some variables – such as time and the degree of urbanisation (urbanicity) – we took a different approach to their measurement, including them as a special form of study level variable which we termed as “meta-variables”, in order to maximise the available information included in this systematic review (see Section 3.4.4).

We also differentiated by, and included, all data in citations where more than one rate was published for each group under study (for example, **crude** (unadjusted), **adjusted** or **standardised** rates, **rate ratios** or **odds ratios** – see notes on **confounding** for further information about the differences between these rates generally).

Citations which did not explicitly report an incidence or prevalence rate (or associated risk factor), but did include sufficient data to permit us to derive an estimate of incidence or

prevalence were included. Where no published or derivable rate (or risk factor) data were available, that citation was excluded from this review.

#### **3.4.4 Meta-Variables (time, urbanicity, data quality)**

Meta-variables are a special form of rate-level variable which may not have been explicitly measured in the original citation, but which can be derived from that citation in order to maximise the available information included in this systematic review. Time provides one good example and is central to the objectives of this review (see Objective B, Section 2.2). Few incidence or prevalence studies identified in this review specifically tested whether rates of psychotic disorders changed over time (though there are, of course, notable exceptions).<sup>23-25, 30, 49-64</sup> However, since all studies were conducted at a particular cross-sectional point in time, or over a period of time, we can potentially use this information to assess whether rates of psychoses have changed. For time, we classified each citation according to the midpoint of the study period and fitted this year as a continuous predictor variable in meta-regression (see below). This approach has some limitations because the original studies were not established to be compared directly in this way. For example, methodological differences, differences in study setting and populations might all account for any apparent changes (or stability) we might observe in this way (for a full account of the limitations of this method, please see the discussion in Section 5). Nevertheless, these meta-variables permit an extra source of information which should be considered in parallel with more direct evidence from citations which sought to directly assess the impact of the corresponding rate-level variable (for example, time).

We also considered urbanicity as a meta-variable, since this variable is known to be associated with the incidence, and possibly prevalence, of some psychotic disorders.<sup>65</sup> Assigning a level of urbanicity to different citations was not straightforward given changes in levels of urbanisation over time and often sparse data from the original citation on the study setting and population at-risk. As such, it was not possible to quantify an objective measure of urbanicity, such as population density, and we chose instead to adopt a multidisciplinary, expert-led approach to assigning urbanicity instead. The following approach was taken:

- (1) Citations which pertained to specialist populations (prisons, institutionalised settings, etc) and citations which purported to cover the whole of England were excluded from this analysis
- (2) The remaining citations were sorted by study ID and a list of unique study settings established. The study setting was defined as reported by the original authors.
- (3) Five of the authors of this report [JBK, PBJ, RMM, CM, TJC] were asked to independently rank study settings [1... $n$ ] according to their perceived level of urbanisation, where 1 was most urban and  $n$  was the least urban (most rural). These authors were from a multidisciplinary background, including a geographer and sociospatial epidemiologist [JBK], sociologist and epidemiologist [CM], a psychometric epidemiologist [TJC] and two Professors of Psychiatry with epidemiological training and considerable experience in conducting studies across a variety of settings in the UK [PBJ, RMM]. These authors are all British citizens and have lived in a variety of UK settings for the majority of their lives
- (4) The mean ranking for each study setting was calculated and study settings sorted in mean rank order. These studies were then re-ranked 1... $n$ , where 1 denoted most urban, with ties assigned the same ranking.
- (5) This variable was used in the meta-regression

This led to the creation of a composite urbanicity variable used in meta-regressions (see Section 3.5.5). We acknowledge that this approach is subjective. We attempted to minimise this by using independent rankings from 5 multidisciplinary researchers. We also acknowledge that this approach does not attempt to differentiate between the urbanicity of the same study setting across different periods of time. However, this approach provided a pragmatic way of assessing urbanicity when it was impossible to obtain a more objective measure. When our urbanicity variable was entered into specific analyses (where only a subset,  $n_s$ , of the study settings 1... $n$  might have been included), the variable was not recoded 1... $n_s$ , but the original ranking was preserved in order to maximise the amount of data available in relation to urbanicity.

The third meta-variable we considered related to the quality of the study conducted from each citation. This allowed us to determine whether estimated incidence or prevalence rates could have been affected by methodological issues. We rated each citation according to whether they had reported seven methodological criteria we considered as important markers of epidemiological rigour. A description of these items is given in Box 3.2. Each quality criterion was assessed dichotomously (reported: 1, not reported: 0) with a score of 7 being the highest possible quality score attainable by any individual citation.

Box 3.2: Description of study quality criterion		
Criterion	Description	
1. <i>Defined catchment</i>	Did the study have a well-defined catchment area to ensure that the numerator (case) and denominator populations came from the same source? Evidence of a defined catchment was needed to meet this criterion.	
2. <i>Accurate denominator</i>	Did the study report how it estimated the denominator population from which the cases came? Was the source known to be accurate, reliable and valid? Evidence of an accurate denominator was needed to meet this criterion.	
3. <i>Population-based case finding</i>	Did the study employ a population-based case finding approach? This includes identifying cases from community-based settings and service contact points, including <b>primary</b> , <b>secondary</b> and <b>tertiary</b> facilities. Studies which only considered hospital-based admissions, for example, would not meet this quality criterion as they would be likely to underestimate the true rate of disorder in the community. Evidence of a broad case-finding approach was needed to meet this criterion.	
4. <i>Standardised research diagnoses</i>	Did the study use standardised research diagnoses to ensure that the cases met comparable diagnostic criteria for psychotic disorder? Studies reliant on clinician-led chart diagnoses may introduce bias into diagnoses given inter-clinician variation in making diagnoses. Applying standardised criteria, by using a method such as the Schedule for the Clinical Assessment in Neuropsychology [SCAN] or using <b>OPCRIT</b> -generated diagnoses would reduce such problems. Evidence of attempts to standardise diagnoses was needed to meet this criterion.	
5. <i>Blinding to demographic factors</i>	Did the study blind the person/panel who diagnosed cases to certain demographic characteristics? For example, ethnicity, where it has been argued that raised rates of psychosis in migrants and their offspring <sup>7</sup> may be due to misunderstanding of cultural differences in symptomatology or, worse, institutionalised racism. Blinding, or partially blinding diagnosticians to this information will reduce the likelihood of this explanation. Some evidence of blinding was needed to meet this criterion.	

6.	<i>Inclusion criteria</i>	Did the study use inclusion criteria to accurately define their study population (numerator and denominator)? Were these criteria sufficient? Standard criteria in epidemiological research include age limits, residency within catchment area at time of disorder, absence of an <b>organic basis</b> to the disorder and no previous episode of disorder (incidence studies only). Inclusion criteria needed to be present <i>and</i> of sufficient relevance/quality to meet this criterion.
7.	<i>Leakage study</i>	Did the study conduct any kind of <b>leakage study</b> ? A leakage study is an attempt by the investigators to identify any cases that may have been missed during original case identification. Leakage studies may be formal (systematic, regular consultation with mental health and other service providers in the region) or more informal (sampling a proportion of such services to estimate possible “leakage”). Evidence of any kind of leakage study was needed to meet this criterion.

Although we recognised that *reporting* aspects of methodological quality may be a different construct from *conducting* those same criteria, we nonetheless considered that this approach minimised introducing bias into our ratings<sup>x</sup> and it could be argued that a failure to report methodological quality criteria is of itself an indication of lower methodological rigour. Ratings were conducted by consensus by AE and JBK.

To assess the impact of meta-variables (time, urbanicity, data quality) on rates of a given psychotic disorder, we performed meta-regression (see Section 3.5.5) on the appropriate dataset, fitting each meta-variable univariately. This allowed us to quantify any association between the incidence or prevalence rate and the meta-variable under study. Where there was sufficient data, we also considered the bivariate and multivariate extensions to the meta-regression model to permit control for confounding of other meta-variables (for example, the effect of time independent of urbanicity effects). Where possible, we compared results for consistency from the standard rate-level variable approach and corresponding meta-variable method.

### 3.4.5 Research streams, themes and blocks

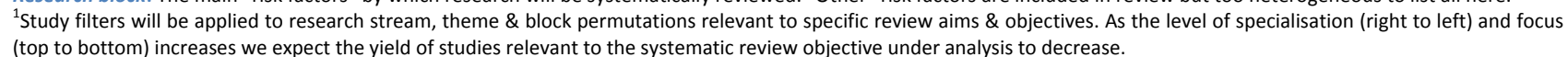
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<sup>x</sup>An alternative approach would have been to attempt to contact all authors of these studies to assess quality criteria independently of what had been reported. This approach, however, may have unduly given higher quality ratings to more recent studies, not because of improving methodological approaches over time (which one might expect), but because asking authors about studies conducted further back in time (as far back as 1950) would become increasingly difficult, due to recall problems or because the author(s) no longer works in the field or have since died.

#### **3.4.5.1 Overview**

To address the six objectives of this review we organised our extraction of rate data from relevant citations according to three broad, interacting and non-mutually exclusive categorisations of citations: by research “streams”, “themes” and “blocks”. All citations included in this review were coded according to the relevant streams, themes and blocks to which they provided rate data. This allowed us to develop a citation matrix from which we could identify relevant citations for specific analyses germane to the objectives of this review. A conceptual overview of this citation matrix is provided in Figure 3.1. Below, we give more detail about **research streams**, **research themes** and **research blocks**.





### 3.4.5.1 Research Streams (study setting)

**Research streams** provided the broadest hierarchical organisation of citations included in this review. Within the research stream hierarchy citations were broadly classified according to studies which pertained to the general adult population (aged 15 years old or older) or what we considered “special” population settings, such as prisons, the judicial system, care institutions and hostels, homeless populations, the armed forces and studies identified based on primary care settings. In each of these examples, there is good theoretical and empirical evidence to suggest that the incidence and prevalence rates in such “specialised” settings may differ dramatically from the rates one would observe in population-based, observational epidemiology studies of the general adult population. Since the risk factors for psychoses may also differ according to these streams, we decided it was important to distinguish *a priori* between such settings.

Within each research stream, citations could be further subdivided into studies providing rate data on **incidence**, **prevalence** or data from such studies pertaining to **risk factors** for psychotic disorder (i.e. **effect sizes**). Prevalence rates could further be distinguished as rates relating to **point**, **period** or **lifetime prevalence** (see Box 3.3).

Box 3.3: Overview of incidence and prevalence types		
	Term	Definition
1.	<b>Incidence</b>	Number of new cases of disorder in a defined period of time and population
2.	<b>Prevalence</b>	Number of new and existing cases with the disorder at a defined point or over a defined period of time in a given population
<i>Of which subtypes:</i>		
2a.	<b>Point prevalence</b>	Prevalence of disorder at a single point in time
2b.	<b>Period prevalence</b>	Prevalence of disorder over a defined period, typically annually
2c.	<b>Lifetime prevalence</b>	Number of new and existing cases known to have had the disorder at some point over their lifetime (usually expressed up to a given age)

#### *3.4.5.2 Research themes (diagnostic hierarchy)*

Citations were also categorised according to the diagnostic classification for which rates were provided (Figure 3.1). This allowed us to investigate incidence and prevalence rates of different sets of disorders, for example, schizophrenia, bipolar disorder or substance-induced psychoses. At the broadest level we considered any citation presenting rates for “all clinically relevant psychoses”. At the next level of hierarchy we considered citations which presented rates by broad diagnostic groups, non-affective psychotic disorders, affective psychotic disorders and substance-induced psychotic disorders. The lowest level of hierarchy allowed us to analyse rates for specific non-affective psychotic disorders (i.e. schizophrenia) and specific affective psychotic disorders (bipolar disorder and psychotic depression). We chose not to analyse non-affective disorders other than schizophrenia as a separate category of disorders due to likely heterogeneity in this group.

One important issue in assigning citations to different diagnostic categories was to ensure our classification allowed us to synthesise rates from different studies which preserved meaningful comparison of similar disorders. This task is not straightforward given different studies use different diagnostic classification systems (International Classification of Disease [ICD], Diagnostic and Statistical Manual [DSM], CATAGO, Research Diagnostic Criteria [RDC], Feighner and others), which differ in the symptomatic criteria required for different psychotic disorders and which are subject to changing diagnostic criteria over time (ICD is in its tenth revision, DSM is in its fourth revision). Our objective in assigning the diagnostic hierarchy we adopted (Figure 3.1) to citations included in this review was to maximise the internal homogeneity of each research theme, and maximise external heterogeneity between different research themes. All diagnostic information presented in the original citation was extracted (AE). This information was reviewed by an experienced academic psychiatrist (PBJ), who developed an algorithm for applying the diagnostic hierarchy we used in the review (Figure 3.1) to the myriad of diagnostic classifications used in the original citations included in this review. The algorithm was independently verified by other members of the research team with experience in psychiatric epidemiology (TJC, JBK). Full details of this algorithm are provided in Appendix III.

### 3.4.5.3 Research Blocks (sociodemographic and environmental variables)

Citations were also coded according to the broad sociodemographic or socioenvironmental categories to which extracted rates pertained. We have termed these **research blocks** (see Figure 3.1) Citations which presented rates for several different sociodemographic groups could be coded to more than one research block. At the broadest level, we coded all citations which presented an overall rate of psychotic disorder for the entire study population (all sexes, all ages, all ethnic groups and so forth). We also coded citations according to whether they presented rates for various sociodemographic variables relevant to the objectives of the study, including time, age, sex, age and sex, ethnicity, migration (country of birth), geography, urbanicity, and other variables pertaining to the social environment (for example, deprivation and ethnic density, where enough studies permit meaningful analyses).

## 3.5 Data analysis and presentation

### 3.5.1 Analysis filters (research streams, themes and blocks)

We applied filters to our **citation matrix** (Figure 3.1) to identify relevant rate data for specific analyses pertinent to the objectives of this review. For each analysis, we recorded the filters that had been applied and the citation IDs and corresponding study IDs of each citation contributing relevant rate data to that analysis. A copy of this **analysis matrix** will be made available online subject to funder's permission (Appendix IV). From this list, we then identified:

- Citations which provided unique rate data for a single study for the analysis in question (**unique citations**)
- Two or more citations from the same study which provided comparable estimates for a given demographic group of interest (**duplicate citations**)

### 3.5.2 Decision tree for selection of the relevant “duplicate” citation

All data from unique citations were included in the analysis. For duplicate citations, we applied a systematic hierarchy to determine which citation would provide the rate data for the analysis. Citations which provided this data were termed “**core**” citations, while the remaining duplicate citations were termed “**satellite**” citations. Rates from duplicate citations were chosen according to the following preference criteria:

- Data presented with a corresponding estimate of the standard error (see Section 3.5.4)
- Data most closely relating to the entry criteria of the study (for example, for age, data on 16 to 64 years would supersede a duplicate citation presenting the same data for people aged 16 to 99+ years)
- Published data (journals supersede books which supersede unpublished data)
- Citations published in highest ranked journal

This process was repeated for each analysis presented in the systematic review. Thus, because citations presented different rates, a citation which was selected as the **core citation** in one analysis was not necessarily considered the **core citation** for another analysis, if an alternate from the same study had stronger data.

### **3.5.3 Decision tree where a single citation presented several usable rate estimates**

In some situations, an included citation may have presented several possible rates which could be used in a specific analysis (for example, where a study published rates of schizophrenia according to different diagnostic classification systems – ICD, DSM or RDC). Where this situation arose, we applied the following preference criteria:

- *Standard error information*: Rates published with some measure of their standard error were preferred over other published rates (see Section 3.5.4.1).
- *Type of rates*: Published crude rates superseded **derived** and **standardised rates**. Derived rates (by us from data available in the original citation) superseded standardised rates.
- *Age*: Some citations presented rates for the total population (i.e. all ages) and rates for the adult population. Where such a choice existed, we used rates which corresponded most closely to the entry criteria for this review (16 to 64 years old). Where studies only published “total” rates (i.e. “all ages” or “16 years to death”), we took a pragmatic approach to include such rates to avoid excluding relevant data.
- *Diagnosis*: Where a study published estimated rates of disorder under different diagnostic classification systems (i.e. DSM Schizophrenia, ICD Schizophrenia, Feighner Schizophrenia, we included rates for the most commonly used classification at the time of writing this report (DSM, ICD, RDC, CATEGO, Feighner, other).

- *Geography*: Rates presented for England or its regions superseded rates for England and Wales, though the latter was included if this was the only data provided.

### 3.5.4 Data preparation and synthesis

After the relevant analysis filter had been applied to the citation matrix, and all unique and core citations identified, the rate estimates relevant to the analysis were extracted to a separate spreadsheet, recorded with an analysis-specific identifier (for a full list of analyses and the corresponding filters included in this review, see Appendix IV).

For each analysis, we systematically reviewed the rates from the available, relevant literature. This included descriptively reporting the number of studies and rates identified, the spread (or variation) of the estimated rates, the settings in which these studies were conducted, sample sizes and any other relevant information (where available). Where there was a sufficient number of rate estimates for specific analyses, we considered using meta-techniques (meta-analysis and meta-regression) to obtain pooled rate estimates, or where appropriate inspect differences in rates according to the sociodemographic and environmental factors identified as *a priori* risk factors for psychosis (see “Research Blocks”, Figure 3.1).

To facilitate meta-techniques (see Section 3.5.5) it was first necessary to transform the extracted rate data onto the appropriate logarithmic scale (depending on whether incidence or prevalence). For incidence rates we transformed estimates to their natural logarithm, appropriate for the analysis of count based data under Poisson processes. For prevalence-based estimates we transformed the rate to the logit scale, appropriate for the analysis of data based on proportions.

Rate estimates included in any meta-analytical techniques must also have a corresponding estimate of the statistical variation around that rate, known as the **standard error**. This gives a measure of precision as to how confident one is that the observed rate accurately estimates the true, unknown underlying rate in the population. Therefore, where possible we calculated the **standard error** associated with any incidence/prevalence rates. The formula for the estimation of the standard error of a rate depends on the type of rate (incidence vs. prevalence) and the

availability of other data from the citation (**standard errors**, **numerators**, **denominators** or **confidence intervals**). Further details are given in the next sections.

#### 3.5.4.1 Estimation of standard errors for a log incidence rate

The preferred method for the estimation of the standard error of an incidence rate,  $\lambda$ , is obtained using the **delta method**:

$$(1) \text{ s.e.}(\log \lambda) = \frac{1}{\sqrt{d}}$$

where  $d$  is the number of cases with the disorder (the **numerator**) for the corresponding incidence rate.

Where studies did not produce an estimate of  $d$ , we used the following alternative methods, in order of preference, to obtain an estimate of the standard error:

$$(2) \text{ s.e.}(\log \lambda) = \frac{[\ln(\text{upper CI of } \lambda) - \ln(\text{lower CI of } \lambda)]}{2Z_{\alpha}}$$

Where  $\ln$  is the natural logarithm of the estimated value, and the *upper CI* and *lower CI* correspond to the upper and lower estimates of the confidence interval surrounding a rate, where published, and  $Z_{\alpha}$  is the value corresponding to the confidence interval used. For 95% CI,  $Z_{\alpha} = 1.96$ .

$$(3) \text{ s.e.}(\log \lambda) = \frac{[\ln(\text{upper CI of } \lambda) - \ln(\lambda)]}{Z_{\alpha}}$$

Formula (3) was used to estimate the s.e. error of the incidence rate where the reported lower confidence interval was close to zero. Since the natural logarithm of values close to zero tend towards negative infinity, this formula overcame problems of estimating standard errors where this situation arose.

$$(4) \text{ Extension to (1): estimation of } d \text{ from other data}$$

Where an incidence rate and the denominator population,  $N$ , for that rate was reported, but no corresponding numerator population,  $d$ , citations reported, it was possible to estimate  $d$ , since:

$$\lambda = \frac{d}{N}$$

where  $\lambda$  is the incidence rate,  $d$ , is the number of new cases (**numerator**) and  $N$  is the number of person-years at risk (**denominator**), therefore

$$d = \lambda N$$

Thus, it was possible to estimate the number of new cases,  $d$ , for a given rate and therefore estimate the standard error using the delta method (1), as before. Incidence rates and their corresponding standard errors (where available) were transformed onto the natural logarithm scale to allow estimates to be pooled in meta-analyses.

#### 3.5.4.2 Estimation of standard errors for a logit prevalence rate

The following formulae were used, in order of preference, to estimate standard errors for the logit prevalence rate,  $p$ :

$$(1) \quad s.e.(\logit p) = \sqrt{\left(\frac{1}{d}\right) + \left(\frac{1}{[N-d]}\right)}$$

Where  $d$  is the total number of cases with the disorder and  $N$  is the total number of people in the population.

If studies did not publish estimates of  $d$  or  $N$ , but provided confidence intervals around a prevalence estimate, the following formula was used:

$$(2) \quad s.e.(\logit p) = \frac{\logit(\text{upper CI of } p) - \logit(\text{lower CI of } p)}{2Z_{\alpha}}$$

or

$$(3) \quad s.e.(\logit p) = \frac{\logit(\text{upper CI of } p) - \logit(p)}{Z_{\alpha}}$$



Where  $p$  is the prevalence rate and  $Z_{\alpha}$  is the value corresponding to the confidence interval used. For 95% CI,  $Z_{\alpha} = 1.96$ . Formula (3) was used where the lower prevalence limit was close to zero, for the analogous reason as described for incidence rates (see Section 3.5.4.1).

### **3.5.5 Meta-analyses and meta-regression**

Where there was sufficient data to pool estimates of incidence or prevalence rates we employed a variety of meta-analytic techniques, depending on the form of the data and the questions of primary interest. Our approach here was guided and conducted by an expert meta-analytical group, led by Dr Dan Jackson and Mr Ian White at the MRC Biostatistics Unit, Cambridge.

In order to assess the magnitude of the overall rates, univariate random effects meta-analyses were performed using the standard method originally proposed by DerSimonian and Laird.<sup>66</sup> However, it was found that the  $I^2$  statistics<sup>44</sup>, which provide an estimate of the heterogeneity of estimates, were generally extremely large (typically these were 90% or greater). Where this situation arose, our primary method of presenting the results from this kind of analysis was to show forest plots, omitting the pooled estimate. Because an indication of a typical rate is of genuine interest however, we refer to the pooled estimate and confidence intervals where an indicative rate or range is required for interpretation. The coverage probability of the confidence intervals can be much lower than the nominal value of 95% when the number of studies is small and the heterogeneity is large,<sup>67</sup> so the pooled rates and accompanying intervals are presented as descriptive rather than inferential statistics.

For studies which investigated the rates of psychotic disorders by gender, we employed a bivariate extension of DerSimonian and Laird,<sup>68</sup> where the two outcomes in the analysis are the rates for each gender. This allowed us to estimate pooled rate estimates for men and women from the same model, and determine whether any differences were significant. Rates are assumed independent within studies because they are computed from different individuals. The between-study variation allows the rates to be correlated. This method facilitates a direct test of whether the rates are the same for men and women, but because the between-study heterogeneity dominates the within-study heterogeneity, the assumptions of the paired two-

sample t-test are almost satisfied. Hence, when testing differences in rates between men and women, we report both the statistical test from the bivariate model, as well as inferences from the much simpler and more transparent t-test, demonstrating that both are in good agreement.

The *a priori* empirical literature in relation to the incidence of psychotic disorders by age strongly suggested an interaction between age-at-onset and gender for certain disorders (see Hafner *et al.*<sup>69</sup> or Kirkbride *et al.*<sup>11</sup> for examples). In order to analyse citations that gave information on rates by sex and age, an innovative approach was adopted. We fitted meta-regression models with fractional polynomials to account for possible interaction between age and sex. Trends by age did not necessarily appear linear so we fitted the following model:

$$\text{Incidence rate } (\lambda) \sim \text{study effect} + \text{fractional polynomial for age} + \text{male effect} \\ + \text{post menopausal female effect}$$

We regressed the rate on study effect, age, male effect and post menopausal female effect, where the model for age was the best fitting fractional polynomial.<sup>70</sup> This allows flexible shapes for the effect of age, but still enables us to identify other effects of interest. The necessary fractional polynomial meta-regressions were fitted as described by Thompson and Sharp,<sup>71</sup> and a purpose-built R program was developed for this purpose.<sup>72</sup> Where incidence rate data from different citations were available by age stratum we assumed the midpoint of each stratum was representative of that age group. We specified, *a priori*, the age at which we hypothesised there would be a secondary peak of psychotic disorders in women (45 years) and classified all women above this age as “post-menopausal”. This allowed us to test whether there were statistically significant differences in rates of psychosis for men and women before and after this point. The models accounted for between-study variation using fixed effects.

We considered meta-analyses to inspect pooled rates by different ethnic groups. For the purposes of synthesis we included any citation which provided separate rates of psychosis for different ethnic groups or according to country of birth, which is a proxy for first generation migration. The citation yield revealed several studies which had published rates by

ethnicity/country of birth, using different terminologies<sup>xi</sup> and classifications in relation to ethnicity. In order to assess whether rates were different for various ethnic groups, we restricted our meta-analyses to three broad, commonly reported ethnic minority groups in England (black Caribbean, black African and South Asian) in comparison to the published rates for the white (or white British) population. Rates were meta-analysed using separate univariate random effects meta-analyses. Had more data been available the multivariate extension of the bivariate modelling used for gender could have been more usefully employed, but this was not attempted here. Where there was insufficient data to pool rates for specific ethnic groups, we reported our findings descriptively in the text.

Finally, it is of interest to know if meta-variables (such as time, urbanicity or data quality) can be used to explain some of the heterogeneity in the raw rates analysed using random effects meta-analysis as described above. Meta-regressions were therefore applied using the generalisation of DerSimonian and Laird's procedure which allows for covariate effects.<sup>71</sup> Meta-regression techniques have their limitations,<sup>73</sup> which we acknowledge, but where there was considerable unexplained variation in rates, there are good *a priori* reasons to wish to investigate whether such variation is explained by potentially important confounding factors. We considered two main risk factors as *a priori* covariates to investigate through meta-regression; time and urbanicity. We also used this approach to inspect variation in rates according to the study quality criteria described above (Section 3.4.4)

Only a handful of studies directly provided estimates of rates over time, with many not providing standard errors. Thus the data was not easily amenable to formal meta-analyses. These studies still provided insight so these results were carefully examined and described but no formal statistical analysis was attempted. To overcome this problem, it is possible to instead

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<sup>xi</sup> For example, the social and political acceptability of different terms for ethnic groups has changed over the study period. Thus, reported rates of psychosis in the black Caribbean population in England might have been reported for "Afro-Caribbean" or "African-Caribbean" groups in the literature. We identified all such changes in terminology to allow pooling of results, independent of the terminology used at the time of original publication.

adopt a meta-regression approach. This allows us to use rate information from several cross-sectional studies of the incidence or prevalence of a given psychotic disorder and fit the midpoint of the study period into a meta-regression as a continuous covariate. Using this approach, we could test whether there was any evidence for changing incidence or prevalence rates of psychotic disorder over time. An analogous approach was used to inspect whether there was any evidence that rates of psychotic disorder varied according to urbanicity (using our composite urbanicity ranking variable) or by data quality (see Section 3.4.4).

Given the paucity of information for some subgroup analyses we adopted a judicious approach to the employment of meta-analyses and meta-regressions. We only considered their use when there was sufficient data to permit analysis. We defined this as follows: for **meta-analyses** a minimum of two citations providing independent rate data were required for univariate analyses (i.e. when analysing “overall” rates of a disorder), and a minimum of three citations providing independent rate data were required when we were interested in bivariate analyses (rates of psychosis by gender, age, ethnicity etc). For **meta-regressions**, our approach was more conservative and a minimum of four citations providing independent rate data were required for analyses. Further, results of any meta-analysis or meta-regression were only considered in supplement to the appraisal of citations which sought to directly test for evidence of variation in incidence (and prevalence) rates by time and urbanicity.

#### 3.5.5.1 Implementation of statistical models

Data extraction and database management was handled in Microsoft Excel. Meta-analyses were performed in Stata version 10 using the package *metan* and *mvmeta1* for multivariate random-effects meta-analysis<sup>74</sup> (*mvmeta*; downloadable from <http://www.mrc-bsu.cam.ac.uk/Software/stata.html>. Type net from [http://www.mrc-bsu.cam.ac.uk/IW\\_Stata/](http://www.mrc-bsu.cam.ac.uk/IW_Stata/) and follow links to meta). Meta-regressions were also performed in Stata using the package *metareg*, developed by Harbord and Higgins<sup>75</sup> for random effects meta-regressions (available at <http://ideas.repec.org/c/boc/bocode/s446201.html>). Fractional polynomial meta-regressions were fitted as described by Thompson and Sharp,<sup>71</sup> and a purpose-built R program was developed for this purpose.<sup>72</sup> We used second order fractional polynomials in a similar manner as Rota *et al.*<sup>76</sup> using the predefined set  $P = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ . We, however, modelled the

between-study variability using fixed study effects which facilitated a one stage approach. We assume the same fractional polynomial for all studies when adopting a one-stage approach.

### **3.5.6 Economic analysis methodology [Objective F]**

We will estimate the economic costs of psychosis in England based on the prevalence estimates we report in this review. This work is conducted in collaboration with Professor Paul McCrone at the Centre for the Economics of Mental Health (Institute of Psychiatry). Professor McCrone's group have recently estimated the cost of care for schizophrenia and bipolar disorder in England up until 2026, and this data is available and has been used previously in the *Paying the Price* report commissioned by the King's Fund.<sup>3</sup> Annual prevalence data for both non-affective psychoses and bipolar disorder will be combined with 2009 mid-year population figures (obtained from the Office for National Statistics) to estimate the number of people with these conditions in the UK. It is worth noting that the best economic cost data available to us were for the UK as a whole. Our economic analyses are therefore not restricted to England, but provide cost estimates for the entire UK. Prevalence estimates will be provided from all relevant citations which made available data on schizophrenia and bipolar disorder, stratified by age and gender. The numbers of cases by age and gender will then be combined with per-person service and lost employment costs to provide cost estimates. These costs include primary and secondary care, social care, care from family members, and the costs of lost employment.

### **3.5.7 Data Presentation**

We stratify the presentation of results in this report according to broad [research streams](#). Thus, results of this systematic review for incidence rates in the general population are provided in Chapter 4, corresponding prevalence findings in Chapter 5 and incidence & prevalence findings from specialist populations in Chapter 6. The economic cost implications of our findings to health services and society are evaluated in Chapter 7. For each stream, we then organise the results by each psychotic disorder under study (i.e. [research themes](#), Figure 3.1), reporting the results from relevant [research blocks](#) for each disorder.

Unless otherwise stated, all incidence rates are expressed per 100,000 [person-years](#), and all prevalence rates are expressed as a percentage. Both are presented to one decimal place with [95% confidence intervals](#), where sufficient information was available to estimate a

corresponding **standard error**. **Rate ratios** [RR] and **hazard ratios** [HR] for incidence, and **odds ratios** [OR] for prevalence studies, are presented with **95% confidence intervals** to one, two or three decimal places as appropriate to aid interpretation of the results.

We have largely limited the presentation of results in this report to rates presented in the text and, where appropriate the use of forest plots or graphs. The presentation of raw data from individual studies in tables has been included for some key analyses, but given the volume of data included in this report; we have attempted to retain clarity by limiting the number of tables used. We have not included an overview table of the 147 studies identified in this report, given size limitations. However, this table, along with all raw extracted data, and details of our analyses will be made freely available online at [www.psychiatry.cam.ac.uk/epicentre](http://www.psychiatry.cam.ac.uk/epicentre) upon publication of this report. We hope that this dataset will provide an important repository for the academic and mental health community.

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## **Chapter 4: Summary Results & Incidence Rates in the General Population**

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## **4.0 SUMMARY RESULTS & INCIDENCE IN THE GENERAL POPULATION**

### **4.1 Search Strategy Results**

A flow diagram of the search strategy and citation yields at relevant stages is shown in Figure 4.1. At Stage 1, we identified 8282 initial citations from the published literature and a further 227 citations from the grey literature. After identification and removal of duplicate citations (n=3133 and 59, respectively) and citations without original data (n=55), a total of 5262 unique citations met potential inclusion for the review. The defined inclusion criteria (see Section 3.3.1) were applied to the titles, and where available, abstracts for these citations by two researchers (JBK and TJC), independently. Inter-rater agreement was high (96.6%); the reviewers agreed that 67 citations “met inclusion criteria” and a further 5014 citations “did not meet inclusion criteria” for the review. The reviewers disagreed about the remaining 181 citations, which were considered as having “possibly met inclusion criteria”. Thus, at Stage 2, full text articles were obtained for any citation which “met” or “possibly met” inclusion for the review (n=248), and reviewed by consensus between JBK and TJC. Discrepancies (n=13) were resolved by a third reviewer (PBJ). One hundred and thirty three citations (56.6%) met inclusion criteria for the systematic review following scrutiny of the full text.

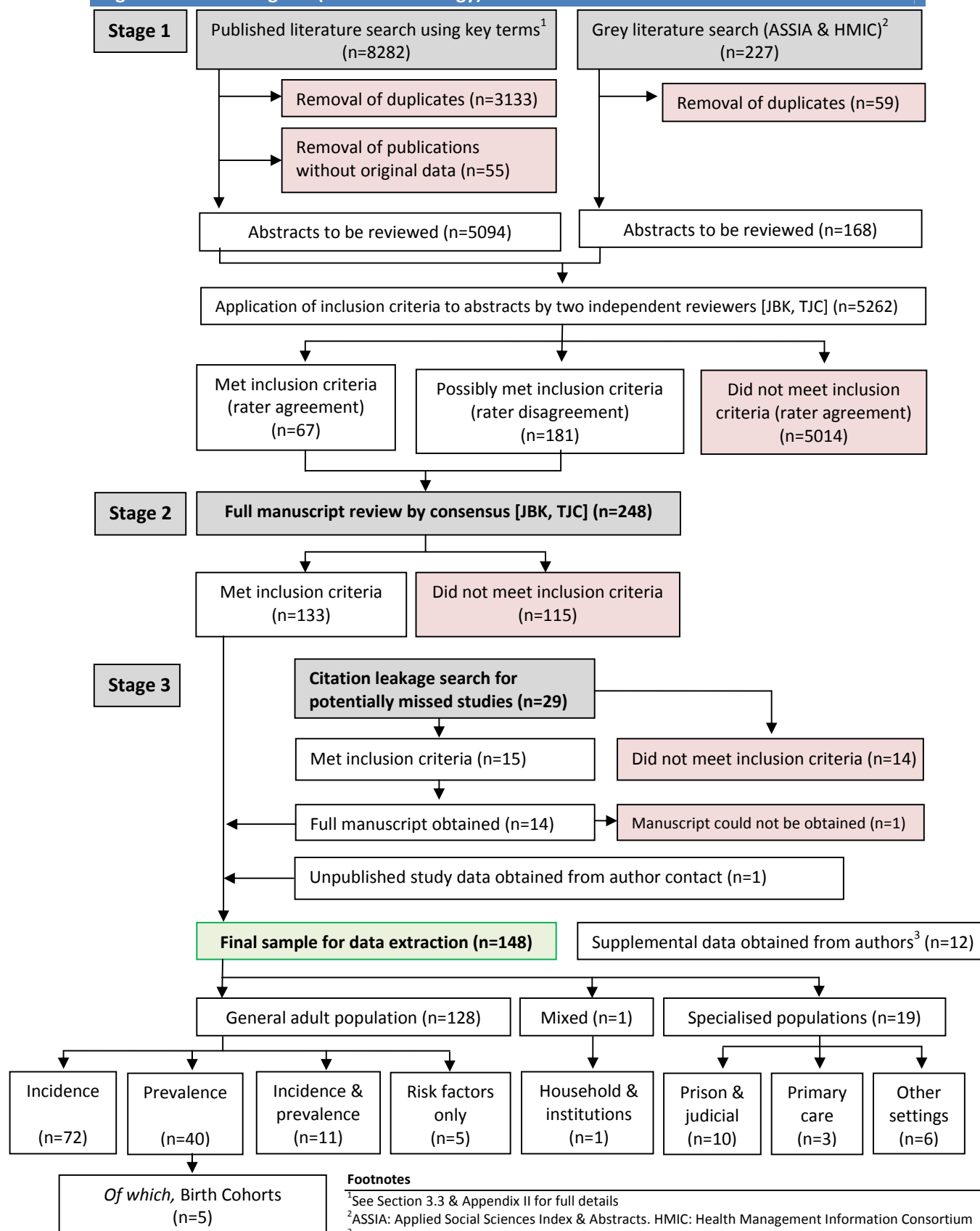
Twenty-nine further studies were identified from our citation and author searches. Of these, 15 (52%) met inclusion for the review, although the full text for one citation<sup>77</sup> could not be obtained following exhaustion of all known sources. One further citation was identified for inclusion in the final sample which consisted of data unpublished at the time of this review identified following contact with the authors.<sup>78</sup> These 15 citations were combined with the 133 previously identified citations to give a final yield of 148 citations from 70 unique studies. Our author contact yielded supplemental data on 12 of these included studies. Full details of all included citations (Appendix V) and studies (Appendix VI) are given in the appendices.

### **4.2 Incidence rates in the general population**

We identified seventy-two citations which provided information about the incidence of psychotic disorders in the general population over the time period under study. From these



**Figure 4.1: Flow diagram (selection strategy) of included studies**



**Footnotes**

<sup>1</sup>See Section 3.3 & Appendix II for full details

<sup>2</sup>ASSIA: Applied Social Sciences Index & Abstracts. HMIC: Health Management Information Consortium

<sup>3</sup>Supplemental data was obtained in instances where the authors stated or alluded to the availability of additional relevant data, not originally published. These data were not entered as separate citations.

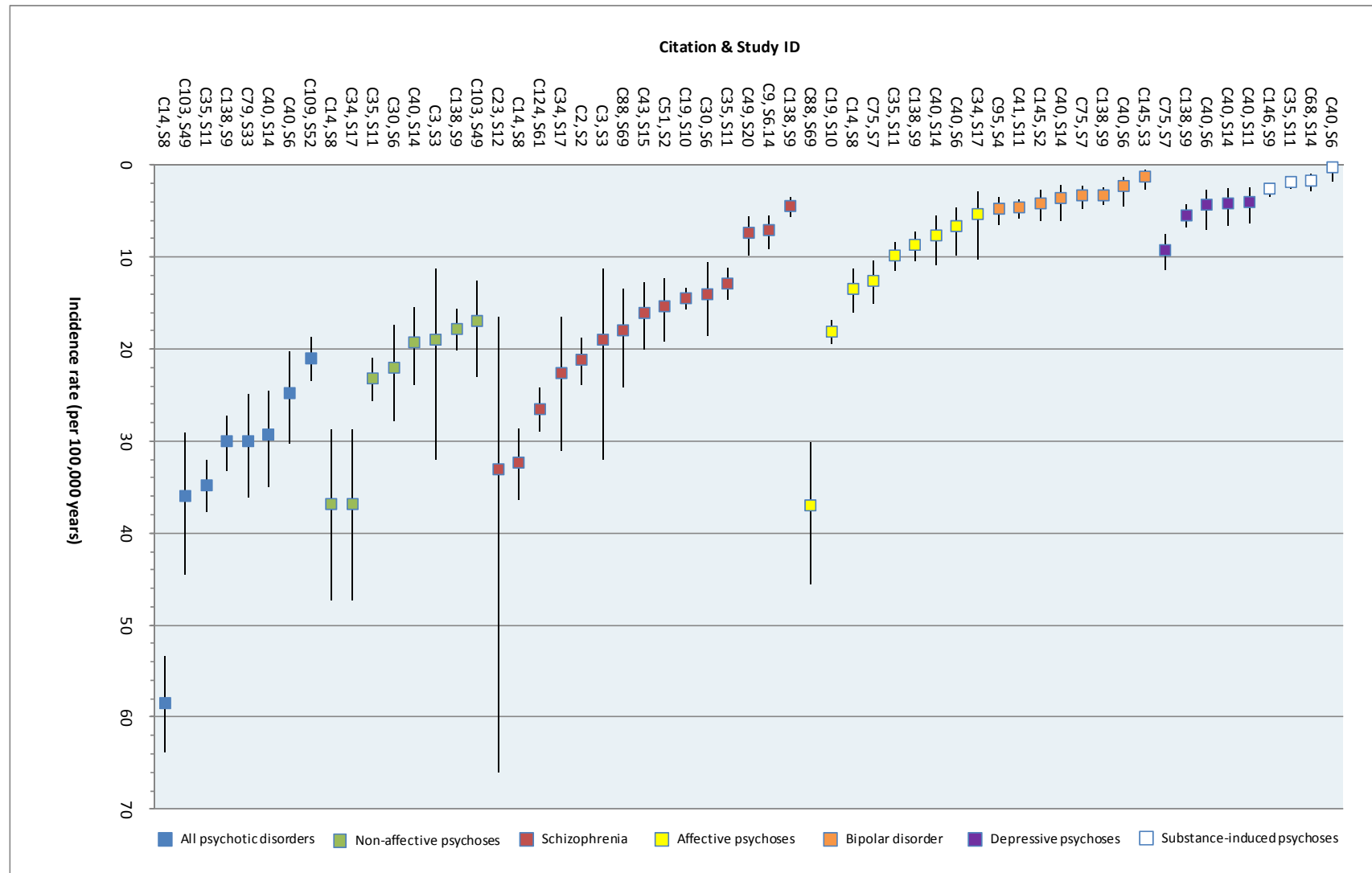
studies, we identified 57 published estimates of the overall incidence of a given psychotic disorder. These rates are broken down by psychotic disorder and presented in Figure 4.2. For each disorder studied there is variation in the estimate incidence rate. This variation might be explained by important characteristics of the sample (age, sex, ethnicity, urbanicity) and these issues will be considered in more detail, below. Overall, however, this figure helps to quantify relative differences in the incidence of different psychotic disorders, a point easily overlooked with the study of specific diagnoses. Largest incidence rates are generally reported from studies of all psychotic disorders, broadly defined, with rate estimates decreasing as the specificity of diagnosis increases. Reported rates are higher for non-affective psychotic disorders than their affective counterparts, consistent with observations from individual studies,<sup>11</sup> and rates of a narrow classification of schizophrenia are higher than corresponding rates of narrow definitions of bipolar disorder, the depressive psychoses and substance-induced disorders. The pattern of these results is generally consistent with what we would expect given the psychiatric literature.<sup>8</sup> We consider the incidence of each of these disorders in more detail, below.

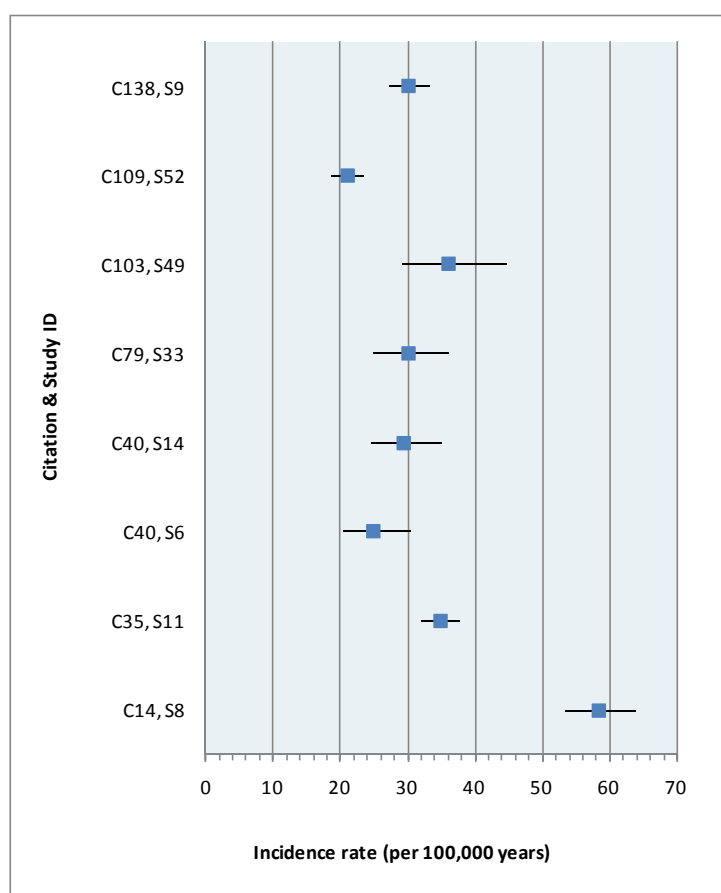
#### **4.2.1 All clinically relevant psychotic disorders**

##### *4.2.1.1 Overall incidence rate of all psychotic disorders*

Fourteen citations provided overall incidence rate data for a broad definition of all psychotic disorders. From these citations, we identified 5 **unique citations** [C14, C79, C103, C109, C130] and a further 3 **core citations** [C35, C40, C138] which provided the rate estimates from nine unique studies (one citation [C40] contained core data from two studies [S6, S14]). An overview of pertinent data from these citations is provided in Table 4.1. The incidence of all clinically relevant psychotic disorders varied from 21 per 100,000 person-years [C109] to 100 per 100,000 person-years [C130]. This latter rate, however, was from an early intervention in psychosis service [EIS] which only included people aged up to 35 years and was excluded from this meta-analysis. Although there was considerable between-study heterogeneity in estimates ( $I^2=0.97$ ), the pooled incidence of broadly defined psychotic disorder was 31.72 per 100,000 person-years (95% CI: 24.63, 40.85) (see Figure 4.3). Interestingly, the four of the five largest incidence estimates published (Table 4.1), were from studies conducted wholly, or partially in London, one of the most urban conurbations in England.

Figure 4.2: Reported overall incidence of various psychotic disorders in England, 1950-2009



**Figure 4.3: Forest plot of incidence rates of all clinically relevant psychotic disorders****Table 4.1: Data summary for overall incidence of all psychoses from identified citations (Section 4.2.1.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Rate per 100,000 <sup>6</sup>	95% CI
<b>C138, S9</b>	Reay	2009	Northumberland	36	2002 (7)	4	<u>411</u>	30.1 <sup>c</sup>	27.2, 33.2
<b>C130, S65</b>	Mahmood	2006	Lambeth (London)	8	2003 (3.2)	3	303	100.0 <sup>c</sup>	NA
<b>C109, S52</b>	Singh	2003	W & SW London	22	2000 (1)	2	295	21.0 <sup>c</sup>	18.7, 23.5
<b>C103, S49</b>	Rowlands	2001	N Derbyshire	31	1999 (1)	2	84	36.0 <sup>c</sup>	29.1, 44.6
<b>C79, S33</b>	Gould	2006	N London	10	2002 (1)	6	111	30.0 <sup>c</sup>	24.9, 36.1
<b>C40, S14</b>	Kirkbride	2009	Nottingham	25	1993 (2)	6	97	29.3 <sup>d</sup>	24.6, 35.0
<b>C40, S6</b>	Kirkbride	2009	Nottingham	25	1979 (2)	6	122	24.8 <sup>d</sup>	20.3, 30.3
<b>C35, S11</b>	Kirkbride	2006	ÆSOP	21	1998 (2)	7	568	34.8 <sup>c</sup>	32.1, 37.8
<b>C14, S8</b>	Coid	2008	E London	1	1998 (2)	7	484	58.4 <sup>d</sup>	53.4, 63.9

<sup>1</sup>Compass abbreviations used (N, S, E, W), ÆSOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban

<sup>3</sup>Mid-year of case ascertainment period, duration in years shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

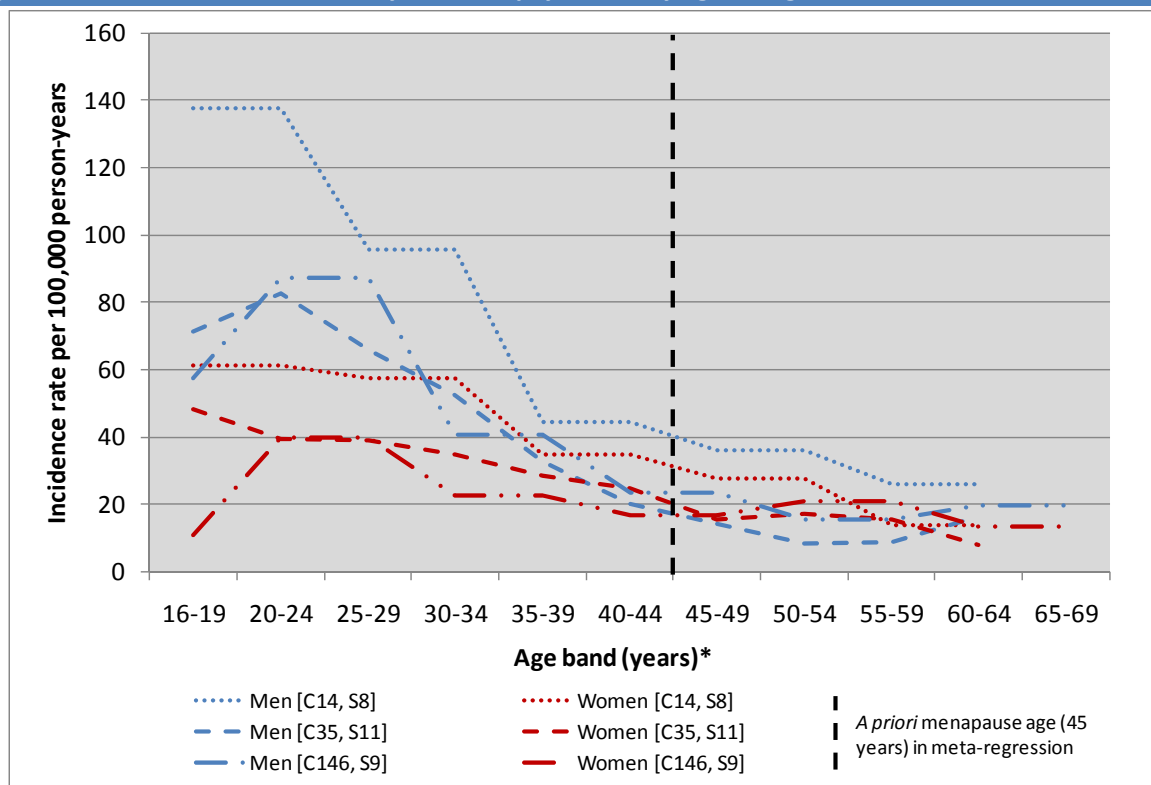
<sup>6</sup>c=crude rate, d=derived crude rate (not reported in citation but derivable from other data)

NA=No further information provided or derivable

#### 4.2.1.2 Incidence of all psychotic disorders by gender and age

Only two citations [C9, C14] provided an estimate of the incidence of all clinically relevant psychoses by gender, from two unique studies [S14, S8, respectively]. In both studies, the crude incidence of psychotic disorder was elevated in men (38% and 67%, respectively) compared with women. Three citations [C14, C35, C146] provided further information on the incidence of all clinically relevant psychotic disorders stratified by age and gender, allowing us to investigate possible interactive effects between these variables in a meta-regression approach using fractional polynomial modelling (see Section 3.5.5). There was evidence of an interaction between age and sex (Figure 4.4), such for those less than 45 years old, the incidence of all clinically relevant psychoses were greater in men compared with women over (**Hazard Ratio** [HR]: 1.67; 95% CI: 1.50, 1.87). However, for those aged over 45 years, there was no evidence that men were at increased risk of psychotic disorders compared with women (HR: 1.12; 95% CI: 0.89, 1.41).

**Figure 4.4: Incidence of all clinically relevant psychoses by age and gender from identified studies**



\*Citations C14 & C146 provided estimates in 10-year age bands and were imputed for each 5-year age band. Only C146 provided an estimate of incidence beyond 64 years old (60-69 years)

#### 4.2.1.3 Incidence of all psychotic disorders by ethnicity

We identified three citations [C21, C29, C38] which had published rates of all psychotic disorders separately by ethnic group. Given the paucity of data, no formal attempt to meta-analyse these results was made. Two of these studies [C21, C38] inspected rates of psychotic disorder across

detailed ethnic groups and in each case observed that incidence rates were elevated for nearly all ethnic minority groups when compared with the white British baseline group. In both studies rates were greatest amongst the black Caribbean and black African populations. The most conservative estimates, from C38, suggested that compared with the white British group, rates were between 3.0 to 5.4 times greater in the black Caribbean population and 2.4 to 4.3 times greater in the black African population. In the *ÆSOP* study [C21], the observed rates for the black Caribbean and black African groups were even more elevated, respectively, between 5.4 to 8.3 and 3.2 to 5.3 times greater than the rates for their white British counterparts. The third citation [C29] we identified which also considered rates of all psychotic disorders by ethnicity was restricted solely to analysis of rates in the black Caribbean population compared with the entire remaining population (i.e. all other ethnic groups). This study also observed elevated rates in the black Caribbean community, placing the estimate between 6.6 and 14.4 times greater than in the background population, consisting of all other ethnic groups.

Citations C21 and C38 also revealed that rates of all psychotic disorders were elevated for other ethnic minority populations in their samples, though to a lesser extent than for the black Caribbean and African groups. Both studies observed that incidence rates were approximately 50% higher in non-British white groups than their British counterparts, while mixed ethnicity populations also had significantly increased rates of psychosis. The *ÆSOP* study [C21] consider all people of mixed ethnicity as a single group and found rates were approximately three times elevated in this group, while the *ELFEP* study [C38] differentiated between mixed white and black Caribbean and all other mixed groups, finding an elevated rate of psychosis (RR: 5.5; 95% CI: 3.0, 9.9) in the former, but not the latter (RR: 0.4; 95% CI: 0.4, 1.1) when compared with the white British population.

Inspection of data from these two studies generally showed that these patterns held for men and women separately. However, in the *ELFEP* study, rates of psychoses in the Pakistani and Bangladeshi groups were raised for women (Pakistani women RR: 4.9; 95% CI: 1.9, 13.0; Bangladeshi women RR: 4.4; 2.2, 8.9), but not men, compared with their white British counterparts. No such differences were observed in the *ÆSOP* study, but the study may not have had sufficient power to detect such differences given the relatively small South Asian population in its catchment areas.

These findings were not explained by differences in the age and sex structures of different ethnic groups in these three studies. Further, the *ELFEP* study (though not the others) was able to adjust for the additional potential confounding effect of socioeconomic status, but this did not alter the

pattern or significance of the results, as described.<sup>20</sup> No studies were identified which had inspected the overall incidence of all psychotic disorders by country of birth or by ethnicity, age and sex. We only identified one study [C21] which published an estimate of the increased risk of all psychoses in ethnic minority groups at different age periods. This data, from the AEsOP study showed that rates were significantly raised for both black Caribbean and black African groups at every age period between 16 and 64 years old, when compared with their white British counterparts.

#### 4.2.1.4 Incidence of all psychotic disorders over time

We identified three citations which had attempted to look directly at incidence rates of all psychotic disorders over time [C9, C40, C147]. C9 and C40 used the same dataset at two time periods (studies S6, S14). We considered C40 to provide the [core](#) citation because it used data from a third, later time period (S11) in the same catchment area. This study found no evidence from three time points over a twenty-year period (1978-80, 1992-94, 1997-99) to suggest the incidence of all clinically relevant psychoses had changed ( $p=0.19$ ).<sup>23</sup> C147 is included here for comparison but is not a true incidence study because it uses data from the General Research Practice Database [GPRD], a database of all contacts with primary care services which are part of the GPRD. Since we know that primary care is only one possible route through which people with first episode psychosis may present to health services it is important to be aware that such a dataset may be unrepresentative of the true incidence rate in the population at-risk. Nevertheless, C147 estimated the annual incidence of first episode psychosis *in primary care* between 1996 and 2005 (see Frisher *et al.*<sup>79</sup>), but did not observe any significant overall change in the incidence of all psychotic disorders.

We also used meta-regression to inspect whether there was any change in the incidence of all psychotic disorders reported over time, using data from seven of the eight cross-sectional studies identified in Section 4.2.1.1 [C14, C35, C40, C79, C103, C109, C138], which provided eight unique estimates of incidence at different time periods (as before, C40 contained data from 2 unique studies), from 1979 to 2003. Data from C130 was not used in this meta-regression because it was not possible to derive a standard error estimate from the information provided by the citation. The meta-regression of the remaining eight rates failed to reveal any change in the incidence of all clinically relevant psychosis over this time period (RR per annum: 1.01; 95% CI: 0.96, 1.06;  $p=0.63$ ).

#### 4.2.1.5 Geographical variation in the incidence of all psychotic disorders

Studies which considered the geographical variation in the incidence of all clinically relevant psychosis in England were few in number and highly heterogeneous in methodological approach. For

this broad diagnostic category, most of the evidence comes from our own work on the ÆSOP study [C35, C36, C44]. Here [C35], we observed that rates of disorder were significantly higher in the most urbanised centre of the study (Southeast London) when compared with either the Nottingham (RR: 1.3; 95% CI: 1.1, 1.7) or Bristol (RR: 1.4; 95% CI: 1.1, 2.0) study centres (C44 provided comparable data). This finding was not confounded by differences in age, sex or ethnicity between the study centres. Further analysis of the within-centre variation in incidence rates between small neighbourhoods in the Southeast London study centre showed that rates of psychosis varied between neighbourhoods independent of differences in their age, sex and ethnic composition [C36]. In a different dataset from Nottingham, Croudace and colleagues [C68] observed that the incidence of broad psychotic disorders increased with more neighbourhood socioeconomic deprivation. This was non-linear such that incidence rates increased exponentially with greater socioeconomic deprivation at the neighbourhood level. One final citation [C69] reported incidence rates of “functional psychoses”, including schizophrenia, bipolar disorder and endogenous depression, in two towns in southern England, Chichester and Salisbury. Incidence rates were high in both settings (Chichester: 293 per 100,000 person-years; Salisbury: 215 per 100,000 person-years), but of interest here is the relative difference between rates, which we calculated to be non-significant (RR Chichester vs. Salisbury: 1.14; 95% CI: 0.95, 1.38).

To further inspect whether urbanicity was associated with the incidence of all clinically relevant psychotic disorders we fitted a meta-regression to the eight incidence rates we identified from relevant citations in Section 4.2.1.1 (and as described in Section 4.2.1.4), using the composite urbanicity ranking for each study setting we had derived (see Section 3.4.4). Overall, we did not find a statistically significant increase in the incidence of all clinically relevant psychotic disorders in more urban environments, though point estimates were in the direction we would expect (Per rank increase in urbanicity: RR: 1.02; 95% CI: 0.99, 1.04;  $p=0.17$ ). Furthermore, four of the five largest estimates of incidence of clinically relevant psychoses (Table 4.1) came from studies wholly [C14, C79, C109, C130] or partially [C35] conducted in London, England’s most urban conurbation.

#### *4.2.1.6 Incidence of all psychotic disorders by study quality*

We fitted a meta-regression on the eight overall incidence rates of all clinically relevant psychoses identified in Section 4.2.1.1. Data quality scores (see Section 3.4.4) varied from 2 to 7 (out of 7), but there was no suggestion from meta-regression that the incidence of all psychotic disorders changed with greater methodological quality studies (RR: 1.07; 95% CI: 0.94, 1.22).



## 4.2.2 Non-affective psychoses

### 4.2.2.1 Overall incidence rate of non-affective psychoses

Eight citations provided relevant rate data on the overall incidence of non-affective psychoses in England [C3, C14, C30, C34, C35, C40, C103, C138] (see Table 4.2). There was variation in incidence rates, from 17 [C103] to 37 per 100,000 [C34] (Figure 4.5), confirmed by meta-analysis ( $I^2=0.935$ ). The pooled estimate for these rates from the meta-analysis was 23.2 per 100,000 person-years (95% CI: 18.3, 29.5). As for all clinically relevant psychoses, the three largest estimates of incidence were from studies conducted in London (see also Section 4.2.2.5).

**Table 4.2: Data summary for overall incidence of non-affective psychoses from identified citations (Section 4.2.2.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Rate per 100,000 <sup>6</sup>	95% CI
<b>C138, S9</b>	Reay	2009	Northumberland	36	2002 (7)	4	<u>243</u>	17.8 <sup>c</sup>	15.7, 20.2
<b>C103, S49</b>	Rowlands	2001	N Derbyshire	31	1999 (1)	2	42	17.0 <sup>c</sup>	12.6, 23.0
<b>C40, S14</b>	Kirkbride	2009	Nottingham	25	1993 (2)	6	80	19.2 <sup>d</sup>	15.4, 23.9
<b>C35, S11</b>	Kirkbride	2006	ÆSOP	21	1998 (2)	7	378	23.2 <sup>c</sup>	21.0, 25.7
<b>C34, S17</b>	King	1994	E London	4	1992 (1)	7	62	36.9 <sup>d</sup>	28.8, 47.3
<b>C30, S6</b>	Jablensky	1992	Nottingham	25	1979 (2)	6	57	22.0 <sup>c</sup>	17.3, 27.9
<b>C14, S8</b>	Coid	2008	E London	1	1998 (2)	7	362	36.8 <sup>a</sup>	33.2, 40.8
<b>C3, S3</b>	Bamrah	1991	Salford	23	1984 (1)	7	14	19.0 <sup>c</sup>	11.3, 32.1

<sup>1</sup>Compass abbreviations used (N, S, E, W), ÆSOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban

<sup>3</sup>Mid-year of case ascertainment period, duration in years shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

<sup>6</sup>c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

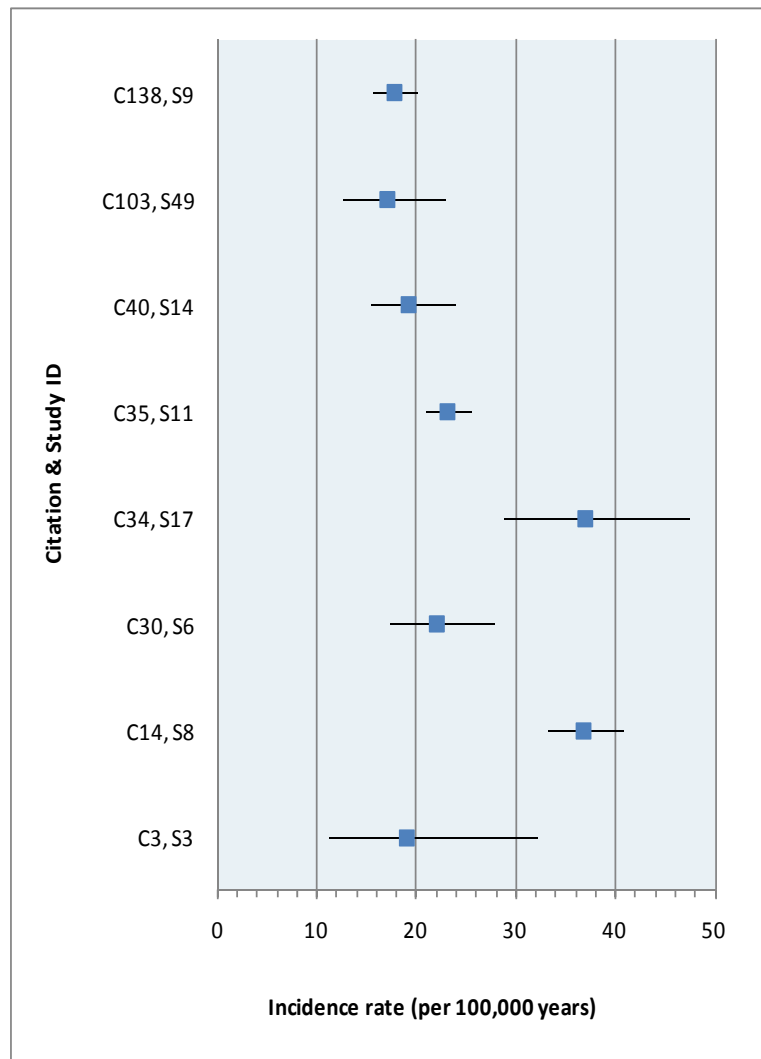
### 4.2.2.2 Incidence of non-affective psychoses by gender and age

Five citations [C9, C15, C19, C37, C102] provided incidence rates of non-affective psychoses broken down by men and women separately. When we entered rate estimates into a multivariate meta-analysis, we observed extremely high between-study correlation of estimates for men and women ( $r=1$ ), suggesting that studies which reported higher estimates for men, also reported higher rates for women. One interpretation of such high correlation is that the factors driving higher rates in those studies are similar for both men and women. The pooled incidence rate ( $\lambda$ ) of non-affective psychosis for men ( $\lambda=21.6$ ; 95% CI: 18.0, 25.9) was significantly greater than for women ( $\lambda=15.3$ ; 95% CI: 11.0, 21.1). There was less evidence of heterogeneity of rates between studies ( $I^2=0.73$ ). Six citations [C9, C14<sup>xii</sup>, C15, C35, C74, C146] provided incidence data stratified by age and sex.

<sup>xii</sup> Supplemental original data made available by authors, not part of publication but was part of the study

Fractional polynomial meta-regression suggested there was a significant interaction between age and sex, such that the incidence of non-affective disorder was higher in men under 45 years of age than their female counterparts (HR: 1.87; 95% CI: 1.67, 2.12), but not in men of older ages (HR: 1.12; 95% CI: 0.83, 1.52) (see Figure 4.6).

**Figure 4.5: Forest plot of incidence of non-affective psychoses**

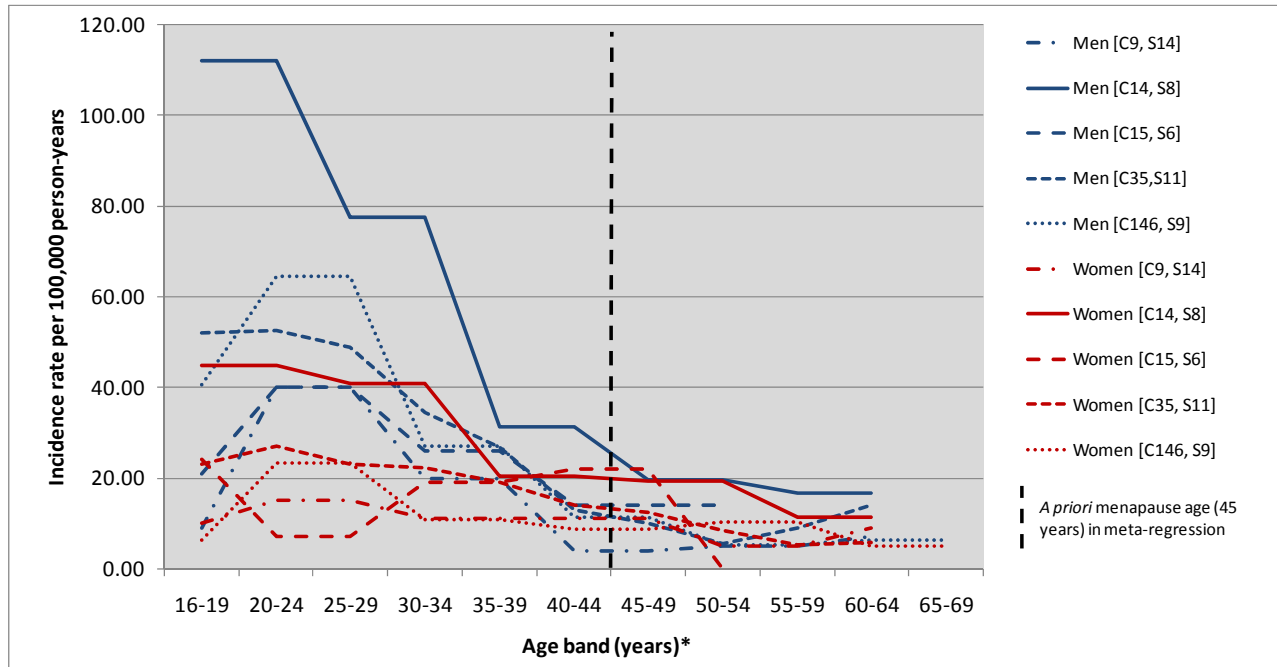


#### 4.2.2.3 Incidence of non-affective psychoses by ethnicity and country of birth

We identified eight citations which reported incidence rates of non-affective psychoses for different ethnic groups, of which four provided **unique/core** data from individual studies [C5, C14, C21, C34]. Inspection of individual results showed that most ethnic minority groups were at elevated risk of non-affective psychosis than their white or white British counterparts. Two studies [C5, C34] used a

broad “white” ethnic group as their baseline group and both reported significantly elevated rates of non-affective psychosis in the black Caribbean group, with rate ratios varying from 1.7 (95% CI: 1.1,

**Figure 4.6: Incidence of non-affective psychoses by age and gender from identified studies**



**Figure Legend:** All identified rates of non-affective psychoses identified by age and sex. Although difficult to interpret individual studies, the patterns of results show that prior to 45 years old, rates of non-affective psychosis tend to be higher in men than women. Until this age, rates decline for men and women, thereafter rates for women stabilise and become greater than the corresponding rates for older men.

\*Some citations provided estimates in 10-year age bands and were imputed for each 5-year age band. Only C146 provided an

2.8) [C5] to 4.3 (95% CI: 3.1, 6.0) [C34]. The two remaining studies [C14, C21] used the “white British” group as the baseline, reporting rate ratios in the black Caribbean group of 4.2 (95% CI: 3.0, 5.8) [C34] and 5.9 (95% CI: 3.9, 8.9) [C34], respectively. All three studies [C14, C21, C34] which estimated incidence rates of non-affective psychoses in black African groups found similarly elevated rates when compared with the white denominator, however defined. All four studies estimated incidence rates of non-affective psychosis in the South Asian group, with two observing statistically significant increased risk in this group [C14, C34] (both East London), and two which found no elevated risk of psychosis in this group [C5, C21]. There were sufficient data to permit random effects meta-analyses, taking the white/white British group as the baseline group for the analysis. The pooled effect size for the black Caribbean group was 4.0 (95% CI: 2.5, 6.3), though considerable heterogeneity was observed within the sample ( $I^2=0.78$ ). Pooled rates were also significantly elevated in the black African (RR: 3.5; 95% CI: 2.7, 4.7;  $I^2=0.00$ ) population, with some weak evidence of raised rates in the South Asian population group (RR: 1.6; 95% CI: 1.0, 2.5;  $I^2=0.64$ ).

We identified two citations which estimated overall rates of non-affective psychoses according to country of birth [C85, C139]. The first study [C85] observed higher rates of psychoses in non-UK-born groups in Bradford compared with the UK born population (estimated RR: 4.6; 95% CI: 2.9, 7.3). The second study [C139], set in London, also found significantly higher rates in non-UK-born groups, specifically, for black Caribbean (estimated RR: 7.7; 95% CI: 4.8, 12.1) and black African (estimated RR: 4.5; 95% CI: 2.5, 8.4) populations in the study region.

Two citations had published incidence rates of non-affective psychoses in different ethnic groups by age and sex [C5, C99], with a further citation [C21] presenting rate ratios for the increased risk in ethnic minority populations in different age groups. Rates of non-affective psychoses were significantly elevated for men and women of black Caribbean in one study [C21, C99] and black African [C21] origin at every age group inspected, with these increased rates just beyond statistical significance in the remaining study [C5]. One study found elevated rates in older Asian migrant women (aged 30-64 years) compared with their white (English) counterparts (RR: 2.7; 95% CI: 1.0, 7.1) [C5].

#### *4.2.2.4 Incidence of non-affective psychoses over time*

We identified seven citations which provided incidence rates of non-affective psychoses over time, of which four contained **unique/core** data [C10, C19, C40, C72, C147], and two which provided **satellite** data [C9, C11]. The data were highly heterogeneous and no attempt to pool the findings was made. C10 estimated the incidence of non-affective psychoses in Camberwell (London) over a 20 year time period, by estimating the incidence in successive 5-year periods from 1965-1984.<sup>24</sup> The authors used a case register which records all first episode psychosis cases to make contact with mental health services in a defined catchment area. The authors found some weak evidence that incidence rates rose over this period (varying from  $p=0.06$  under an ICD-9 classification to  $p=0.10$  under a DSM-III classification), but demonstrated that this was largely due to an increase in the proportion of people of black Caribbean ethnicity moving into the area during this time (i.e. the findings were confounded by ethnicity). Using a population-based case finding approach, C40 observed that the incidence of non-affective psychoses in Nottingham at three time points over a twenty year period (1979 -1999) had remained constant (RR: 1.00; 95% CI: 0.98, 1.02;  $p=0.96$ ). One study of first admission rates [C72] using the Health Survey for England data noted a decline in rates of non-affective psychoses for both men and women separately from around 1970. These rates declined rapidly in men (from 16 to 9 new case per 100,000 person-years, between 1970 and 1978), and more steadily in women (15 to 8 per 100,000 person-years between 1970 and 1978). A further

study [C19] in Oxfordshire over the same period reported a similar decline in rates. Given changes in the structure of mental health care over this time period it is possible that this rapid decline in first admissions did not correspond to a true decline in the incidence of non-affective psychosis during this time, as suggested by studies C10 and C40. Finally, C147 used general practice data (subject to the same caveats as described in Section 4.2.1.6) to examine change in the incidence of non-affective psychoses between 1996 and 2005 in *primary care*. The authors found no evidence to suggest rates had significantly changed in primary care during this time period.<sup>79</sup>

We also fitted a meta-regression using time as a covariate to the nine identified citations which estimated the overall incidence of non-affective psychoses in England between 1984 and 2002. There was no evidence that these rates varied over time (RR per annum: 1.00; 95% CI: 0.96, 1.53). We performed a second, multivariate meta-regression on citations which provided the incidence of non-affective psychoses by gender [C9, C15, C19, C37, C102], but found no evidence of an effect of time from these studies for men ( $p=0.50$ ) or women ( $p=0.99$ ).

#### 4.2.2.5 *Geographical variation in the incidence of non-affective psychoses*

Three citations [C24, C35, C36] had investigated the incidence of non-affective psychoses according to some metric of geographical variation. In general, the methodologies and findings from these studies were too heterogeneous to permit pooling of results. Instead, we summarise the main findings here. The earliest study [C24] inspected the distribution of the incidence of non-affective psychoses in Nottingham between 1975 and 1980. They observed that the incidence of non-affective psychoses were highest in neighbourhoods which were typically more socioeconomically deprived; concentrated in both inner-city and suburban (council-owned estate) areas. The remaining two citations [C35, C36] were conducted by one of the authors of the present report and examined spatial variation in the incidence of non-affective psychoses using data from the ÆSOP study. One citation observed significantly higher rates of non-affective psychoses in Southeast London compared with Nottingham (RR: 2.7; 95% CI: 2.2, 3.4) or Bristol (RR: 1.9; 95% CI: 2.7, 3.8), not explained by differences in age or sex. Further unpublished data (obtained from the ÆSOP and ELFEP studies) has shown that rates of DSM-IV non-affective psychoses remain significantly lower in Nottingham (RR: 0.54; 95% CI: 0.39, 0.73) and Bristol (RR: 0.59; 95% CI: 0.39, 0.90) than Southeast and East London, after adjustment for age, sex, their interaction, individual-level socioeconomic status and ethnicity. The remaining citation [C36] relevant to this analysis examined variation between smaller neighbourhoods within the Southeast London centre of the ÆSOP study. The study

demonstrated that rates of non-affective psychoses varied significantly between neighbourhoods in Southeast London, after adjustment for age, sex and ethnicity.

To further explore the possible effect of urbanicity, we employed a meta-regression analysis to consider whether the overall incidence of non-affective psychoses, as identified by citations in Section 4.2.2.1 [C3, C14, C30, C34, C35, C40, C103, C138], showed any association with our composite urbanicity ranking. Here, we found some evidence that rates of non-affective psychoses were higher in studies conducted in settings which were rated as more urban (RR per 1 rank increase in urbanicity: 1.022; 95% CI: 1.017, 1.028). This translates to an approximately 2% increase in rates per rank increase in urbanicity. We then inspected whether this finding was apparent for men or women separately by performing a second meta-regression on incidence data stratified by gender [C9, C15, C19, C37, C102], but we found no evidence of an effect of urbanicity for men ( $p=0.68$ ) or women ( $p=0.63$ ).

#### 4.2.2.6 Incidence of non-affective psychoses by study quality

We conducted a meta-regression on the eight studies providing an estimate of overall incidence of non-affective psychoses [C3, C14, C30, C34, C35, C40, C103, C138] to consider whether study quality influenced the observed incidence of disorder. Quality scores ranged from 2 to 7 (mean = 5.8). No association between study quality and incidence rates was observed (RR per point increase in quality: 1.12; 95% CI: 0.97, 1.30;  $p=0.09$ ).

### 4.2.3 Schizophrenia

#### 4.2.3.1 Overall incidence rate of schizophrenia

Twenty-three citations provided data on the incidence of schizophrenia, of which we identified 15 **unique/core** estimates of incidence rates [C2, C9, C14, C19, C23, C30, C34, C35, C43, C49, C51, C88, C124, C138] (see Table 4.3). There was considerable between-study heterogeneity ( $I^2=0.97$ ) in crude incidence rates, which ranged from 4.4 per 100,000 person-years [C138] to 33 per 100,000 person-years [C23] (see Figure 4.7). The pooled estimate for the incidence of schizophrenia was 15.2 per 100,000 person-years (95% CI: 11.9, 19.5).

#### 4.2.3.1 Incidence of schizophrenia by gender and age

Seven citations [C9, C15, C26, C37, C102, C119, C145] provided estimates of incidence rates for men and women separately. One citation [C119] was excluded from the meta-analysis because it was not possible to obtain corresponding estimates of standard error for the published rates, but one

**Table 4.3: Data summary for overall incidence of schizophrenia from identified citations (Section 4.2.3.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Rate per 100,000 <sup>6</sup>	95% CI
<b>C138, S9</b>	Reay	2009	Northumberland	36	2002 (7)	4	<u>60</u>	4.4 <sup>c</sup>	3.4, 5.7
<b>C124, S61</b>	Giggs	1973	Nottingham	25	1965 (7)	2	478	26.5 <sup>d</sup>	24.2, 29.0
<b>C88, S69</b>	Jones	1991	Nottingham	25	1982 (1)	2	44	18.0 <sup>c</sup>	13.4, 24.2
<b>C51, S2</b>	van Os	1996	Camberwell	5	1990 (5)	4	79	15.3 <sup>c</sup>	12.3, 19.1
<b>C49, S20</b>	Shepherd	1989	Aylesbury	32	1977 (1.5)	2	49	7.4 <sup>c</sup>	5.6, 9.8
<b>C43, S15</b>	McNaught	1997	Hampstead	25	1991 (~1)	5	35	16.0 <sup>c</sup>	12.8, 20.0
<b>C35, S11</b>	Kirkbride	2006	ÆSOP	21	1998 (2)	7	209	12.0 <sup>c</sup>	11.2, 14.7
<b>C34, S17</b>	King	1994	E London	4	1992 (1)	7	38	22.6 <sup>d</sup>	16.5, 31.1
<b>C30, S6</b>	Jablensky	1992	Nottingham	25	1979 (2)	6	48	14.0 <sup>c</sup>	10.6, 18.6
<b>C23, S12</b>	Gater	1995	S Manchester	15	1990 (1)	3	<u>68</u>	33.0 <sup>a</sup>	16.5, 66.0
<b>C19, S10</b>	de Alarcon	1993	Oxfordshire	35	1981 (12)	2	593	14.4 <sup>c</sup>	13.3, 15.6
<b>C14, S8</b>	Coid	2008	E London	1	1998 (2)	7	268	32.4 <sup>d</sup>	28.7, 36.5
<b>C9, S6.14</b>	Brewin	1997	Nottingham	25	1993 (2)	7	57	7.0 <sup>c</sup>	5.4, 9.1
<b>C3, S3</b>	Bamrah	1991	Salford	23	1984 (1)	7	14	19.0 <sup>c</sup>	11.3, 32.1
<b>C2, S2</b>	Allardyce	2001	Camberwell	5	1988 (12)	7	265	21.2 <sup>d</sup>	18.8, 23.9

<sup>1</sup>Compass abbreviations used (N, S, E, W), ÆSOP: SE London, Nottingham, Bristol

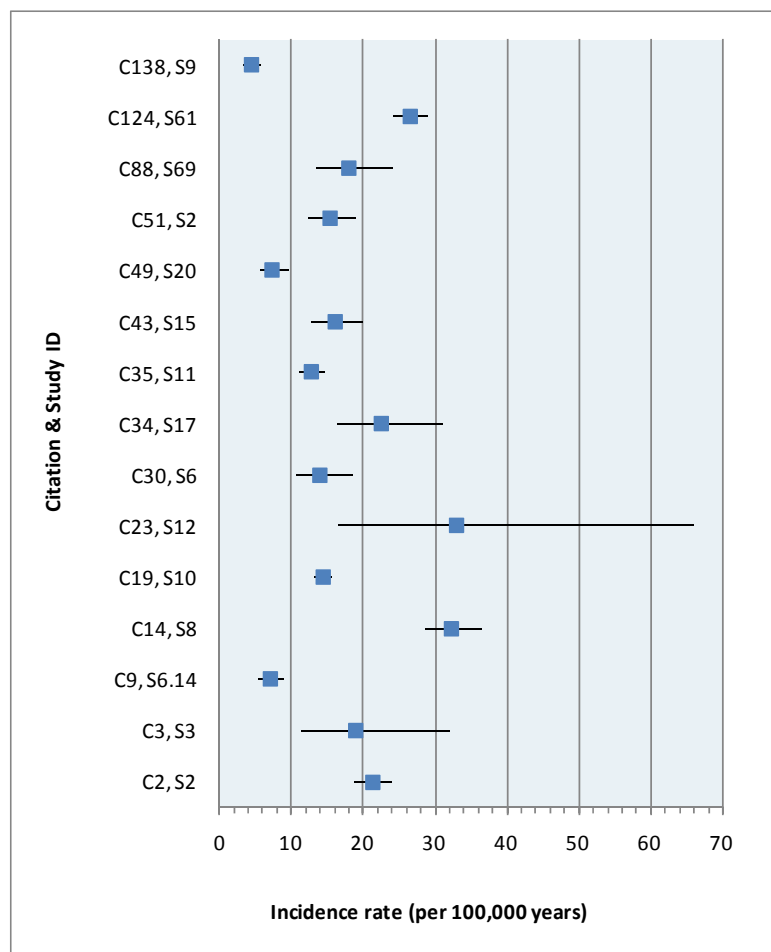
<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section3.4.4). 1=most urban, 6=least urban

<sup>3</sup>Mid-year of case ascertainment period, duration in years shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

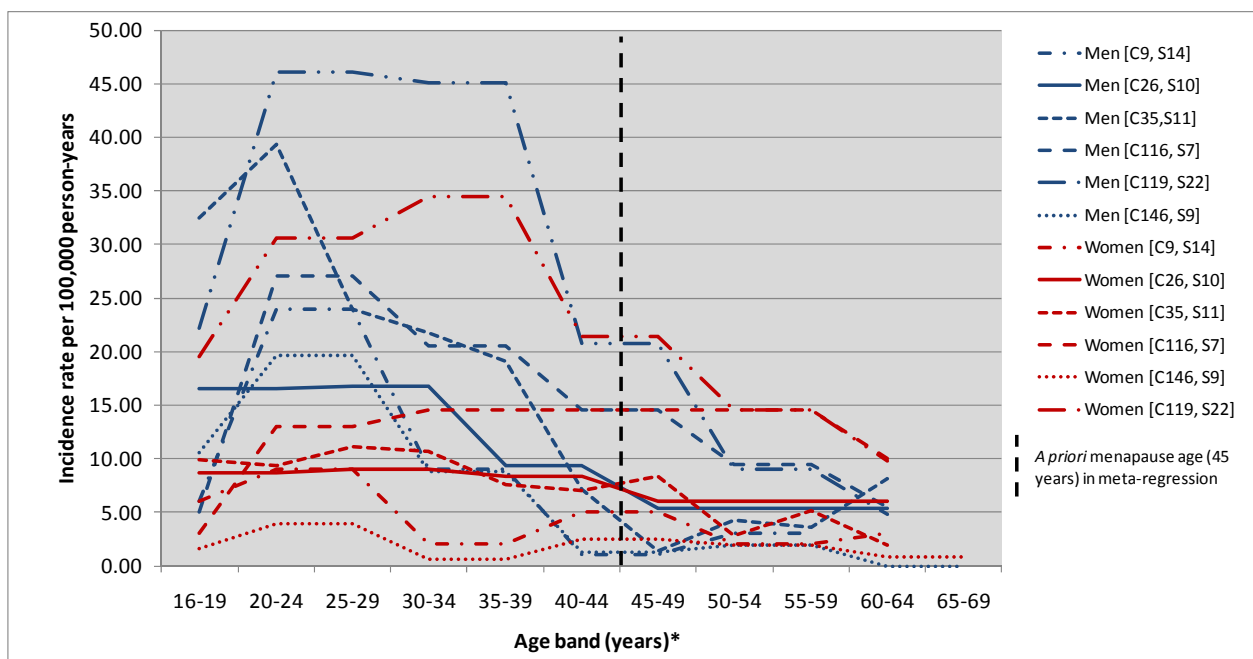
<sup>6</sup>c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

**Figure 4.7: Forest plot of incidence of schizophrenia**

citation [C145] provided rate estimates from two studies [S2, S3], meaning a total of seven estimates of incidence for men and seven estimates of incidence for women were included in the meta-analysis. Random effects multivariate meta-analysis suggested that the pooled incidence rate for men ( $\lambda=13.3$ ; 95% CI: 10.1, 17.6) was greater than for women overall ( $\lambda=9.0$ ; 95% CI: 6.3, 12.9).

Between-study correlation was high (0.89), suggesting that studies which reported higher incidence rates for men, also reported higher incidence rates for women. Between-study heterogeneity was, however, also high ( $I^2=0.90$ ), suggesting that estimates of the incidence of schizophrenia for men and women varied considerably across studies. Six citations [C9, C26, C35, C116, C119, C146] provided incidence data for schizophrenia stratified by age and sex. Fractional polynomial meta-regression revealed a strong, significant association between age and sex, such that the incidence of schizophrenia was elevated for men under 45 years of age compared with their female counterparts (HR: 1.99; 95% CI: 1.70, 2.33), but incidence rates were similar at older ages (HR: 0.98; 95% CI: 0.70, 1.36) (Figure 4.8).

**Figure 4.8: Incidence of schizophrenia by age and gender from identified studies**



**Figure Legend:** The graph shows all rates of schizophrenia identified by age and sex. Although difficult to interpret individual studies, the patterns of results show that prior to 45 years old, rates of schizophrenia tend to be higher in men than women. Until this age, rates tend to decline for both men and women. Around 45 years old, however, rates for women appear to stabilise and become greater than corresponding rates for older men. \*Citations providing estimates in 10-year bands were imputed for each 5-year band. C146 estimated incidence beyond 64 years (60-69 years).



#### 4.2.3.2 Incidence of schizophrenia by ethnicity and country of birth

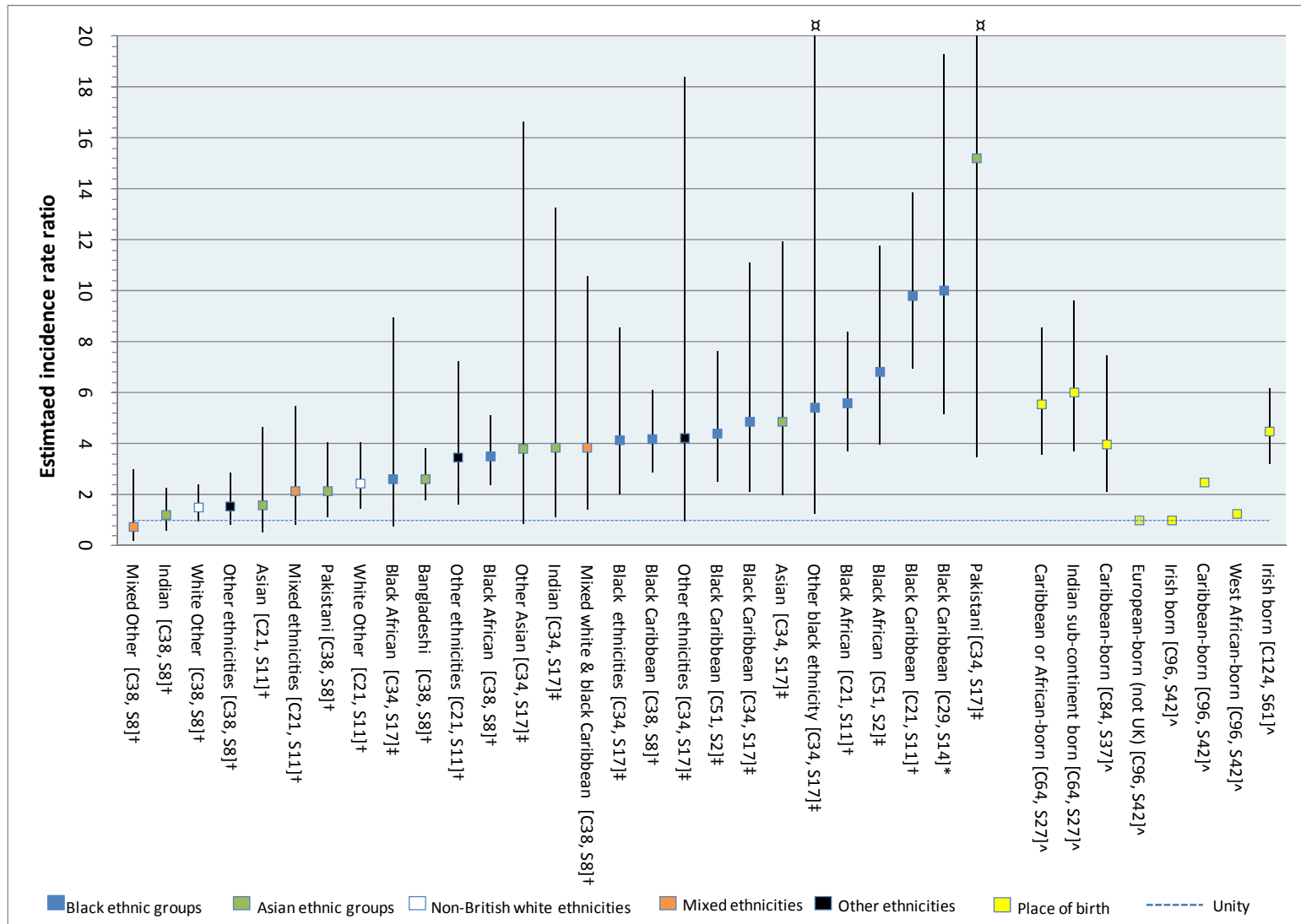
We identified 16 citations which reported the incidence of schizophrenia by ethnic group or country of birth, of which ten provided **unique** or **core** data to facilitate random effects meta-analysis [C21, C27, C29, C34, C38, C51, C64, C84, C96, C124]. In each study, we estimated incidence rate ratios using the extracted incidence data for each ethnic minority group in comparison with the white or white British baseline (see Figure 4.9). Five of the ten citations presented rates for specific ethnic groups, one presented rates for the black Caribbean group only, but no comparison group (data not shown in Figure 4.9), and a further four citations [C64, C84, C96, C124] provided incidence rates according to country of birth. One of these citations [C96] provided an incidence rate, but no further data in order to derive an estimate of standard error. As for the non-affective psychoses, inspection of the graph suggested that incidence rates were most elevated in black Caribbean and black African populations in England. Rates were also raised for some other ethnic groups, such as the non-British white group or some mixed and Asian populations, but effect sizes were generally lower and the size of these differences did not always reach statistical significance.

To further investigate differences in the incidence of schizophrenia by ethnicity we performed random effects meta-analyses on data from the five studies which presented rates of psychosis by ethnic group. Overall, rates of schizophrenia were 5.6 times greater in black Caribbean groups than the white or white British population (95% CI: 3.4, 9.2), with some evidence of heterogeneity in estimates between individual studies ( $I^2=0.77$ ). We also found evidence that rates of schizophrenia were raised in both the black African (RR: 4.7; 95% CI: 3.3, 6.8;  $I^2=0.47$ ) and Asian groups (RR: 2.4; 95% CI: 1.3, 4.5;  $I^2=0.42$ ) with less evidence of heterogeneity between estimates.

#### 4.2.3.1 Incidence of schizophrenia over time

We identified 10 citations [C2, C6, C9, C10, C11, C19, C28, C40, C45, C137] which had attempted to examine changing incidence rates in schizophrenia over time. A summary of these citations, their relevant details, main findings and the authors' primary explanation of these result(s) is provided in Box 4.1. Four citations [C2, C6, C10, C11] reported an increase in the incidence of schizophrenia between 1965 and 1997 in Camberwell, London, after adjustment for age and sex. Between 1965 and 1984 [C10, C11] there was a trend towards an increased rates ( $p=0.06$ ). When data was included up until 1997 [C6], this increase became strongly significant with a suggestion that rates had doubled during this time period. All citations directly [C6, C10, C11] or indirectly [C2] proposed that underlying increases in the proportion of ethnic minority groups in the population at-risk, known to be at increased risk of schizophrenia (see, for example, Section 4.2.3.3) was likely to have accounted

Figure 4.9: Estimated incidence rate ratios of schizophrenia for different ethnic groups compared with the white or white British baseline



†white British baseline; ‡ white baseline; \*Non-black Caribbean baseline; ^UK-born baseline ([C96, S24] did not provide data to enable estimation of confidence intervals) ∞Upper confidence limit truncated on graph for clarity. Actual values were 23.6 for the “other black ethnicities” category [C34, S17] and 66.5 for the “Pakistani” category [C34, S17]

for these changes in incidence. Indeed, no other study (Box 4.1) outside of the Camberwell region, reported a significant increase in the incidence of schizophrenia.

Prince and Phelan [C137] presented data on first admissions in England over the period 1970-85 which suggested a decline in rates of schizophrenia admitted to psychiatric settings in England. In response to Der *et al.*'s [C72] publication<sup>xiii</sup> which raised the possibility that this decline was genuine, Prince and Phelan suggested that the decline in admission rates of schizophrenia should be placed in the context of admission rates for other psychiatric diagnoses, which had also fallen over this period. They suggested that changes to the structural organisation of health service provision, from inpatient to outpatient care, as well as possible shifts in the attitude of the general public as to the treatment of people with mental illness could explain such declines. Two citations [C9, C40], using data collected from three methodologically-similar samples obtained during 1978-80, 1992-4 [C9, C40] and 1997-9 [C40] in Nottingham, reported declines in incidence over time. Both studies reported a corresponding increase in the incidence of other non-affective psychotic disorders over the same time periods, but the primary interpretation of these changes differed between studies. The former study [C9] suggested this reflected a genuine change in the syndromal presentation of psychotic disorders, while the authors of the latter study [C40] attributed this change to shifts in diagnostic fashion over time. This explanation was also proposed by the authors of a third study [C28], conducted in Oxfordshire between 1975-86, which observed a similar decline in the incidence of schizophrenia paralleled by a small increase in other non-affective disorders.

Finally, two citations [C28, C45] using further data from Nottingham found no evidence of a change in the incidence of schizophrenia over time; one study assessing the change in rates over three time periods 114 years apart. Intriguingly the authors of both studies questioned their findings in relation to the importance of understanding possible changes in the denominator population in terms of ethnicity. The authors of the 114-year study [C45] suggested that given the increase in black and minority ethnic populations in their study population between 1881 and 1994 it was curious that no corresponding increase in incidence rates had been observed.

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<sup>xiii</sup> Under our classification of diagnostic outcomes, C72 reported rates for non-affective psychoses (broad schizophrenia), and changes over time reported therein are provided in [Section 4.2.2.4](#)

Box 4.1: Citations addressing incidence of schizophrenia over time in England, by study						
Study	Citation	Time period(s)	Setting	Contact type	Findings <sup>^</sup>	Author explanations
S2	C2 <sup>†</sup>	1979-84; 1992-7	Dumfries & Galloway; Camberwell, London	Case register & first contact	Increased rate in Camberwell over time, adjusted for age & sex (+)	Increase in ethnic minority population in Camberwell over time period. Rate in white group in 1992 was comparable between rural & urban settings
S2	C6	1965-97	Camberwell, London	As above	As above (+)	Increase in ethnic minority population in Camberwell over time period.
S2	C10, C11 <sup>*</sup>	1965-84	Camberwell, London	Case register	Trend towards increased rates (p=0.06) (+)	As above
S6	C28	1975-87	Nottingham	Case register	No change in rate (~)	Changes elsewhere might be explained by migration
S6.11.14	C40	1978-80; 1992-4; 1997-9	Nottingham	Case register + first onset	Decline in rate (-)	Diagnostic changes over time. Decline matched by corresponding increase in other non-affective psychoses. Overall, stable rates of non-affective psychosis
S6.14	C9	1978-80; 1992-4	Nottingham	Case register	Decline in rate (-)	Genuine change in the syndromal presentation of disorder
S6.11	C45 <sup>*</sup>	1881-1902; 1978-80; 1992-4	Nottingham	Case register + re-diagnosis of historical records	No change over 114 years (~)	Stability of aetiologically-relevant social factors over time, though not across sociodemographic groups, may explain constant rate
S10	C19	1975-86	Oxfordshire	First contact	Decline in rate (-)	Diagnostic changes over time, partially evidenced by increases in diagnosis of other "paranoid states" (i.e. other non-affective disorders)
S68	C137	1970-85	England	First admissions	Decline in rate (-)	Change of organisation of healthcare from inpatient to outpatient and possible population attitude shift in treatment of mentally ill may explain decline. Decline of schizophrenia set against parallel declines over same period for many types of mental illness. Argues against "true" decline (see C72)

<sup>†</sup>Results from Dumfries & Galloway (Scotland) not officially part of present review but included as part of study

<sup>\*</sup>C10 and C11 report the same data as a peer-reviewed publication & monograph, respectively

<sup>\*</sup>First time period lies outside the scope of this review, but results presented in Table for completeness

<sup>^</sup>(+) Increase in rate; (-) decrease in rate; (~) no change in rate observed

They proposed that the aetiologically-relevant social factors which increase psychosis risk might be stable over time, such that the most socially marginalised groups at different temporal periods face the greatest risk of schizophrenia, but which sociodemographic group which is exposed to this risk is not temporally stable. Harrison and colleagues [C28] suggested that the stable rates of schizophrenia observed in their sample between 1975-87 may have differed from other studies [C10, C11] because these studies had not adequately controlled for changes in the ethnic structure of their populations at-risk over time. One more recent study [C40] was able to control for increases in the proportion of ethnic minority groups in its study setting between two time periods (1992-4 & 1997-9), but this did not alter its findings.

To further inspect possible changes in the incidence of schizophrenia over time we conducted a meta-regression on data from citations providing estimates of the overall incidence of schizophrenia at different cross-sectional points in time (those citations identified in Section 4.2.3.1: C2, C3, C9, C14, C19, C23, C30, C34, C35, C43, C49, C51, C88, C124, C138). The median time points from these studies ranged from 1965 to 2002. Overall, there was no evidence that the incidence of schizophrenia had increased during this time (RR per year: 0.99; 95% CI: 0.95, 1.02).

#### *4.2.3.2 Geographical variation in the incidence of schizophrenia*

We identified ten studies which had investigated the incidence of schizophrenia in relation to geographical variation and societal-level risk factors [C7, C8, C12, C24, C25, C35, C37, C39, C44, C69]. Two citations [C35, C69] had examined variation in incidence rates between geographical locales. Published data from the ÆSOP study [C35] suggested that the incidence of schizophrenia was significantly higher in the Southeast London centre of this study, than in either the Nottingham (RR: 2.5; 95% CI: 2.0 3.3) or Bristol (RR: 2.0; 95% CI: 1.7 5.0) centres, after adjustment for age and sex. Data from a separate study [C69] suggested there were no significant differences in the crude incidence rates of schizophrenia between two small cities in the south of England, Chichester and Salisbury (RR for Salisbury vs. Chichester: 1.44; 95% CI: 0.91, 2.29).

The remaining eight citations [C7, C8, C12, C24, C25, C37, C39, C44] had all investigated geographical variation in the incidence of schizophrenia within study settings at a smaller

geographical level, and putative socio-environmental factors which might explain this variation. Typically these studies inspected variation in incidence rates at the neighbourhood level, as defined by administrative boundaries such as the electoral ward or enumeration district. All studies observed some significant variation in the incidence of schizophrenia across neighbourhoods attributable to higher-level (non-individual) effects. Data from the AESOP study [C37, C39] suggested the proportion of variance attributable to the neighbourhood level in Southeast London remained significant ( $\chi^2$  (12df):  $p < 0.001$  [C37]) after adjustment for potential differences between neighbourhoods in age, sex and ethnicity. This variation was, on average, however, typically small, in the region of 4% [C37],<sup>xiv</sup> though varying by sociodemographic group. In one study [C37], rates of schizophrenia were observed to be significantly higher in neighbourhoods with lower levels of social cohesion, as indexed by voter turnout at local elections. The study also found that schizophrenia incidence was independently higher in neighbourhoods with greater levels of ethnic fragmentation (a potential marker of social isolation). These findings were independent of age, sex, ethnicity and socioeconomic deprivation at the neighbourhood level. In a follow-up study [C39] the authors attempted to address the putative association between social cohesion and schizophrenia in more detail, by measuring social cohesion directly using a cross-sectional household survey instead of using the proxy measure of voter turnout. Here, the association between ethnic fragmentation and schizophrenia remained, but the authors found a non-linear association between social

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<sup>xiv</sup>Using multilevel Poisson modelling, the authors [C37] initially estimated this variation to be ~23%, based on random effects parameter estimates from this model. Since publication however, advances in multilevel statistical modelling have proposed a revised, more accurate method for interpreting these parameter estimates. While the estimate itself remains unchanged (and significant), the proportion of variance attributable to neighbourhood level factors is now thought to be closer to 4%, but will vary according to demographic subgroup. This concurs with the estimates published in a very recent study (from Sweden) by Zammit *et al.*<sup>6</sup> Zammit S, Lewis G, Rasbash J, Dalman C, Gustafsson J-E, Allebeck P. Individuals, Schools, and Neighborhood: A Multilevel Longitudinal Study of Variation in Incidence of Psychotic Disorders. *Archives of General Psychiatry*. September 1, 2010 2010;67(9):914-922. This study also observed an association between social fragmentation at the school-level and the incidence of non-affective psychosis, suggesting that higher-level socio-environmental factors are likely to be important in explaining the association between urbanicity and the incidence of non-affective psychoses.

cohesion and the incidence of schizophrenia, such that schizophrenia was significantly elevated in neighbourhoods which had both the lowest and highest levels of social cohesion. The authors proposed that one possible explanation for this non-linear relationship could be that areas with high social cohesion may foster higher rates of schizophrenia if certain vulnerable groups were excluded from accessing that social cohesion.

This argument is predicated on the hypothesis that social stress, exacerbated by a range of potential socioenvironmental factors including social isolation, negative life events, discrimination and socioeconomic inequality, is implicated in the onset of schizophrenia and other psychoses (see Section 8.5 for a fuller discussion on this).<sup>80</sup> It underpins a number of explanations in regard to the association between schizophrenia risk and a number of factors including urbanicity, ethnicity and migration. For example, several studies have also considered whether ethnic density (the proportion of people in your neighbourhood who come from a similar ethnic group) is associated with the incidence of schizophrenia [C7, C12, C39]. Two studies conducted in separate samples in Southeast London [C7, C39] observed that as the proportion of black and minority ethnic groups in a neighbourhood decreased, the incidence of schizophrenia for members of those groups increased disproportionately relative to the corresponding rate for their white British neighbours. One earlier citation [C12] also investigated this hypothesis using all first admission data in England from the Mental Health Enquiry in 1981. The study did not observe any association between ethnic density and schizophrenia (except for a negative correlation between the incidence of schizophrenia in Irish-born groups in England and their ethnic density). However, the study considered ethnic density in relation to two levels of geography – England and Regional Health Authorities – both of which could have been too broad to detect important associations between ethnic density and schizophrenia risk at smaller, neighbourhood levels. Further, there is support for the ethnic density hypothesis from studies conducted outside of the UK, for example in the USA<sup>81, 82</sup> and the Netherlands.<sup>83</sup>

Two citations [C24, C25] reported data from a study conducted in Nottingham which found significant variation in the incidence of schizophrenia across small neighbourhoods (enumeration districts). Higher rates of schizophrenia than would be expected were observed in communities characterised by higher levels of socioeconomic deprivation and social fragmentation, both in inner-city areas and newer (i.e. 1960s) housing estates in suburban

areas. One further citation [C8] considered the role of socioeconomic inequality, in a study conducted in Southeast London. The study found no overall association between inequality and the incidence of schizophrenia, but in the most deprived neighbourhoods greater inequality was associated with higher rates of schizophrenia, over and above potential confounding factors including absolute deprivation. This finding, as others highlighted here, points to the complex interaction of social and economic factors in the aetiology of schizophrenia: here, the authors observed relative deprivation is associated with rates of schizophrenia, but only in neighbourhoods where there are marked levels of absolute socioeconomic deprivation.

To supplement these studies we also considered whether the overall incidence of schizophrenia, as identified in the 15 citations in Section 4.2.3.1, varied according to the urbanicity of their study setting. We entered the data into a meta-regression, fitting our composite urbanicity ranking as a covariate. We found evidence that per rank increase in urbanicity, there was an observed increase in the incidence of schizophrenia (RR: 1.03; 95% CI: 1.01, 1.05).

#### *4.2.3.3 Incidence of schizophrenia by study quality*

We entered the 15 overall incidence rates of schizophrenia identified in Section 4.2.3.1 [C2, C9, C14, C19, C23, C30, C34, C35, C43, C49, C51, C88, C124, C138] into a meta-regression to consider the possible effects of study quality on overall incidence rates. Quality ratings ranged from 2 to 7 (mean = 4.8) but a meta-regression suggested this was not associated to the observed incidence of schizophrenia (RR per point increase in study quality: 1.02; 95% CI: 0.88, 1.20).

### **4.2.4 Affective psychoses**

#### *4.2.4.1 Overall incidence rate of affective psychoses*

We identified 13 citations [C14, C19, C24, C25, C35, C36, C40, C48, C75, C88, C108, C138, C146] which reported the overall incidence of affective psychoses in the literature, of which seven [C14, C19, C35, C40, C75, C88, C138] provided unique rate data from eight studies (C40 provided data for two studies: S6 & S14). summarises key data extracted from these citations. The incidence of affective psychoses varied between studies from 6.6 to 37.0 per 100,000 person-



years ( $I^2=0.97$ ) (see Figure 4.10), with a pooled estimate of 12.4 per 100,000 person-years (95% CI: 9.0, 17.1).

**Table 4.4: Data summary for overall incidence of affective psychoses from identified citations (Section 4.2.4.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Rate per 100,000 <sup>6</sup>	95% CI
<b>C138, S9</b>	Reay	2009	Northumberland	36	2002 (7)	4	<u>118</u>	8.6 <sup>c</sup>	7.2, 10.4
<b>C88, S69</b>	Jones	1991	Nottingham	25	1982 (1)	2	90	37.0 <sup>c</sup>	30.1, 45.5
<b>C75, S7</b>	Gater	1989	S Manchester	21	1977 (10)	2	114	12.6 <sup>d</sup>	10.5, 15.1
<b>C40, S14</b>	Kirkbride	2009	Nottingham	25	1993 (2)	6	32	7.7 <sup>d</sup>	5.4, 10.9
<b>C40, S6</b>	Kirkbride	2009	Nottingham	25	1979 (2)	6	26	6.7 <sup>d</sup>	4.5, 9.8
<b>C35, S11</b>	Kirkbride	2006	ÆSOP	21	1998 (2)	7	160	9.8 <sup>c</sup>	8.4, 11.4
<b>C19, S10</b>	de Alarcon	1993	Oxfordshire	35	1981 (12)	2	740	18.1 <sup>c</sup>	16.8, 19.5
<b>C14, S8</b>	Coid	2008	E London	1	1998 (2)	7	122	13.5 <sup>d</sup>	11.3, 16.1

<sup>1</sup>Compass abbreviations used (N, S, E, W), ÆSOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban

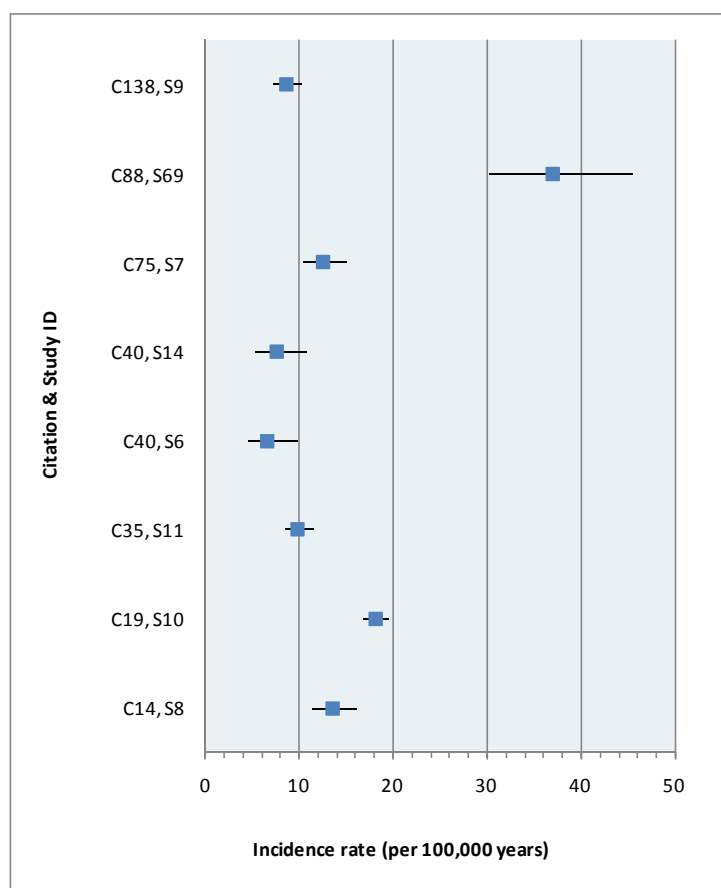
<sup>3</sup>Mid-year of case ascertainment period, duration in years shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

<sup>6</sup>c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

**Figure 4.10: Forest plot of incidence of the affective psychoses**

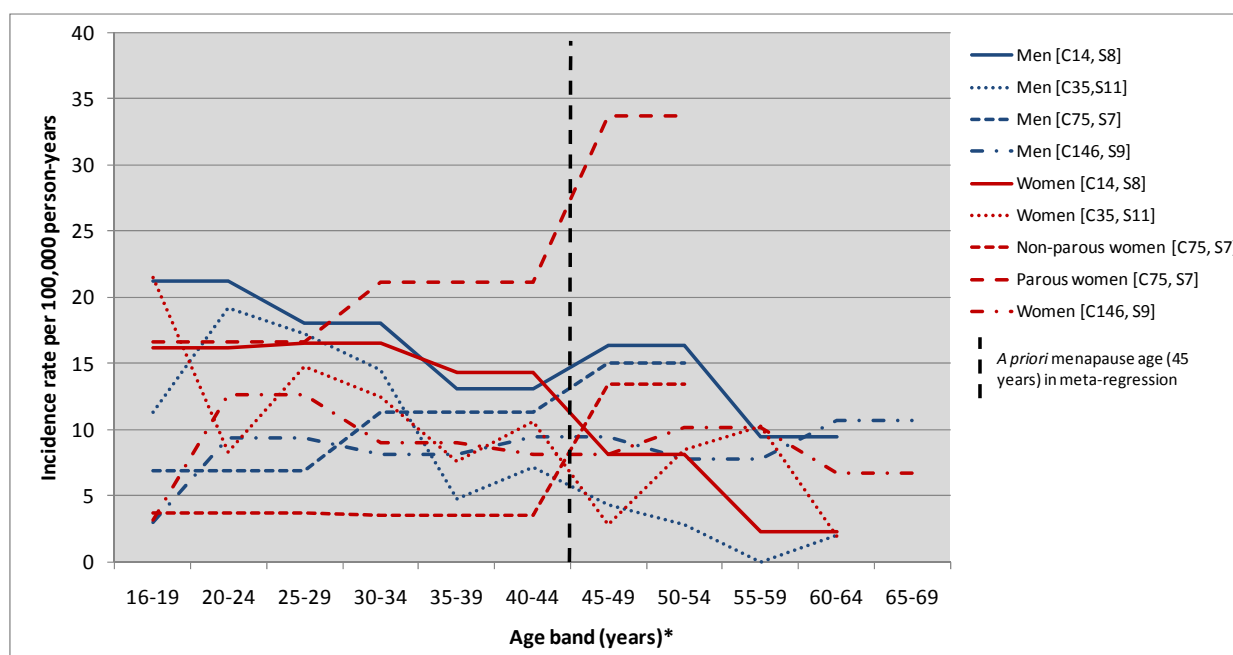


#### 4.2.4.2 Incidence of affective psychoses by gender and age

Only two citations provided unique rate data on the incidence of affective disorders for men and women [C75, C119]. Although there were insufficient data points to perform meta-analyses, both citations found that point estimates of incidence were greater for women than men. For example, C119 reported that the incidence of affective psychoses for women was 31.2 per 100,000 person-years and 19.8 for men (the citation did not provide data to estimate a standard error associated with these rates. C75 also found that rates were higher in women ( $\lambda=15.4$ ; 95% CI: 12.2, 19.5) than men ( $\lambda=9.8$ ; 95% CI: 7.3, 13.1), though overall rate estimates were lower in this study than C119 for both sexes. One further citation [C35] did not provide absolute incidence rates of affective psychosis for men and women, but reported no difference in relative risk between the sexes (RR: 1.0; 95% CI: 0.7, 1.6). Four citations provided incidence data for the affective psychoses stratified by age and sex [C14<sup>xv</sup>, C35, C75, C146]. A fractional polynomial model was applied to the data, though sparse, and there was a suggestion of an interaction between age and sex, such that prior to menopausal age there were no differences in rates between men and women (HR: 0.98; 95% CI: 0.81, 1.19), but after this time there was a suggestion rates of affective psychoses became significantly higher in women compared with men (HR: 1.40; 95% CI: 1.02, 1.91). However inspection of individual studies revealed no consistent pattern (Figure 4.11). The largest two studies suggested rates for men and women declined with age [C14, C35], while one smaller study [C75] recorded an increase in the incidence of affective psychoses for men and both parous and non-parous women over time. Finally, some unpublished data [C146] suggested a sharp increase in incidence for men and women in the youngest age group of the sample (16-19 years) but with both sexes experiencing a constant incidence thereafter. It is difficult to draw firm conclusions from this data, but the largest, most robust studies suggest rates of affective psychoses may decline with age for both men and women [C14, C35].

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<sup>xv</sup> Supplemental original data made available by authors, not part of publication but was part of the study

**Figure 4.11: Incidence of affective psychoses by age and sex from identified studies**

**Figure Legend:** The graph shows all rates of affective psychoses identified, by age and sex. With the exception of C35 [S11], all studies show a decline in rates for men and women over time, but there is little consistent evidence of an interaction between age and sex around 45 years of age, despite weak evidence of such from a fractional polynomial meta-regression. \*Some citations provided estimates in 10-year age bands and were imputed for each 5-year age band. Only C146 provided an estimate of incidence beyond 64 years old (60-69 years).

#### 4.2.4.3 Incidence of affective psychoses by ethnicity and country of birth

We identified two citations [C14, C38] from the same study [S8] which reported the incidence of affective psychoses by ethnic group. C38 provided more usable information and was selected as the core publication. The study observed that black Caribbean, black African and non-British white groups had between two and three times higher rates of affective psychoses than their white British counterparts, after adjustment for age and sex. For all three groups, the increased risk of affective psychoses remained double that of their white British counterparts after further adjustment for socioeconomic status. However, in general the effect sizes for the black Caribbean and African groups were generally lower than corresponding effect sizes observed for the non-affective psychoses (see Sections 4.2.2.3 and 4.2.3.3). This recent study<sup>20</sup> also observed markedly high rates of affective psychoses in the mixed white and black Caribbean group (RR: 10.9; 95% CI: 4.5, 26.3), though this has yet to be replicated. There was no evidence of raised rates of affective psychoses in this citation. Two further citations [C64, C139] analysed rates of

affective psychoses by country of birth. One study [C139] found elevated rates for migrants born in the Caribbean (estimated RR: 1.9; 95% CI: 1.3, 2.8) and African (estimated RR: 8.2; 95% CI: 4.6, 14.6) compared with the UK-born group, but the other study found no differences in rates between these groups, or for people from the Indian subcontinent. Given the paucity of data here, no attempt was made to meta-analyse this data.

#### 4.2.4.4 Incidence of affective psychoses over time

We identified three citations which had investigated the incidence of affective psychoses over time [C19, C28, C40]. Harrison *et al.* reported a significant decline in the incidence of affective psychoses between 1975 and 1987, but this could be directly attributed to the addition of a new diagnostic category in ICD-9 of “311: Depressive Disorders, Not Otherwise Specified”, introduced in 1981. Prior to this point such non-psychotic depressive illnesses had been classified in the affective psychoses category (ICD-8) and this led to a dramatic drop in incidence rates around this time period. This was accounted for in a further study of the affective psychoses [C40] which demonstrated that affective psychoses had remained stable over three time periods between 1978 and 1999 (RR: 1.00; 95% CI: 0.98, 1.03). Finally, although de Alarcon and colleagues [C19] observed a broad-based decline in affective disorders between 1975 and 1986, they did not distinguish between non-psychotic depression and affective psychoses (which accounted for 17% of this category), meaning it was impossible to infer further information from this sample.

We therefore used a meta-regression approach to test whether the overall incidence of affective psychoses had changed over time, as identified by eight rates published from the seven citations identified in Section 4.2.4.1 [C14, C19, C35, C40, C75, C88, C138]. The median time period of these studies varied from 1977 to 2002. There was no evidence that the crude incidence of affective psychoses had changed over time from these estimates (RR: 0.98; 95% CI: 0.93, 1.03).

#### 4.2.4.5 Geographical variation in the incidence of affective psychoses

Five citations from three studies [C24, S6; C25, S6; C35, S11; C36, S11; C69, S29] investigated variation in the incidence of affective psychoses according to socio-spatial gradients. In work conducted in Nottingham in the late 1970s, Giggs [C24] and Giggs and Cooper [C25] found less

evidence of variation in the affective psychoses that for their non-affective counterparts, but higher rates were identified in suburban areas of Nottingham, characterised by recent, rapid population growth, new estates, young families and people involved in the manufacturing industry. More recently, there was no evidence of significant neighbourhood variation in the incidence of affective psychoses from data from the Southeast London centre of the ÆSOP study [C36], or that incidence rates differed significantly between Southeast London, Nottingham or Bristol, after adjustment for age and sex [C35]. These findings are in accordance with the wider research literature.<sup>15, 81, 84, 85</sup> De Alarcon *et al.* [C69] observed higher crude incidence rates of affective psychoses in Chichester than Salisbury (RR: 1.28; 95% CI: 1.04, 1.58), a finding the authors stated was driven by higher rates of such disorders amongst women in the former setting. Unfortunately, no data was available to control for possible sociodemographic differences between the study populations which might have explained this finding.

We fitted a meta-regression model with our composite urbanicity ranking variable to the overall rates of affective psychoses identified in Section 4.2.4.1 [C14, C19, C35, C40, C75, C88, C138]. This model suggested that the crude incidence of affective psychoses was not associated with the level of urbanicity (RR: 1.00; 95% CI: 0.95, 1.05).

#### 4.2.4.6 Incidence of affective psychoses by study quality

A random effects meta-regression of the eight overall rates of affective psychoses [C14, C19, C35, C40, C75, C88, C138] was conducted to inspect whether incidence varied according to study quality. Quality scores ranged from 2 to 7 (out of 7; mean=4.5), but there was no evidence rates of affective psychoses varied significantly by study quality (RR: 0.86; 95% CI: 0.71, 1.04).

### 4.2.5 Bipolar disorder

#### 4.2.5.1 Overall incidence rate of bipolar disorder

We identified 9 citations [C4, C34, C40, C41, C68, C75, C95, C138, C145] which reported the overall incidence of bipolar disorder in the relevant literature. Two of these citations reported duplicate data [C4, S4; C68, S14], with the remaining seven citations providing unique data from 9 studies (C40 and C145 each reported data from two separate studies). Data are summarised in Table 4.5. Heterogeneity between rates was moderate ( $I^2=0.54$ ), varying from 1.2 per 100,000

person-years [C145, S3] to 5.4 per 100,000 person-years [C34] (Figure 4.12). Overall, the pooled incidence of bipolar disorder was 3.7 per 100,000 person-years (95% CI: 3.0, 4.5).

**Table 4.5: Data summary for overall incidence of bipolar disorder from identified citations (Section 4.2.5.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Rate per 100,000 <sup>6</sup>	95% CI
<b>C145, S3</b>	Wing	1976	Salford	23	1971 (5)	2	<u>6</u>	1.2 <sup>c</sup>	0.5, 2.7
<b>C145, S2</b>	Wing	1976	Camberwell	5	971 (5)	2	<u>25</u>	4.1 <sup>c</sup>	2.8, 6.1
<b>C138, S9</b>	Reay	2009	Northumberland	36	2002 (7)	4	<u>44</u>	3.2 <sup>c</sup>	2.4, 4.4
<b>C95, S4</b>	Leff	1976	Camberwell	5	1970 (9)	3	<u>38</u>	4.7 <sup>c</sup>	3.4, 6.5
<b>C75, S7</b>	Gater	1989	S Manchester	21	1977 (10)	2	30	3.3 <sup>d</sup>	2.3, 4.7
<b>C41, S11</b>	Lloyd	2005	ÆSOP	21	1998 (2)	7	75	4.6 <sup>c</sup>	3.7, 5.8
<b>C40, S14</b>	Kirkbride	2009	Nottingham	25	1993 (2)	6	15	3.6 <sup>d</sup>	2.2, 6.0
<b>C40, S6</b>	Kirkbride	2009	Nottingham	25	1979 (2)	6	9	2.3 <sup>d</sup>	1.2, 4.4
<b>C34, S17</b>	King	1994	E London	4	1992 (1)	7	9	5.4	2.8, 10.3

<sup>1</sup>Compass abbreviations used (N, S, E, W), ÆSOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban

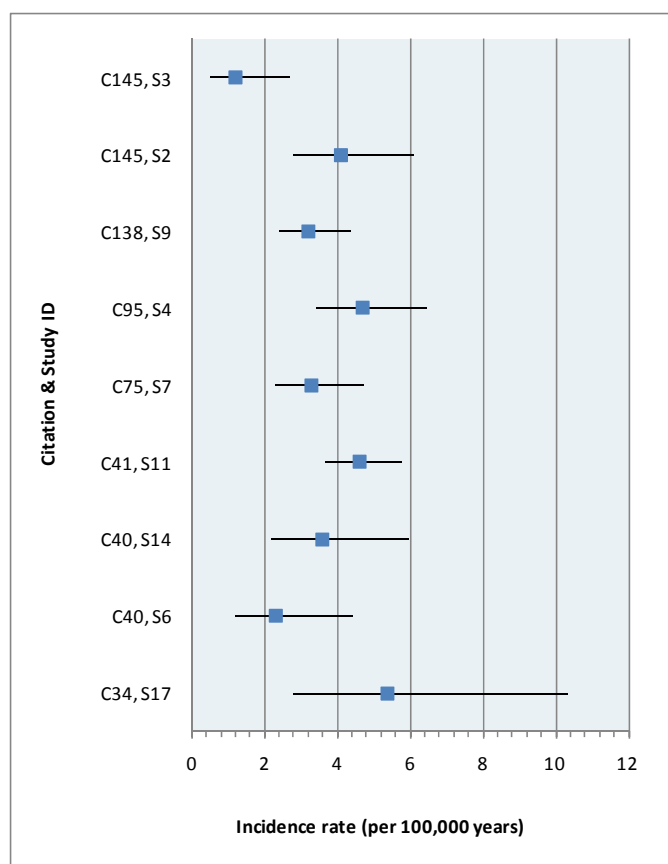
<sup>3</sup>Mid-year of case ascertainment period, duration in years shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

<sup>6</sup>c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

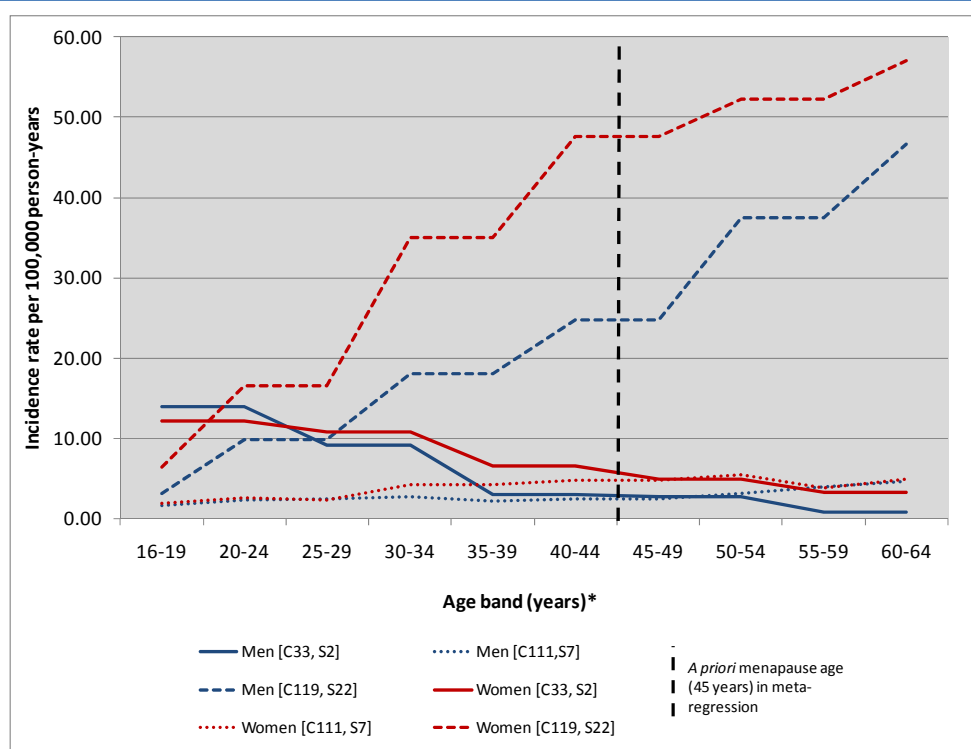
**Figure 4.12: Forest plot of incidence of bipolar disorder**



#### 4.2.5.2 Incidence of bipolar disorder by gender and age

Five citations provided unique incidence rates of bipolar disorder separately for men and women from six different studies [C41, C75, C95, C102, C145] (C145 provided rates for men and women from two studies; S2 & S3). Overall the pooled incidence rates for men ( $\lambda=4.0$ ; 95% CI: 2.9, 5.6) and women ( $\lambda=3.9$ ; 95% CI: 2.1, 7.5) were similar. As for the affective psychoses, there were too few studies to permit pooling of incidence rates by age and sex [C33, C111, C119]. Visual inspection of this data (Figure 4.13) suggested three notable facts. First, all three studies reported that the point estimate incidence rate at every age period was greater for women than men, in contrast to the studies which reported similar rates of affective psychoses between the sexes. Second, there was no consistent pattern in incidence rates with age; one study reported an increase in rates with age [C119], one study reported approximately consistent rates over age [C111] and the third study reported a decline in rates with age [C33]. Only one of these studies [C33] was based on first contact rates; the other studies being based on first admissions. Finally, there was little visual evidence that the incidence of bipolar disorder by age was modified by sex i.e. there was no evidence of an interaction between age and sex in any study.

**Figure 4.13: Incidence of bipolar disorder by age and sex from identified studies**



\*Some citations provided estimates in 10-year age bands and were imputed for each 5-year age band.

#### 4.2.5.3 Incidence of bipolar disorder by ethnicity

We identified five citations which had published rates of bipolar disorder by ethnicity [C11, C21, C27, C41, C52], of which we included data from one **unique** citation [C27] and two further **core** citations [C21, C52]. For the purposes of this analysis, C11 and C41 were classified as **satellite** citations. There were insufficient data to permit meta-analyses and so we limit our analysis to inspection of results from each included citation. Two citations [C27, C52] only reported the incidence of bipolar disorder in the black Caribbean group compared with the remaining population in their study setting. In both instances the studies observed higher rates of bipolar disorder in the black Caribbean group, estimated here to be between 4.1 (95% CI: 1.9, 8.8) [C27] and 12 [C52] (no data published to estimate a confidence interval) times greater than in the background population. The remaining citation [C21] estimated the incidence of bipolar disorder across several ethnic groups and used the white British group as the baseline category to provide a more detailed inspection of incidence rates across ethnic groups. The data, taken from the ÆSOP study [S11], revealed that rates of bipolar disorder were significantly and substantially elevated in the black Caribbean (RR: 8.0; 95% CI: 4.3, 14.8), black African (RR: 6.2; 95% CI: 3.1, 12.1) and mixed ethnicity (RR: 6.2; 95% CI: 2.6, 15.0) groups, after adjustment for age and sex. These patterns held for men and women independently. The study also observed that Asian men (RR: 3.8; 95% CI: 1.1, 13.1) had elevated rates of bipolar disorder in this sample, after adjustment for age. There was no evidence that the rate of bipolar disorder was raised in the non-British white group.

#### 4.2.5.4 Incidence of bipolar disorder over time

Five citations were identified which had considered changes in bipolar disorder over time [C11, C28, C40 C52, C56], summarised in Box 4.2. Three studies observed at least some evidence of an increase in the incidence of bipolar disorders over time, although the strength of this evidence was weak. The strongest evidence for a change in mania incidence was observed by Harrison and colleagues [C28] who observed a small, but statistically significant increase in rates between 1975 and 1987 from 3.66 to 4.47 (test for trend  $p=0.01$ ). However, Harrison and colleagues could not exclude the possibility that the succession of ICD-8 with ICD-9 in 1981 explained this increase. Van Os and colleagues [C52] observed a similar statistically significant increase in mania with schizomania for women (test for trend,  $p=0.03$ ), between 1965 and 1984, although the absolute change in incidence was also low; from 3.0 to 4.4 case per 100,000 person-years.



By contrast, no such corresponding change was observed for men with mania with schizomania, or for either sex when a separate diagnosis of mania was considered. Finally, [C56] Barraclough and Krietman published admission rates of “manic depressive reaction” in England and Wales for men and women, by age group, for the period 1950-60, calculated from data obtained from the Registrar General. The authors made no attempt to analyse these rates and no corresponding sample sizes were published to allow us to estimate standard errors, however we have graphed these point estimates for men and women in Figures 4.14 and 4.15, respectively. The data suggest there was an increase in the admitted rate of bipolar disorder over this time period, for men and women, across all ages, though it is not possible to determine whether this change was statistically significant.

Box 4.2: Citations addressing incidence of bipolar disorder over time in England, by study						
Study	Citation	Time period(s)	Setting	Contact type	Findings <sup>^</sup>	Author explanations
S2	C11, C52 <sup>†</sup>	1965-84	Camberwell, London	Case register	Increase in mania with schizomania in women (+), but not men (~). No increase in mania for either sex (~)	Chance. Possibly due to change in the ethnic structure of the population at-risk (increased migrants). Changes in diagnostic fashion unlikely but impossible to exclude.
S6	C28	1975-87	Nottingham	Case register	Increase (+)	Change in diagnostic classification between ICD-8 and ICD-9
S6.11.14	C40	1978-80; 1992-4; 1997-9	Nottingham	Case register + first onset	No change (~)	-
S22	C56	1950-60	England & Wales	First admissions	Increase (+)	NA <sup>‡</sup>

<sup>†</sup> C11 and C52 report the same data as a monograph & peer-reviewed publication, respectively

<sup>‡</sup> Published data from reference in tabular form only. No analysis or interpretation provided by authors. Impossible to test statistical significance of change.

<sup>^</sup>(+) Increase in rate; (-) decrease in rate; (~) no change in rate observed

One study [C40], which analysed data from Nottingham at three time points between 1978 and 1999, did not observe any change in the incidence of bipolar disorder during this period, after adjustment for age and sex (RR: 1.02; 95% CI: 0.98, 1.06).

Figure 4.14: Incidence of bipolar disorder for men by age group from Citation 56

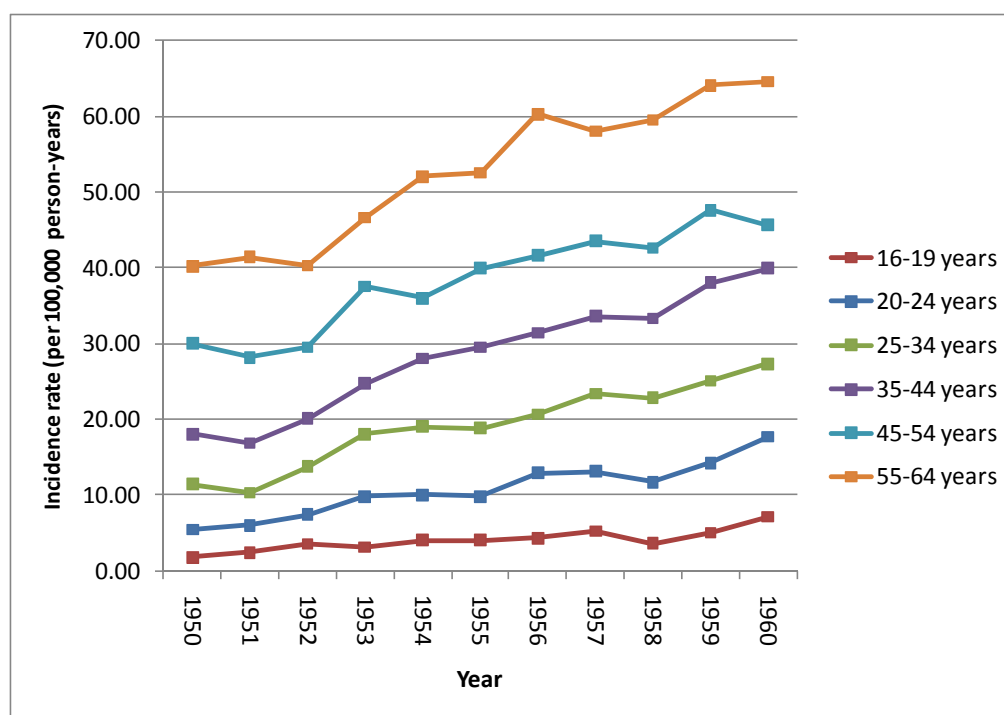
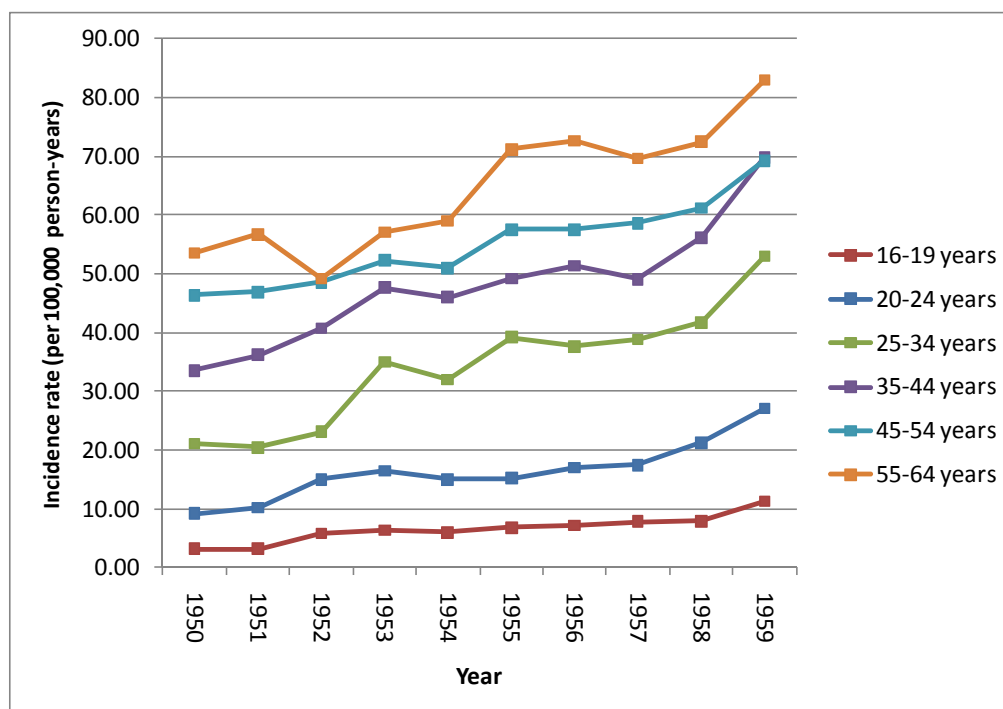


Figure 4.15: Incidence of bipolar disorder for women by age group from Citation 56



To further consider possible changes in the incidence of bipolar disorder over time we considered a random effects meta-regression of the nine overall rates identified in Section 4.2.5.1 [C4, C34, C40, C41, C68, C75, C95, C138, C145], with the mid-point year of each study fitted as a covariate. All studies were conducted between 1971 and 2002 and overall there was no evidence that the crude incidence of bipolar disorder had changed during this time (RR: 1.00; 95% CI: 0.98, 1.03).

#### *4.2.5.5 Geographical variation in the incidence of bipolar disorder*

We identified two citations which had investigated the incidence of bipolar disorder between study settings [C41, C145]. Both studies compared rates in Southeast London against rates in other centres: Nottingham [C41], Bristol [C41] and Salford [C145]. Age and sex standardised rates of bipolar disorder in London were significantly greater than in Nottingham (RR: 1.9; 95% CI: 1.2, 3.2) [C41] or Bristol (RR: 3.6; 95% CI: 1.4, 9.3), and crude rates in London were greater than those in Salford (RR: 3.4; 95% CI: 1.4, 8.4) [C145]. Each study also published these rates stratified by gender allowing us to test whether rates of bipolar disorder were greater for men and women separately in London compared with the other centres. Although power was low, point estimates were generally higher for both men and women separately, though this effect was stronger, and only achieved statistical significance for women, when age-adjusted rates in London were compared with those in Bristol or Nottingham [C41]. However, further published data from that citation [C41] suggested that inter-centre differences disappeared after further adjustment for differences in the ethnic structure of the underlying populations at-risk.

We did not identify any citation from our search strategy which had inspected variation in the rates of bipolar disorder at a finer, neighbourhood –level of spatial resolution.

We conducted a random effects meta-regression on nine rates from seven of the nine citations reporting overall incidence rates of bipolar disorder identified in Section 4.2.5.1 [C34, C40, C41, C75, C95, C138, C145] in relation to the composite urbanicity ranking variable we developed. In contrast to the findings from individual studies, meta-regression suggested that there was no evidence rates of bipolar disorder increased in more urban settings (RR per rank increase in urbanicity: 1.01; 95% CI: 0.99, 1.04;  $p=0.18$ ).

#### 4.2.5.6 Incidence of bipolar disorder by study quality

We also considered whether the citations providing information on overall rates of bipolar disorder showed differed according to study quality [C4, C34, C40, C41, C68, C75, C95, C138, C145]. Study quality varied out of a maximum score of 7 from 2 to 7. We entered data on study quality into a meta-analysis as a covariate but found no evidence that this was associated with incidence rates (RR: 1.05; 95% CI: 0.91, 1.21).

### 4.2.6 Depressive psychoses

#### 4.2.6.1 Overall incidence rate of depressive psychoses

We identified four citations [C40, C68, C75, C138] which provide estimates of the incidence of the depressive psychoses, of which one [C68] provided duplicate data from a more informative citation [C40]. C40 provided rates of depressive psychosis from three separate studies [S6, S11, S14] and so a total of five rates included in the meta-analysis of depressive psychoses here (Table 4.6). Incidence rates varied from 3.9 [C40, S14] to 9.3 [C75] per 100,000 person-years, with some evidence of between-study heterogeneity ( $I^2=0.83$ ). The pooled estimate of incidence of depressive psychosis was 5.3 per 100,000 person-years (95% CI: 3.7, 7.6) (see Figure 4.16).

**Table 4.6: Data summary for overall incidence of depressive psychoses from identified citations (Section 4.2.6.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Rate per 100,000 <sup>6</sup>	95% CI
C138, S9	Reay	2009	Northumberland	36	2002 (7)	4	<u>74</u>	5.4 <sup>c</sup>	4.3, 6.8
C75, S7	Gater	1989	S Manchester	21	1977 (10)	2	84	9.3 <sup>d</sup>	7.5, 11.5
C40, S11	Kirkbride	2009	Nottingham	25	1998 (2)	6	17	3.9 <sup>c</sup>	2.5, 6.3
C40, S14	Kirkbride	2009	Nottingham	25	1993 (2)	6	17	4.1 <sup>d</sup>	2.5, 6.6
C40, S6	Kirkbride	2009	Nottingham	25	1979 (2)	6	17	4.3 <sup>d</sup>	2.7, 7.0

<sup>1</sup>Compass abbreviations used (N, S, E, W), AESOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban

<sup>3</sup>Mid-year of case ascertainment period, duration in years shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

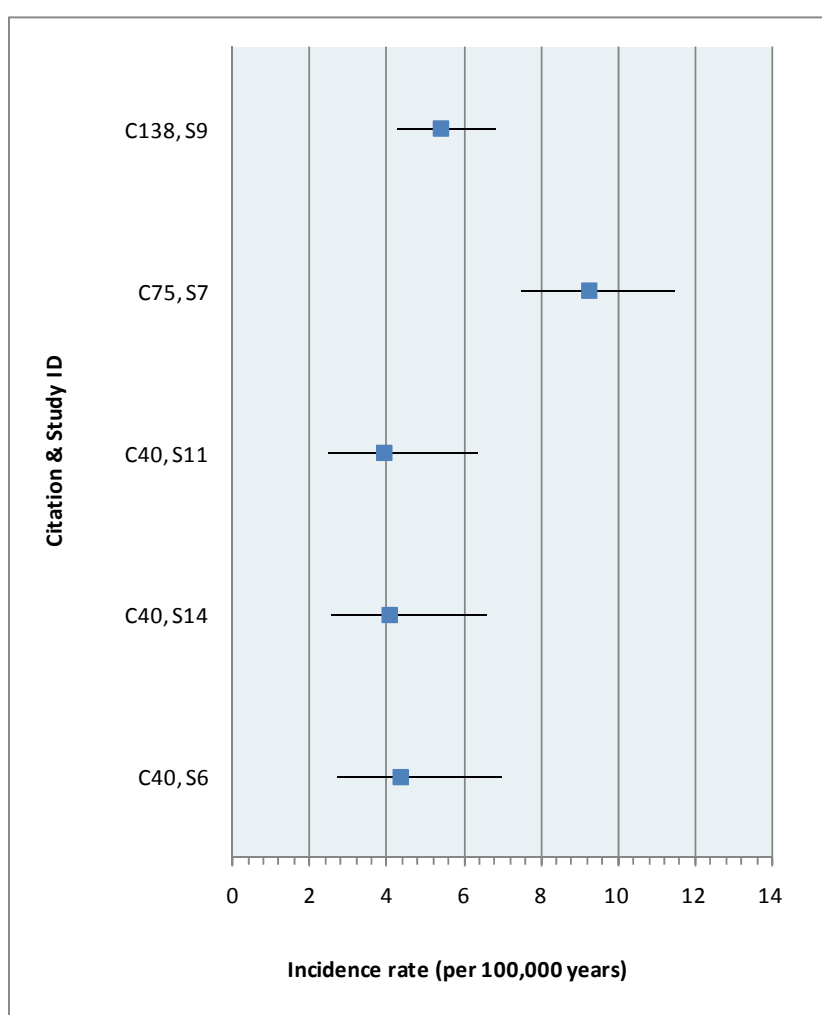
<sup>6</sup>c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

#### 4.2.6.2 Incidence of depressive psychoses by gender and age

Only two citations were identified [C75, C111] which provided separate incidence rates of depressive psychosis for men and women, both of which were from the same study [S7]. Rates were observed to be broadly similar for men ( $\lambda=3.5$ ; 95% CI: 2.1, 5.7) and women ( $\lambda=3.1$ ; 95% CI:

1.8, 5.2) [C75]. We identified one citation which presented incidence rates of depressive psychoses stratified by age and sex [C111]. The study presented estimates of first admission rates of depressive psychoses from the Mental Health Enquiry over a two year period 1965-6. For both men and women the admission rate increased consistently with age until 65 years old (where after rates declined).

**Figure 4.16: Forest plot of incidence of depressive psychoses**



#### 4.2.6.3 Incidence of depressive psychoses by ethnicity

We only identified one citation – from the ÆSOP study – which had presented rates of depressive psychoses by different ethnic groups [C21]. Rates of depressive psychoses were raised in several ethnic groups when compared with the white British group, but point estimates

for rate ratios were generally lower than observed for other diagnostic outcomes considered in this study. Thus, after adjustment for age and sex, the rate of depressive psychosis was 3.1 (95% CI: 1.5, 6.1) higher for the black Caribbean group than their white British counterparts, the latter rate ratio not achieving conventional statistical significance. Notably, rates were significantly raised for the Asian (RR: 3.0; 95% CI: 1.3, 7.1), mixed ethnicity (RR: 4.0; 95% CI: 1.6, 10.2) and “other” ethnic group (RR: 3.0; 95% CI: 1.3, 7.1) categories, though not for the black African and (RR: 2.1; 95% CI: 0.9, 5.0) or non-British white groups (RR: 1.3; 95% CI: 0.5, 3.2). The citation also presented these rates stratified by sex. Rates of depressive psychoses were raised for all ethnic minority men except the black Caribbean and black African groups, but for women only in the black Caribbean groups. One further citation [C71] found evidence of greater than expected numbers of depressive psychoses in migrant women born in Africa in comparison to the UK-born group, but no such differences were observed for their male counterparts or for people born elsewhere.

#### 4.2.6.4 Incidence of depressive psychoses over time

We identified two citations which had investigated possible changes in the incidence of depressive psychoses over time [C40, C56]. Kirkbride *et al.* [C40] did not find any evidence to support a change in the incidence of depressive psychoses across three time points between 1978-99 based on first-onset data from Nottingham (RR: 0.99; 95% CI: 0.96, 1.02). Barraclough and Krietman [C56] also considered whether the hospitalised first admission rate in England had changed between 1950 and 1960. They published annual rates for men and women separately across three age groups between 35 and 64 years, but did not find any evidence to suggest a change in the first admission rates of depressive psychosis (see Figures 4.16 and 4.17), termed in their report “involutional melancholia”. This publication tabulated the data but made no attempt to analyse it. We plotted the reported first admission rates graphically but no corresponding measures of standard error were published to permit formal statistical tests. One limitation of their data is that it is based on hospitalised admissions and may therefore not be representative of true changes in incidence rates in the community. This data should be considered in relation to other data available presented here, and for the affective psychoses more broadly.

Figure 4.16: Incidence of depressive psychoses for men by age group from Citation 56

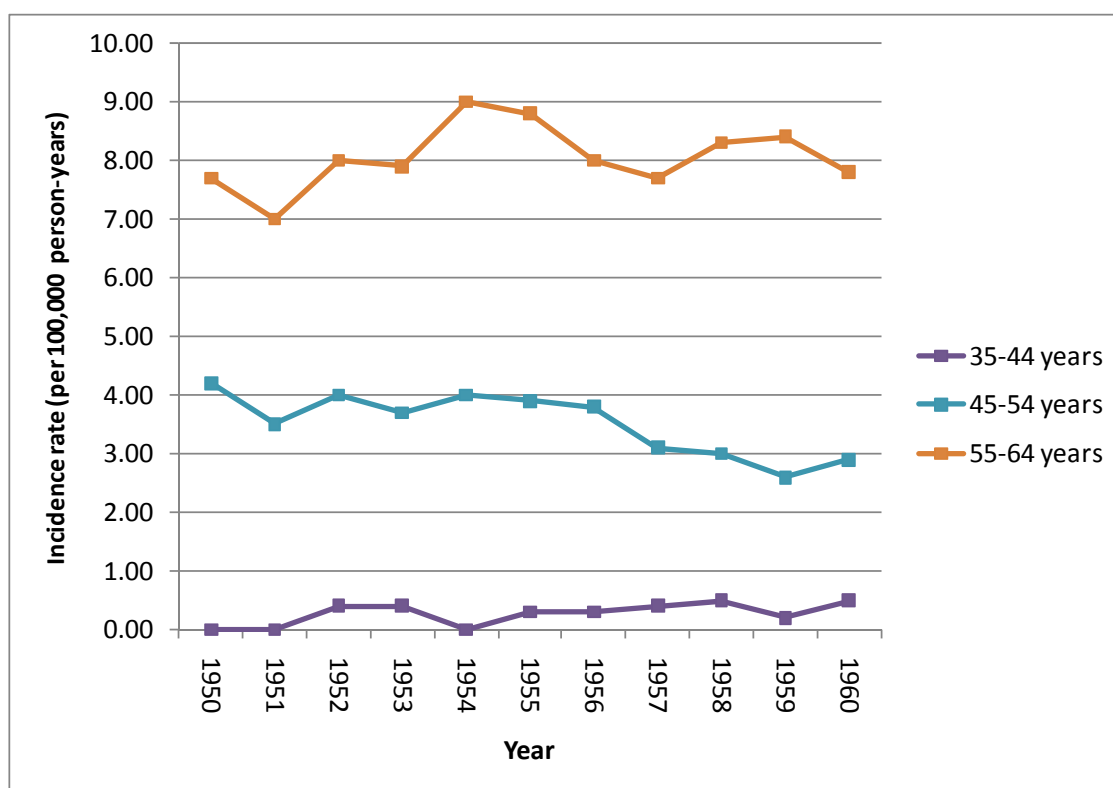
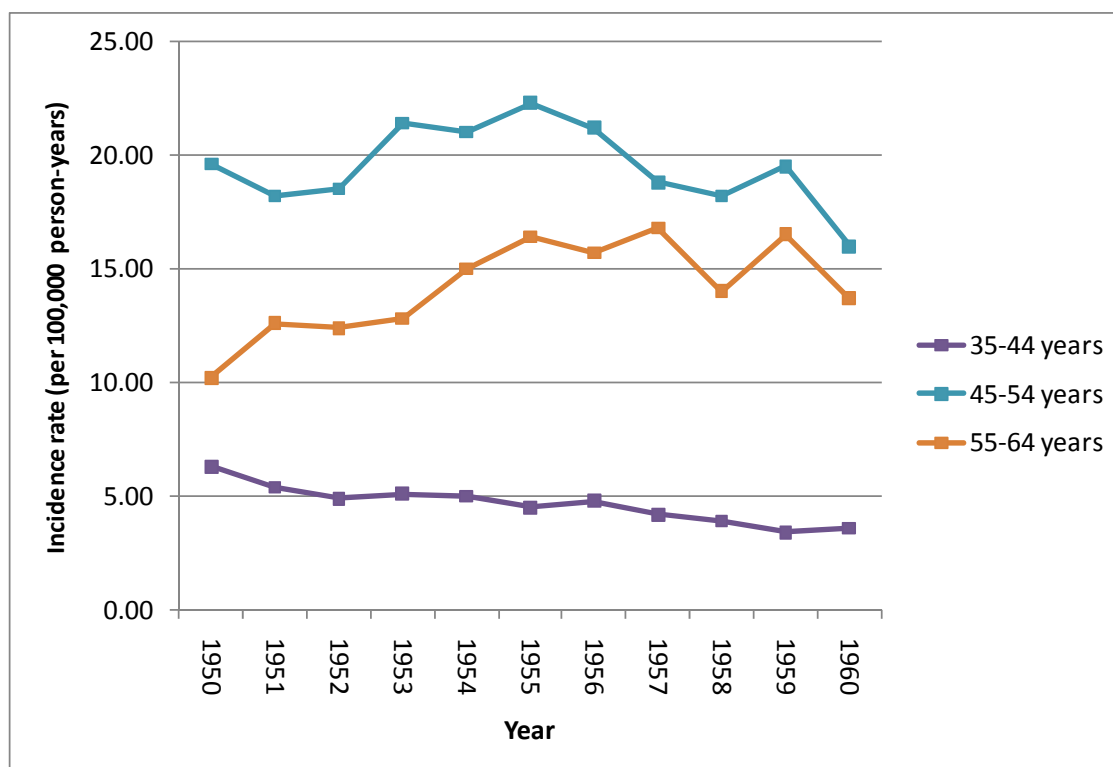


Figure 4.17: Incidence of depressive psychoses for women by age group from Citation 56



To further investigate the possible change in the incidence of depressive psychoses over time we fitted a random effects meta-regression to the five overall rates of depressive psychoses identified in Section 4.2.6.1 [C40, C75, C138]. These studies were conducted between 1977 and 2002 and meta-regression suggested that observed crude rates had not significantly changed during this period (RR per year: 0.98; 95% CI: 0.93, 1.04).

#### *4.2.6.5 Geographical variation in the incidence of depressive psychoses*

We did not identify any study which had directly addressed the socio-spatial distribution of the incidence of depressive psychoses as an independent outcome. We therefore considered a meta-regression of five overall incidence rates of depressive psychoses (as identified in Section 4.2.6.1 from C40, C75, C138) fitting our composite urbanicity ranking variables as a meta-level predictor. The data indicated that there was no association between urbanicity and the incidence of depressive psychoses (RR per rank increase in urbanicity: 1.02; 95% CI: 0.89, 1.16).

#### *4.2.6.6 Incidence of depressive psychoses by study quality*

We assessed whether the observed incidence of depressive psychoses could have been affected by study quality by fitting a random effects meta-regression with study quality score entered as a predictor variable. The analysis was based on the five overall incidence rates of depressive psychoses identified in Section 4.2.6.1 [C40, C75, C138]. Study quality scores ranged from two to six (out of seven) and we found some evidence to suggest that higher quality studies tended to report lower crude rates of depressive psychoses (RR per increase point in study quality: 0.81; 95% CI: 0.71, 0.93).

### **4.2.7 Substance-induced psychoses**

#### *4.2.7.1 Overall incidence rate of substance-induced psychoses*

Five citations [C35, C40, C68, C108, C146] published overall incidence rate estimates for substance-induced psychoses, of which one citation [C108] provided duplicate rates from the same study as another citation [C68, S14]. For the four included citations (Table 4.7), incidence rates varied from 0.3 to 2.6 per 100,000 person-years ( $I^2=0.63$ ) (see Figure 4.18), with a reported pooled estimate of 1.9 per 100,000 person-years (95% CI: 1.2, 2.8).



**Table 4.7: Data summary for overall incidence of substance induced psychoses from identified citations (Section 4.2.7.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Rate per 100,000 <sup>6</sup>	95% CI
<b>C146, S9</b>	Mitford	Unpub	Northumberland	36	2002 (7)	4	46	2.6 <sup>d</sup>	1.9, 3.5
<b>C68, S14</b>	Croudace	2000	Nottingham	25	1993 (2)	7	13	1.6 <sup>d</sup>	1.0, 2.8
<b>C40, S6</b>	Kirkbride	2009	Nottingham	25	1979 (2)	6	1	0.3 <sup>d</sup>	0.0, 1.8
<b>C35, S11</b>	Kirkbride	2009	ÆSOP	25	1998 (2)	7	<u>29</u>	1.8 <sup>c</sup>	1.3, 2.6

<sup>1</sup>Compass abbreviations used (N, S, E, W), ÆSOP: SE London, Nottingham, Bristol

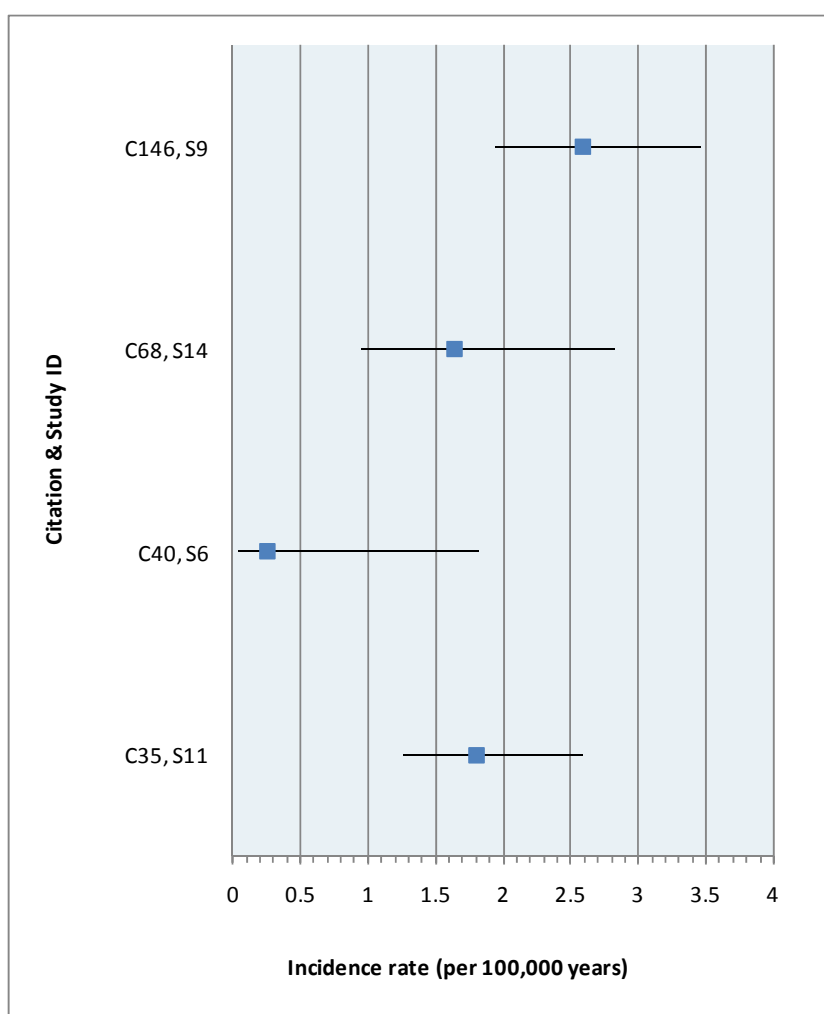
<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban

<sup>3</sup>Mid-year of case ascertainment period, duration in years shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

<sup>6</sup>c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

**Figure 4.18: Forest plot of incidence of substance-induced psychoses**

#### 4.2.7.2 Incidence of substance-induced psychoses by gender and age

No published data was identified on the incidence rates of substance-induced psychosis separately for men and women, but unpublished data from the ÆSOP study [S11] suggested that substance-induced psychoses were more common in men ( $\lambda=2.5$ ; 95% CI: 1.6, 3.8) than women ( $\lambda=0.9$ ; 95% CI: 0.4, 1.8). Two citations [C35, C146] provided incidence rates of substance-induced psychoses by age and sex, too few for meaningful pooling. Data from one of these citations [C35], the ÆSOP study, suggested that the incidence of such diagnoses peaked in the early twenties and declined rapidly thereafter, such that no cases of substance-induced psychoses were observed in people aged over 40 years. Similarly, unpublished data from Northumberland [C146] showed that rates of substance-induced psychoses were highest in people aged under 30 years of age and then declined with every ten-year age band thereafter.

#### 4.2.7.3 Incidence of substance-induced psychoses by ethnicity

We identified one study [C99], based on first admissions in Birmingham between 1980 and 1983, which investigated differences in the first admission rate of “cannabis psychosis” between the white and black Caribbean population. The study found no evidence of such diagnoses in either ethnic group for people aged over 30 years of age, broadly supporting the findings from the previous section. The authors did, however, find that rates of cannabis psychosis were significantly greater for black Caribbean men than their white counterparts, aged 16-29 years old, though confidence intervals were large (RR: 95.0; 95% CI: 12.3, 735.8). Point estimates for black Caribbean women were also raised, but did not reach statistical significance (RR: 5.7; 95% CI: 0.9, 33.8). The authors suggested that the validity of “cannabis psychosis” as a diagnosis – made for nearly 30% of their black Caribbean sample of subjects, was contested. The study did not blind people making diagnoses to the ethnicity of subjects and it would therefore not be possible to exclude diagnostic bias as an explanation of these results. As McGovern and Cope [C99] commented, there is no evidence to suggest that rates of cannabis consumption are greater in black Caribbean groups in England than other groups. Indeed, very recent evidence of *reported* cannabis consumption would lend support to this suggestion.<sup>86</sup> Further, in patient samples cannabis use is comparable across ethnic groups.<sup>87</sup>

We were also able to inspect unpublished data from the ÆSOP study sample, which showed that of the 27 people with a diagnosed first episode of substance-induced psychosis, the majority (92.6%) were of white British ethnicity. The remainder of the sample were of mixed ethnicities.

One further study (data provided in 2 citations, C20, C71) was identified which estimated first admission rates of “alcoholic psychosis and alcoholism” in Irish-born versus UK-born groups using data from four London Health Authorities in 1976. The study area covered an estimated total population of 15 million people. The best data from the study were provided in C71, but it was difficult to directly compare groups because the authors presented age-sex standardised first admission rates for the UK-born group, but crude first admission rates for the Irish-born group. Nevertheless, with this caveat stated, estimation of rate ratios suggested rates were elevated in both Irish-born men (RR: 2.2; 95% CI: 1.8, 2.7) and women (RR: 2.5; 95% CI: 1.8, 3.5) compared with their UK-born counterparts.

#### *4.2.7.4 Incidence of substance-induced psychoses over time*

Two citations were identified which had inspected the incidence of substance-induced psychotic disorders over time [C40, C72]. Data from the former citation found that the incidence of these disorders had risen on average by 15% per year (RR: 1.15; 95% CI: 1.05, 1.25) over the three time periods between 1979 and 1999 in Nottingham, after adjustment for age and sex. It should be noted that the absolute standardised incidence remained low even at the last time point (3.6 per 100,000 person-years; 95% CI: 1.9, 5.2). Der and colleagues [C72] reported the incidence of admitted alcoholic psychoses in England and Wales between 1970-86, using data from the Mental Health Enquiry. Rates were negligible over this period and hovered at around 0-1 per 100,000 person-years (no standard errors provided).

A meta-regression on the overall rates of substance-induced psychoses reported in Section 4.2.7.1 was performed to provide further information on the rates of substance-induced psychoses between 1979 and 2002 [C35, C40, C68, C146], but this did not reveal any increase in rates (RR: 1.08; 95% CI: 0.95, 1.21).

#### 4.2.7.5 *Geographical variation in the incidence of substance-induced psychoses*

We were unable to identify a literature on geographical variation in the incidence of substance-induced psychoses. However, we were able to perform a meta-regression using the overall rates of substance-induced psychoses identified in Section 4.2.7.1 [C35, C40, C68, C108, C146] to inspect whether there was any variation according to our composite urbanicity ranking. There was no evidence this was the case (RR for rank increase in urbanicity: 0.97; 95% CI: 0.79, 1.18).

#### 4.2.7.6 *Incidence of substance-induced psychoses by study quality*

There was no evidence the incidence of substance-induced psychoses varied by study quality from a meta-regression of data presented in Section 4.2.7.1 [C35, C40, C68, C108, C146] (RR: 0.87; 95% CI: 0.35, 2.15).

### 4.3 **Summary of incidence findings**

All clinically relevant psychotic disorders had a pooled incidence rate of 32 cases per 100,000 people at risk, per year (95% confidence interval [95% CI]: 25, 41). Incidence rates were higher in men than in women considering those under 45, but more even, thereafter (Figure 4.4). This pattern was also found for non-affective psychoses, including schizophrenia. Rates of affective psychoses were more evenly distributed between men and women until 45 years old, and declined with age. After this age, rates in women became higher than in men. Rates for black and minority ethnic groups were much higher than in the background population. This was a very consistent finding. We found higher rates of non-affective psychoses in more urban settings, indicated by visual inspection of the data and meta-regressions. No such effect was apparent for the affective psychoses. In general, the incidence rates of affective psychoses were roughly half of those of their non-affective counterparts. There were few studies of ongoing psychotic disorders associated with long-term use, excluding the short-term effects of drug intoxication. The pooled incidence rate was 2 per 100,000 person-years (95% CI: 1, 3), with disorders more common in men and more frequent in those under thirty; there was no evidence that they are more common in black and minority ethnic populations. We found no evidence for any psychotic outcome, that study quality affected the reported incidence rate. There was little evidence incidence had changed over time, other than attributable to changes to the underlying denominator population or changes in diagnostic fashion.

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## **Chapter 5: Prevalence in the General Population**

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## 5.0 RESULTS: PREVALENCE IN THE GENERAL POPULATION

We have arranged this section, as with the previous section on incidence, themed around the main diagnostic outcome of interest. Within each of these subsections we report the overall prevalence rates of disorder, as identified from the literature as well as examining rates, where provided, stratified by age, gender, age and gender, ethnicity, country of birth, geographical variation, time and data quality. Where relevant, we report studies which have published rates stratified by two or more of these variables. Estimations of prevalence have taken various forms between 1950 and 2009 and the same and different authors have presented prevalence distinguishable by type; **point**, **period** and **lifetime**, sometimes in the same citation. We have been diligent to these important distinctions and present results accordingly. All analyses are conducted separately according to prevalence type, and this necessarily adds a further level of stratification of the data. Given the many permutations by which prevalence data could have been presented, data for specific analyses were therefore often sparse. When appropriate, we use meta-analyses and meta-regressions to facilitate and aid our systematic review of the literature, but their employment has been used judiciously.

### 5.1 All clinically relevant psychoses

#### 5.1.1 Overall prevalence rates of all clinically relevant psychotic disorders

We identified just one citation which had estimated an overall point prevalence of all clinically relevant psychotic disorders [C22]. This study estimated the point prevalence rates in the adult population in Salford (aged 16 and over, no upper age limit), on 31<sup>st</sup> December, 1973 to be 4.6 per 1000 (95% CI: 4.2, 5.0). The corresponding point prevalence for in-patient only groups was estimated to be 2.5 per 1000 (no corresponding standard error could be derived). A further citation [C97] estimated the 2-month period prevalence rate in the city of Gloucester in 2000, based on scrutiny of all health and social care contact points in the city for people with mental illness. The study estimated the period-prevalence to be 3.3 per 1000 (95% CI: 3.0, 3.6).

We identified a further 12 citations which had reported an annual (12-month) period prevalence rate [C22, C59, C63, C87, C90, C104, C110, C114, C128, C131, C133, C142], from which we were able to identify seven **unique/core** rates [C22, C59, C90, C104, C110, C131, C133] (see Table

5.1). Point estimates of the annual prevalence varied from 1.2 per 1000 (95% CI: 1.0, 1.4) [C110] for admission rates in a London borough to 7.8 per 1000 (95% CI: 7.2, 8.5) [C104] in the PRiSM study, based on community mental health services (Figure 5.1). The pooled estimate of the annual prevalence rate in England was 4.1 per 1000 (95% CI: 2.6, 6.5), though considerable heterogeneity between estimates was observed ( $I^2 = 0.99$ ).

**Table 5.1: Overall annual prevalence of all psychotic disorders from relevant citations (Section 5.1.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Annual prev. <sup>6</sup>	95% CI
<b>C133, S26</b>	Meltzer	1994	Great Britain	NA	1993 (9m)	5	<u>133</u>	4.0 <sup>c</sup>	3.4, 4.7
<b>C131, S66</b>	Sadler	2009	England	NA	2006 (1)	5	<u>30</u>	4.0 <sup>c</sup>	2.8, 5.7
<b>C110, S53</b>	Soomro	2002	Merton	24	1993 (1)	1	<u>156</u>	1.2 <sup>c</sup>	1.0, 1.4
<b>C104, S18</b>	Ruggeri	2000	Nunhead, Norwood	16	1991 (1)	6	511	7.8 <sup>c</sup>	7.2, 8.5
<b>C90, S40</b>	Kai	2000	Newcastle	17	1997 (2)	2	234	3.7 <sup>d</sup>	3.2, 4.2
<b>C59, S23</b>	Bebbington	2004	Great Britain	NA	2000 (7m)	4	60	5.0 <sup>c</sup>	3.9, 6.4
<b>C22, S3</b>	Freeman	1986	Salford	23	1974 (1)	4	624	6.8 <sup>c</sup>	6.3, 7.4

<sup>1</sup>Compass abbreviations used (N, S, E, W), AESOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban. NA=Not applicable

<sup>3</sup>Mid-year of case ascertainment period, duration in years (or months [m]) shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

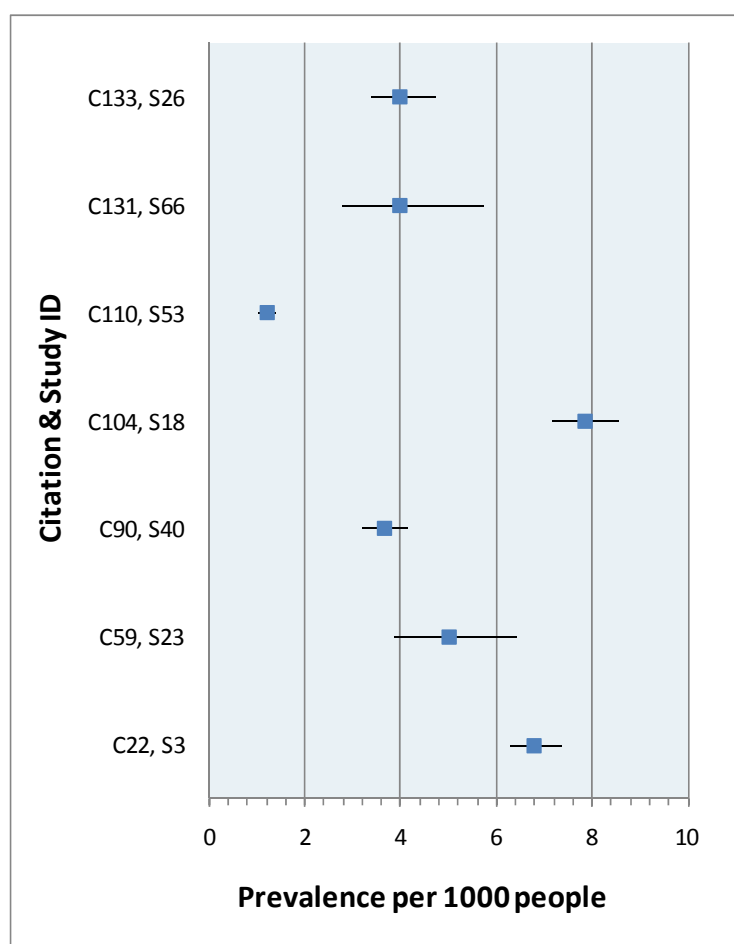
<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

<sup>6</sup>Per 1000. c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

### 5.1.2 Prevalence of all clinically relevant psychotic disorders by gender and age

We identified one citation which had reported the point prevalence of all psychotic disorders for men and women separately [C22], based on data from the Salford Psychiatric Case Register. Point estimates suggested prevalence was similar for both men (7.0 per 1000) and women (6.6 per 1000), but no estimates of standard error were provided to permit us to test whether this small difference was statistically significant. We did not identify any study which had published point prevalence rates of all clinically relevant psychoses by age, or age by gender.

Four citations [C87, 128, C131, C142] had estimated the annual prevalence of all clinically relevant psychoses separately for men and women of which two citations [C87, C128] came from the same study, the latter being identified as the core citation. All four citations provided rate estimates from large, national household surveys of the prevalence of psychiatric disorders in England, Wales and Scotland. All studies suggested that rates were similar between men and women. Data from the first British National Survey of Psychiatric Morbidity [BNSP] [C128]

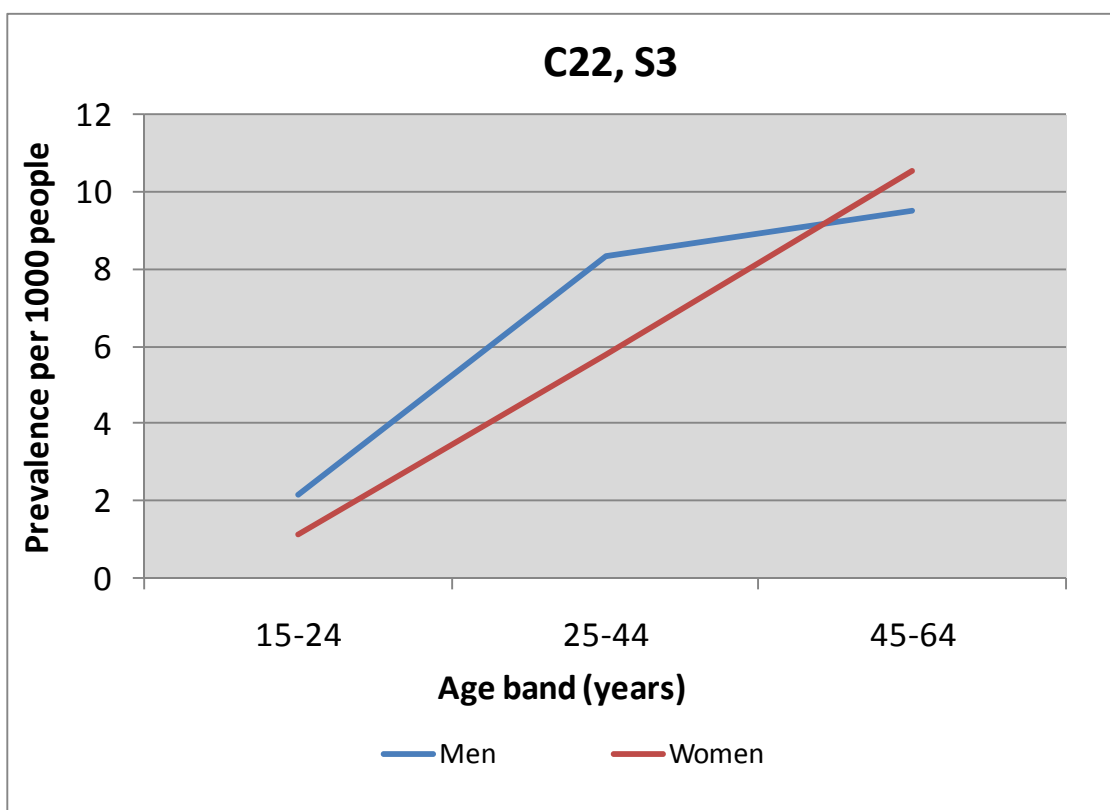
**Figure 5.1: Forest plot of period prevalence of all clinically relevant psychotic disorders**

suggested that the annual prevalence, standardised for age, sex, household size and survey non-response, was estimated to be 4.0 per 1000 for both men (95% CI: 2.3, 6.9) and women (95% CI: 2.3, 6.9) aged 16-64 years in *Britain*. Rates were comparable for people living in English households in the second BNSP survey [C142], conducted seven years later (2000), with crude estimates being placed at 6.0 per 1000 for men (95% CI: 3.8, 9.3) and 5 per 1000 per women (95% CI: 3.2, 7.7), aged 16 to 64 years. Finally data from the most recent national survey of psychiatric morbidity, the Adult Psychiatric Morbidity Survey (2007) [C131] suggested that crude annual prevalence rates for the adult population in Great Britain aged 16 to 74 years were 3.0 per 1000 (95% CI: 1.7, 5.4) for men and 5 per 1000 for women (95% CI: 3.2, 7.8). The corresponding figures for the 16-64 year group were 4 and 6 per 1000 for men and women, respectively. There was no evidence that any of these rate differences were statistically significant. We pooled these data using a random effects, multivariate meta-analysis, which



confirmed the similarity in annual prevalence rates between men (4.3 per 1000; 95% CI: 2.9, 6.5) and women (4.7 per 1000; 95% CI 3.6, 6.2) (OR: 1.1; 95% CI: 0.7, 1.8).

**Figure 5.2: Annual prevalence of all clinically relevant psychoses by age and gender [C22]**



We identified three citations that had also published annual prevalence rates of all clinically relevant psychoses by gender and age [22, 131, 142], the latter two taken from the national household surveys of psychiatric morbidity in 2000 [C142] and 2007 [C131]. The third citation [C22] was based on data from the Salford Psychiatric Case Register. For clarity we have graphed the annual prevalence rate by age for men and women separately in each study (Figures 5.2-5.4). Inspection of these graphs reveals some similarities and differences in findings across the studies. First, the range of prevalence rates by age is broadly similar across studies, with rates in all studies observed to peak at around 10-13 per 1000 persons. Second, all three citations observed an increase in the prevalence of psychotic disorders for both men and women up to the mid-thirties. Data from the two household surveys [C131, Figure 5.3; C142, Figure 5.4]

suggested that from the mid-thirties, until aged 64 years, annual prevalence rates of psychoses began to decline for both men and women. This observation held true for both definite (ICD-10 confirmed) psychotic disorder and the studies' broader "probable psychosis" category which included all individuals who initially screened positive for psychosis. By contrast, prevalence rates in the Salford Psychiatric Case Register [C22, Figure 5.2] increased with age for both men and women until 64 years of age. Finally, we did not observe any clear consensus as to whether rates at different age periods were elevated more for one group than another. C22 suggested rates were similar for men and women over the entire adult age range until 64 years. Data from the household surveys suggested prevalence rates of psychosis for men and women were roughly similar at each period until the early to mid-forties, where after rates for men and women tended to diverge. However, in the earlier study [C142, Figure 5.4] point estimates of annual prevalence rates for probable psychosis appeared to be greater for men than women at later ages; a pattern that was reversed in the later study [C131, Figure 5.3]. C22 and C131 also presented combined prevalence estimates for men and women, by age, but we have not presented these here given the similarities in rate estimates between both sexes.

Figure 5.3: Annual prevalence of all clinically relevant psychoses by age and gender [C131]

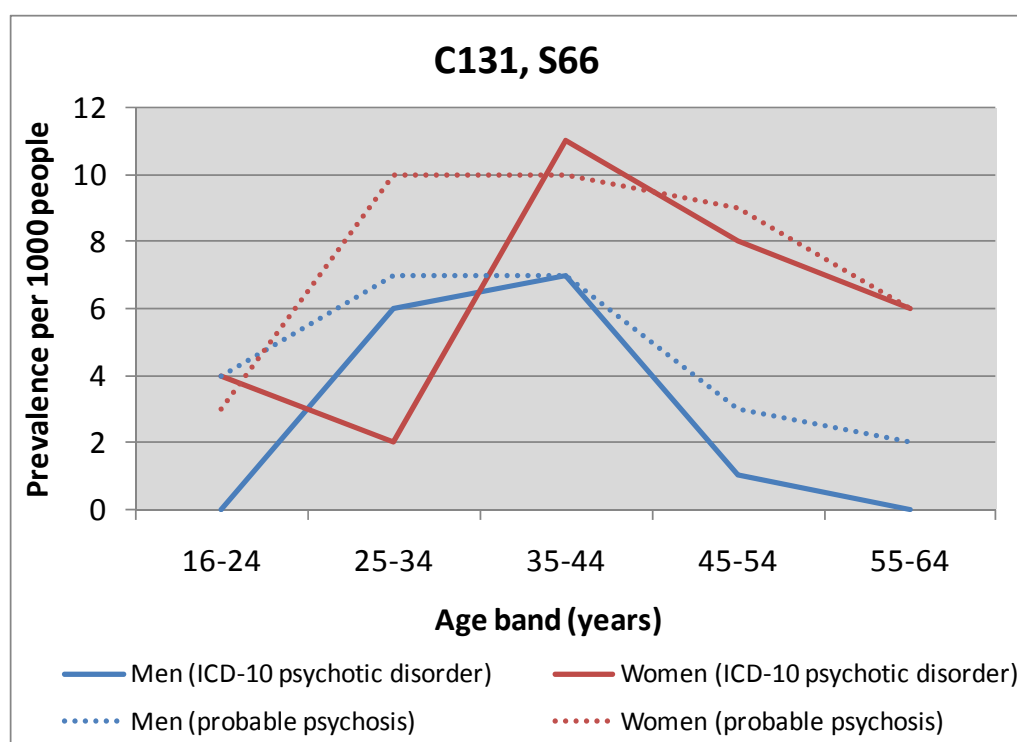
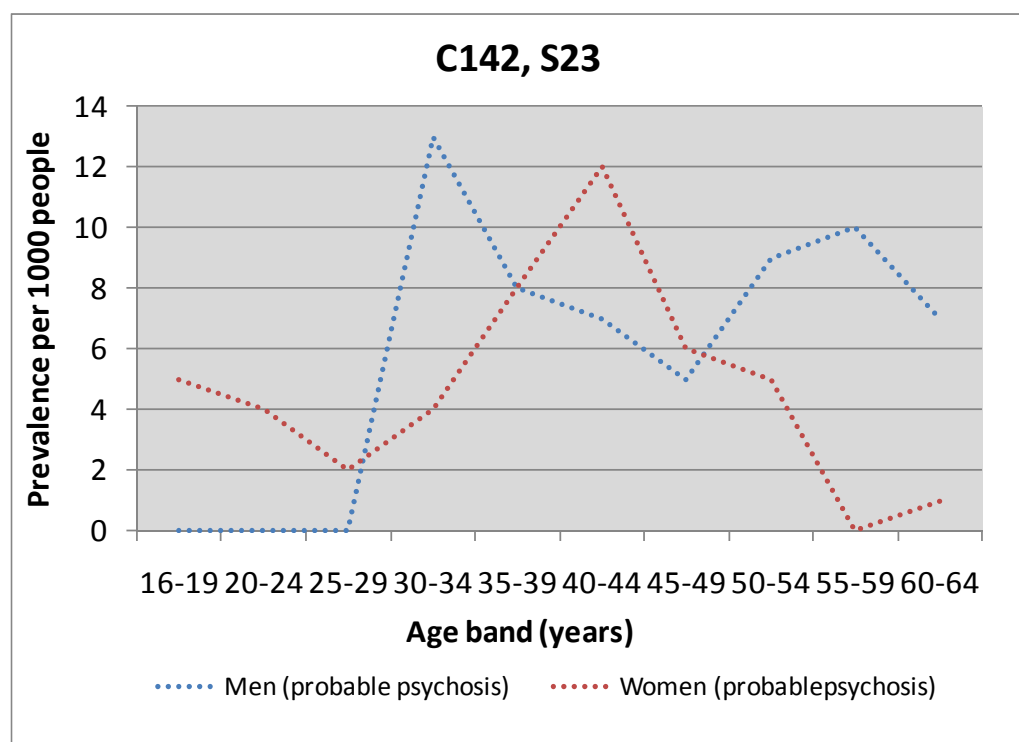


Figure 5.4: Annual prevalence of all clinically relevant psychoses by age and gender [C142]



### 5.1.3 Prevalence of all clinically relevant psychotic disorders by ethnicity and country of birth

We identified six citations which had presented overall annual prevalence rates of all clinically relevant psychoses by ethnic group [C32, C62, C101, C131, C142, C143] of which C32 was excluded as a **satellite** citation of a preferred **core** citation [C143] from the same study [S16]. Data from the first British National Psychiatric Survey [C62] presented by Brugha and colleagues<sup>88</sup> suggested that the annual prevalence of probably psychotic disorder (either confirmed psychosis or probable psychosis at an initial screen) was raised in black Caribbean and black African groups (combined as a single category) (18.9 per 1000; 95% CI: 5.0, 68.9) compared with the white population (4.2 per 1000; 95% CI: 3.0, 3.8). We estimated the associated prevalence ratio here as 4.6 (95% CI: 1.4, 14.5). By contrast, the authors found no evidence that prevalence was elevated in people of Asian ethnicity (OR: 0.38; 95% CI: 0.01, 9.59), though numbers were low. Finally, although the point estimate prevalence ratio was raised for all other ethnic groups compared to the white group (OR: 3.2), but the confidence interval for this effect did not suggest this difference was statistically significant (95% CI: 0.5, 21.0).

Elevated rates of probable psychosis were also raised in people from black ethnicities in the second British National Psychiatric Morbidity Survey [C142] (OR: 3.6; 95% CI: 1.4, 9.4), and age-standardised rates of definite (ICD-10) psychotic disorder were also raised in these groups compared with the white group, just outside of conventional statistical significance (OR: 3.54; 95% CI: 0.98, 12.81), in data published from the third, most recent such national study; the Adult Psychiatric Morbidity Survey [C131]. No other differences in prevalence rates were reported between other ethnic minority groups and the baseline white group in either of these studies. The fourth National Survey of Ethnic Minorities [C101] observed that annual psychosis prevalence was roughly doubled in the black Caribbean group compared (14.0 per 1000) with the white group (8.0 per 1000), though no measure of standard error was published from this study to test whether this difference was statistically significant.<sup>89</sup> Finally, complementary and more detailed rates of prevalence of psychotic disorder by ethnic group were published by Nazroo and King [C143] from the Ethnic Minority Psychiatric Illness Rates in the Community [EMPIRIC] study,<sup>90</sup> conducted in 2000 and based on a sample from the Health Survey for England. The study estimated the annual, age-standardised prevalence of psychotic disorder in the white group (excluding white Irish groups) was 8.0 per 1000 (95% CI: 3.8, 17.3) compared with a rate of 16.0 per 1000 (95% CI: 9.0, 29.4) in the black Caribbean group. These differences did not achieve statistical significance (OR: 2.0; 95% CI: 0.8, 5.3).

We employed a meta-analysis in an attempt to synthesise the data above. Given the heterogeneity between samples we suggest caution in the interpretation of these results, but believe they may be informative in assessing the general direction of results. We inspected the data according to three broad ethnic categorisations; white, black (black Caribbean and African combined) and Asian (Indian, Pakistani and Bangladeshi). There was not sufficient resolution in the data to permit analysis by more specific ethnic groupings. Our meta-analysis for the annual prevalence of all clinically relevant psychosis in the black versus white group included data from four citations [C62, C131, C142, C143]. The pooled data showed only weak evidence of heterogeneity ( $I^2=0.31$ ) and suggested the annual prevalence rate was significantly greater in people of black ethnic groups than their white counterparts (OR: 2.1; 95% CI: 1.2, 3.6). For the Asian versus white group meta-analysis, we were able to include data from three citations [C62, C131, C143]. There was no evidence of heterogeneity across these studies ( $I^2=0.0$ ) and no

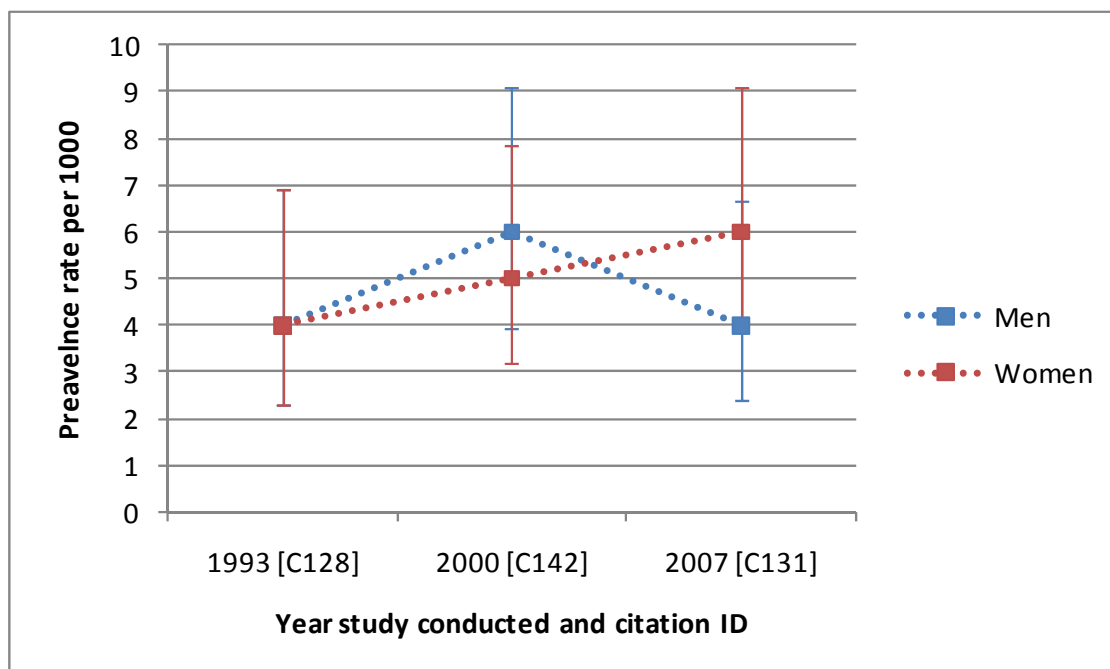
evidence that the annual prevalence rate in the Asian group differed from that in the white population in England (OR: 1.2; 95% CI: 0.8, 1.7).

Three of these citations [C131, C142, C143] reported the annual, age-standardised prevalence of psychotic disorders by ethnic group for men and women separately. Raised point estimates in black ethnic groups were generally observed for both men and women in all three studies compared with the baseline white group, though these differences only achieved statistical significance in one study [C131] for men (OR: 18.2; 95% CI: 3.8, 86.3) (no cases observed for women). In the remaining two studies point estimates for prevalence ratios in black Caribbean men and women were much smaller, ranging between 1.6 (men, C143) and 3.4 (women, C142). We suggest caution in the interpretation of these findings given the small numbers of cases involved.

#### **5.1.4 Prevalence of all clinically relevant psychotic disorders over time**

Comparisons in prevalence rates over time are not straightforward given potential methodological differences under-pinning estimates of rates between studies. As with other comparisons of incidence over time, the use of meta-regressions should only be used to supplement data available from surveys which have more directly attempted to assess changing rates using similar methodologies. The best evidence regarding possible changes in the prevalence of all psychotic disorders over time comes from the three national household surveys of Great Britain conducted in 1993 [C128], 2000 [C142] and most recently in 2007 [C131]. Data from the three studies were available for the adult population aged 16-64 years old to allow us to inspect possible changes in the annual prevalence of all psychotic disorders over time. Inspection of the available data from these studies suggested no significant change in the prevalence of all psychotic disorders between 1993 and 2007 (Figure 5.5). In the 2009 publication of the latest national survey [C131] the authors also published a comparison of the annual prevalence of psychosis by age between the second and third studies (2000, 2007) and showed that at each age period there was little evidence that the prevalence rate of psychosis had changed (see their report [C131 – Figure 5B]).

**Figure 5.5: Annual prevalence of all clinically relevant psychoses over time in the three major national household surveys of psychiatric morbidity**



From the overall annual prevalence rates identified in Section 5.1.1 we were able to perform a meta-regression to examine whether the period prevalence of psychotic disorders had changed over time. The seven relevant citations [C22, C59, C90, C104, C110, C131, C133] were conducted between 1974 and 2006, a period of over 30 years. The data suggested that there had been no change in the period prevalence of all clinically relevant psychotic disorders during this time (OR per year: 0.98; 95% CI: 0.91, 1.06).

### 5.1.5 Geographical variation in the prevalence of all clinically relevant psychotic disorders

Two studies had published prevalence rates of all psychotic disorders by broad geographical region [C1, C142]. C1 inspected point prevalence rates across four community mental health team districts [CMHT] in Luton. The authors reported rates which varied from 3.12 per 1000 to 9.40 per 1000 between CMHTs; a three-fold differences. The authors suggested this variation correlated with socioeconomic deprivation but it was not possible to directly test this from the data present in their publication. Annual prevalence rates from the Second National Psychiatric Morbidity Survey [C142] were published by broad geographical region (NHS Regional Offices)

and for all adults rates varied 1 per 1000 (Southwest) to 10 per 1000 (Trent), but the authors stated that “variation according to region, lacked any consistent pattern and the differences are not large enough to reach statistical significance”<sup>60</sup> (pp.27).

To further investigate the possible effect of urbanicity on prevalence rates of all psychotic disorders we fitted a meta-regression to the citations containing usable data identified as providing overall annual prevalence rates [C22, C90, C104, C110], where our composite urbanicity ranking variable was entered as a covariate. No statistically significant association between the annual prevalence of all clinically relevant psychoses and urbanicity was found (OR: 1.12; 95% CI: 0.65, 1.92).

#### **5.1.6 Prevalence of all clinically relevant psychotic disorders by study quality**

We also inspected whether the overall annual prevalence of clinically relevant psychotic disorder (see Section 5.1.1) varied by study quality [C22, C59, C90, C104, C110, C131, C133]. Quality scores ranged from 1 to 6 (out of 7) and we did find some evidence that higher quality studies reported higher prevalence rates of psychoses (OR per increase in study quality: 1.32; 95% CI: 1.03, 1.69).

### **5.2 Non-affective psychoses**

#### **5.2.1 Overall prevalence rates of non-affective psychoses**

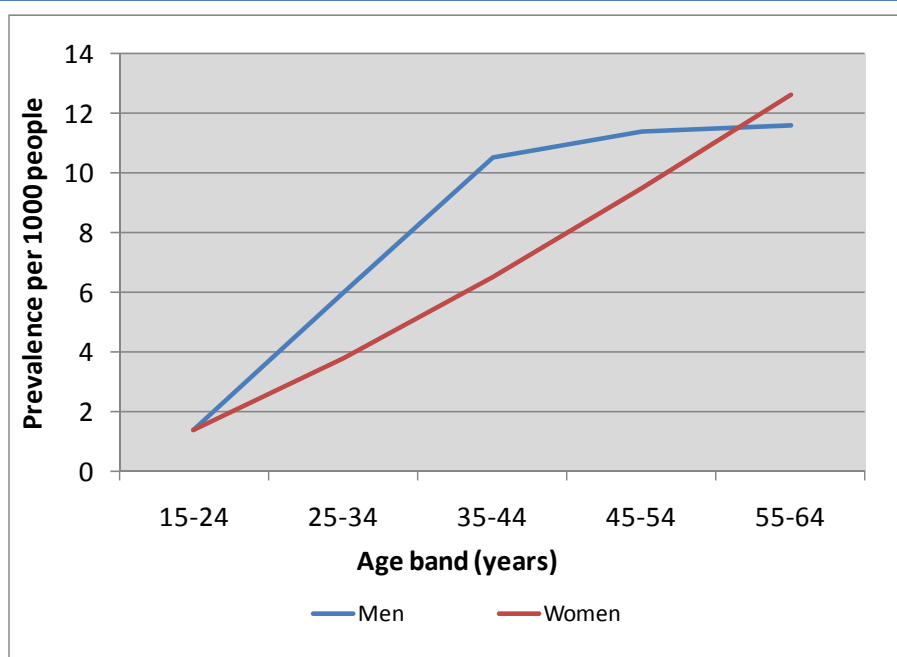
One study [C3] based on data from the Salford Psychiatric Case Register, supplemented by contact with general practitioners to identify further cases, estimated the point prevalence of non-affective psychoses to be 6.3 per 1000 (95% CI: 5.7, 6.9). The same citation placed the annual period prevalence in the same population to be 7.5 per 1000 (95% CI: 6.9, 8.2). We did not identify any other unique/core citation which had estimated the point or period prevalence of non-affective psychoses (though several addressed a narrower definition of schizophrenia, see Section 5.3.1). Finally, we identified two citations [C73, C89] from the 1958 and 1946 birth cohorts, respectively, which allowed us to report the estimate lifetime prevalence of non-affective psychotic disorders at ages 28 and 43, respectively. Done and colleagues [C73] provided two definitions of non-affective psychoses under the PSE-CATEGO system. Using the broader of these definitions (S+, S?, P+, P?, O+, O?) data provided by the study allowed us to

estimate a lifetime prevalence at 28 years of 0.48% (95% CI: 0.39, 0.60). The more restrictive definition of non-affective psychoses used by the authors (S+/S?, P+/P?, O+/ O?) led to an observed lifetime prevalence estimate of 3.5 per 1000 (95% CI: 2.7, 4.5). At 43 years of age, *Jones et al.* [C89] estimated the lifetime prevalence of non-affective psychoses was 6.3 per 1000 (95% CI: 4.4, 9.0).

### 5.2.2 Prevalence of non-affective psychoses by gender and age

One citation [C3] reported the annual prevalence of non-affective psychoses for men (7.7 per 1000) and women (7.4 per 1000) separately using data taken from the Salford Psychiatric Case Register. Rates were similar for both groups but no formal statistical test was possible given absence of corresponding estimates of standard error. This citation was also the only study we identified which reported these rates by gender and age (Figure 5.6). Inspection of the data suggested that the annual prevalence of non-affective psychoses increased with age between 15 and 64 years. This increase appeared to be more pronounced in men at younger ages, but prevalence rates for men appeared to begin to level out after 35 years of age. In contrast rates appeared to constantly increase for women at every age group, and by 55 to 64 years of age, rates were comparable between the sexes.

**Figure 5.6: Annual prevalence of non-affective psychoses by gender and age from published literature [C3]\***



\*No corresponding data were published to allow estimation of standard errors and confidence intervals.



We identified only one further study had published prevalence rates for the non-affective psychoses by gender [C89]. Using data for people aged 43 years old, Jones *et al.*<sup>91</sup> estimated that the lifetime prevalence of non-affective psychoses was significantly higher in men (8.8 per 1000; 95% CI: 5.7, 13.6) than women (4.4 per 1000; 95% CI: 2.4, 8.2) (estimated OR: 2.4; 95% CI: 1.1, 3.0).

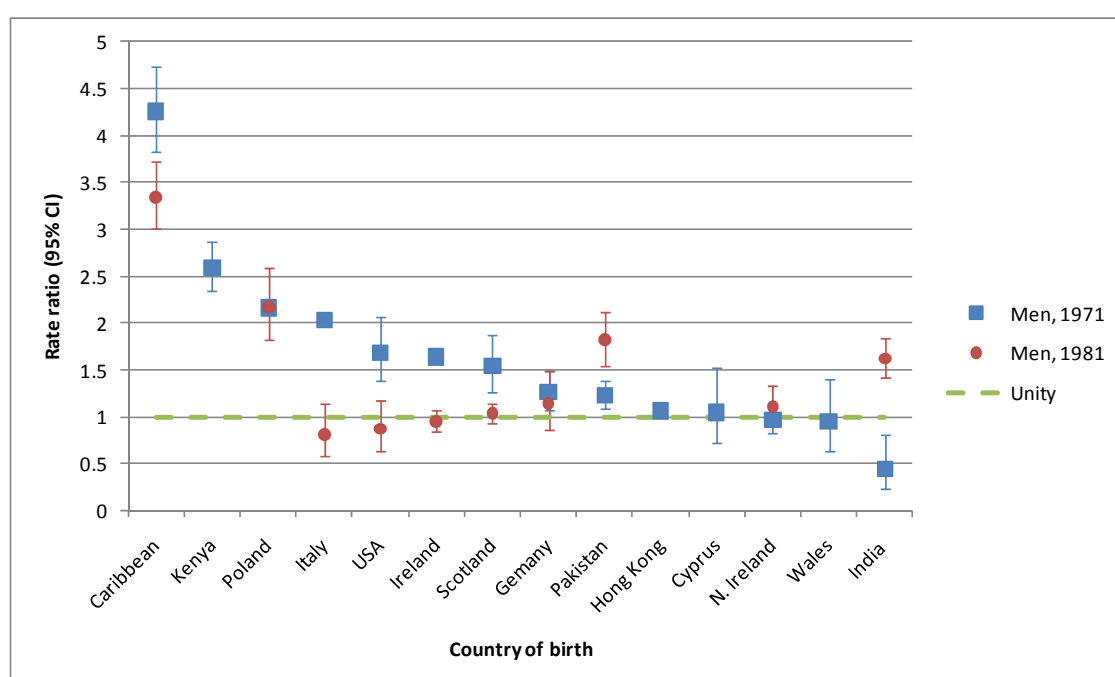
### **5.2.3 Prevalence of non-affective psychoses by ethnicity and country of birth**

We identified one citation [C135] which had reported the annual prevalence of non-affective psychoses in different ethnic groups in England and Wales [C135] using data from the Fourth National Survey of Ethnic Minorities. There were no statistically significant differences in prevalence rates by ethnic group, though point estimates were raised in the black Caribbean group (14 per 1000; 95% CI: 6, 21) compared with the white population baseline (8 per 1000; 95% CI: 4, 12). This difference appeared to be stronger for women (17 per 1000 in black Caribbean women versus 8 per 1000 in the white group) than men (10 and 8 per 1000, respectively). There was also a suggestion of raised prevalence rates in Irish men compared with their non-Irish white counterparts (21 per 1000 vs. 8 per 1000). No data related to standard error was published to allow us to assess whether these differences were statistically meaningful.

Two further citations [C66, C13] published annual prevalence rates of hospitalised admissions of non-affective psychoses by country of birth and sex in England and Wales using from the Mental Health Enquiry [S7] in 1971 and 1981, respectively. We have summarised this data diagrammatically in Figure 5.7 (men) and Figure 5.8 (women), respectively. Of note, the baseline comparator group is slightly different between 1971 (people born in England) and 1981 (people born in England and Wales). At both time periods, for men and women, the prevalence of admitted non-affective psychosis in England and Wales is highest in the Caribbean-born population (i.e. first generation Caribbean migrants), roughly four times greater than for people born in England or England and Wales. Polish-born immigrants (both sexes) also had highly elevated prevalence rates compared with the baseline group at each time period. Kenyan-born and Pakistani-born men, but not women, appeared also to have elevated prevalence rates of non-affective psychosis at both time periods. Pakistani-born women at 1971 but not 1981 had

significantly lower prevalence rates than their English-born counterparts. Otherwise, rate ratios between 1971 and 1981 were consistent for women, where foreign-born women from Ireland, Italy, Northern Ireland and India had significantly elevated prevalence rates of non-affective psychoses. Rates for women born in other European settings (Scotland, Wales, Germany, Cyprus), Hong Kong and the USA did not appear to be consistently elevated. For men, a less consistent pattern emerged with several foreign-born groups being at elevated risk of psychosis in 1971, but not 1981 (see for example Italian, USA, Irish, Scottish and German men) or *vice versa* (see for example Indian-born men).

**Figure 5.7: Annual prevalence of non-affective psychoses in England & Wales in 1971 and 1981 for men from C135\***



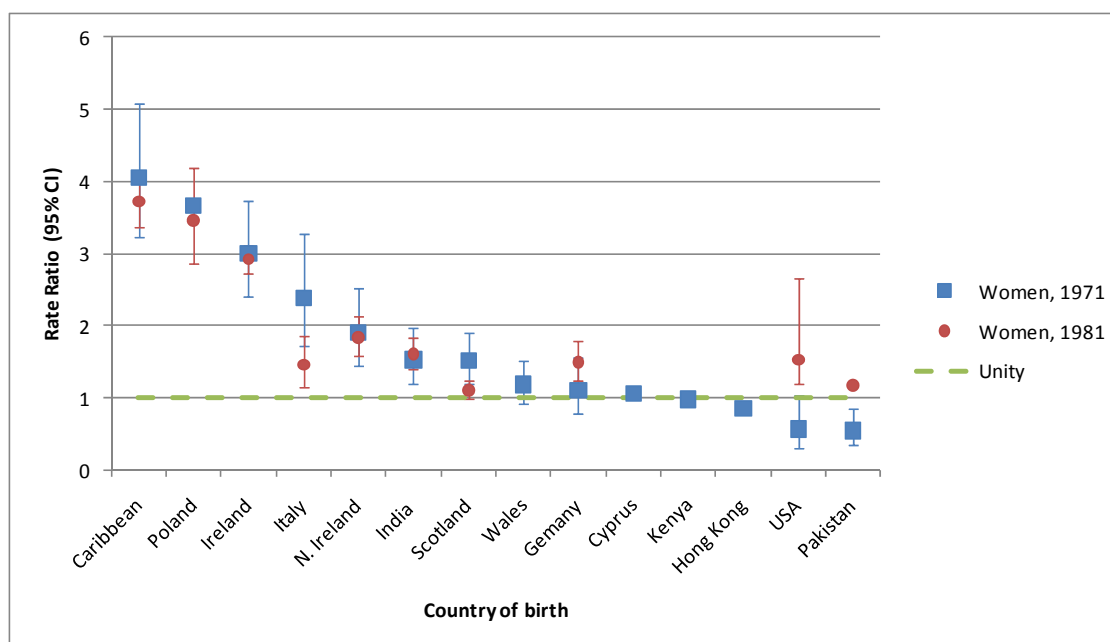
\*Baseline group is English-born in 1971 and English- & Welsh-born in 1981. Rates were not available for every country of birth group at each time period and standard errors were sometimes not reported

## 5.2.4 Prevalence of non-affective psychoses over time

One study [C118] reported point and annual prevalence rates at three time periods between 1976 and 1982 for people using “community psychiatric nursing services”, using data from the Salford Psychiatric Case Register. The study found that rates increased significantly over this time period, but they assigned this increase to greater staffing of the service rather than a true change in the prevalence of disorder. A more recent study of the prevalence of non-affective

psychoses in England in *primary care*, another non-population based sample [C147], found that the annual prevalence had remained close to 0.9 per 1000 people between 1996 and 2005, fairly low compared with overall rates reported above. There was insufficient data for the non-affective sample to permit meta-regression analyses on time.

**Figure 5.8: Annual prevalence of non-affective psychoses in England & Wales in 1971 and 1981 for women from C135\***



\*Baseline group is English-born in 1971 and English- & Welsh-born in 1981. Rates were not available for every country of birth group at each time period and standard errors were sometimes not reported

## 5.2.5 Geographical variation in the prevalence of non-affective psychoses

We did not identify any study which had considered geographic variation in the prevalence of non-affective psychoses. There was also insufficient data for the non-affective sample to permit meta-regression analyses on urbanicity.

## 5.2.6 Prevalence of non-affective psychoses by study quality

There was insufficient data for the non-affective sample to permit meta-regression analyses by study quality.

## 5.3 Schizophrenia

### 5.3.1 Overall prevalence rates of schizophrenia

We identified five **unique/core** estimates of the point prevalence of schizophrenia from four citations [C3, C31, C83, C145] (see Table 5.2). Point prevalence rates varied from 2.0 per 1000 (95% CI: 1.7, 2.2) [145] to 5.9 per 1000 (95% CI: 5.3, 6.4). We excluded one rate [C31, prevalence = 3.5 per 1000] from a meta-analysis because no corresponding measurement of standard error was provided. The pooled point prevalence of schizophrenia from the remaining four citations (Figure 5.9) was estimated to be 3.1 per 1000 (95% CI: 2.0, 5.0), though we noted considerable heterogeneity between the four point estimates included here ( $I^2=0.99$ ).

**Table 5.2: Overall point prevalence of schizophrenia from relevant citations (Section 5.3.1)**

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Point prev. <sup>6</sup>	95% CI
<b>C145, S3</b>	Wing	1976	Salford	23	1971	2	<u>270</u>	2.8	2.5, 3.1
<b>C145, S2</b>	Wing	1976	Camberwell	5	1971	2	<u>238</u>	2.0	1.7, 2.2
<b>C83, S36</b>	Harvey	1996	Camden	11	1995	6	538	2.9	2.7, 3.2
<b>C31, S15</b>	Jeffreys	1997	Hampstead	25	1991	5	NA	3.5	NA
<b>C3, S3</b>	Bamrah	1991	Salford	23	1984	7	436	5.9	5.4, 6.4

<sup>1</sup>Compass abbreviations used (N, S, E, W), ÆSOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban.

<sup>3</sup>Mid-year of case ascertainment period.

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

<sup>6</sup>Per 1000. c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

NA=Not able to derive.

We identified seven **core/unique** citations providing an estimate of the annual prevalence of schizophrenia [C3, C23, C82, C90, C114, C123, C144] (see Table 5.3). These rates varied from 2.1 [C123] to 7.0 per 1000 (95% CI: 6.5, 7.6) [C3].<sup>46</sup> Excluding C123 from a meta-analysis because of the absence of a standard error, the remaining six rates (Figure 5.10) were pooled to give an overall estimate of the annual prevalence of schizophrenia as 4.1 per 1000 (95% CI: 2.9, 5.6). We noted evidence of heterogeneity between rates in the sample ( $I^2=0.98$ ).

Figure 5.9: Forest plot of point prevalence of schizophrenia

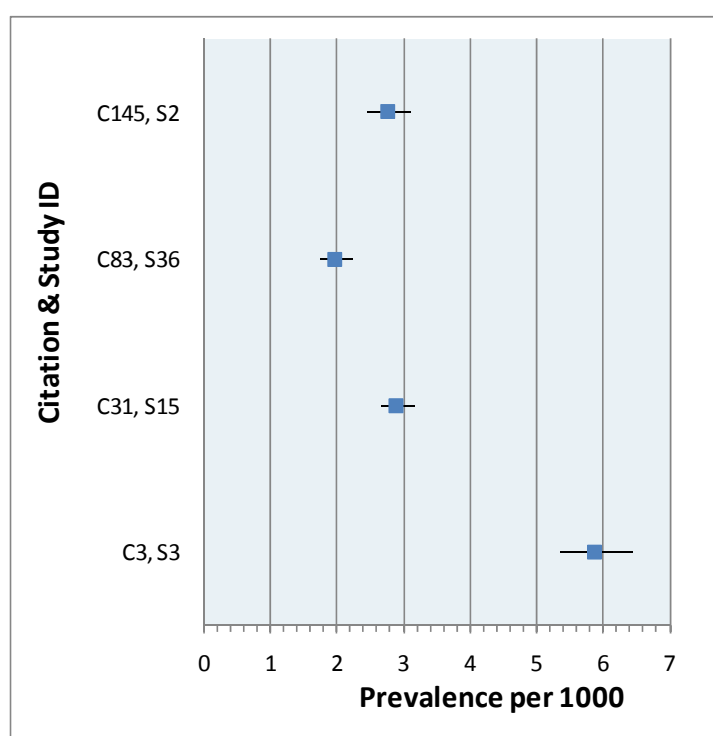


Table 5.3: Overall annual prevalence of schizophrenia from relevant citations (Section 5.3.1)

Study ID	First author	Pub. year	Setting <sup>1</sup>	Urban rank <sup>2</sup>	Mid-year (duration) <sup>3</sup>	Quality rank <sup>4</sup>	N <sup>5</sup>	Annual prev. <sup>6</sup>	95% CI
<b>C144, S2</b>	Wing	1967	Camberwell	5	2000 (1)	1	595	3.4	3.1, 3.7
<b>C123, S60</b>	Gibbons	1985	Southampton	29	NA (NA)	1	NA	2.1	NA
<b>C114, S18</b>	Thornicroft	1999	S London	16	1991 (1)	5	238	3.0	2.6, 3.4
<b>C90, S40</b>	Kai	2000	Newcastle	17	1997 (2)	2	159	2.5	2.1, 2.9
<b>C82, S35</b>	Harris	1984	Inner London	7	1980 (1)	1	<u>163</u>	5.0	4.3, 5.8
<b>C23, S12</b>	Gater	1995	S Manchester	15	1990 (1)	3	<u>68</u>	5.7	4.5, 7.2
<b>C3, S3</b>	Bamrah	1991	Salford	23	1984 (1)	7	520	7.0	6.5, 7.6

<sup>1</sup>Compass abbreviations used (N, S, E, W), A&SOP: SE London, Nottingham, Bristol

<sup>2</sup>Composite rank of perceived urbanicity by 5 raters (JBK, PBJ, TJC, CM, RM) of all settings. (See Section 3.4.4). 1=most urban, 6=least urban.

<sup>3</sup>Mid-year of case ascertainment period, duration in years (or months [m]) shown in brackets

<sup>4</sup>Study quality according to criteria outlined in Box 3.2. (See Section 3.4.4). Min=0, Max=7

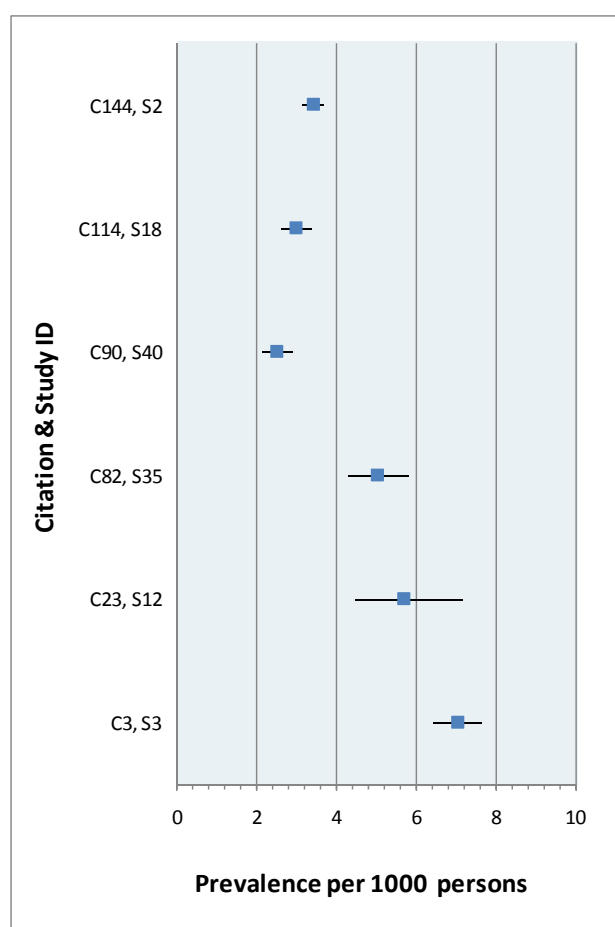
<sup>5</sup>Numbers underlined in italics denote a derived N – not reported in original citation but possible to derive from other provided data

<sup>6</sup>Per 1000. c=crude rate, d=derived crude rate (not provided in citation but possible to derive from other data), a=adjusted rate

NA=Not able to derive.

Data from two birth cohorts, the 1946 and 1958 birth cohorts, allowed us to estimate the lifetime prevalence of schizophrenia at ages 43 [C94] and 28 [C73, C93], respectively. At 28 years the lifetime prevalence of schizophrenia was derived to be 2.3 per 1000 (95% CI: 1.7, 3.1) [C93] and at 43 years of age, the corresponding lifetime prevalence was estimated to be 6.7 per 1000 (95% CI: 4.7, 9.6).

**Figure 5.10: Forest plot of annual prevalence of schizophrenia**



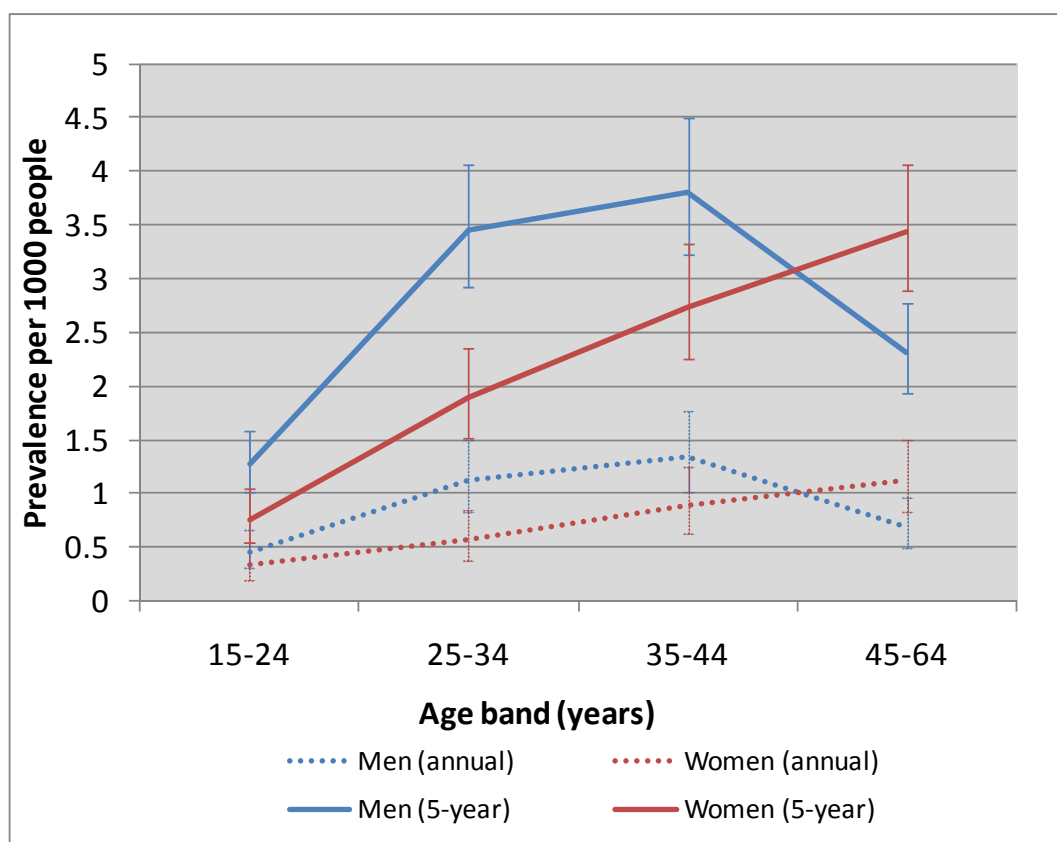
### 5.3.2 Prevalence of schizophrenia by gender and age

The point prevalence of schizophrenia was identified in one study of two case registers (Camberwell and Salford) [C145]. In Camberwell the point prevalence of schizophrenia was placed at 2.0 per 1000 people for both men (95% CI: 1.6, 2.4) and women (95% CI: 1.7, 2.4). In Salford rates were slightly elevated for men (3.0 per 1000; 95% CI: 2.5, 3.5) compared with women (2.6 per 1000; 95% CI: 2.2, 3.0), but this difference did not reach statistical significance

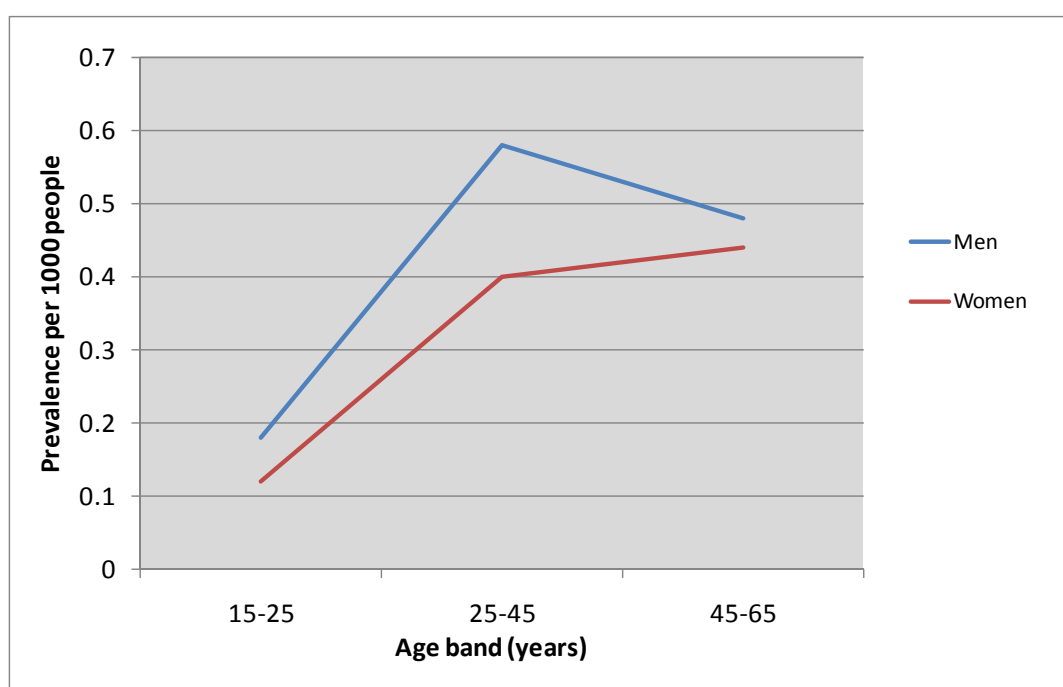
(OR: 1.2; 95% CI: 0.9, 1.5). Annual prevalence estimates for men and women were published in one study [C26], and were observed to be very low for both men (0.6 per 1000; 95% CI: 0.5, 0.7) and women (0.4 per 1000; 95% CI: 0.4, 0.6). These differences were not statistically significant (OR: 1.22; 95% CI: 0.97, 1.53). One possible explanation for their extremely low values (lower, for example than the point prevalence estimates above, or the overall pooled rate for all groups (see Section 5.3.1)), is that the study was based on treated prevalence rates in the previous year. It is possible that these data did not reflect the true prevalence rate in the community. The study also reported the 5-year treated prevalence rate of schizophrenia between 1981-6. The reported rates for men (1.9 per 1000; 95% CI: 1.7, 2.1) were significantly higher than for women (1.6 per 1000; 95% CI: 1.5, 1.8) (OR: 1.15; 95% CI: 1.01, 1.31). These rates were broadly comparable to rates from a second citation [C100] which had also published 5-year prevalence rates of schizophrenia for men (2.0 per 1000; 95% CI: 1.9, 2.1) and women (0.90 per 1000; 95% CI: 0.87, 0.93) for England and Wales between 1994-8, again with rates being statistically significantly greater for men (OR: 2.2; 95% CI: 2.1, 2.3). It is possible that the treated prevalence rates from C26 reflect more plausibly the true rate in the community than the corresponding period prevalence estimates, since people with schizophrenia might be more likely to come into contact with services at least once over a five-year period, than over the course of a given year. This study also published both annual and 5- year prevalence rates by age and gender (Figure 5.11). For both types of prevalence, point estimates were higher for men than women at each age group until 45 to 64 years old, a finding that bears resemblance to the classic age-sex distribution of incidence of schizophrenia. Notably, there was a peaking and subsequent decline of prevalence rates for men, but a more-or-less constant increase in prevalence for women across each age period. Differences in prevalence rates between genders only achieved statistical significance in the 5-year prevalence rate, where from 25-44 years old prevalence rates there was at least some evidence rates were greater in men than women. After 45 years old, however, the reverse became apparent; the 5-year prevalence rate was significantly higher for women than men.

Fascinatingly, point estimates (standard errors not provided) from two further studies of the annual [C144] (see Figure 5.12) and 5-year prevalence [C100] (Figure 5.13) from the only two other studies to have published results on the prevalence of schizophrenia by gender and age, suggested near identical patterns to the one presented above.

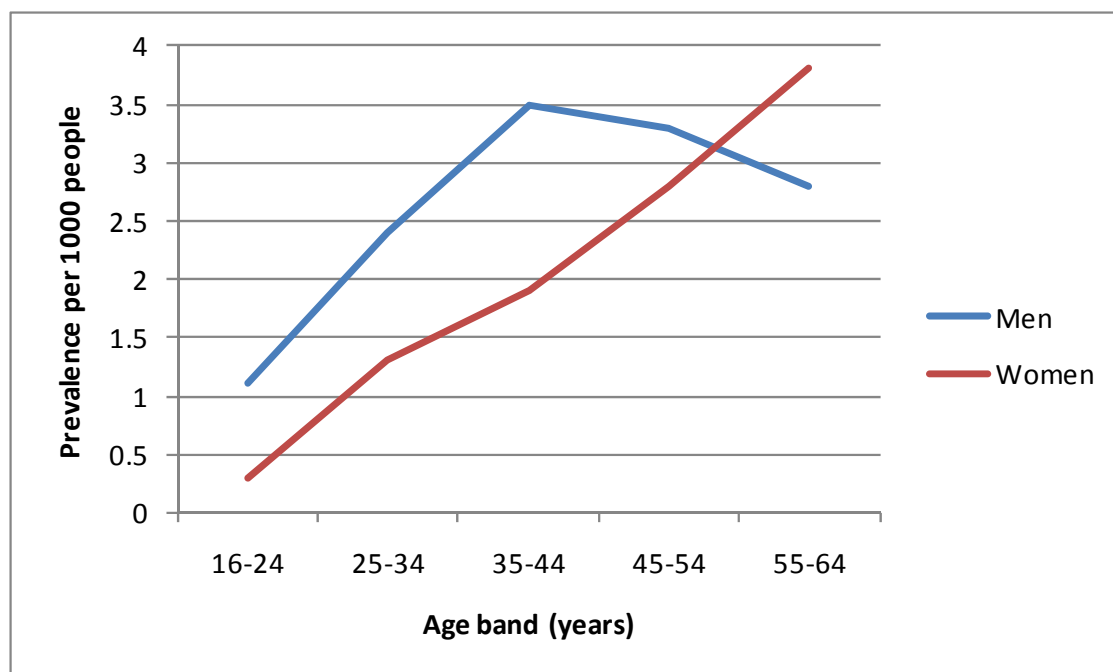
**Figure 5.11: Period prevalence rates of schizophrenia by gender and age from C26**



**Figure 5.12: Annual prevalence rate of schizophrenia by gender and age from C144**





**Figure 5.13: Annual prevalence rate of schizophrenia by gender and age from C100**

### 5.3.3 Prevalence of schizophrenia by ethnicity and country of birth

One citation we identified present estimates of the point prevalence of schizophrenia stratified by country of birth and sex [C58] using data from the Camberwell Psychiatric Case Register in December 1970.<sup>92</sup> The study differentiated between point prevalence rates based on “current” contact with services and rates based on all admissions up until 1978. Under both definitions, the study found no evidence that the point prevalence was raised in Caribbean-born or Irish-born men compared with their UK-born counterparts. For women, however, the authors observed Caribbean-born women (4.2 per 1000; 95% CI: 2.4, 7.2) had significantly higher prevalence rates than their UK-born counterparts (0.7 per 1000; 95% CI: 0.5, 1.0) when “all admissions” were considered (OR: 6.0; 95% CI: 3.1, 11.5), with a suggestion of this effect when the study was restricted to “current contacts” (OR: 1.83; 95% CI: 0.96, 3.49). These findings were standardised for age.

A further two citations were identified which presented the annual prevalence of schizophrenia by country of birth and sex [C12, C54], with a further study providing 6-month period rates

stratified in the same way [C67]. C54 also provided rates by country of birth for both sexes but in the interests of brevity, these results are not presented here. Heterogeneity between samples and small sample sizes prevented formal meta-analysis of these data. The best data was presented from the Camberwell Psychiatric Case Register [C54], which suggested prevalence rates were significantly elevated in Caribbean-born (OR: 4.1; 95% CI: 2.3, 7.3) and African-born men (OR: 34.7; 95% CI: 18.5, 64.9), compared with their British-born counterparts. Corresponding rates for women were equivocal across groups. Inspection of data from the Mental Health Enquiry [C12] broadly ratified this observation (Caribbean-born men vs. English-born men OR: 4.3; Caribbean-born women vs. English-born women OR: 1.2), though the study did not publish standard errors to determine the statistical significance of these rate ratios. Other prevalence rates from this study suggested rates between English-born and foreign-born groups were broadly comparable, with the exception of possibly elevated rates for Polish (OR: 3.7) and Irish-born women (OR: 3.0). The final study [C67] observed no statistically significant differences in the 6-month prevalence of schizophrenia between Irish-born or English-born groups, whether men or women, aged either between 16-44 years or 45-64 years.

Finally, we identified one citation [C42] which published annual prevalence rates of schizophrenia for white versus non-white groups in Norwood and Nunhead (South England). The authors<sup>93</sup> observed that the annual prevalence of ICD-9 schizophrenia was 3.46 per 1000 in Nunhead and 2.24 per 1000 in Norwood for the white group. Rates were significantly elevated for the non-white group in both settings (Nunhead non-white OR: 2.1; 95% CI: 1.6, 2.9; Norwood non-white OR: 2.5; 95% CI: 1.7, 3.5). This difference remained statistically significant when different diagnostic classifications – DSM-III-R or ICD-10 – were also considered. The authors reported that the largest non-white ethnic minority group in the population at-risk in both these settings was the black Caribbean group.

#### **5.3.4 Prevalence of schizophrenia over time**

We were able to perform meta-regressions on both the overall point and prevalence rates of schizophrenia identified in Section 5.3.1 to assess whether there was any evidence that rates of schizophrenia had changed over time. In respect to point prevalence, we included four rate estimates from three studies [C3, C83, C145], but found no evidence to suggest there was a

change in rates over the period these studies were conducted, 1971-1995 (OR per year: 1.02; 95% CI: 0.90, 1.15). Similarly, for annual prevalence rates [C3, C23, C82, C90, C114, C123, C144], conducted between 1980 and 2000, we failed to observe any change in rates over time (OR per year: 0.96; 95% CI: 0.91, 1.02).

### 5.3.5 Geographical variation in the prevalence of schizophrenia

We identified five citations which had estimated the prevalence of schizophrenia according to some measure of geographical variation [C42, C83, C100, C122, C145]. These studies were heterogeneous with respect to type of prevalence and geographical measure used. However two citations [C83, C145] published estimates of point prevalence in two locations each; North and South Camden [C83] and Camberwell and Salford [C145]. The former study did not provide standard errors to make meaningful comparisons possible but did estimate the point prevalence of schizophrenia to be 4.9 per 1000 for residents of South Camden compared with 2.2 per 1000 for residents of North Camden, equivalent to an odds ratio of 2.2. The latter study [C145] observed significantly higher rates of schizophrenia in Salford compared with Camberwell for all groups (OR: 1.4; 95% CI: 1.2, 1.7), men (OR: 1.5; 95% CI: 1.2, 1.9) and women (OR 1.3; 95% CI: 1.0, 1.7). One further study [C42] did not find any significant differences between Norwood and Nunhead in the annual prevalence of schizophrenia for either the white or non-white group. Moser *et al.* [C100] observed a strong gradient in the 5-year prevalence of schizophrenia for men and women in England and Wales, such that the rate in the lowest quintile of deprivation for men was 0.9 per 1000 (95% CI: 0.8, 1.0) and for women 1.1 per 1000 (95% CI: 1.0, 1.2), increasing for both sexes in a dose-response fashion until the fifth quintile where rates were 3.0 per 1000 (95% CI: 2.8, 3.1) and 2.2 (95% CI: 2.1, 2.4). Finally, Congdon *et al.* [C122] also observed higher admission rates of schizophrenia in more deprived wards in Barking and Havering.

We employed meta-regressions for data on both the point and period prevalence rates of schizophrenia identified in Section 5.3.1 to inspect whether prevalence rates varied significantly by our composite urbanicity ranking. No such association was observed for either point ( $p=0.27$ ) or period ( $p=0.64$ ) prevalence.

### **5.3.6 Prevalence of schizophrenia by study quality**

Data on study quality from the citations providing overall point and period prevalence rates identified in Section 5.3.1 were included in meta-regressions, but there was no evidence that study quality affected the observed prevalence rate for either point ( $p=0.22$ ) or period prevalence rates ( $p=0.64$ ).

## **5.4 Affective psychoses**

### **5.4.1 Overall prevalence rates of affective psychoses**

We did not identify any study which reported the point prevalence of the affective psychoses, given our search criteria. Two citations [C55, C114] were identified which provided estimates of the annual prevalence rate for the affective psychoses, both of which were conducted in London, in 1967 [C55] and 1991 [C114] respectively. The prevalence of affective psychoses was generally lower than for their non-affective counterparts (see Section 5.3), with annual prevalence rates varying from just 0.02% (95% CI: 0.01, 0.03) [C114] to 1.0 per 1000 (95% CI: 0.9, 1.1) [C55]. Finally, data provided by Done and colleagues [C73] from the 1958 birth cohort allowed us to derive an estimate of the lifetime prevalence of affective psychoses at 28 years of age to be 2.1 per 1000 (95% CI: 1.5, 3.0).

### **5.4.2 Prevalence of affective psychoses by gender and age**

We were unable to identify any study which had presented any types of prevalence rate of all affective psychoses by gender, age or gender and age. For studies of the affective psychoses along these sociodemographic dimensions, please refer instead to the sections reporting the prevalence of bipolar disorder (Section 5.5) and the depressive psychoses (Section 5.6) separately.

### **5.4.3 Prevalence of affective psychoses by ethnicity and country of birth**

No study presented prevalence rates of affective psychoses by ethnic group. However, we identified three studies [C55, C58, C66] which had reported the point [C58] or annual [C55, C66] prevalence of affective psychoses by country of birth.

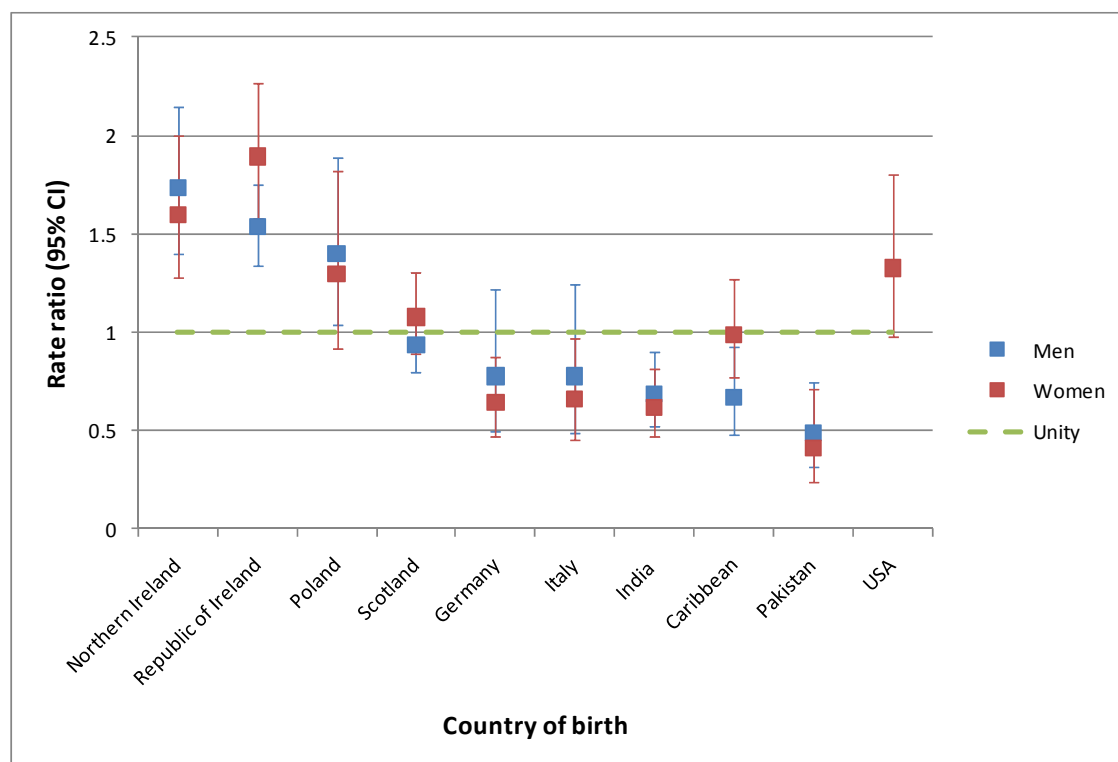
Turning first to the point prevalence, there was no evidence from the Camberwell Psychiatric Case Register [C58] the rate of affective psychosis based on total admissions was 1.2 per 1000 for men (95% CI: 0.9, 1.6) and 2.6 per 1000 for women (95% CI: 2.1, 3.1), and there was no evidence that these rates were significantly different for either the Caribbean-born or Irish-born population in the study.

We were able to derive annual prevalence rates of affective psychoses for immigrants according to country of birth from data published by Bagley [C55] from the Salford Psychiatric Case Register in 1966. These estimates have been derived from that publication by the authors of the present review. We have made no attempt to compare rates between groups, because the study did not report data to allow us to derive a point prevalence rate in the UK-born group. Prevalence rates were lowest for those people born in the Caribbean (1.3 per 1000; 95% CI: 0.7, 2.4) and highest in people born in India and Pakistan (4.5 per 1000; 95% CI: 1.4, 14.0) and Africa (8.6 per 1000; 95% CI: 3.9, 19.3). Data derived from the Mental Health Enquiry [C66] could illuminate these findings to a greater extent (Figure 5.14). The data suggested that rate ratios for each group were similar for men and women in each country of birth category. Thus annual prevalence rates of hospitalised admissions of affective psychoses were significantly elevated for men and women from both the Republic of Ireland and Northern Ireland compared to their English-born counterparts. There was a suggestion that prevalence rates for Polish-born groups were also elevated but this only achieved statistical significance in men. The hospitalised prevalence of affective psychoses were significantly lower for women born in Germany, Italy, India and Pakistan and for men born in India, the Caribbean and Pakistan than their English-born counterparts. Rates were equivocal for men and women born in Scotland and women from the Caribbean and the USA.

#### **5.4.4 Prevalence of affective psychoses over time**

We did not identify any study which had considered the prevalence of affective psychoses (as a single category) over time. There was also insufficient data to look at changes in prevalence in relation to time from a meta-regression of cross-section surveys.

**Figure 5.14: Annual prevalence of affective psychoses by country of birth for men and women from the Mental Health Enquiry, 1971 [C66]**



#### 5.4.5 Geographical variation in the prevalence of affective psychoses

We did not identify any study which had considered the prevalence of affective psychoses (as a single category) by a measure of geography. There was also insufficient data to look at changes in prevalence in relation to urbanicity from a meta-regression of cross-section surveys.

#### 5.4.6 Prevalence of affective psychoses by study quality

There were insufficient studies to permit assessment of whether the prevalence of affective psychosis was influenced by study quality.

### 5.5 Bipolar disorder

#### 5.5.1 Overall prevalence rates of bipolar disorder

One citation [C145] was identified which had estimated the point prevalence of bipolar disorder in England. The citation provided two independent rates, from the Salford and Camberwell case

registers, respectively, in 1968. Reported prevalence rates were very low: 0.20 per 1000 (95% CI: 0.13, 0.30) in Camberwell and 0.07 per 1000 (95% CI: 0.03, 0.14) in Salford.

We also identified two citations [C90, C144] which had estimated the annual prevalence of bipolar disorder. The most recent study [C90], conducted in Newcastle in 1997, published data which allowed us to derive an annual estimated prevalence rate of 0.9 per 1000 (95% CI: 0.7, 1.1) for people aged 16 to 64 years old. The earlier study, by Wing *et al.* [C144], was based on the Camberwell psychiatric case register in 1965. Here, the age range of the study included all people, not restricted to those aged 16-64 years, and the estimated annual prevalence of bipolar disorder was much higher, placed at 3.8 per 1000. Further data were not provided in this study to permit us to place a confidence interval around this estimate. Finally, data from Done *et al.* [C73] allowed us to estimate the lifetime prevalence of bipolar disorder at 28 years old, placed at 0.6 per 1000 (95% CI: 0.3, 1.1).

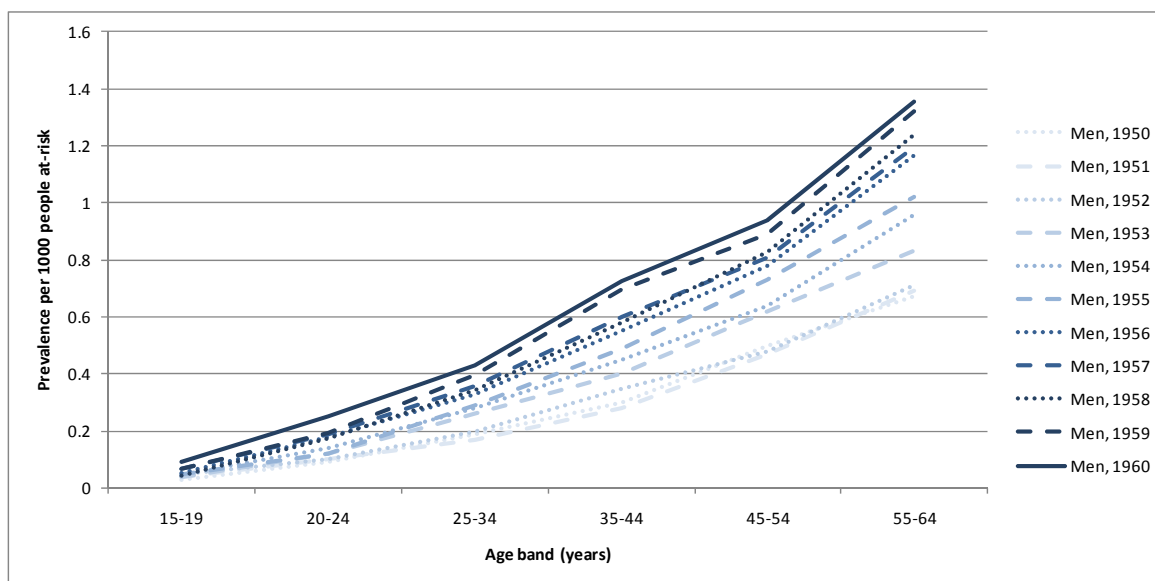
### **5.5.2 Prevalence of bipolar disorder by gender and age**

Published point prevalence rates of bipolar disorder were estimated separately for men and women in one citation [C145], which published separate rates from two psychiatric case registers; Salford and Camberwell. In both centres point estimates were low and similar for men and women (Camberwell men: 0.19 per 1000 (95% CI: 0.10, 0.35), Camberwell women: 0.21 per 1000 (95% CI: 0.12, 0.36) and Salford men: 0.07 per 1000 (95% CI: 0.02, 0.21), Salford women: 0.08 per 1000 (95% CI: 0.03, 0.21)). We note here that although prevalence rates were higher in Camberwell compared with Salford, for both men (OR: 2.7; 95% CI: 0.8, 9.4) and women (OR: 2.1; 95% CI: 0.9, 7.9), these differences did not reach statistical significance.

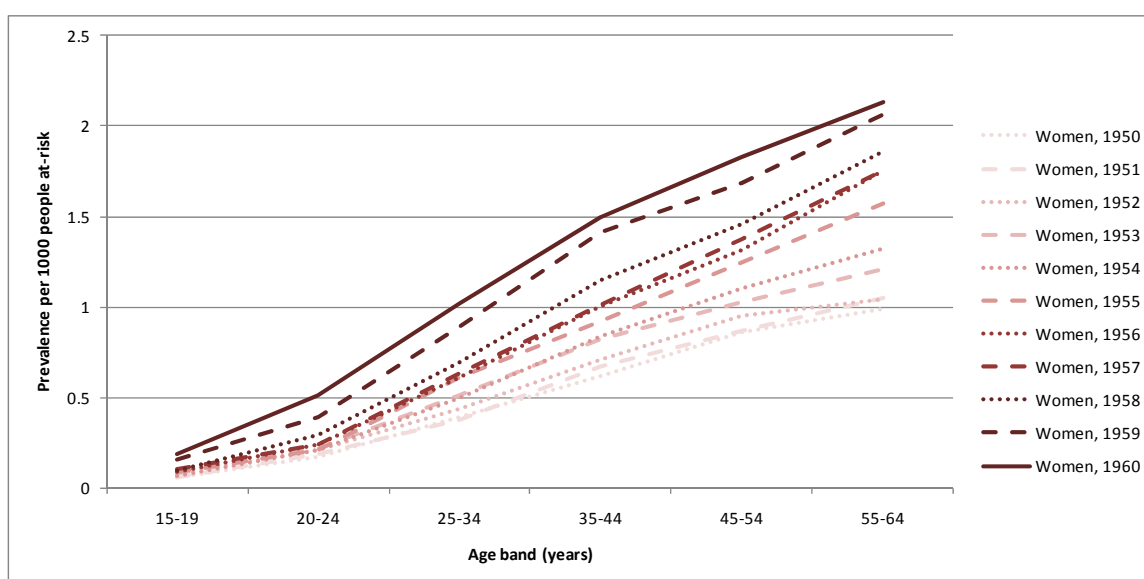
Two further citations had published the period prevalence of bipolar disorder stratified by gender and age [C144] and gender, age and year [C56]; the latter for 10 years based on total admissions to psychiatric facilities in England and Wales between 1950 and 1960. In this study, the annual admitted prevalence of bipolar disorder increased with age, up until 64 years of age for both men and women separately (Figures 5.15 and 5.16, respectively). In each year of observation, at each age group, point estimates of rates were higher for women than men. We were unable to test these differences because the authors did not publish corresponding

standard error estimates. Analogous findings were observed in C144. Finally, of note in regard to these findings (see also Section 5.5.4), the admitted prevalence of bipolar disorder increased, more-or-less, year-upon-year over this 11-year period for both men and women (see Figures 5.15 and 5.16).

**Figure 5.15: Annual prevalence of bipolar disorder by age and year for men from C56**



**Figure 5.16: Annual prevalence of bipolar disorder by age and year for women from C56**





### **5.5.3 Prevalence of bipolar disorder by ethnicity and country of birth**

Our search strategy did not identify any citation which had published prevalence rates of bipolar disorder by ethnicity or country of birth.

### **5.5.4 Prevalence of bipolar disorder over time**

We only identified one citation [C56] which observed trends in the prevalence of bipolar disorder over time. As reported in Section 4.3.5.4, this study published annual prevalence rates of total admissions in England and Wales between 1950 and 1960. For both men and women, admission prevalence rates increased over this time period, an effect which was perhaps more exaggerated with increasing age (see Figures 5.15 and 5.16). For both men and women, there was a suggestion this increase may have accelerated after 1957. It was not possible to determine whether these changes were statistically significant or whether they indeed reflected genuine changes in the true (community) prevalence of bipolar disorder at this time.

### **5.5.5 Geographical variation in the prevalence of bipolar disorder**

Data are sparse and will be populated in the final version of this review

### **5.5.6 Prevalence of bipolar disorder by study quality**

Data are sparse and will be populated in the final version of this review

## **5.6 Depressive psychoses**

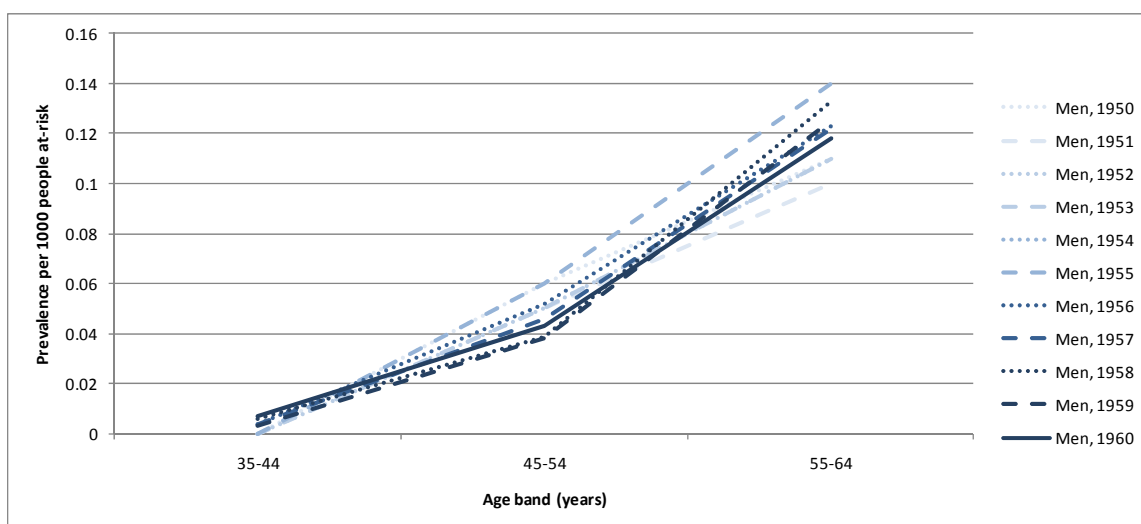
### **5.6.1 Overall prevalence rates of depressive psychoses**

We identified one citation [C73] which provided data to allow us to estimate the (lifetime) prevalence of depressive psychoses. This data came from the 1958 British birth cohort, which suggested that the lifetime prevalence of depressive psychoses at 28 years of age was 0.4 per 1000 (95% CI: 0.2, 0.8).

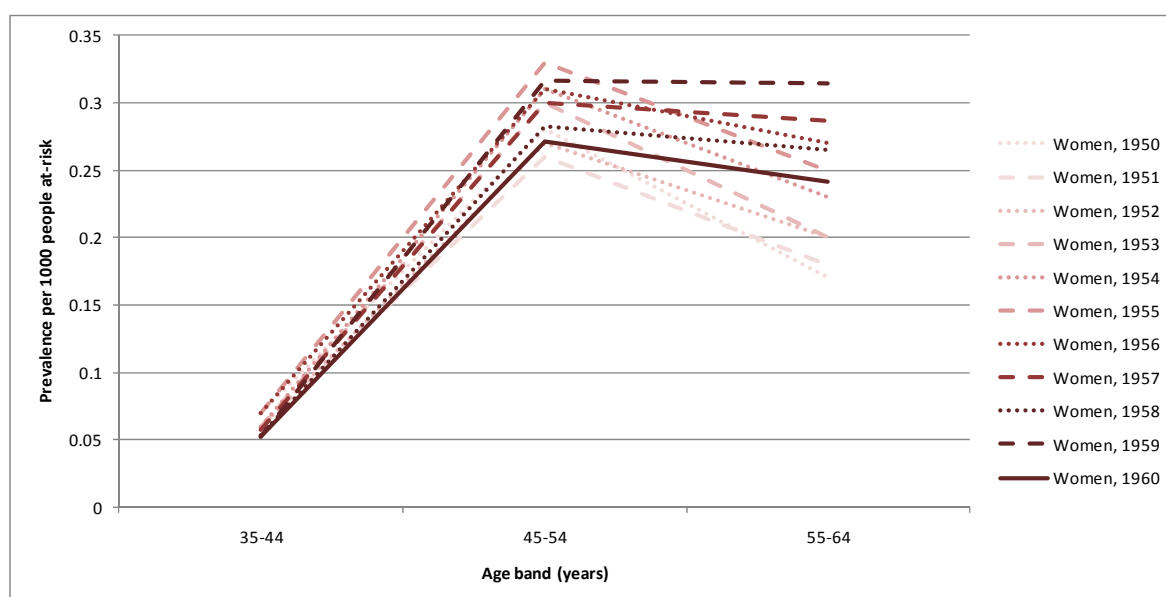
## 5.6.2 Prevalence of depressive psychoses by gender and age

One citation [C56] had published annual prevalence rates of admitted depressive psychoses, or “involuntional melancholia”, in people aged 35 -64 years in England and Wales, for each year over the period 1950-60. For men, prevalence rates appeared to increase constantly with age (Figure 5.17), however for women this increase plateaued, and possibly declined after 45 to 54 years of age (Figure 5.18). There was no suggestion from this data (unlike the corresponding data from this study for bipolar disorder, see Section 5.5.2), that admitted prevalence rates increased (or decreased) with any discernable pattern over the time period.

**Figure 5.17: Annual prevalence of depressive psychoses by age and year for men from C56**



**Figure 5.18: Annual prevalence of depressive psychoses by age and year for women from C56**



### **5.6.3 Prevalence of depressive psychoses by ethnicity and country of birth**

Our search strategy did not identify any citation which had published prevalence rates of depressive psychoses by ethnicity or country of birth.

### **5.6.4 Prevalence of depressive psychoses over time**

We identified, as stated in Section 5.6.2, one citation which had considered the annual admitted prevalence of depressive psychoses – “involitional melancholia” over time in England and Wales [C56]. This study did not suggest that the prevalence rate had changed in a discernible fashion for men or women at any age period between 35 and 64 years of age (see Figures 5.17 and 5.18).

### **5.6.5 Geographical variation in the prevalence of depressive psychoses**

Our search strategy did not identify any citation which had published prevalence rates of depressive psychoses according to geographical variation.

### **5.6.6 Prevalence of depressive psychoses by study quality**

Data are sparse and will be populated in the final version of this review

## **5.7 Substance-induced psychoses**

We were unable to identify a literature on the prevalence (any type) of substance-induced psychoses, save for one study which had published rates of alcoholic psychoses and alcoholism for men and women according to country of birth [C66]. We have not reported these results in great detail because the study did not differentiate between these two outcomes, meaning we could determine with any degree of confidence the prevalence of alcoholic psychoses versus “alcoholism”. Data are available on request. Thus, we were unable to identify any study which had published overall prevalence rates, or rates stratified by age, gender, ethnicity, country of birth, time or by any permutation of the aforementioned dimensions. Given the increased evidence for the role of illicit substances such as cannabis in the aetiology of psychotic disorder, this absence is both surprising and important.

## 5.8 Summary of prevalence findings

Studies of the prevalence of psychotic disorders show considerable variation in methodology and so in results. Overall, annual prevalence estimates (i.e. those with active disorder in the past year) were in the region of 4 per 1000 (95% CI: 3, 7) for all psychotic disorders and similar for the non-affective psychoses. The corresponding lifetime prevalence rate of non-affective psychosis at 43 years old was 6 per 1000; this is consistent with the typically-reported 10 per 1000 (1%) prevalence over the life course. For all clinically relevant psychoses, population surveys indicated similar prevalence for men and women with a peak between 30 and 40 years of age; case registers indicate increasing prevalence with age up to 65 years. There is no indication of changes in prevalence with time. These effects were similar for studies of *non-affective psychosis*, for which there was some evidence of increased prevalence in older women, and for schizophrenia. There were too few studies of affective psychosis to draw meaningful conclusions. Studies which addressed *bipolar disorder* (Section 5.5), specifically, suggested that despite being relatively chronic from a clinical viewpoint, the annual prevalence is less than 1 per 1000, a reflection of its relatively low incidence compared with other psychoses (Section 4.2.5). Prevalence is similar in men and women, and increases with age. Prevalence of *depressive psychosis* was addressed by very few studies and, remarkably, there was none estimating prevalence of substance-induced psychosis. Single studies of depression suggested similar prevalence for men and women, increasing with age monotonically for men and reaching a plateau in middle-age for women. There was no evidence the prevalence of any psychotic disorder had changed over time.

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## **Chapter 6: Incidence & Prevalence in Specialised Populations**

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## **6.0 INCIDENCE AND PREVALENCE RATES IN SPECIALISED POPULATIONS**

Special Populations Overall prevalence rates of all clinically relevant psychotic disorders We identified 21 citations from populations other than general populations, these were described in a variety of terms (General practice/Primary Care, the British Army, puerperal cohorts, prison populations, the homeless, judicial system samples including young offenders, those in residential care or hostel accommodation, care homes (and one of convicted murderers). Four were incidence studies, 2 were incidence and prevalence studies, and the remainder (15 studies) were prevalence. Of the six incidence studies, two were first admission studies, two first contact, and two other types of contact. Of the prevalence studies four were annual, one lifetime, and seven point-prevalence. Importantly, we note that included here were the British National Survey of Psychiatric Morbidity (Homeless), British National Survey of Psychiatric Morbidity (Household + Prison) and British National Survey of Psychiatric Morbidity (Institutional) samples; also the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness and the Survey of Psychiatric Morbidity among Prisoners in England and Wales. Due to the variety of case-finding methods, no decision has yet been made on the synthesis of estimates from these samples, particularly the criminal justice system studies, where there may be sufficient data for a meta-analytic pooling of rates.

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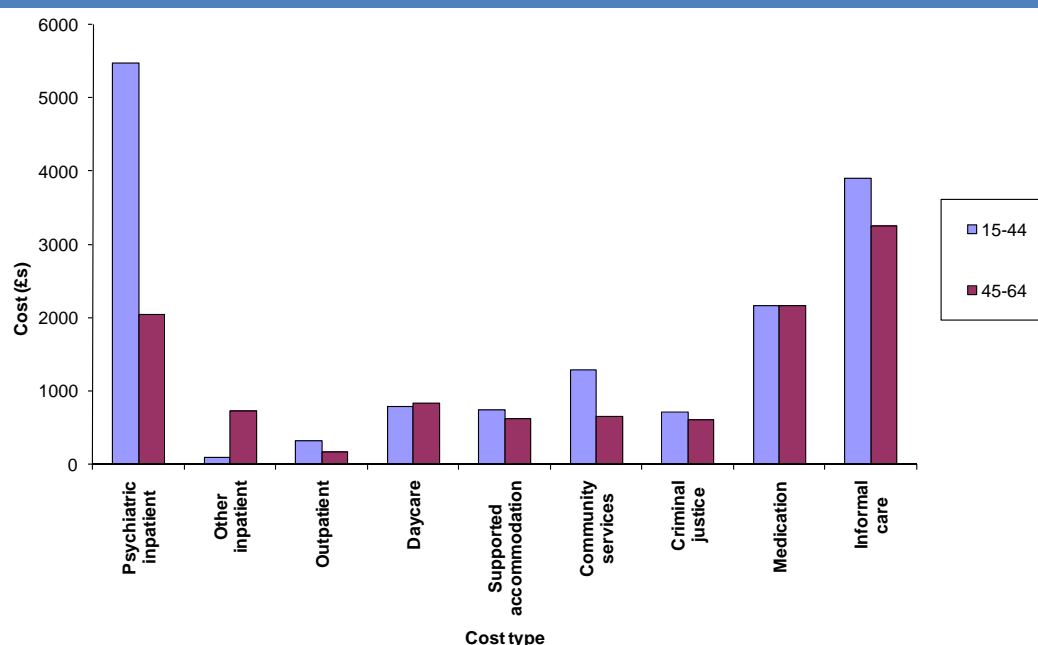
## **Chapter 7: Economic cost implications for health services and society**

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## 7.0 ECONOMIC COST IMPLICATIONS FOR HEALTH SERVICES AND SOCIETY

We were able to estimate the economic costs to services and society in the UK for various psychotic disorders (see Sections 7.2-7.4). Our estimates are based on published annual prevalence rate data, stratified by age and sex, and adjusted to the mid-year 2009 census population. This data was then combined with economic cost data made available for this report by the Centre for the Economics of Mental Health,<sup>3</sup> which detailed the estimated mean annual cost per patient with non-affective psychosis (including schizophrenia) (Figure 7.1) and bipolar disorder (Figure 7.2) to services and society in the UK (Figure 7.1).

**Figure 7.1: Mean annual service costs, by age, per patient for non-affective psychoses in the UK†**



†Data estimated by the Centre for the Economics of Mental Health for the King's Fund. See *Paying the Price* by McCrone *et al.*<sup>3</sup>

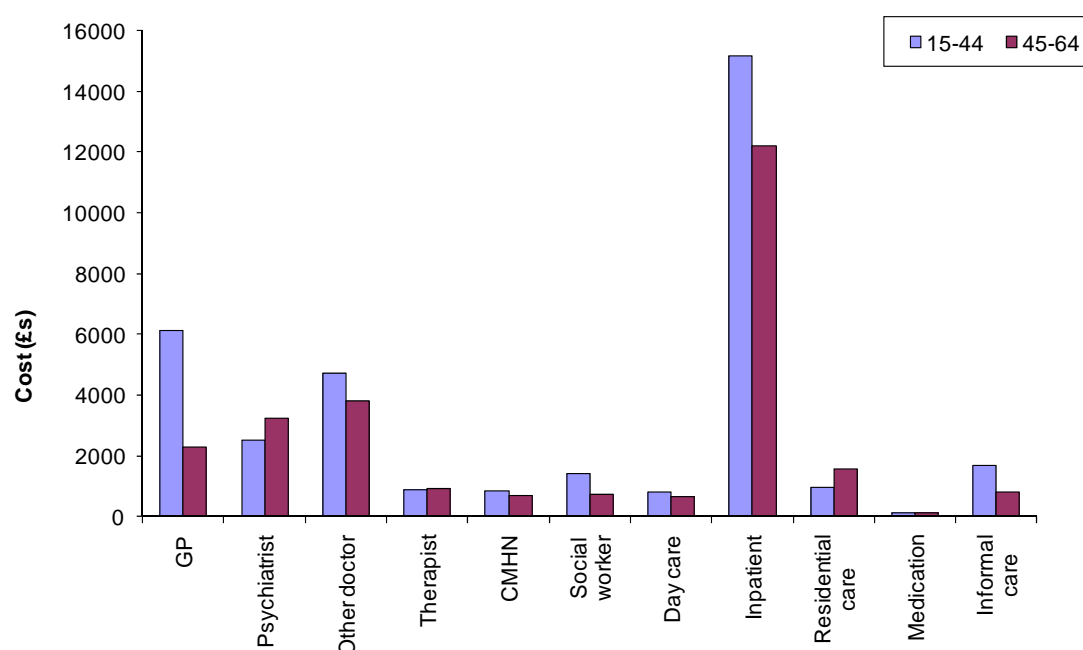
For the non-affective psychoses (Figure 7.1), psychiatric inpatient costs represent the largest single service cost. These costs are considerably higher for people under 45 years of age (£5,479 per annum) than those aged 45 to 64 years (£2,040 per annum). For this older group, informal care costs present the largest single cost to services (£3,252). Medication costs are also



considerable in both age groups, while a range of other service costs, though smaller, also contribute substantially to the total costs of mental healthcare in the UK. In terms of societal costs, the estimated cost of days of employment lost (data not shown in Figure 7.1) represents the single largest economic burden associated with non-affective psychosis.<sup>3</sup> Per annum, this cost is estimated to be £13,607 per individual with a non-affective psychosis aged 15-44 years, and £10,942 for people aged 45-64 years old.

Inpatient costs also reflected the largest single per annum service cost for bipolar disorder in the UK, irrespective of age (see Figure 7.2). Per annum, per patient these costs were £15,171 for people age 15-44 years and £12,200 for people aged 45-64 years. These costs were considerably higher than for non-affective psychoses (see above).

**Figure 7.2: Mean annual service costs, by age, per patient for bipolar disorder in the UK†**



†Data estimated by the Centre for the Economics of Mental Health for the King's Fund. See *Paying the Price* by McCrone *et al.*<sup>3</sup>

## 7.1 Non-affective psychoses

We identified only one citation [C3] which had made available the annual prevalence of non-affective psychoses by age and sex (see Section 5.2.2). This data was taken from a well-conducted (quality rating: 7/7) prevalence survey of psychiatric disorders using the Salford Psychiatric Case Register in 1984.<sup>49</sup> Given that there is little data to suggest the prevalence of non-affective psychoses in England varied significantly over time (see Section 5.2.4) or by study setting (see Section 5.2.5), we assumed that these data were representative of the rate in the English population as a whole.

**Table 7.1: Annual economic cost estimates of non-affective psychosis in the UK\***

Age range	UK population estimate (1000s), 2009	Annual prev. rate per 1000 [C3]	Number with disorder	Service costs (£m) <sup>†</sup>	Informal care costs (£m) <sup>†</sup>	Lost employment costs (£m) <sup>†</sup>	Total costs (£m) <sup>†</sup>
<b>Men</b>							
15-24	4,210.9	1.4	5,895	68.3	23.0	80.2	171.5
25-34	4,047.1	6.0	24,283	281.2	94.8	330.4	706.4
35-44	4,465.7	10.5	46,890	543.1	183.0	638.0	1,364.1
45-54	4,116.9	11.4	45,933	543.6	183.1	638.6	1,365.3
55-64	3,585.3	11.6	41,589	481.7	162.3	565.9	1,209.9
<b>Subtotal</b>	<b>20,425.9</b>		<b>165,590</b>	<b>1,917.9</b>	<b>646.1</b>	<b>2,253.1</b>	<b>4,817.2</b>
<b>Women</b>							
15-24	4,009.6	1.4	5,613	65.0	21.9	76.4	163.3
25-34	3,946.2	3.8	14,996	173.7	58.5	204.0	436.2
35-44	4,546.3	6.5	29,551	342.3	115.3	402.1	859.7
45-54	4,232.7	9.5	40,211	465.7	156.9	547.1	1,169.8
55-64	3,729.9	12.6	46,997	544.3	183.4	639.5	1,367.2
<b>Subtotal</b>	<b>20,464.7</b>		<b>137,367</b>	<b>1,591.0</b>	<b>536.0</b>	<b>1,869.1</b>	<b>3,996.1</b>
<b>Total</b>	<b>40,890.6</b>		<b>302,957</b>	<b>3,508.8</b>	<b>1,182.2</b>	<b>4,122.3</b>	<b>8,813.2</b>

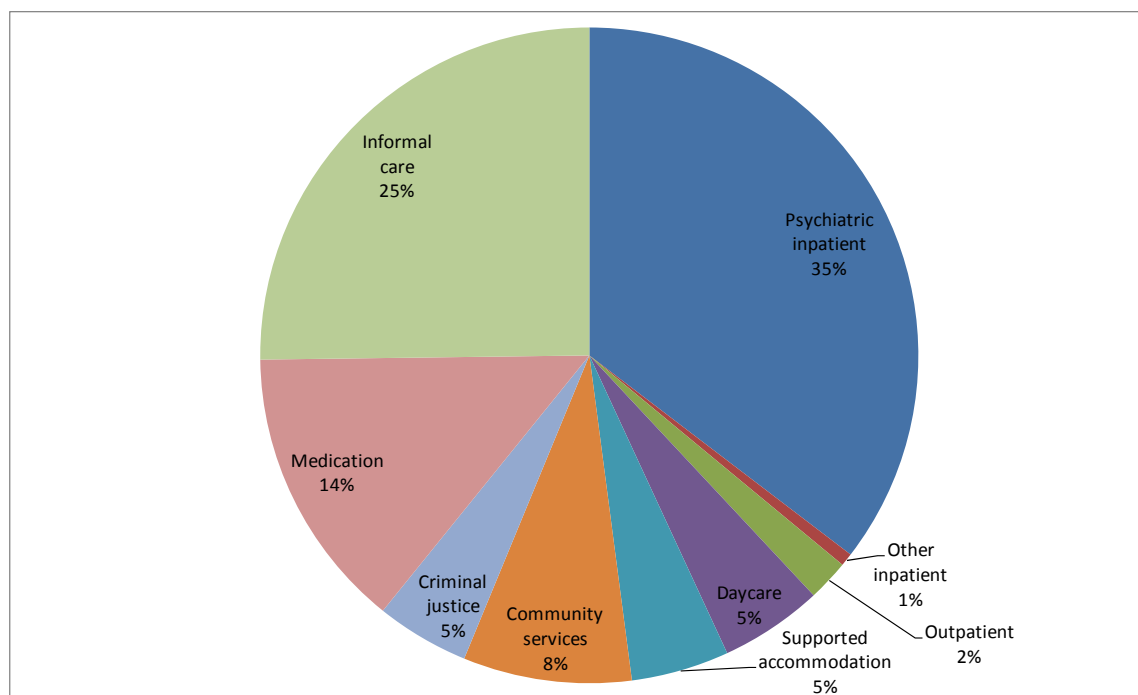
\*Based on citation C3

<sup>†</sup>See Figure 7.1 for cost per person estimates. Subtotals and totals might differ due to rounding

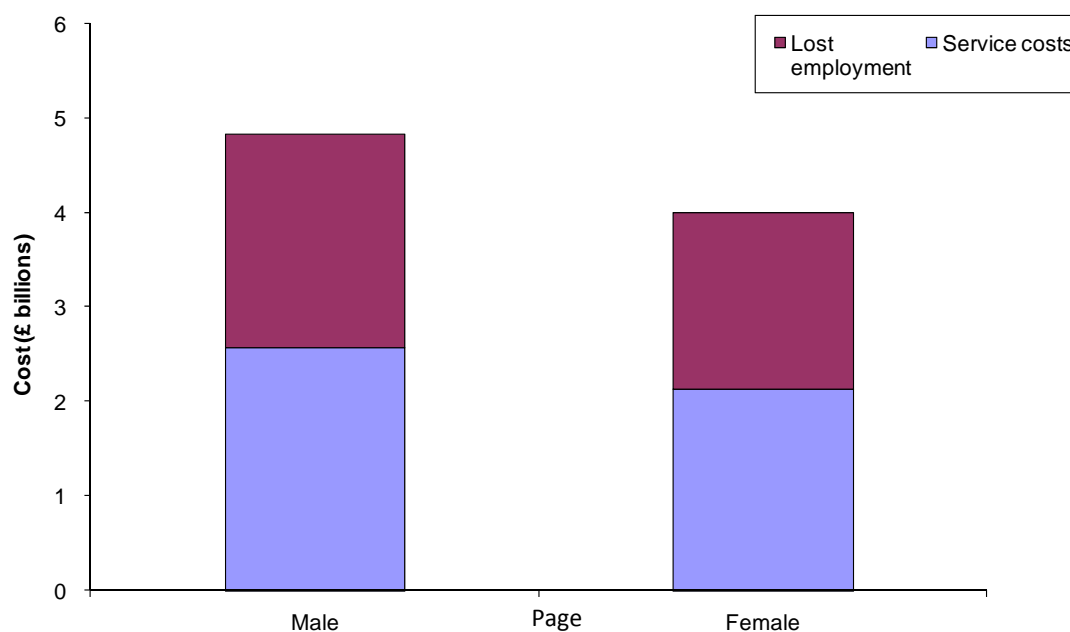
Using the prevalence rates from citation C3, we estimated the total number of people in the UK who were currently diagnosed with a non-affective psychosis, adjusted for the estimated 2009 population (see Table 7.1). We then applied the cost data (Figure 7.1) to these numbers to estimate the total economic costs of non-affective psychoses to services and society in the UK per annum. Total service costs (not including informal care costs) were placed at a little over £3.5bn per annum, with informal care costs placed at nearly £1.2bn. A full breakdown of the distribution of these costs by service type (not including lost employment) is given in Figure

7.3. The cost of lost employment was the single largest cost to society, placed at over £4.1bn. In total, the cost to UK services and society of non-affective psychoses was estimated at over £8.8bn. Both service costs and lost employment costs were slightly greater for men than women (see Figure 7.4).

**Figure 7.3: Distribution of non-affective psychosis & schizophrenia service costs in the UK**



**Figure 7.4: Estimated annual cost of non-affective psychosis, by sex, to services & society in UK**



## 7.2 Schizophrenia

We identified only two citations in the English literature which had provided estimates of the annual prevalence of schizophrenia by age and sex [C26 and C144] (see Section 5.3.2). From these data, we were then able to estimate the total annual cost of schizophrenia in England, using the estimates provided in Figure 7.1. Here, we only report data from C144 because it also provided prevalence estimates of bipolar disorder (see Section 7.3), making cost estimates more comparable. C144 was based on case register data from the Camberwell Psychiatric Case Register in 1965. Although the age of the data provides a caveat to the interpretation of our data, we found no evidence to suggest the prevalence of schizophrenia had changed over time.

**Table 7.2: Annual economic cost estimates of schizophrenia in the UK\***

Age range	UK population estimate (1000s), 2009	Annual prev. rate per 1000 [C3]	Number with disorder	Cost estimates			
				Service costs (£m) <sup>†</sup>	Informal care costs (£m) <sup>†</sup>	Lost employment costs (£m) <sup>†</sup>	Total costs (£m) <sup>†</sup>
Men							
15-24	4,210.9	1.8	7,580	87.8	29.6	103.1	220.5
25-34	4,047.1	5.8	23,473	271.9	91.6	319.4	682.9
35-44	4,465.7	5.8	25,901	300.0	101.1	352.4	753.5
45-54	4,116.9	4.8	19,761	228.9	77.1	268.9	574.9
55-64	3,585.3	4.8	17,209	199.3	67.2	234.2	500.6
Subtotal	20,425.9		93,924	1,087.8	366.5	1,278.0	2,732.3
Women							
15-24	4,009.6	1.2	4,812	55.7	18.8	65.5	140.0
25-34	3,946.2	4.0	15,785	182.8	61.6	214.8	459.2
35-44	4,546.3	6.8	30,915	358.1	120.6	420.6	899.3
45-54	4,232.7	4.4	18,624	215.7	72.7	253.4	541.8
55-64	3,729.9	4.4	16,412	190.1	64.4	223.3	477.4
Subtotal	20,464.7		86,547	1,002.4	337.7	1,177.6	2,517.7
Total	40,890.6		180,471	2090.2	704.2	2,455.6	5,250.0

\*Based on citation C144

†See Figure 7.1 for cost per person estimates. Subtotals and totals might differ due to rounding

An overview of the annual economic costs of schizophrenia to healthcare services and society in the UK is given in Table 7.2. The number of people with schizophrenia in the UK is based on the prevalence estimates from study C144 adjusted to the mid-year 2009 census population. The total cost of schizophrenia to services and society in the UK was estimated at £5.25bn. Nearly half of this figure was attributable to costs associated with lost employment (£2.46bn; 46.8%), with service costs and informal care costs placed at £2.1bn (39.8%) and £700m (13.4%),

respectively. Because we used the same economic costings for schizophrenia and the non-affective psychoses (Figure 7.1), the total breakdown of service costs is assumed to be identical to those provided in Figure 7.3). In terms of costs by age group, the greatest costs to the UK, in terms of both service and societal (employment) costs were associated with men aged 25-44 years old (£1.4bn) and women aged 35-54 years old (£1.4bn).

### 7.3 Bipolar disorder

We used prevalence data, stratified by age and sex, from one suitable citation [C144] to estimate the annual costs of bipolar disorder to services and society in the UK (see Section 5.5.2). Data came from the Camberwell Psychiatric Case Register. Although this citation used data from 1965, we did not find any evidence to suggest the annual prevalence of bipolar disorder had changed over time (or by study setting), and so we assumed these estimates could be generalised to the 2009 UK population. We used the mean cost estimates per person with bipolar disorder (Figure 7.2), provided by the Centre for the Economics of Mental Health.

**Table 7.3: Annual economic cost estimates of bipolar disorder in the UK\***

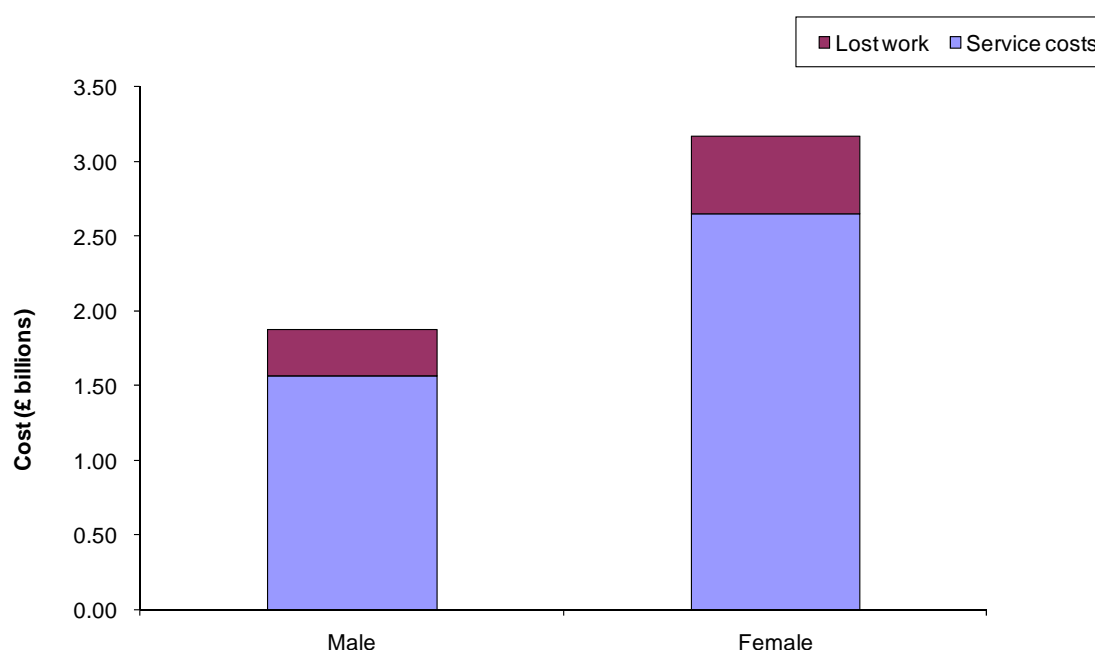
Age range	UK population estimate (1000s), 2009	Annual prev. rate per 1000 [C3]	Number with disorder	Cost estimates			
				Service costs (£m)†	Informal care costs (£m)†	Lost employment costs (£m)†	Total costs (£m)†
Men							
15-24	4,210.9	1.2	5,053	169.3	8.5	30.7	208.4
25-34	4,047.1	2.0	8,094	271.1	13.6	49.2	333.9
35-44	4,465.7	2.0	8,931	299.2	15.0	54.3	368.4
45-54	4,116.9	3.8	15,644	409.7	12.5	95.0	517.2
55-64	3,585.3	3.8	13,644	356.8	10.8	82.8	450.4
Subtotal	20,425.9		51,347	1,506.1	60.3	311.9	1,878.3
Women							
15-24	4,009.6	2.0	8,019	268.6	13.4	48.7	330.8
25-34	3,946.2	4.2	16,574	555.2	27.8	100.7	683.7
35-44	4,546.3	4.2	19,094	639.6	32.0	116.0	787.6
45-54	4,232.7	5.2	22,010	576.4	17.5	133.7	727.6
55-64	3,729.9	5.2	19,935	507.9	15.4	117.8	641.2
Subtotal	20,464.7		85,093	2,547.8	106.2	516.9	3,170.9
Total	40,890.6		136,440	4,053.8	166.5	828.9	5,049.2

\*Based on citation C144

†See Figure 7.2 for cost per person estimates. Subtotals and totals might differ due to rounding

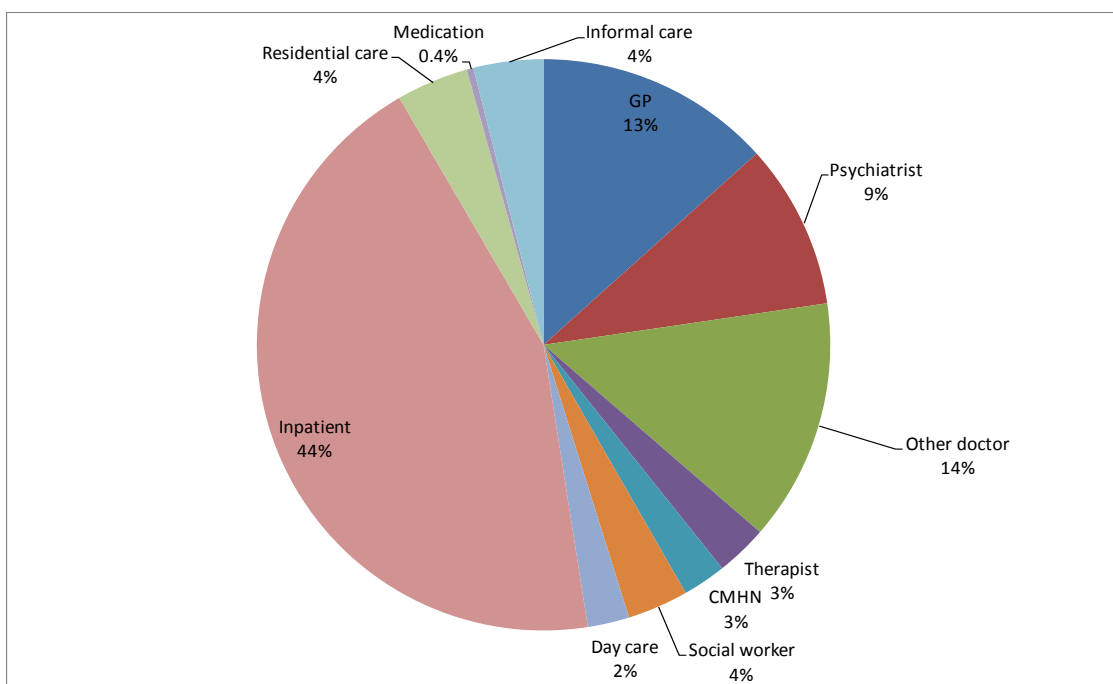
The total annual cost of bipolar disorder to the UK in 2009 was estimated to be £5.05bn (Table 7.3). In contrast to schizophrenia (Section 7.2), a much higher proportion of these costs were associated with service provision (£4.05bn; 80.3%), compared with either informal care costs (£166.5m; 3.3%) or costs due to lost employment (£828.9m; 16.4%). This is reflected in Figure 7.5, which also shows that, unlike schizophrenia and the non-affective psychoses, the costs of bipolar disorder are greater in women than men, reflecting the higher prevalence rates observed in our data sample [C144]. The cost of bipolar disorder was greatest in men aged over 45 years old and women aged 35-54 years old (see Table 7.3)

**Figure 7.5: Estimated annual costs of bipolar disorder, by sex, to services and society in the UK**



A breakdown of the distribution of costs by service type is given in Figure 7.6. Costs of inpatient care present the largest proportion of total service costs (44%), followed by other forms of clinical care from GPs (13%), other doctors (14%) and psychiatrists (9%).

Figure 7.6: Distribution of non-affective psychosis & schizophrenia service costs in the UK



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## **Chapter 8: Discussion**

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## **8.0 DISCUSSION**

### **8.1 Overview**

This is the largest, most comprehensive systematic review of the incidence and prevalence of schizophrenia and other psychotic disorders ever undertaken on the research literature – published and unpublished – in England. Such is the scope and breadth of the data included in this report, that it may more accurately be considered a series of interconnected systematic reviews than a single body of evidence. We have developed and implemented a thorough, expert-led systematic research strategy to identify all citations reporting original incidence or prevalence data on no fewer than seven broad diagnostic psychiatric outcomes: all clinically relevant psychotic disorders, the non-affective psychoses, including a narrower definition of schizophrenia as a separate outcome, the affective psychoses and their two principle diagnostic groups – bipolar disorder and psychotic depression, and those disorders meeting criteria for inducement by substances both licit and illicit. For each of these outcomes, we have summarised the available literature with regard to the overall incidence and prevalence rates observed in England since 1950. With respect to prevalence data we have further differentiated studies according to prevalence type; point, period or lifetime. Where justifiable we have implemented meta-analytical methods to obtain pooled estimates of these rates. We have sought, for each diagnostic outcome, to determine whether these incidence and prevalence rates showed meaningful variation across a number of important domains, including age, sex, ethnicity, country of birth, urbanicity, geographical local and time. Finally, we have inspected the available data to ascertain the degree of support for biases in observed rates, by examining whether rates varied according to study quality, type of rate (for example, first admission versus first-onset in regard to incidence data).

We have identified and confirmed existing understanding of the variation in the incidence and prevalence of these psychotic disorders, as well as discovering important new sociodemographic, geographic and societal domains where rates may vary. In some instances, we have highlighted areas where there is a paucity of data to permit firm conclusions to be drawn regarding the incidence and prevalence of psychotic disorders, and in other areas still, we

have brought to light findings which run counter to the prevailing understanding of the distribution of schizophrenia and other psychotic disorder in terms of incidence and prevalence.

We have set out our discussion section to bring to bear the main findings of this review in relation to the initial aims and objectives outlined in Section 2. We present our principal findings in this way in Section 8.2. Our systematic review of the literature is no different to other such reviews or original pieces of research in that it should be subject to open, critical interpretation of our findings in relation to the strengths and weaknesses of our methodological approach. We address these in Section 8.3. Delineating the incidence and prevalence of psychotic disorders in England over the last 60 years, their unequal distribution in the population at-risk and changes over time will provide valuable information for effective service planning and resource allocation to ensure appropriate services are provided for those people who most need them. We develop these ideas in light of our findings in Section 8.4. The data from England we have identified in this report can also make valuable contributions to the aetiological understanding of the causes of psychotic disorders. In this regard, however, it is critical that the research presented here is considered in relation to the wider aetiological research from around the world – within and outside of epidemiology, not restricted to incidence- or prevalence-based study designs – which seeks to identify the causes of psychosis. While the prevention, management and treatment of people with psychosis may demand localised, sub-national, healthcare policies and prevention strategies, the social, psychological and biological factors which underpin the development and maintenance of various psychotic disorders are unlikely to respect geopolitical boundaries. In Section 8.5 we therefore consider the meaning of our findings in aetiological terms in reference to the existing global literature. We conclude our report by identifying areas where there is currently a knowledge gap, in respect to informing health services research, aetiology or both (Section 8.6).

## 8.2 Principal findings in relation to aims and objectives

### 8.2.1 Principal findings from the incidence study

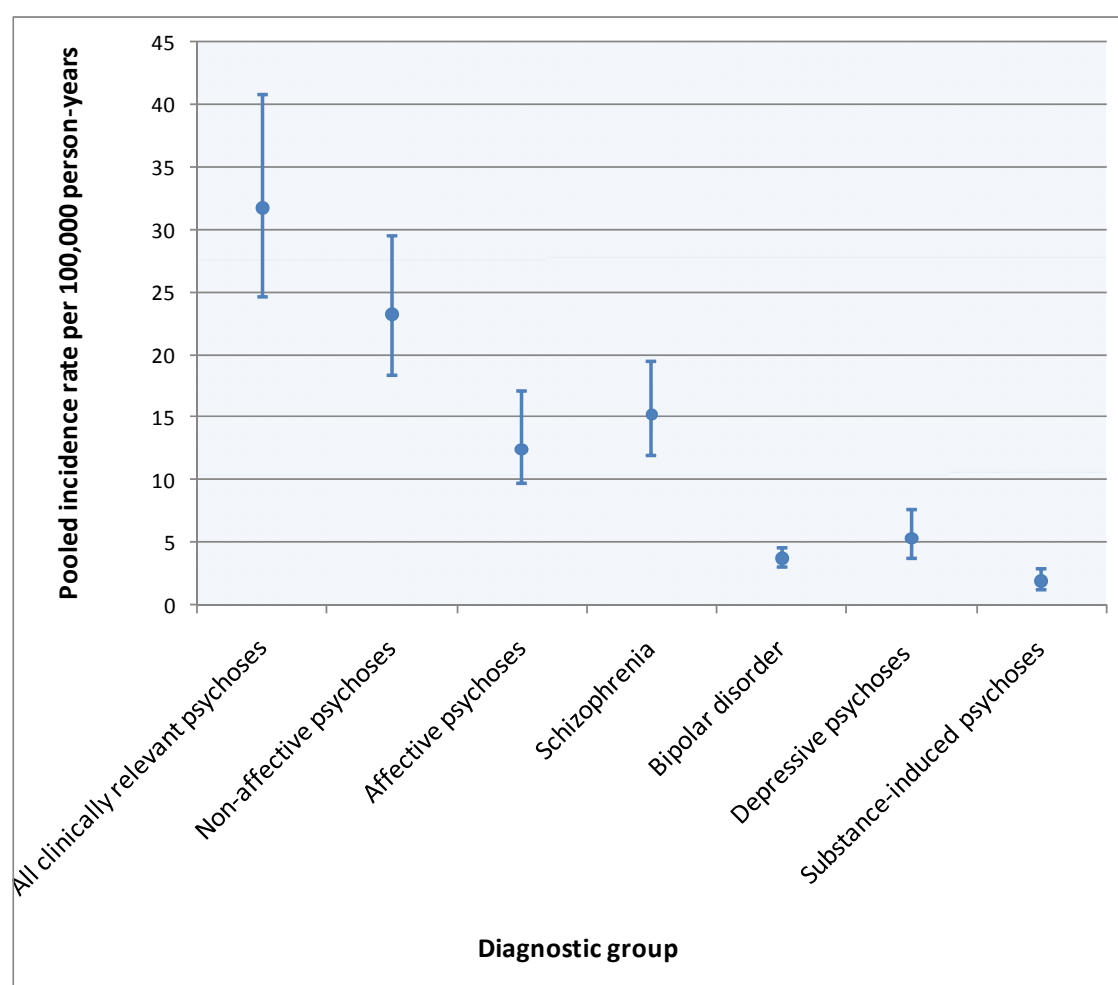
*Objective A: Is the literature on the epidemiology of psychotic disorders in England consistent with the epidemiological landscape?*

The overall pooled incidence of all clinically relevant psychoses in England was broadly in keeping with what we would expect from the psychiatric epidemiological literature (31.72 per 100,000 person-years; 95% CI: 24.63, 40.85). This figure, of course, belies considerable heterogeneity in the incidence of psychotic disorders, both by specific outcome and by sociodemographic and socioenvironmental subgroups. It is this heterogeneity which emerges as the primary finding from the incidence-based systematic review; we found support for variation in the rates of psychotic disorders according to the classical dimensions of age and gender<sup>69</sup>, ethnicity and migrant status<sup>94</sup> and for schizophrenia, urbanicity.<sup>65</sup> We were able to identify several studies which had attempted to explore the possible socio-environmental factors which underpinned the urbanicity effect, and these studies have highlighted putative factors, including ethnic density and social fragmentation, which might be important to our understanding of the aetiology of psychoses. We will briefly summarise the evidence presented in this review along these dimensions (for urbanicity and related findings, we will summarise these in relation to Objective E of this review).

We first emphasise the importance of understanding the relative incidence rates of different psychotic disorders, something often overlooked in epidemiological and health services planning research. Our summary figure (Figure 4.2) in this regard is a salient reminder of the relative incidence rates of different psychotic disorders, broadly categorised. Though there is overlap and variation between rates in England, influenced in part by sociodemographic differences between settings as well as the important epidemiological tenets of chance and bias, the results presented here suggested that the pooled incidence rate of non-affective psychoses (23.2 per 100,000 person-years; 95% CI: 18.3, 29.5) was almost double the observed pooled rate of affective psychoses in England (12.4; 95% CI: 9.0, 17.1). Within these two broad categorisations of disorder, the pooled incidence rate of schizophrenia was, similarly, an order of magnitude

higher than corresponding estimates for bipolar disorder and the depressive psychoses, as well as substance-induced disorders, which were generally extremely rare (see Figure 8.1). That said, we note that substance misuse, when seen in the context of ongoing psychotic disorder, is an extremely serious concern in terms of its association with poor outcome and high service use.<sup>95</sup>  
<sup>96</sup> We believe these findings will be informative for health service provision and public health.

**Figure 8.1: Pooled incidence rates of psychotic disorders by diagnostic category**



The incidence of psychotic disorders by age and gender are best understood when stratified simultaneously along both dimensions, since it has long been observed that the typical, age distribution of some psychotic disorders, such as schizophrenia differs between men and women.<sup>11, 69</sup> Here, our analyses of the data from England between 1950 and 2009 broadly supported this hypothesis, and indeed shed new light on this finding. Thus, using the latest

developments in meta-analytical techniques (fractional polynomial random effects meta-regression), we were able to demonstrate that incidence rates of all psychotic disorders, non-affective psychoses and schizophrenia as a separate outcome were higher for men than women prior to 45 years of age, but that after this age no statistically significant differences in rates were observed. Interestingly, a fractional polynomial meta-regression of the available incidence data for the affective psychoses suggested that prior to 45 years of age rates were comparable for men and women, but that after this age rates became significantly higher amongst females. These findings are broadly supportive of hypotheses which suggest a broadly protective effect of oestrogen in women until around the time of menopause, where after the incidence rates observed in women mirror more closely the observed rates in men. As has been previously and frequently observed (see also McGrath *et al.*<sup>8</sup> for a comprehensive appraisal of the global literature in this regard), the peak incidence rates of non-affective psychoses was typically before 30 years of age, with most studies reporting peak rates in the early twenties or late teens for both men and women. The incidence data in regard to the affective psychoses was more mixed. Studies which investigated the affective psychoses as a broad outcome generally upheld this observation, with findings for bipolar disorder more mixed (though there were also fewer studies conducted here). The one study which appraised the incidence of depressive psychoses by age and gender suggested incidence rates generally increased with age for both sexes, but this study was based on hospitalised cases and may have reflected service-side practices in admissions rather than true population-based epidemiology. We would conclude there is too little data for bipolar disorder and the depressive psychoses separately to be definitive as regard to their typical age-sex distribution, though rates for the affective psychoses offer more clues. Very little data was available in regard to the age-sex distribution of the incidence of substance-induced, but two studies suggested such diagnoses were greater in men than women and declined sharply after 30 years of age for both sexes.

Our study also observed, replicated and extended findings regarding the incidence of psychotic disorders according to ethnic group. As mentioned at the start of this report, earlier studies tended to use country of birth instead of ethnicity as the domain of interest; a pragmatically acceptable approach given that a large majority of ethnic minority population in England were first generation migrants. As these migrant groups aged and had children, country of birth was superseded by more direct assessment of ethnicity (usually via self-ascription of both the

numerator and denominator). Thus, studies reporting rates according to country of birth can probably be regarded as reasonably assessing rates in first generation migrants compared with the white, UK-born population. Later studies either presented rates of psychoses by ethnic group, or ethnic group and country of birth (or sometimes age) to assess potential differences in incidence rates between first- and later-generation migrants.

The literature on migration/ethnicity and the incidence of psychotic disorder was fairly consistent between diagnostic groups. Thus, there is good evidence in England that the rates of all outcomes under study in this review, with the exception of substance-induced psychoses, are most highly elevated in the black Caribbean and black African populations.<sup>10, 20, 24, 54, 97-104</sup> Thus, pooled rate ratios for the black Caribbean group ranged from 4.0 (95% CI: 2.5, 6.3) for non-affective psychoses to 5.6 (95% CI: 3.4, 9.2) for schizophrenia. Rates of affective psychoses were also elevated though point estimates were of the order of two to three for this group.<sup>10, 20</sup> Corresponding pooled rate ratios in the black African population in England were 3.5 (95% CI: 2.7, 4.7) for the non-affective psychoses and 4.7 (95% CI: 3.3, 6.8) for schizophrenia, with significantly elevated rates also observed for the affective psychoses, typically of around three times the rate in the baseline white group.<sup>20, 62</sup> The size of this effect has largely persisted in these groups, notwithstanding improved methodological study designs, including the use of standardised diagnostic criteria, better estimation of the denominator population by ethnic group, broad categorisation of psychotic disorders (not limited to schizophrenia), adjustment for age, sex and other confounders, including socioeconomic status<sup>20</sup> and at least partial blinding of psychiatrists to the ethnicity of the case.<sup>10</sup> That some studies, such as the ÆSOP study<sup>10</sup> or ELFEP study<sup>98</sup> have observed raised rates in these groups across the spectrum of psychotic disorders also argues against possible misdiagnosis as an explanation of higher rates in these groups.

For other ethnic groups, findings have been more mixed. The data regarding the incidence of psychotic disorders in first generation migrants and their offspring from the Indian subcontinent have been equivocal, with small sample sizes often prohibiting sensitive analysis of differences between and within people of Indian, Pakistani and Bangladeshi origin. When considered as one group, two studies have found raised rates of schizophrenia in the “Asian” group (defined by ethnicity<sup>102</sup> and place of birth) between four and six times that of the baseline white/UK-born population. However, more recent data from the ÆSOP study did not observe significantly

elevated rates in the broad Asian group.<sup>10</sup> Inspection of data for specific migrant groups and their offspring from the Indian subcontinent have begun to unravel these effects. Although findings for the Indian group have been mixed,<sup>20, 102</sup> both these studies have demonstrated significantly raised rates in the Pakistani population in England, while the latter citation also found raised rates in Bangladeshi groups.<sup>20</sup> Interestingly, when stratified by gender, rates of schizophrenia were particularly pronounced for Pakistani and Bangladeshi women, but not men, with an order of magnitude comparable to black Caribbean and black African women in the same sample after adjustment for age, sex and socioeconomic status. When we pooled the data relating to the incidence of schizophrenia in the Asian group, our meta-analysis suggested that this group were at more than twice the risk of developing psychosis than their white or white British counterparts (OR: 2.4; 95% CI: 1.3, 4.5). Recent studies have also report some elevation in rates for the non-British white group and people of mixed ethnicity.<sup>10, 20</sup>

*Objective B: Have incidence rates of schizophrenia and other psychoses changed over time in England?*

One of the most frequently asked hypotheses within psychiatric epidemiology is whether the incidence of psychotic disorders has changed over time. Designing studies to measure such change over time is fraught with difficulties. To avoid attributing genuine changes to artefactual changes in the administrative incidence of psychoses over time, or *vice versa*, all possible variables with the exception of changes in the numerator and denominator need to remain stable over time. This very rarely happens given fairly frequent revisions of diagnostic classifications, updated diagnostic practices in response to scientific discovery (for examples unrelated to this review, see the introduction of seasonal affective disorder or attention deficit hyperactivity disorder; ADHD) or fashion, changes in nomenclature, definition of disorders with successive versions of ICD and DSM, or changes in the provision of health services (for example the movement from inpatient to outpatient care during the course of the review period). Other explanations, such as inadequate adjustment for confounders, which also change over time, such as the proportion of ethnic minority groups living in a catchment area, may also have an effect on determining whether incidence rates have changed over time.

The forthcoming publication of the next iterations of the Diagnostic and Statistical Manual (DSM-V) and the International Classification of Diseases (ICD-11) may also have an impact on the future administrative incidence (and prevalence) of psychotic disorders. The movement towards a diagnostic category of at-risk mental states [ARMS], people who may have a high predisposition to psychosis, would likely artificially increase both the incidence and prevalence of psychosis in the community. Identification of such groups in England has increasingly become a challenge for Early Intervention in Psychiatry Services [EIS], and early indications suggest that rates of psychotic disorder in these services are higher than anticipated (see Principal Findings in regard to Objective C, below, and Cheng *et al.*<sup>105</sup>). Thus, future assessments of whether the true (population) incidence and prevalence of psychotic disorders has changed over time will require careful consideration of the diagnostic criteria used at different time periods, across different models of mental health services provision. While we acknowledge the importance of delaying diagnosis in EIS, it will nevertheless be important to ensure – at least for epidemiological, public health and health services research – that continual efforts to provide accurate, reliable diagnoses are made.

Prefaced by these caveats, we will summarise the evidence relating to changes of disorder over the time period of this review. For all clinically relevant psychoses – perhaps the ultimate outcome for which changes of rates should be assessed over time – we found no evidence to suggest rates had changed over time, either from the two studies which directly tested this hypothesis across three methodologically-similar first episode samples from the same catchment area<sup>23</sup> and primary care,<sup>79</sup> or via indirect testing of the broader literature using a meta-regression based approach (see Section 4.2.1.4). It should be acknowledged that the maximum extent of this data covered the period 1973-2003 and we were unable to address changes in the incidence of all clinically relevant psychoses over time. For the non-affective psychoses (Section 4.2.1.4), results were more mixed. The same study by Kirkbride *et al.* did not observe any change in the incidence of non-affective psychoses between 1979 and 1999.<sup>23</sup> Castle *et al.*<sup>24</sup> observed a small increase in rates over a 20-year period (1965-84), but attributed this change to increases in the proportion of ethnic minority populations over the same time period. By contrast, data from the Mental Health Enquiry<sup>25</sup> – and others<sup>53</sup> – showed that the admitted incidence of non-affective psychoses fell sharply for both men and women during the 1970s, but as noted by Prince and Phelan<sup>106</sup> these changes can be best understood by changes in



the structure of mental health services during this period, with a movement towards outpatient care. An analogous finding for schizophrenia was found with studies more-or-less equally divided between those finding an increase, finding a decrease and remaining stable over time (see Box 4.1). Overall our meta-regression did not suggest rates of schizophrenia had changed significantly over time.

Observed declines in the early 1980s in affective psychoses<sup>53, 55</sup> could be readily attributed to a movement from ICD-8 to ICD-9 and a change in how people with non-psychotic depression were classified (away from the affective psychoses category). Overall, for the affective psychoses, there was no evidence incidence rates had changed between the 1970s and the early 21<sup>st</sup> century, either from empirical observation<sup>23</sup> or our meta-regression. For bipolar disorder and the depressive psychoses evidence was again mixed. In the 1950s Barraclough and Kriemann<sup>107</sup> presented some evidence from England and Wales that admitted rates of bipolar disorder were increasing for men and women at every age group, but whether these changes reflected increases in the true incidence rate is unclear. Two further studies observed a small, but significant increase in mania between the 1960s and mid-1980s,<sup>55, 62</sup> but absolute rates remained low and possible diagnostic changes and confounding could not be excluded. One study found no evidence rates had risen between 1979-1999.<sup>23</sup> Overall there was no evidence that the incidence of depressive psychoses had changed since the 1950s.

*Objective C: Are incidence rates higher when established through early intervention services than other types of studies and services?*

This objective was incorporated into the review, but because we only identified one citation [C130] which had published rates from an EIS setting we have reported findings related to this objective here rather than in the main results section. This citation was included in the main body of results for all other relevant analyses. For clarity, we have structured this subsection of the discussion like a short report, given the centrality of Objective C to the PRP.

### *Background*

Early intervention in psychosis services [EIS] were introduced across the UK in 2002 as a new model within the National Health Service [NHS] for the management and treatment of young people, aged 14-35 years, presenting with symptoms of psychosis. Since their introduction there has been anecdotal evidence that services are inundated with people meeting criteria for psychosis, with numbers greatly exceeding those used to define commissioning guidelines, where anticipated incidence rates were placed in the region of 12 to 15 per 100,000 person-years.<sup>38, 39</sup> If confirmed, these anecdotal reports would perhaps suggest that the EIS model may identify previously unmet need in the community, or that such services were accepting clients with broader psychiatric morbidity than suggested by the narrow rates of schizophrenia upon which EIS was founded.

Either way, confirmation of these reports would have important implications for service planning, public health and resource allocation. We therefore recognise the importance of addressing this objective, which was one of the NIHR policy research programme's (PRP) key requirements in the original tender for this project.

### *Identification of relevant EIS data from the systematic review*

Our systematic search strategy (see Chapter 3) allowed us to be confident that we had identified all relevant literature on published incidence rates from EIS and other service types. Unfortunately we could only identify one published citation [C130] which had estimated incidence rates of psychotic disorder from Early Intervention Services since their introduction. This citation was an abstract published as part of a set of conference proceedings in *Schizophrenia Bulletin* in 2006. The authors (Mahmood *et al.*<sup>108</sup>) published the incidence rate of all clinically relevant psychoses for people aged 16-35 years based on accepted referrals to the Lambeth Early Onset [LEO] psychosis service in South London between 2002-5. The authors estimated the crude incidence rate in LEO to be 100 per 100,000 person years (95% CI: 89.5, 111.9). Although extremely high, it is important to place this rate in context to other rates for this age group in South London, since we know empirically that this age period spans the peak onset of psychosis and that incidence rates observed in South London are amongst the highest ever recorded globally.<sup>14</sup>

#### *Comparison of EIS rate with other incidence rates from non-EIS settings: Methods*

We therefore decided to compare this incidence rate with the corresponding crude incidence rate for the age group 16-34 years old in Lambeth as identified through the ÆSOP study between 1997-1999 (unpublished data). We considered this direct comparison was suitable and important because:

- The two time periods between the ÆSOP study (1997-9) and the LEO study (2002-5) were temporally close to minimise possible changes in the underlying population at-risk
- The 2001 Census was recorded exactly mid-way between the two studies ensuring accurate estimation of the population at-risk aged 16-35 years
- Both studies took place in the London borough of Lambeth so we could ensure the catchment area of both datasets was conterminous
- Importantly, the former study (ÆSOP) was conducted prior to the introduction of EIS services,

Given these similarities in the catchment population of the two samples, a direct comparison of incidence rates between the two studies would provide reasonable evidence of whether this EIS was observing higher than expected rates of psychotic disorder in the community. We extracted all first episode subjects from the ÆSOP database, aged 16-35 years old, who came into contact with services in South London and presented with an address in Lambeth at first contact (n=127). As per Mahmood *et al.* we excluded all subjects from the ÆSOP study who were of no fixed abode at first contact. We then recalculated the denominator population aged 16-35 years in Lambeth using 2001 census data and adjusting for the 2-year study period and used this to recalculate incidence rates from the ÆSOP study. We used a Mantel-Haenszel test to determine whether the differences in observed rates between ÆSOP and LEO met statistical significance.

#### *Comparison of EIS rate with other incidence rates from non-EIS settings: Results*

We identified 127 subjects with a clinically relevant first episode psychosis, aged 16-35 years and living in Lambeth at the onset of their disorder over the two year study period. This corresponded to an incidence rate of 58.3 per 100,000 person-years (95% CI: 49.0, 69.4). Comparing the crude rate in LEO [C130] with this rate, we found that the incidence reported through LEO was significantly higher than observed in the pre-EIS ÆSOP study (OR: 1.72; 95% CI: 1.39, 2.11). In other words, the estimate crude rate of psychosis observed through one EIS in

South London was between 39% and 111% greater than the observed crude rate of clinically relevant psychosis in the ÆSOP study.

*Comparison of EIS rate with other incidence rates from non-EIS settings: Discussion*

We would advise caution in the interpretation of this one finding. It does not refute anecdotal reports that EIS are experiencing a higher case load than expected. Despite the strengths of the comparison of this data which we outlined above there are a number of important caveats. First, we have no way of ratifying the validity of the data published by Mahmood and colleagues [C130].<sup>108</sup> We have no reason to doubt their findings, but given data was taken from an abstract some important information is missing to allow us to fully the quality of their research. For example, we do not know how cases were ascertained, whether the 2001 Census denominator was used (and properly adjusted for the length of their study) or how diagnoses were made, by whom and using which classification system. Such information would be needed to fully assess whether the difference in rates between the non-EIS rate and the EIS rate were genuine differences in rates.

Nevertheless, these issues might be the very contributing factors which have led to anecdotal reports of higher than expected caseloads in EIS in England. For example, we know that EIS tend not to diagnose clients immediately after acceptance by the service in order to allow full evolution of symptoms and avoid the stigma which can be associated with severe mental illness. Indeed, such is the diagnostically agnostic approach within EIS that the term schizophrenia has generally been subsumed into the term “psychosis” in both the full title of such early intervention in *psychosis* services and in the language and management of service users. In principle, schizophrenia is seen as an outcome of a process of symptom evolution that can in some cases be avoided if the intervention is early enough; this fits with current operational diagnostic criteria for schizophrenia that retain a time period over which symptoms have to exist. Furthermore, the only place that the diagnosis has a use is in the product licences for antipsychotic drugs; the drugs are antipsychotic regardless of diagnosis. Some people may receive no formal diagnosis other than of “psychosis” in EIS until they are discharged, up to three years after being accepted by the service; very few subjects may be discharged with that diagnosis replaced by another such as OCD or personality disorder. We do not suggest that this approach should be changed as it has many positive benefits in clinical practice. However, a

diagnostically agnostic approach inevitably leads to some blurring of the threshold for psychiatric morbidity in the community which demands attention from early intervention in psychosis services. Should they, for instance, try and engage individuals who have not, themselves (or by proxy through others), sought help from services? Furthermore, where EIS were originally commissioned on estimates of incidence more typical of narrowly-defined schizophrenia than the incidence of all clinically relevant psychoses as estimated in this review,<sup>38</sup> it is perhaps unsurprising that there have been murmurs from such services regarding the inundation of clients.

Further epidemiological data from EIS is only just beginning to be published in the medical academic press. Given issues of case ascertainment and diagnosis, persuading peer-reviewed journals to accept such evidence is understandably difficult. Two of the authors of the current report (JBK, PBJ) currently have recently been involved in the publication of the first epidemiological data from EIS.<sup>105</sup> This study was not included in the review because it was published outside of the time period we used in our inclusion criteria. Using data from the CAMEO early intervention in psychosis service, Cambridgeshire, the data broadly support and extend the findings from Mahmood *et al.*<sup>108</sup> We found that the crude incepted incidence rate of psychosis in CAMEO over a seven-year period (2002-2007) was 50.0 per 100,000 person-years (95% CI: 44.5, 56.2). This rate only included incepted cases (not people defined as ARMS) and was considerably higher than the anticipated incidence rate of schizophrenia (15 per 100,000 person-years)<sup>38</sup> upon which EIS in England were originally commissioned. Thus, the results of Mahmood *et al.*<sup>108</sup> and Cheng *et al.*<sup>105</sup> are of considerably importance to health care planning in England, providing the first empirical epidemiological evidence observed through EIS. We also have much more detailed empirical investigations underway to delineate the precise epidemiology of psychotic disorders in early intervention in psychosis services (see, for example, the Social Epidemiology of Psychoses in East Anglia [SEPEA] study, [www.sepea.org](http://www.sepea.org), PI: Dr Kirkbride). The authors of the present review echo the PRP's demand for an evidence base from early intervention in psychosis services; however, it is apparent that these calls forerun the empirical data.

*Objective D: What are the candidate socioenvironmental factors that may account for: a) variation in incidence by geographical area, ethnicity and gender; and b) trends in rates over time?*

*(A1) Geographical variation and candidate socioenvironmental factors*

We have inspected the data identified in this systematic review for variation according to the urbanicity of study setting. Studies which have addressed geographical variation in incidence rates were often diverse in location, methodology, exposure of interest and outcome variable studied. Findings for a geographical gradient in the incidence of psychotic disorder were generally strongest for the non-affective psychoses, including schizophrenia, with less evidence of variance by geographical location for the affective psychoses. It was interesting to note that the highest overall incidence rates of all psychoses and non-affective psychoses were consistently found in studies based in London; arguably England's most urban conurbation. Published data from the ÆSOP study suggested higher rates of non-affective psychoses and schizophrenia were observed in the London centre of this study compared with the less urban settings in Nottinghamshire and Bristol, after adjustment for age and sex,<sup>11</sup>. Unpublished analysis of pooled data from this study and the contemporaneous and methodologically-similar ELFEP study indicated that these differences persisted following further adjustment for ethnicity and socioeconomic status (data available from authors). The only other study to report differences in incidence rates of non-affective psychoses [C69], did not observe any difference in rates between two rural cities in South England.<sup>109</sup>

To supplement interpretation of this data we also developed a composite urbanicity ranking variable to assess whether overall incidence rates of psychotic disorder conducted *across* studies were associated with the level of urbanicity. Per rank increase in urbanicity, we observed a statistically significant increase in the incidence of both broad non-affective psychoses (OR: 1.022; 95% CI: 1.017, 1.028;  $p < 0.001$ ) and schizophrenia (OR: 1.03; 95% CI: 1.01, 1.05;  $p = 0.01$ ). By contrast, for the affective psychoses, including bipolar disorder and the depressive psychoses, meta-regressions of our composite urbanicity ranking variable did not reveal any association between incidence rates and urbanicity (respective  $p$ -values for affective psychoses, bipolar and depressive psychoses:  $p = 0.94$ ,  $p = 0.18$ ,  $p = 0.73$ ). Of the individual studies to have inspected the spatial distribution of the affective outcomes, the ÆSOP study found no evidence

of a geographical gradient either *between*<sup>11</sup> or *within* study centres<sup>14</sup> after adjustment for individual-level covariates. Giggs observed some patterning in Nottingham, but less than for non-affective psychoses.<sup>110</sup> Two studies [C69, C145] published significantly different crude rates of affective psychoses and bipolar disorder between Chichester and Salisbury [C69],<sup>109</sup> and Camberwell and Salford [C145],<sup>111</sup> respectively, but it is difficult to assess the validity of these results given the potential effect of unadjusted confounders, including age, sex and ethnicity. Therefore, we suggest that the best evidence for geographical variation in the incidence of affective psychoses is compatible with the broader literature which has not reported any geographical or urban gradient to the affective psychoses.<sup>15, 65, 81, 84, 85</sup> This difference between the two broad sets of disorders – affective and non-affective – has potentially important implications for aetiology (see Section 8.5).

We identified several studies which had attempted to explain the geographical variation in the incidence of non-affective psychoses. Although these studies were generally heterogeneous with respect to methodology and the measurement of socioenvironmental factors some consistent findings emerged:

- Differences in age, sex and ethnic composition of the population did not generally explain variation in incidence rates by geographical gradients, at the small neighbourhood level, or between towns and cities.<sup>11, 14, 30, 31, 112, 113</sup>
- We did not identify any incidence study during our search strategy which had attempted to investigate whether aspects of the physical (by this we include potential environmental toxins, transmission of viruses shown to increase later schizophrenia risk<sup>114-116</sup> or other dimensions of the physical environment such as noise pollution) or aspects of the built environment were associated with the incidence of psychotic disorder. This is a notable omission here.
- Thus, studies had focused on aspects of the social environment as the putative risk factors to explain geographical variation in the incidence of non-affective psychoses.
- The strongest evidence for an effect of a socio-environmental risk factor was in relation to ethnic density, shown by two studies<sup>30, 31</sup> to be associated with the incidence of schizophrenia in an urban area. Simply put, the risk of schizophrenia for ethnic minority

individuals increased significantly as they lived in neighbourhoods with smaller proportions of people of similar ethnicities. One further study which investigated ethnic density in relation to psychotic disorder failed to observe such an association,<sup>117</sup> but the level of geographical analysis in this study (Health Authorities) can be considered too broad to detect subtle neighbourhood effects (for a full discussion, please see Section 4.2.3.5)

- Given that the ethnic density effect might have its impact on incidence rates through individual-level psychosocial stressors, further studies have addressed other social risk factors at the level of the neighbourhood which might add weight to this hypothesis. One study has shown that social cohesion might be associated with the incidence of schizophrenia, though this relationship was nonlinear.<sup>31</sup> This study also found that in addition to an independent ethnic density effect, there was an additional effect of ethnic fragmentation on the incidence of schizophrenia in Southeast London. Thus, in neighbourhoods where ethnic minority groups lived in less cohesive residential patterns, observed incidence rates were significantly higher. These findings were independent of age, sex, ethnicity, ethnic density and socioeconomic deprivation.
- Two studies have also addressed more material aspects of socioenvironmental deprivation in relation to the incidence of schizophrenia. Croudace and colleagues<sup>118</sup> found a non-linear relationship with deprivation such that deprivation was associated with higher rates of schizophrenia in Nottingham, but only in the most deprived communities. Similarly, Boydell and colleagues<sup>112</sup> measured socioeconomic inequality between neighbourhoods in Southeast London (a relative measure of socioeconomic disparity rather than an absolute measure of deprivation) and found that inequality was associated with the incidence of schizophrenia, but only in the most deprived communities, perhaps where the contrast between rich and poor becomes more stark.
- These findings are consistent with the international literature on the role of social factors in non-affective psychoses (see Section 8.5)
- One important limitation with the literature from England conducted in this area is that the observed findings from these studies are largely cross-sectional. That is, the exposure (the social environment) was measured close to, during or even after the onset of psychosis in the individual. Thus, it is difficult from this literature alone to



exclude the possibility of reverse causation; that is, people with schizophrenia, or in the prodromal phases of the disorder who have increasing difficulty gaining or keeping employment or securing affordable housing drift socially into more marginalised and fragmented communities. Large scale longitudinal datasets from predominantly European settings have been able to mitigate this problem to an extent by testing the association between urban birth and upbringing and later psychosis risk<sup>5, 18, 119</sup>; the relationship still holds. It should be noted that social drift (reverse causation) and social causation are not two mutually exclusive possibilities as they are often framed in the literature. It is possible that one leads to the other, such that an individual vulnerable to psychosis who drifts socially is then exposed to a perpetuating cascade of negative life events and social stressors which lead to the frank manifestation of psychosis. At present there is no evidence to support or refute this hypothesis. To overcome and disentangle the competing and possibly interactive effects of the social milieu will require prospective, longitudinal studies capable of investigating the critical periods over the life course when exposure to social environmental factors, negative life events or even substance abuse, might be most detrimental to the development of psychosis.

*(A2) Variation in incidence rates by ethnicity and candidate socioenvironmental factors*

Raised rates of psychotic disorder in ethnic minority groups are one of the most frequently replicated and controversial findings in contemporary psychiatric epidemiology. As stated above, these rates have been consistently replicated for ethnic minority groups in England over the last 60 years. These rates are elevated to the greatest extent in black populations in the UK, but there is evidence that all ethnic minority and migrant groups have some increased risk of psychoses compared with the white British population. The most recent findings, taken from the East London First Episode Psychosis study<sup>20, 98, 99</sup> have illuminated this area in three important ways:

- First, rates in ethnic minority groups were partially confounded by socioeconomic status, but this did not explain all the excess risk in migrant groups and their offspring
- Second, rates in Pakistani and Bangladeshi women were as elevated as rates for black Caribbean and black African women, after adjustment for age and socioeconomic status. Further inspection of this data suggested this effect was even more pronounced

in non-UK-born women, raising the possibility that the combined effect of migration, minority status and even the minority cultural position of certain women might be important sociocultural dimensions of schizophrenia risk. We should be clear that there is currently no empirical evidence to support or refute this hypothesis.

- Third, rates appear to be elevated to the same extent in the offspring of migrants as the first generation migrants. This finding is consistent with other literature in the UK (and beyond) which has observed elevated rates of psychosis in second-generation migrants,<sup>100, 120, 121</sup> but it *does not* support the notion that rates are *even* higher in second generation groups as has sometimes been suggested.<sup>122</sup>

The ethnic density effect, discussed above, is clearly an important potential explanation of the raised incidence rates of schizophrenia in ethnic minority groups. However, evidence from the two main studies in England to have addressed this hypothesis<sup>30, 31</sup> found that rates of psychosis remained significantly elevated in ethnic minority groups compared to the white or white British baseline group, even in neighbourhoods with the greatest levels of ethnic density.

In the wider academic community there have been several hypotheses which have attempted to explore the possible drivers of higher rates of psychoses in ethnic minority groups in England, as well as in most other international settings where this hypothesis has been tested.<sup>21, 123-129</sup> The main hypotheses to explain these rates, and the degree of support for and against them, is summarised in Box 8.1.

Incidence (or prevalence) data in England to directly test many of these hypotheses – beyond those explanations we have refuted above – are relatively sparse; a reflection of testing these explanations in incidence-based studies, where one usually lacks the stratification of the denominator population by the exposure of interest (for example the census does not ask people about their level of cannabis consumption; see section on the difficulty of estimating incidence rates due to cannabis use in Section 8.3 and Section 8.5.1 for a discussion of the likely effects of cannabis on incidence rates, assuming a causal relationship). However, data from the case-control arm of the AEsOP study has shed useful light on the potential increased risk of psychoses in black and minority ethnic groups.<sup>13, 130, 131</sup> Through such designs, the authors –

Box 8.1: Principle hypotheses to explain raised rates of psychotic disorder in migrant groups and their offspring							
	HYPOTHESIS TITLE	HYPOTHESIS DESCRIPTION	TYPE OF HYPOTHESIS <sup>†</sup>	PROPOSED BY (YEAR)	EVIDENCE FOR <sup>‡</sup>	EVIDENCE AGAINST <sup>‡</sup>	NOTES
H1	Predisposition to migrate	People at genetic disposition to psychosis were more likely to migrate	Reverse causality	Ødegaard <sup>132</sup> (1932)	Initial observations of Ødegaard <sup>132</sup>	Selten <i>et al.</i> 's natural experiment rejected hypothesis <sup>133</sup> Raised rates in second- (& later-? i.e. <sup>20</sup> ) generation groups [i.e. <sup>21, 98, 101, 121</sup> ] Migration highly complex task for people predisposed to psychosis <sup>91</sup>	
H2	High rates in sending country	Elevated rates in country of origin would explain higher rates in immigrants	Reverse causality	Cochrane & Bal <sup>134</sup> (1987)	None	Incidence rates of schizophrenia in the Caribbean comparable to those in host UK & Dutch population <sup>135-138</sup> . Hospitalised rates in Ireland higher than those for Irish migrants to UK <sup>134</sup>	Few comparative studies have been conducted other than the UK vs. Caribbean studies noted. Irish comparative study <sup>134</sup> only based on hospitalized rates. Other studies would be informative i.e. rates in Morocco vs. Moroccans in the Netherlands
H3	Socio-demographic differences	Age, sex, marital status & socioeconomic status [SES] differences between host & immigrant groups explain differences	Confounding	Cochrane & Bal <sup>134</sup> (1987)	Young, male groups over-represented in initial migrant groups. Also known to be at increased risk of psychosis <sup>69</sup>	Control for age & sex <sup>10, 21, 94, 98, 101, 104, 120, 129, 139</sup> , latterly SES <sup>20, 123, 126</sup> . Marital status a consequence, not cause of psychosis <sup>134</sup>	
H4	Misdiagnosis of psychotic symptoms	Psychiatrists in host country may misdiagnose psychotic symptoms in migrant groups, unfamiliar with their socio-cultural norms, or tendency to over-diagnose migrants with schizophrenia vs. other psychotic disorders	Bias	Cochrane & Bal <sup>134</sup> (1987)	Early evidence of institutionalized racism in mental health services <sup>140</sup> , particularly with regard to pathways to care <sup>141</sup> . Psychotic symptoms may be more prevalent in Caribbean migrants <sup>142</sup> Poor inter-rater reliability between English & Jamaican psychiatrist <sup>143</sup>	Standardized diagnoses used in research, often quasi-blind to ethnicity of subject <sup>11</sup> Raised rates of psychotic disorders not limited to schizophrenia <sup>10, 62, 98</sup> Inter-rater reliability was poor but not racially biased <sup>143</sup>	Rates of psychotic disorders in migrants persisted despite improved study designs & standardized diagnoses. Separate to the problem of institutionalized racism – see <sup>144</sup> for controversies surrounding this area. Cultural variation in symptom interpretation needs further research
H5	Migratory & post-migratory factors	Several, but involving negative consequences of migration, acculturation & post-migratory living as relevant. Stress/vulnerability is posited as potential biological mechanism.	Confounding	Cochrane & Bal <sup>134</sup> (1987), Bhugra <sup>145, 146</sup> (2000), Jones & Fung <sup>147</sup> (2005)	Ethnic density effect implicates social support as protective <sup>30-32</sup> Higher rates of psychosis in BME groups which experience greater discrimination <sup>148</sup> Neighbourhoods with more ethnic fragmentation have higher rates of psychosis <sup>113</sup> Social adversity confounds relationship between psychosis & migrancy <sup>149</sup> Greater impact of social disadvantage in black Caribbean migrants than white British <sup>34</sup>	Other purportedly stress-induced disorders not raised for immigrants (i.e. depression) <sup>134, 150</sup> Immigrants experience similar levels of stress but variation in rates of psychosis is marked <sup>134</sup>	Cochrane & Bal's <sup>134</sup> assertion that experience of migratory factors is similar across all immigrants is unlikely to now hold given likely genetic variation in stress vulnerability & differential experiences of migration along other socio-demographic & -cultural dimensions (i.e. family structure, social support, networks)

	HYPOTHESIS TITLE	HYPOTHESIS DESCRIPTION	TYPE OF HYPOTHESIS <sup>†</sup>	PROPOSED BY (YEAR)	EVIDENCE FOR <sup>‡</sup>	EVIDENCE AGAINST <sup>‡</sup>	NOTES
H6	Life course factors & neuro-development	Factors across the life course, including pre- & peri-natally, and through childhood have greater impact in migrants. Includes vitamin D hypothesis: a change in maternal vitamin D exposure after migration alters offspring neurodevelopment	Confounding	Eagles <sup>151</sup> (1991), McGrath <sup>152</sup> , Jones & Fung <sup>147</sup> (2005)	Separation from parents during childhood has greater impact in black Caribbean migrants than white British <sup>13</sup> Prenatal hypovitaminosis D associated with schizophrenia risk in general, <sup>153</sup> but...	No evidence that pre- & peri-natal problems have greater role in migrant than native groups <sup>150</sup> No current evidence directly linking migration, hypovitaminosis & psychosis	Evidence is mixed, depending on type of risk factor & period of life course. Further research required.
H7	Substance abuse	Greater substance misuse in migrants accounts for higher rates	Confounding	Jones & Fung <sup>147</sup> (2005)	None	Little evidence cannabis used more in black Caribbean than white patients <sup>154</sup> or general population [i.e. <sup>155-157</sup> , or substance use more generally <sup>158</sup> ]	Putative link between cannabis & schizophrenia <sup>33</sup> combined with misconception that cannabis consumption was more prevalent in black Caribbean fuelled "hypothesis"
H8	Psychological hypotheses	Interpretation of life events have greater impact on psychosis in migrant groups	Mediating factor	Jones & Fung <sup>147</sup> (2005)	Tendency to attribute life events to an external locus may lead to onset of paranoid symptoms in some migrant groups. Evidence is weak. <sup>159</sup>	No differences in number of life events experienced by UK white vs. black Caribbean migrants <sup>160</sup>	Difficult to exclude this hypothesis & may mediate or have some overlap with other hypotheses (i.e. H5, H6, H10).
H9	Genetic predisposition	Genetic factors explain higher rates in migrant groups	Genetic confounding	Jones & Fung <sup>147</sup> (2005)	None	Morbid risk is similar for offspring of both black Caribbean migrants & white group in UK <sup>161, 162</sup> . Larger morbid risk in second-generation migrants suggests environmental, not genetics pressures alone. Rates of psychosis in Caribbean comparable to those in host UK population <sup>135-137</sup>	Genetic factors alone are unlikely to explain differences in rates between migrants & host population but genetic susceptibility in combination with environmental exposures (i.e. interaction – see Hypothesis 10 might be important)
H10	Gene-environment interactions & epigenetic processes	People with underlying susceptibility genes for psychosis at increased risk if exposed to stressful environmental factors i.e. migration & other post-migratory factors. May be regulated epigenetically i.e. changes to gene expression following changes to environmental stimuli after migration	Interaction	Rutter <sup>163</sup> (2002), Broome <i>et al.</i> <sup>164</sup> (2005), Dealberto <sup>165</sup> (2007)	Little explicit evidence either way. Ethnic density effect is proxy for interaction between individual phenotype (i.e. BME status) & exposure to environmental stressors [i.e. <sup>30-32</sup> ]. No direct study of genes vs. environment in psychosis & migrants but studies are underway <sup>166</sup>	Little explicit evidence either way.	Promising avenue for future research. More studies required.

some of whom are authors of the present review – were able to investigate whether aberrant parental separation and loss (death of a parent) during childhood,<sup>13</sup> as well as measures of cumulative social disadvantage,<sup>34</sup> were associated with an increased risk of developing psychotic disorder. The authors observed that both parental separation/loss and greater social disadvantage were significantly associated with greater risk of schizophrenia in the black Caribbean and white British group. However, the prevalence of these loss/disadvantage factors was significantly greater for the black Caribbean group – in both cases and controls – suggesting that the impact of these events in ethnic minority populations might be a partial explanation of the raised rates of psychotic disorders in these groups.

Finally, we acknowledge the important issue of institutional racism in health and other public services, whereby black and minority ethnic populations do not receive culturally, religiously and ethnically sensitive services in the same way as the majority population.<sup>144</sup> This issue is quite separate from the observations of raised rates of psychotic disorders in ethnic minority populations, which the evidence presented here and outside of the UK, overwhelming suggests are real and demand sensitive mental health service provision and public health attention. Conflation of these two distinct mechanisms can only hinder progress to resolve each important issue.

*(A3) Variation in incidence rates by gender and candidate socioenvironmental factors*

Our review has demonstrated an interaction between age and gender (see above). This finding generally persists in spite of introduction of other risk factors into explanatory models of schizophrenia risk. One hypothesis to explain the secondary peak of psychosis for women around and after the age of menopause is that estrogen is protective against psychosis before this point (see Grigoriadis and Seeman,<sup>167</sup> Riecher-Rossler<sup>168</sup> and Seeman<sup>169</sup> for greater detail on this hypothesis).

*(B) Variation in incidence rates by time and candidate socioenvironmental factors*

Given our failure to find any good evidence of increasing or decreasing rates of psychotic disorder attributable to genuine changes in the underlying rates in the population in England, we not consider a discussion on candidate socioenvironmental factors in relation to incidence

rates is warranted here. Given the stability in incidence of all clinically relevant psychoses over time (see Section 4.2.1.4) we suggest that any changes in specific outcomes are most likely due to changes in diagnostic fashion over time. The recent movement towards service models based on early intervention in psychosis [EIS], where often services avoid making an initial diagnosis at first presentation to allow symptom evolution and avoid stigmatisation of service users, is a contemporary example of how service-side practices might directly influence the measurement of psychotic disorders over time.

*Objective E: Have geographical, ethnic and gender differences in incidence become more (or less) marked over time in England?*

It is difficult to assess whether changes in the strength of associations between psychotic disorders and candidate risk factors for them have changed over time, and whether such changes indicate a genuine change in risk, or are instead due to chance, bias or other methodological differences between studies. With respect to incidence, we have generally observed that patterns of rates by age and gender over time have remained fairly consistent. With respect to ethnicity and immigration, elevated rates of psychotic disorders in immigrants and their offspring has been consistently replicable in some groups, such as the black Caribbean and black African populations in England, over time. Nevertheless, earlier studies tended to report rates that were ten or more times greater than those in the white population in England,<sup>101</sup> but more recent studies have suggested the size of this risk is closer to five to eight-fold.<sup>10, 20</sup> While this may reflect genuine changes in excess risk, it seems more likely that improved methodological study designs (more accurate estimation of the denominator population, standardised research diagnoses, partial blinding of clinical diagnosticians to ethnicity of the subject, better control for confounding) account for some of this reduction. Conversely, for other smaller migrant groups and their offspring in the UK, it has been harder to determine whether they also have an increased risk of psychosis. Here, more recent, powerful studies have shown that some groups, including first and second generation South Asian women, non-British white groups and people of mixed ethnicity, are also at increased risk of psychotic disorder.

In terms of detecting possible changes in the geographical distribution of psychotic disorders over time, this issue is even more fraught with methodological difficulty. Nevertheless, data from Nottingham obtained using a similar methodology over a 40 year period suggests that the geographical patterning of schizophrenia (in inner city areas) has remained relatively stable over time.<sup>170, 171</sup> This potentially suggests that exposure to putative socio-environmental factors important in the aetiology of psychotic disorders (for example, discrimination, deprivation, social disadvantage) may be relatively constant in some neighbourhoods. Our [citation matrix](#) of extracted data according to research stream, theme and block is 4000+ x 200+ entries wide (although not every cell is populated with data) and this provides a rich dataset for further exploration of citations according to possible changes in effect sizes over time. This will be the focus of ongoing research.

### **8.2.2 Principal findings from the prevalence study**

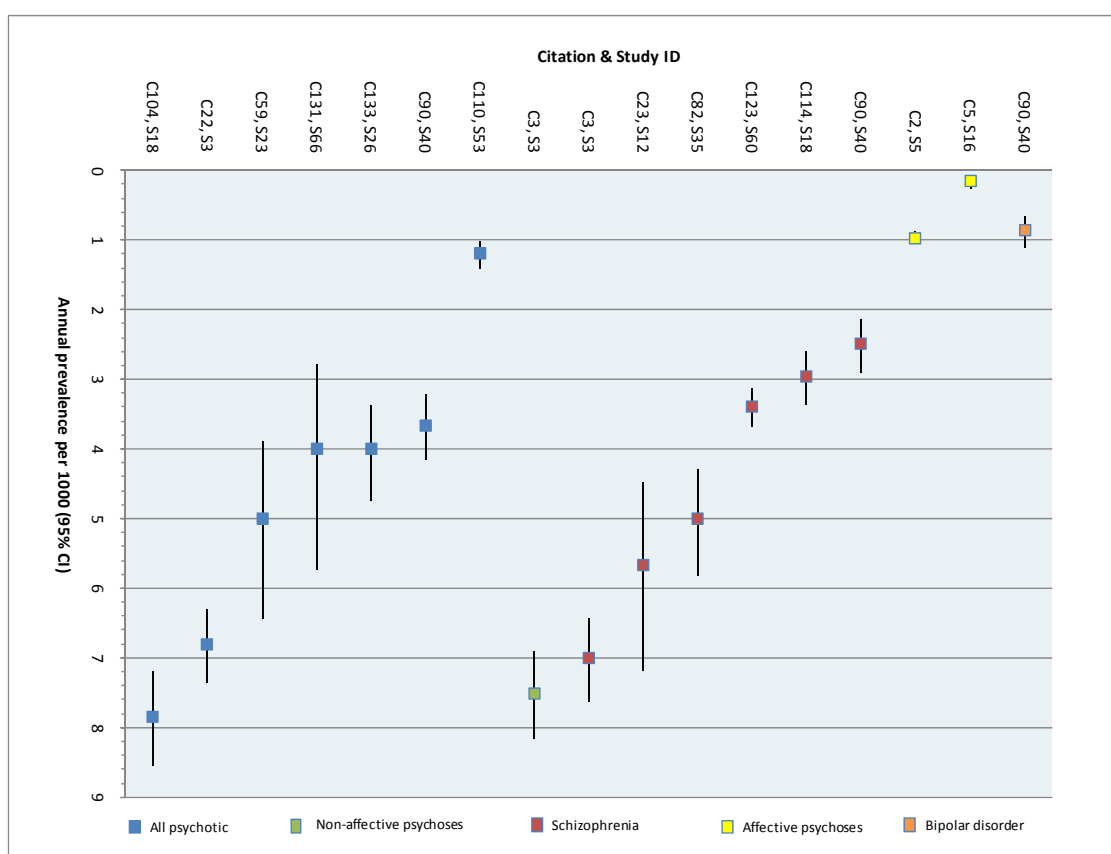
Studies of the prevalence of psychotic disorders show considerable variation in methodology and so in results. However, overall there was evidence that the distribution of annual prevalence rates (for which there was most information) followed the expected gradient across diagnostic boundaries, with considerably lower prevalence rates of the affective psychoses than their non-affective counterparts (Figure 5.2). Cross-sectional surveys of the general population have considerable problems of measurement and definition, and those based on service databases (case registers) tend to accumulate cases as there is no indication of when people get better. The period over which prevalence is estimated varies between studies from a point prevalence to a whole lifetime. Most studies used only one definition, in contrast to studies of incidence where narrowly defined diagnoses were often a subset of broader categories that were also reported. Overall, annual prevalence rates were in the region of 0.4% for all psychotic disorders and similar for the non-affective psychoses. The corresponding lifetime prevalence rate of non-affective psychosis at 43 years old was 0.63% and this is probably consistent with the typically-reported 1% prevalence over the life course.

*All clinically relevant psychosis (Section 5.1)*

The pooled estimate of annual prevalence was 4 per 1000 (95% CI: 3, 7). Population surveys indicate similar prevalence for men and women with a peak between 30 and 40 years of age; case registers indicate increasing prevalence with age up to 65 years. There is no indication of changes in prevalence with time. Studies vary far more by type and definition than by quality that, unlike the former, did not appear to affect the conclusions that could be drawn.

These effects were similar for studies of *non-affective psychosis* (Section 5.2) for which there was some evidence of increased prevalence in older women, and for schizophrenia (Section 5.3). There were too few studies of affective psychosis (Section 5.4) to draw meaningful conclusions.

**Figure 8.2: Distribution of annual prevalence of different diagnostic outcomes in England by citation**



Studies of *bipolar disorder* (Section 5.5) suggested that, despite bipolar disorder being relatively chronic from a clinical point of view), the annual prevalence is less than one per 1000, a reflection of its relatively low incidence compared with other psychoses (Section 4.2.5). Prevalence is similar in men and women, and increases with age.



Prevalence of *depressive psychosis* (Section 5.6) was addressed by very few studies and, remarkably, there was none estimating prevalence of substance-induced psychosis (Section 5.7; in contrast to drug dependence). Single studies of depression suggested similar prevalence for men and women, increasing with age monotonically for men and reaching a plateau in middle-age for women.

### **8.2.3 Principal findings from specialist settings**

The data relating to special populations was extremely heterogeneous in terms of setting, population and methodology. The most appropriate ways to analyse and present this data are currently being explored by the research team and these data will be synthesised into the next version of this report, following peer-review.

### **8.2.4 Principal findings in regard to economic cost implications for services and society (Objective F)**

Using available, limited, period prevalence estimates of psychotic disorder in England we were able to estimate the annual costs of these disorders to services and society in the UK (see Chapter 7). Total cost estimates for the UK were placed at £8.8bn and £5.25bn per annum for non-affective psychoses and bipolar disorder, respectively. Excluding the estimated cost of lost employment and informal care costs – both of which were particularly substantial for non-affective psychoses – the direct service costs of non-affective psychoses, schizophrenia and bipolar disorder were £3.5bn (Table 7.1), £2.0bn and £4.05bn (Table 7.3), respectively. It is interesting, and perhaps surprising to note that service costs associated with bipolar disorder were greater than those for either the non-affective psychoses or schizophrenia; the latter being based on the same study [C144] upon which the bipolar disorder estimates were obtained. Despite the lower prevalence of bipolar disorder than non-affective psychoses, per patient service costs associated with care are much higher than estimated for people with non-affective psychosis.<sup>3</sup> For example, for people aged 15-44 service costs are estimated to be £11,582 for people with a non-affective psychosis per annum, compared with £33,498 for people with bipolar disorder. A similar discrepancy is observed in the 45-64 year old group. However, there are substantial informal care and loss of employment costs associated with the non-affective psychoses, which tend to be more debilitating and demanding than their affective counterparts.

Given, the median age at onset of non-affective psychoses is in the mid-twenties, and the chronicity of such disorders, these annual estimates of costs to services and society take on increased meaning; they are likely to be incurred annually for the remainder of the patient's life – on average another 30 years.<sup>172</sup>

Unfortunately we were unable to identify any suitable citations providing the prevalence of affective psychoses by age and sex (see Section 5.4.2) to enable us to estimate the overall cost of these disorders. The totals presented here may therefore underestimate the true cost of psychotic disorders to services and society, though a number of other caveats need also to be considered when interpreting these estimates (see Section 8.3). There was also insufficient prevalence data to investigate the economic cost implications of any variation in psychosis by other key variables, such as ethnicity or geographical locale. Understanding such variation, and associated costs, will remain an important priority for health services research.

### **8.3 Methodological aspects**

In this section we consider the methodological aspects of the study, that might have a bearing on the results and conclusions, and hence on the connections to be made from this work to emerging policy issues of health service organisation and funding issues. Since these are quite general and wide ranging, we have organised them as bullet pointed paragraphs, so as not to convey any priority via numbering.

- **Epidemiology and Systematic Review**
  - The conclusions of our review clearly depend on the comprehensiveness of our enumeration, and accuracy of definition of relevance, for studies conducted in English catchment areas over the period (1950-2009). We believe that our methodological approach provided a broad, inclusive screening of potentially relevant literature.
  - Our decision to use four published literature databases and two covering grey literature was influenced by our library and information services collaborators, whose judgement we accepted (and to whom we are very grateful, since their input

ensured the success and timely completion of the first stage of the research – enumerating the superset of possible studies and citations.

- We used published incidence and prevalence rates from citations spanning over six decades. During this time changes to nomenclature, health service organisation, diagnostic classifications and research methodologies are all likely to have had some bearing on the likelihood of complete case ascertainment and the extent to which reported incidence and prevalence rates can be considered true rates within the community. We took the pragmatic assumption for this report that measured incidence and prevalence represented true rates. Our study quality variable included assessments of the extent to which case ascertainment was likely to be complete (entry criteria, defined catchment area, leakage study and so forth), and we identified little evidence to support any systematic under- or over-estimation of rates in the literature along these lines of enquiry. We did differentiate between incidence (i.e. first contact versus first admission) in our data extraction process, meaning this data is available for future inspection by interested stakeholders ([www.psychiatry.cam.ac.uk/epicentre/review](http://www.psychiatry.cam.ac.uk/epicentre/review)).
- Abstract and paper review was conducted by two team members, since this seemed most efficient, and it worked in practice. In practice very few studies had to be referred to the third adjudicator (PBJ) who was tasked with resolving decisions that diverged.
- Any missed studies that come to our attention will be able to be included when the reviews are updated (as systematic reviews tend to be, over coming years). In order to facilitate speedy incorporation of any missed studies, we will have section on the website where “potentially omitted in error) studies can be brought to our attention by national (or international) scientists. The first wave of peer review (following submission of the first version (Version 1.00) to the Department of Health) praised the comprehensiveness of included papers; no erroneously omitted citation was brought to our attention by our peers.
- We acknowledge that limiting the geographical scope of this review to studies conducted wholly or partially in England represents a limitation in terms of generalisability to other settings. Nevertheless, it was beyond the remit of this

review to appraise the wider literature. Where relevant, we have drawn comparisons and similarities between patterns in England and those observed elsewhere, and referenced key citations accordingly. Given the heterogeneity in figures within England, one should also be sensitive to the likely international heterogeneity of findings which may provide important aetiological clues to our understanding of psychotic disorders. Nevertheless, there are also some findings which bare replication across settings, and these should be acknowledged: age-at-onset and distribution of psychoses by sex, greater risk in migrant groups and their offspring and higher rates in more urban populations.

- The urgency with which this review is updated may well relate to a possible area of policy interest i.e. the speed with which EIS developments increase the number of small, service-catchment based epidemiological studies of (early-) psychosis coming to join the existing literature. This will also add a more interesting twist to the temporal questions about rates (since EIS services date back to only 2002). However such studies will have to confront considerable challenges to validity (for example, to case-definition) and also potentially be smaller in scale than many existing reported studies. Nevertheless, this will enable new frontiers in understanding the micro-epidemiology of psychosis to be navigated, as well as increasing the number of register/routine data-based multi-centre epidemiological studies of schizophrenia, other psychoses (and we suspect other serious and common mental disorders).
- In terms of **Research Streams**, the most sparsely populated section of the results was that relating to special populations (Chapter 6) (i.e. those in specific residential situations – hostels, sheltered accommodation, prisons or the criminal justice system, the Army, or further unique cohorts; for example, the study of pregnancy termination(s) and psychiatric outcomes). Here, other than for the more forensic settings, there appears to be relatively little data available. We also note that prior international reviews have included the majority of existing studies (e.g. the review of SMI in prisons by Fazel and Danesh<sup>173</sup> and that of Fazel *et al.*<sup>174</sup> on the prevalence of mental disorders in the homeless).

- Although we are not aware of any bias that might have arisen in this systematic review, we should at least make this point ourselves, although the process of the review should be described in sufficient detail for possible bias to be identified: we do not think that this is likely. Also previous reviews, more international in scope, have also provided equal impetus to the heterogeneity of incidence perspective, for both epidemiological incidence and prevalence data.
  
- **Statistical and meta-analytic issues**
  - We think that our application of meta-analysis and meta-regression methods is at one level, fairly conventional, but for the meta-regression analyses we note that we are using a newly developed (multivariate and fractional polynomial trend based) procedures, that are only just becoming established in the biostatistical literature supporting evidence synthesis, although for our study the method was recommended by and all analyses conducted by an international centre of excellence in the biostatistical aspects of meta-analysis research (the MRC Biostatistics Unit). Also our meta-analytic statistician (Dan Jackson) has been mentored and supervised during this project by two experts in the field (Ian White and Julian Higgins, who are both MRC Senior Scientists of international repute).
  - One key variable used in the meta-regression modelling was the measure used to relate “degree of urbanicity” to study rates. Here we took a bold but novel approach, using “expert judgement” which involved the majority of the study team rating /ranking study catchment areas in terms of most versus less urban. Although subjective, and new, this approach yielded a gradient of urbanicity against which we could relate potential study between study rate variation(s). The stability of this ranking over a larger number of raters would be a valuable addition to our claims for the reliability and validity of this approach. No other single number summary was available for use in the same way in our analyses, so once again we invented something pragmatic. However, this is also an area where personal (subjective) bias could arise.

- Our measure of data quality did not suggest that reported study data quality significantly affected the incidence or prevalence rate of psychotic disorders. Our measure had some psychometric validity (Appendix VII), though we acknowledge that *reported* study quality from individual citations may not be the same as *actual* study quality.
- Clearly the methodological community may contribute to the debate over the most appropriate methods for exploring age-related variation in study rates, and the focus of this review on time trends in rates is also (relatively) unusual. As we have noted in our methods, the dating of studies for use of this between study variation in rates, is a little less than ideal, but once again proved pragmatically useful. An appendix to this report (Appendix VII) includes a possible psychometric extension of the meta-regression modelling using study quality (to be clear, *reported* study quality, see Section 3.4.4) summary variables, producing an alternative continuous measure that arguably has stronger scaling properties than the sum score (although a sensitivity analysis of the meta-regression findings using this alternative has yet to be undertaken, since it currently relies on only 6 of the 7 quality criteria (omitting “leakage study”, since leakage study ratings were unavailable for ~10% of studies).
- We extracted all data relating to incidence or prevalence from relevant citations. This included, where published, estimates of the **numerator** and **denominator**. Where possible we used the published rates and standard errors provided by the citation. Where these were not published, we estimated these (“derived”) figures from other information provided by the study. Similarly, when inspecting differences in rates between subpopulations (by estimating **rate ratios**) we sometimes had to derive these from the available data if rate ratios were not reported in the original citation. We have no reason to doubt the accuracy of our estimates from these citations, but presented results may differ slightly from the original citation in a few instances, due to rounding and small methodological differences in the calculation of rates (we used a Mantel-Haenszel approach to compare (usually crude) rates, where original studies might have adopted multivariate regression-based techniques to compare adjusted rates). Where available, we published rates and rate ratios as published in the original citation.

- **Cannabis use and psychosis**

- We did not include substance use, and in particular cannabis, as a risk factor along which the incidence or prevalence of psychotic disorder may vary. This omission may at first seem surprising since the prevalence of both licit and illicit substances, including cannabis, alcohol and amphetamines is known to be extremely high in clinical samples of people experiencing a first episode of psychosis.<sup>95, 96</sup> Cannabis, particularly, has been the focus of much scientific research and media attention over the last decade, and there is now good evidence that use is associated with a greater risk of developing psychosis,<sup>175, 176</sup> something which may be particularly harmful during adolescent brain development.<sup>177</sup> We have not included substance use (or cannabis as a separate risk factor) in this review because in the UK it is impractical to obtain estimates of either incidence or prevalence of psychotic disorder according to this risk factor. Obtaining incidence estimates is not possible because although substance use data is often collected on clinical samples (the **numerator**), data on substance use is not routinely collected on the general population which make up the **denominator** of any incidence estimate. Obtaining prevalence estimates according to substance use is more feasible, but issues of recall, exposure frequency and dose make it difficult to estimate such rates. We acknowledge that substance use is an extremely important issue in both clinical practice and research and this review does not attempt to downplay that. Rather, such risk factors generally do not fall within the scope of this review. We have attempted to provide information on substance-induced psychoses (usually diagnosed as a result of acute intoxication). For a comprehensive and detailed systematic review of the effects of cannabis on psychosis, we refer readers to Moore *et al.*<sup>33</sup>

- **Other general limitation of our review**

- Finally, clearly an area not addressed by the research team is the role of any routine NHS data to be used for epidemiological research on psychosis. Although potential

for such work may be changing in recent years, the authors experience of routine data systems since the relative demise of the (at one time, well managed) Case Registers, is not generally positive with respect to population prevalence of incidence estimation. Perhaps new NHS IT initiatives will enable us to revise our views in coming years and include more routine data estimates of relevant psychosis epidemiology data. Indeed, we suspect that the Public Health Observatories will engage with this agenda the moment that data coverage and quality appears to allow.

- **Health Economics and Cost Implications**

- The economic and cost implications outlined above were based on several caveats which we should note.
- Estimating the cost of mental illness to health services and society is extremely difficult and reliant upon a number of assumptions.<sup>178</sup> We were able to base our estimates of cost upon some of the best available data in the UK, conducted by the Centre for the Economics of Mental Health, based at the Institute of Psychiatry. This data was, however, only available for the UK as a whole, and therefore the costs implications reported in this study pertain to this level of geography, and are not solely limited to England.
- Accurately estimating the costs of psychotic illness to health services and society is reliant upon high quality prevalence data, stratified by important sociodemographic variables such as age and sex. In this review, we were often restricted to a handful of well-conducted studies which had published such stratified prevalence rates. These studies were often based on data more than 20 years old, and while we have no reason to suspect these estimates have changed over time, it would be clearly of interest from a public health and health economics perspective to have up-to-date, detailed and comprehensive estimates of the prevalence of psychotic disorders in England. We suggest that this data should be stratified by several demographic factors, not limited to age and sex, but including ethnicity, social class (occupation) and marital status. We



attempted to minimise this issue in our analyses by adjusting prevalence estimates to the 2009 mid-term census population to establish the number of people suffering from psychotic disorders in the UK.

- We used the same cost data to underpin our models of both non-affective psychoses and schizophrenia, separately. In reality, we acknowledge that the costs of services for different psychotic disorders will differ. Nevertheless, our results provide ballpark estimates of the costs incurred in the UK for these disorders.
- There was insufficient data in England to examine the cost implications of variations in rates by variables other than age and sex. We were unable to draw firm conclusions as to whether the prevalence of psychotic disorder varies by geographical setting, though there is evidence of this from incidence studies. Notwithstanding the excellent EMPIRIC study and British National Survey of Psychiatric Morbidity,<sup>37, 60</sup> we will require large surveys to detect such possible variation and estimate healthcare cost implications accordingly. These surveys suggested the prevalence of psychotic disorder was elevated in some ethnic minority groups, but we did not have cost data available to look at the economic implications of this variation. This presents a future challenge for healthcare economics.

#### **8.4 Meaning of our findings for health services research**

These systematic reviews have considered a great deal of evidence, almost certainly more than has ever been brought together with relevance to psychotic illness in England and of relevance to the NHS.

The reviews yield relatively precise estimates of the incidence of the main diagnostic groups, particularly for the broadest categories that have most relevance for service planning and clinical practice, the latter being based more on symptoms than diagnoses within the psychotic disorders that are all relevant to early intervention services in the NHS. Service planners and commissioners must also acknowledge that these estimates will be accurate in the round, but there may be year on year variation in count data such as this.

Most psychotic disorders comprise so called non-affective illnesses closest to the concept of schizophrenia. These conditions most commonly arise in young adults than older people, in men, in cities and in black and minority ethnic groups. While we condone clinical services acknowledging all individual diversity, the data suggest that service planning needs to take these factors into account, perhaps the last in particular, when planning services. We recommend that our work is taken further in terms of developing practical prediction tools for commissioners and those providing mental health services; this would now be a relatively simple step.

Inner city areas with a high a proportion from black and minority ethnic communities will definitely yield higher numbers of young people with these disorders per unit of population than will rural areas. However, the review also suggests that some of the largest variation may be quite local and population needs assessment needs to be commensurately sophisticated. Furthermore, evidence of increases in the incidence of these disorders over time is most likely to be due to changes in the composition of communities in terms of black and minority ethnic groups than any intrinsic changes to the disorders, themselves, or to other determinants. We do not know what is happening in the recently migrated populations from the former USSR or Eastern Europe; further research is required.

For affective psychotic disorders such as depressive psychosis and bipolar disorder, precise estimates of incidence were possible, with little or no variation according to sex or socioeconomic factors. There is evidence that, as above, black and minority ethnic populations are at higher risk but the evidence is less secure and the effects probably smaller than for illnesses like schizophrenia; furthermore, there will almost certainly be differences between ethnic groups.

There were fewer differences within and between estimates of prevalence of psychotic disorders, over and above the fact that non-affective psychoses such as schizophrenia represent the main burden, something that does not detract from the needs of those with other disorders in terms of their personal characteristics or the particular service requirements for the health conditions.

The reviews have generated precise estimates of prevalence but these do not differ greatly from previous information. That said, there are few studies of this basic parameter; improved and

coordinated NHS clinical information systems could be central to improving our knowledge of this area.

The economic costs to mental health care and other services of psychotic disorder are considerable and should not be overlooked. Our data indicate that these costs appear to be particularly high for bipolar disorder. However, when we factor in the substantial cost of informal care for people experiencing non-affective psychotic disorders (£1.1bn pa), the total cost of service provision for non-affective psychoses and bipolar disorders is more similar; just over £4bn each. These findings serve as a salient reminder that of the importance of recognising the substantial burden of informal care placed upon caregivers of people experiencing psychotic disorder. From a health services and public health perspective, the cost of both non-affective psychoses in the UK is particularly pronounced given the typically young age at onset and poor outcome for people with psychosis. Efforts to prevent the onset of psychosis or improve outcome may reduce the associated direct (service) and indirect (employment) costs of such disorders, but the evidence regarding the success of initiatives designed to tackle these issues (such as Early Intervention in Psychosis Services [EIS]) remains equivocal.<sup>179-182</sup>

## **Recommendations**

1. Service commissioners and planners should take into account the detailed variation in incidence of psychotic disorders, particularly non-affective psychoses (schizophrenia) at the local population level.
2. The greatest driver of variation in incidence, once the age, sex and socio-economic structure of a population is taken into account, is the proportion of people from BME communities. This has to be acknowledged at the service planning and political level, with more research being required to understand this important phenomenon. Future changes regarding recent migrant groups need to be studied.
3. DH should commission the development of a prediction tool that integrates small-area (local) population data and the findings from the review. This would produce information about the numbers of people each year who will develop a psychotic illness (population need) in any given area. This would ensure that services can be designed to meet population need and would greatly help commissioners and service providers.

4. In addition to the prediction tool (Recommendation 3), the numbers of people being treated for first onset psychosis (administrative incidence) should be studied through EIS so as to refine prediction and to ensure that services are being planned and delivered properly. Some EIS may have much higher caseloads than were expected; others may have lower caseloads. A prediction tool and the routine monitoring of administrative incidence would reduce the likelihood of a mismatch between population need, commissioning and the services provided.
5. New NHS information systems should be routinely used to collect current and future information on the variation in (administrative) incidence and prevalence of these disorders. This will support service delivery and research into the causes of illness.
6. Social factors in the urban environment, including indicators of low community cohesion, were associated with increased incidence rates of schizophrenia. Further research into these factors may reveal prevention opportunities and help unravel the multilevel causes of psychosis. This is a public health priority.

### **8.5 Comparison of findings with the wider literature**

This review has focused on the incidence and prevalence of psychotic disorders in England between 1950 and 2009. As such, it has revealed variation in rates along several dimensions, which will be important for the continued planning of appropriate, sensitive mental health services (see Section 8.4). Our review may also have a bearing on aetiological research of psychotic disorders, and in this sense, its findings need positioning in context to the wider epidemiological literature. Understanding similarities and differences in the epidemiological landscape of psychoses in England *vis-à-vis* other settings provides an opportunity to learn more about the possible causes of psychosis. Furthermore, our review has been restricted to incidence- and prevalence-based studies. This necessarily ignores a much wider epidemiological literature utilising other study designs, such as case-control studies, to elicit risk factors for psychosis which could not be discovered easily or at all from studies of incidence or prevalence. Such risk factors include major life events in childhood and adulthood, substance abuse, social disadvantage, paternal age and malnutrition. In this section, therefore, we also highlight how the findings observed in this report fit in with the broader concept of psychosis risk, illustrated

through other epidemiological studies, both national and international. This is to say nothing of the importance of genetic risk, possible gene-environment interactions or the potentially important role of epigenetic factors in determining psychosis risk, but it is beyond the scope of this review to cover these themes (but see O'Donovan *et al.*<sup>183</sup>, van Os *et al.*<sup>184</sup>, and McGowan *et al.*<sup>185</sup> and Meaney *et al.*<sup>186</sup>, respectively).

### 8.5.1 Comparison with international incidence rates of psychotic disorders

The incidence rate of all first episode psychotic disorders in England appears to fall within the range of observed rates across the world, though direct comparisons are difficult and one should be careful not to preclude important heterogeneity in rates, both between and within different settings. Nevertheless, the overall rate in England is comparable to the rate observed in one area of the Netherlands,<sup>139</sup> lower than observed in Sweden,<sup>187</sup> but higher than observed in Sao Paulo, Brasil.<sup>188</sup> For schizophrenia, our pooled estimate of incidence in England (15.2 per 100,000 person-years) was identical to the median incidence observed from 170 studies in McGrath *et al.*'s systematic review of the international schizophrenia incidence literature.<sup>8</sup> Importantly however, these figures obscure important heterogeneity within England and globally. The WHO Ten-Country study found a threefold variation in the incidence of schizophrenia across different countries,<sup>4</sup> providing important though often overlooked clues to aetiology.

Less international data is published on the incidence of the affective psychoses, and given that incidence rates of such disorders are an order of magnitude lower than for the non-affective psychoses (see Figure 8.1) comparisons are difficult. Nevertheless our pooled incidence of bipolar disorder in England fell within the range of rates observed internationally, comparable to rates observed in the Netherlands<sup>139</sup> and one Danish study,<sup>189</sup> but lower than the rate observed in another Danish study,<sup>190</sup> and greater than rates observed in the Czech Republic as part of the International Pilot Survey of Schizophrenia [IPSS].<sup>189</sup> We are aware of very few studies conducted outside of the UK which have published the incidence of depressive psychoses, but the pooled rate we report here was significantly greater than observed in one Dutch study.<sup>139</sup>

Incidence rates of the psychotic disorders under study in this review according to age and sex followed a highly replicable pattern, seen in many epidemiological samples across the globe.<sup>8, 11, 69, 191</sup> Our findings confirm that the incidence of all psychotic disorders increase for women compared with men around the age of menopause. Prior to this point, rates of non-affective psychoses tend to be elevated amongst men, while rates of affective psychoses appear similar for both sexes. These findings putatively support the hypothesis that estrogen may operate to protect women from psychosis during their premenopausal adult life.<sup>168</sup> This hormone also appears to lower symptomatology, but despite some animal evidence which suggests estrogen may be neuroprotective, the latest Cochrane Review did not find enough evidence to promote its use as an intervention.<sup>192</sup> Furthermore, since the general pattern in men and women until menopause is a decline in incidence rates from the early to mid twenties, other factors which change as a function of age must also be implicated in psychosis aetiology. These could be neurogenetic changes over time, potentially mediated by or due to epigenetic changes following accumulated social and toxological environmental insults.

The raised rates of psychotic disorders in ethnic minority groups in England fits within the wider literature from Northern Europe, the USA, Canada and the Middle East, which have all identified migrant and ethnic minority groups as having higher incidence rates of psychotic disorder. The patterning of this risk is closely linked with country-specific migration histories, thus rates are elevated for Caribbean and African migrants (and their offspring) in the UK,<sup>10, 101, 193</sup> Moroccan, Turkish, Surinamese and Antillean migrants (and offspring) in the Netherlands,<sup>21, 139, 194</sup> European and East African migrants (and offspring) in Scandinavia,<sup>94, 127, 129, 149</sup> European migrants to North America,<sup>123, 195</sup> and African-American groups in the USA.<sup>132, 196</sup> The migration effect has been less fully explored in other countries; in Australia<sup>197, 198</sup> and Israel<sup>126, 199</sup> the current evidence is equivocal. These findings emphasise the role of addressing contextual factors which may operate differential on the risk of psychosis in migrant groups and their offspring. The magnitude of increased risk seems to be dependent on the degree to which people can be identified as a “visible minority”<sup>7</sup>; something which may not be limited to ethnicity or migration status alone. Ethnicity and migration provide one of the leading candidate demographic factors through which to explore socioenvironmental risk; this is discussed in greater detail in Section 8.5.3.

Our review, incorporating available data from nearly 60 years of research, has suggested that overall incidence rates of psychotic disorder in England have not significantly changed over time. We acknowledge diagnostic shifts have led to some decline in rates of certain conditions (such as schizophrenia), but as far as the evidence allows us to determine, these declines have been matched by corresponding increases in the incidence of other non-affective psychoses. These patterns likely reflect changing diagnostic practices, movements to new classifications and the sensitive issue of stigmatisation; the latter being particularly relevant to how EIS currently operate. Service-side changes from inpatient to outpatient care in the 1980s and 1990s also likely explain a large degree of the decline in hospitalised admission rates over this period. True, population-based measures of incidence do not tend to reveal similar declines in rates.<sup>23</sup> These English findings are broadly echoed in the wider literature. Thus, in Finland the incidence of schizophrenia has tended to fall over time, but this appears to have been compensated for by increases in the rate of other non-affective psychoses.<sup>200</sup> In Denmark<sup>201</sup> and New Zealand,<sup>202</sup> changes in the organisation of services has also been proposed to account for the decline in hospitalised incidence rates during the 1980s.<sup>203</sup>

Recent international studies have posited that rates of psychosis might even be rising, with speculation that increases in substance use may be responsible. As noted in Section 8.3, estimating the incidence of psychotic disorder attributable to substance use is fraught with methodological issues. Although there appears to be a causal link between substance use and psychosis risk,<sup>33</sup> whether this results in raised rates of disorder is unclear. If we assume that previous cannabis use doubles psychosis risk,<sup>176</sup> even this may only have a small effect on incidence rates, given that not all individuals who develop psychosis have used cannabis and given that the absolute incidence of psychotic disorders is low. Thus, a risk factor which has a strong relative risk (in this example, a RR of 2), may only lead to small changes in incidence, which may be particularly difficult to detect. This problem is exacerbated if those subjects who smoked cannabis and developed psychosis would have gone on to do so anyway in the absence of substance use. The limited data available from England suggest that rates of substance-induced psychoses in Nottingham have increased over a 20 year period,<sup>23</sup> but whether this reflects a genuine change or is an artefactual reflection of changes in diagnostic practice is

unclear. However, one Canadian study has reported increases in the incidence of all psychotic disorders in the 1990s,<sup>204</sup> while a further study in Zurich found increased rates amongst teenagers over the same time period,<sup>205</sup> which the authors suggested may be due to changing patterns of substance abuse. Model-based projections in England suggest that if changes in substance use have led to raised rates psychosis, this should be detectable from 2010 onwards in incidence samples.<sup>206</sup> We suggest carefully designed epidemiological research should be established to monitor this important public health concern.

### **8.5.2 Comparison with international prevalence rates of psychotic disorder**

As with incidence, the prevalence of psychotic disorders is known to vary worldwide.<sup>9</sup> Acknowledging this heterogeneity, however, some comparisons can be made between our findings and those from the wider literature. Saha and colleagues placed the median point and period prevalence of schizophrenia at 4.6 (10<sup>th</sup> – 90<sup>th</sup> percentile: 1.9, 10.0) and 3.1 per 1000 persons (10<sup>th</sup> – 90<sup>th</sup> percentile: 1.3, 8.2), respectively. Though corresponding estimates in England were heterogeneous, they fell within this range (Point prevalence: 2.0, 5.0; annual prevalence: 2.9, 5.6). The lifetime prevalence of schizophrenia at 28 and 43 years was also estimated in two British Birth Cohorts to be 2.9 per 1000 and 6.7 per 1000, respectively. These rates lie in the range of lifetime risk estimates identified in Saha et al.'s international systematic review.<sup>9</sup> Interestingly, these rates highlight heterogeneity in the lifetime prevalence of schizophrenia worldwide. Emphasising this, two major US epidemiological studies, the Epidemiological Catchment Area study and the National Comorbidity Survey, estimated the lifetime prevalence of schizophrenia at 14 and 7 per 1000,<sup>207, 208</sup> respectively. A more recent Finnish study placed lifetime prevalence at 8.7 per 1000.<sup>35</sup> However, two meta-analyses have suggested that the pooled lifetime prevalence is closer to 4.5 or 5.5 per 1000 persons.<sup>9, 36</sup>

The prevalence of affective psychoses in England was generally observed to be lower than for the non-affective disorders, with estimates of the annual prevalence of bipolar disorder placed between 1.0 and 3.8 per 1000 persons [C90, C144]. These rates appear to be lower than observed elsewhere in Europe.<sup>209</sup> We did not have sufficient data to make meaningful comparisons between the lifetime prevalence of bipolar disorder and depressive psychoses in



England and other settings (but see Perala *et al.*<sup>35</sup> and Pini *et al.*<sup>209</sup> for the international literature).

### **8.5.3 Integrating our findings with wider literature on risk factors for psychosis**

Despite the heterogeneity in the rates of psychotic disorder presented in this report, some consistent findings do emerge which lend support the wider, emerging epidemiological literature in regard to the etiology of psychosis. Most pertinent in this context are the incidence findings in relation to ethnicity and urbanisation. We have already summarised the main findings and risk factors identified in the English incidence and prevalence literature (see Section 8.2.1). Here, we draw upon the wider international literature and other epidemiological study designs to frame the potential etiological implications of our findings in wider context.

Raised rates of psychosis amongst migrants and their offspring putatively suggest that the risk of psychotic disorder is related to the migratory process or socioenvironmental exposures encountered after migration. There is increasing evidence against many other putative hypotheses (see Box 8.1), including a purely genetic explanation for raised rates in migrants and their offspring, since incidence is lower in the sending countries of those migrants who later develop higher rates of psychosis.<sup>135-137</sup> Selective migration does not account for this phenomenon either.<sup>133</sup>

The ethnic density effect, observed in England,<sup>30, 31</sup> the Netherlands<sup>32</sup> and the USA,<sup>81</sup> suggests that psychosis risk in migrants and their offspring is conditional upon the proportion of people from similar ethnic groups living in their neighbourhood. This indirectly implicates social factors as putatively important in governing psychosis risk, something for which there is accumulating evidence, for both ethnic minority groups specifically and in the population as a whole. Pursuing this idea, using an ecological study design, Veling *et al.*<sup>148</sup> found that ethnic groups who experienced greater levels of discrimination also had higher rates of psychosis. However, attempts to replicate this finding at the individual-level have so far proved unsuccessful<sup>210</sup>; perhaps suggesting the relationship between discrimination, ethnicity and psychosis is complex and context dependent. Indeed, recent evidence from the same group emphasises this issue.<sup>211</sup>

In a case-control design, individuals who identified less with their own ethnic group had a greater risk of developing schizophrenia. Put another way, individuals with stronger ethnic identity had a lower risk of developing schizophrenia. This suggests that in the face of social stressors (often more prevalent for minority groups), such as discrimination, living in a new, unknown country or living in poorer environments, individuals with stronger ethnic identity were more able to buffer themselves from developing psychosis. This could be due to increased levels of self-esteem conferred from perceptions of a strong ethnic identity, or because such individuals could draw more directly on strong social ties in the community to buffer social stress following exposure to negative life events, or indeed both.

Interestingly, studies which have examined psychosis risk according to neighbourhood social composition tend to find that neighbourhoods indexed by greater social fragmentation and isolation have higher rates of psychosis. Thus, the highest rates of psychosis in English cities tend to occur in the most socially fragmented communities.<sup>14, 31, 113, 170, 212</sup> This effect persists after controlling for socioeconomic deprivation. Similar reports have been published in Scotland,<sup>29</sup> the USA,<sup>213</sup> and the Netherlands<sup>214</sup> where the rate of schizophrenia was higher in settings characterised by greater social fragmentation, residential turnover and proportions of single individuals, respectively. Given the association between urban birth and upbringing and schizophrenia,<sup>5, 119</sup> it is unlikely (though possible) that social drift entirely accounts for these associations.

If, as evidenced, social support is protective against psychosis, it should follow that adverse life events at the individual level would impact negatively on psychosis risk. Data from several studies now bear this out. Adverse life events in childhood seem to be particularly pervasive on later psychosis risk. For example, lower socioeconomic position during childhood has been found to be associated with greater psychosis risk in a large Swedish population sample.<sup>215</sup> Traumatic events in childhood including physical and sexual abuse,<sup>130, 216</sup> parental death,<sup>13</sup> separation from a parent<sup>13</sup> and institutionalised care and victimisation<sup>216</sup> have all been associated with an increased odds of experiencing psychosis. Severity of abuse experienced appears to increase psychosis risk in a dose-response fashion.<sup>217</sup>

Cumulative exposure to a range of negative life events in both childhood and adulthood may increase the risk of later psychosis, particularly where individuals may lack the social support required to buffer the detrimental effects of stress. Interestingly, some social adversities, including aberrant parental separation and death, and markers of adult social disadvantage, appear to be more prevalent in some ethnic minority groups, which may in part explain the increased risk of psychosis in migrants and their offspring.<sup>13, 34</sup> These social adversities fit well into a hypothesised causal mechanism of social defeat,<sup>218</sup> which potentially operates via chronic changes in stress response to disrupt dopaminergic pathways, eventually leading to the onset of positive psychotic symptoms such as delusions and hallucinations. Although direct proof of this mechanistic pathway is still missing, some commentators now suggest that psychotic disorders may be the result of permanent aberrant salience disruption.<sup>80, 219, 220</sup>

We should, however, recognise that a sociodevelopmental model of psychosis, as outlined is not the only possible mechanism through which environmental factors increase psychosis risk. Although not directly part of this review, we also know that early life events, including obstetric complications<sup>221</sup> and maternal influenza<sup>114</sup> and malnutrition<sup>222, 223</sup> during gestation increase later psychosis risk (see Brown and Susser for a review<sup>224</sup>). Vitamin D deficiency may also be important in increasing psychosis risk<sup>153</sup> (see, for a discussion, McGrath *et al.*<sup>225</sup>), and putatively may explain differences in incidence and prevalence rates by ethnicity, migration and level of urbanisation. Advanced paternal age also increases the risk of psychosis in offspring.<sup>226, 227</sup> These factors highlight the likely multifactorial aetiology of psychosis, and it is important to recognise that there will be a clear overlap between neurodevelopmental and social risks, as well as interplay with genetic susceptibility and epigenetic mechanisms.<sup>228</sup> Studies of the potential interactive effects of genetic and broadly defined environmental exposures are just beginning.<sup>229</sup>

## 8.6 Future directions for epidemiological research

Although conceivably within the scope of this research, it has proved beyond the reasonable limits of the research team to populate the results with results sections presenting data on every possible permutation from our researchable questions roadmap, which is how we think of the [citation matrix](#) presented in Figure 3.1. Currently, the main body of this report includes results from all analyses completed to date. As these results, and this report, are shared with

reviewers and dissemination audiences, it is of course highly likely that requests for, or opportunities for more data arise. With an unlimited resource, clearly a wide range of other analyses are possible. It remains for the research team to negotiate with the research commissioners to specify appropriate avenues for completing further work, or making the research resources of the study team available so that more permutations from the matrix can be pursued.

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## **Chapter 9: Conclusion**

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## **9.0 CONCLUSION**

We have demonstrated considerable heterogeneity in both the incidence and prevalence of psychotic disorders in England over the last 50 years. Overall, the findings from England support the wider research literature that the epidemiological landscape is rich with contours and gradients,<sup>230</sup> which have potentially important implications for both health service planning and our aetiological understanding of psychotic disorders. In this regard we have demonstrated that the typical age-sex distribution of the incidence of psychotic disorders is upheld, with a significant secondary peak in incidence for women after 45 years of age. Incidence rates of psychotic disorder are elevated for migrant groups and their offspring, a finding that is particularly pronounced in the black Caribbean and black African groups. There was less variation in the prevalence of psychotic disorders, but rates were raised in some ethnic minority groups, particularly the black Caribbean and black African groups. We have demonstrated the first strong evidence that migrants from the Indian Subcontinent and their offspring – particularly Pakistani and Bangladeshi women – are at elevated risk of schizophrenia. These findings persist with control for socioeconomic status. The incidence data with regard to the spatial distribution of psychosis broadly support an association with urbanicity for non-affective psychoses and a growing number of studies implicate putative neighbourhood-level factors including ethnic density and social cohesion/fragmentation as important in this regard. There is limited evidence regarding the incidence of psychosis observed through EIS, but early reports appear to confirm anecdotal suggestions that such services have higher than expected caseloads. We have made some tentative recommendations to the PRP to inform policy and we will update these in light of further analyses and peer-review.

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## APPENDIX I – GLOSSARY OF SCIENTIFIC TERMS

This glossary is divided into three sections:

- Terminology used to aid the structural organisation of this report [A]
- Organisations referred to by acronyms of studies and databases [B]
- Information sources/references/resources/manuals [C]
- Glossary of scientific and methodological terms [D]

### A. Terminology used to structure the review and organise the results presented in this report:

**Research blocks** – The term given to our coding of citations according to the broad sociodemographic or socioenvironmental categories to which extracted rates pertained

**Research streams** – The broadest hierarchical organisation of citations included in this review. Within the research stream hierarchy citations were broadly classified according to studies which pertained to the general adult population or what we considered special populations

**Research Themes** – The term used to delineate the diagnostic outcome under consideration.

See Figure 3.1 for diagrammatic representation of how research blocks, streams and themes form our **citation matrix**.

**Citation matrix:** The product of research blocks, streams and themes allowing us to identify relevant citations contributing original data for a given analysis. This matrix is available from the authors and will be made freely available subject to agreement with the funding body of this work.

**Citation** – In this report a citation refers to a published or unpublished resource containing potentially relevant information for the review. A **study** may have several citations associated with it, if the study has multiple publications of relevance. Thus, citations could be defined as **unique** or **duplicate** (**core** or **satellite**) references of usable rate data.

**Unique citation** – the only citation from a single study included in this report. Note that the citation is unique to this report. More than one citation from the same study may exist, but were not relevant to the present systematic review.

**Duplicate citations** – two or more citations providing similar/same rate data from a single study. These were identified as either **core** or **satellite** citations

**Core citation** – Defined as a citation from a study which provides the primary information for a given analysis, when multiple citations from a single study exist. A citation can be core for one analysis and satellite for another, depending on the specific content of that report. Criteria for deciding whether a citation was considered core or satellite is provided in Section 3.5.2.

**Satellite citation** – Defined as a citation from a study which provides secondary or duplicate information for a given analysis, when multiple citations from a single study exist. Data is not used directly in the analysis, except where it could supplement or clarify data from the **core citation**. A citation can be core for one analysis and satellite for another, depending on the specific content of that report. Criteria for deciding whether a citation was considered core or satellite is provided in Section 3.5.2.

**Study** – a study is defined in this review as the scientific investigation or database which has contributed one or more citations regarding the incidence, prevalence or associated risk factors for psychotic disorders to this review. A study may have multiple **citations** associated with it, while on some occasions a single citation may have also presented results from more than one study (for example C145 presents rates of psychotic disorder from two studies, the Camberwell and Salford Psychiatric Case Registers).

## **B. Organisations referred to by acronym**

### **Cambridge**

**CPFT** – Cambridgeshire & Peterborough Foundation Trust, Cambridgeshire

**EAC** – Evidence Adoption Centre, Cambridge

**IPH** – Institute of Public Health, Forvie Site, Cambridge

**MRC Biostatistics Unit [BSU]**

### **London**

**CEMH** – Centre for the Economics of Mental Health, Kings College, London

**IoP** – Institute of Psychiatry, De Crespigny Park, London

## **C. Information sources/reference/resources/manuals**

**ASSIA** – Abbreviation for the Applied Social Sciences Index and Abstracts, an indexing and abstracting tool covering health, social services, psychology, sociology, economics, politics, race relations and education.

**CINAHL** – Abbreviation for the Cumulative Index to Nursing and Allied Health Literature

**DSM** – Abbreviation for the Diagnostic and Statistical Manual of the American Psychiatric Association, Washington. A reference volume for diagnostic criteria for research and clinical practice containing an attempt to standardize the definitions of mental disorders. Currently awaiting release of its fifth version.

**EMBASE** – Acronym for a bibliographic database in the area of biomedicine the Excerpta Medica database (EMBASE) produced by Elsevier. It is a major biomedical and pharmaceutical database indexing over 3,500 international journals in the following fields: drug research, pharmacology, pharmaceuticals, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering/instrumentation

**HMIC** – Acronym for Health Management Information Consortium database of clinical medicine and public health literature. >300k citations. Combines Department of Health Library and Information Service and King's Fund Information and Library Service. Includes journals, official reports and grey literature.

**ICD** – Abbreviation for the International Classification of Diseases of the World Health Organisation. A non-US reference volume for diagnostic criteria for research and clinical practice. Currently awaiting release of its 11<sup>th</sup> version.

**MEDLINE** – An electronic database produced by the United States National Library of Medicine (NLM). It indexes millions of articles in selected journals, available through most medical libraries, and can be accessed on the Internet

**OPCRIT** – Acronym/abbreviation for the Operational Criteria (OPCRIT) diagnostic checklist. OPCRIT is a checklist built up of operational criteria defined by a comprehensive glossary. It is designed to assign reliable diagnoses from case notes, but the validity of such a procedure compared with procedures involving prospective assessment is rarely tested.

**PSycINFO** – Acronym/abbreviation for the PsycINFO Psychological Abstracts database which provides access to the international literature in psychology and related behavioral and social sciences, including psychiatry, sociology, anthropology, education, pharmacology.

## D. Glossary of scientific and methodological terms

**95% confidence interval** – see **Confidence interval**

**Adjusted rates** – Rates that control for the effects of artefacts or confounding factors, such as the age, race, ethnicity, sex, or other characteristic composition of a population to allow comparisons between these populations independent of their structure. (Adapted from the glossary of the Department of Health of the states of New Jersey and Washington

[[www4.state.nj.us/dhss-shad/home](http://www4.state.nj.us/dhss-shad/home) & [www.doh.wa.gov/Data/guidelines/Rateguide.htm](http://www.doh.wa.gov/Data/guidelines/Rateguide.htm)]

**Confidence interval** – “a range of values calculated from the sample observations that is believed, with a particular probability, to contain the true parameter value. A 95% CI, for example, implies that if the estimation process was repeated again and again, the 95% of the calculated intervals would be expected to contain the true parameter value.”<sup>231</sup>

**Crude rates** – Rates calculated by dividing the total number of events in a specified time period by the total number of individuals in the population who are at risk for these events and multiplying by a constant, such as 1,000 or 100,000 [e.g., (numerator/denominator) x constant].

[Adapted from the glossary of the Department of Health of the states of New Jersey and

Washington ([www4.state.nj.us/dhss-shad/home](http://www4.state.nj.us/dhss-shad/home) & [www.doh.wa.gov/Data/guidelines/Rateguide.htm](http://www.doh.wa.gov/Data/guidelines/Rateguide.htm))]

**Denominator population** – “the lower portion of a fraction used to calculate a rate or ratio” Last (2001)

**Derived incidence or prevalence rates** – included as original data, where although the original citation may not have estimate a rate, there was sufficient data within the citation to permit estimation of a rate. Derived rates were reviewed by consensus by PBJ, TJC and JBK, all with expertise in psychiatric epidemiology, biostatistics and psychometrics.

**Effect size** – a difference between means, an odds ratio or a relative risk that is used to communicate treatment differences in clinical trials or associations in epidemiology.

**False negative (citation)** – refers to a citation which was excluded in error (i.e. in reality it met inclusion criteria). This could arise in a systematic review when you make a (false) decision based on only a limited amount of information (i.e. an abstract rather than the full text of a citation). We minimised the number of possible false negatives in our review by ensuring a sensitive search strategy to identify potential false positives at later stages of the review (for example citation and author searches).

**Hazard ratio** – A measure of effect produced by a survival analysis of time to event data. This represents the increased risk with which one group is likely to experience the outcome of interest with respect to another (reference group).

**Heterogeneity** – A phrase used to capture the notion of diversity to some degree or other, or a technical term used to describe a set of studies or participants with sizeable heterogeneity. The opposite of homogeneous (see **Homogeneity**) [[www.cochrane.org/glossary](http://www.cochrane.org/glossary)]

**Homogeneity** – A phrase used to capture the notion of sufficient similarity, or a technical term used specifically to describe the effect estimates from a set of studies where they do not vary more than would be expected by chance [[www.cochrane.org/glossary](http://www.cochrane.org/glossary)]

**I<sup>2</sup>-statistic (or I<sup>2</sup>)** – The I-squared statistic; a measure used to quantify heterogeneity. It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity though interpretation of the statistic is contentious. [[www.cochrane.org/glossary](http://www.cochrane.org/glossary)]

**Incident (or incidence)** – The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year [[www.cochrane.org/glossary](http://www.cochrane.org/glossary)]

**Leakage study** – A leakage study is an attempt by the investigators to identify any cases that may have been missed during original case identification. Leakage studies may be formal (systematic, regular consultation with mental health and other service providers in the region) or more informal (sampling a proportion of such services to estimate possible “leakage”).

**Lifetime prevalence** – Number of new and existing cases known to have had the disorder at some point over their lifetime (usually expressed up to a given age).

**Meta-analysis** – A statistical method of combining the results of a number of different studies

**Meta-regression** – A technique used to explore the relationship between study characteristics and study results in a systematic review [[www.cochrane.org/glossary](http://www.cochrane.org/glossary)]

**Non-organic disorders** – Organic disorders are diseases that can be understood with reference to an alteration in the structure of an organ. Non-organic, in contrast, may be used to refer to disorders that are better understood as psychosomatic or functional in nature, i.e. those in which no evidence of organic problems exist even though some impairment exists.

**Numerator population** – “the upper portion of a fraction used to calculate a rate or ratio” <sup>232</sup>

**Odds ratio** – “the ratio of two odds”<sup>232</sup> Odds may be defined differently depending on epidemiological study design, but broadly describe the probability of an event, usually a disease outcome in epidemiology, taking place, expressed as the number of people in a given group who have the disease/exposure of interest divided by the number of people in that group who do not have the disease/exposure of interest. The odds ratio compares the odds of getting the disease between two groups (for example, men and women). The (natural) log of the odds ratio is used in statistical calculations and in graphical displays of odds ratios in systematic reviews [www.cochrane.org/glossary]

**Original data** – data on incidence, prevalence or an associated risk factor identifiable from a citation. Includes incidence or prevalence data *derivable* (see **derived incidence or prevalence rates**) from a citation, although no rates may have been explicitly published in the original manuscript.

**Period prevalence** – Prevalence of disorder over a defined period, typically annually.

**Point prevalence** – Prevalence of disorder at a single point in time.

**Prevalent (prevalence or prevalence study)** The proportion of a population having a particular condition or characteristic. Hence, a **prevalence study is a** type of epidemiological (cross-sectional) study that measures the prevalence of a characteristic.

**Rate ratio** – The ratio of two rates: the rate among the exposed proportion of the population, divided by the rate in the unexposed portion of the population, gives a relative measure of the effect of a given exposure. (Adapted from The Harvard University Public Health Disparities Geocoding Project Monograph Glossary. [

[www.hsph.harvard.edu/thegeocodingproject/webpage/monograph](http://www.hsph.harvard.edu/thegeocodingproject/webpage/monograph)]

**Risk factor** – An aspect of a person's condition, lifestyle or environment that affects the probability of occurrence of a disease [www.cochrane.org/glossary]

**Standard error** – The standard deviation of the sampling distribution of a statistic. Measurements taken from a sample of the population will vary from sample to sample. The standard error is a measure of the variation in the sample statistic over all possible samples of the same size. [www.cochrane.org/glossary]

**Standardised rate** – rates adjusted for a confounding population factor, such as age or sex, yielding the hypothetical rate that would have been observed if the population being studied had the same distribution as an externally defined standard population. (Adapted from the glossary of the Department of Health of the states of New Jersey and Washington

[[www4.state.nj.us/dhss-shad/home](http://www4.state.nj.us/dhss-shad/home) and [www.doh.wa.gov/Data/guidelines/Rateguide.htm](http://www.doh.wa.gov/Data/guidelines/Rateguide.htm)]

**Systematic review** – A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review [[www.cochrane.org/glossary](http://www.cochrane.org/glossary)]



## APPENDIX II – FULL DETAILS OF SEARCH STRATEGIES

The search strategies were as follows:

MEDLINE:

- 1 Schizo\*.ti,ab.
- 2 (psychotic or psychosis or psychoses).ti,ab.
- 3 (bipolar adj3 disorder\*).ti,ab.
- 4 (delusion\* adj3 disorder\*).ti,ab.
- 5 (dementia adj (praecox or precox)).ti,ab.
- 6 (((severe or serious or chronic) adj mental adj (illness\* or disorder\*)) or SMI).ti,ab.
- 7 (mani\* adj3 depressi\*).ti,ab.
- 8 affective disorders, psychotic/ or bipolar disorder/ or schizoid personality disorder/ or schizotypal personality disorder/ or exp "schizophrenia and disorders with psychotic features"/ or psychoses, alcoholic/ or psychoses, substance-induced/
- 9 1 or 2 or 3 or 4 or 5 or 6 or 8 or 7
- 10 (inciden\* or prevalen\* or epidemiolog\*).ti,ab.
- 11 ((first\* or 1st\* or hospital\*) adj3 (episode\* or contact\* or admission\* or admit\*)).ti,ab.
- 12 (case adj3 register\*).ti,ab.
- 13 case control\*.ti,ab.
- 14 (prospectiv\* or population\* or communit\* or survey\*).ti,ab.
- 15 10 or 11 or 12 or 13 or 14
- 16 exp Great Britain/
- 17 (England or United Kingdom or UK or Britain or GB or British or Wales or Scotland or Ireland).ti,ab.
- 18 (Bath or Birmingham or Bradford or Brighton or Hove or Bristol or Carlisle or Cambridge or Canterbury or Chester or Chichester or Coventry or Derby or Durham or Ely or Exeter or Gloucester or Hereford or Kingston upon Hull or Hull or Lancaster or Leeds or Leicester or Lichfield or Lincoln or Liverpool or London or Manchester or Newcastle upon Tyne or Norwich or Nottingham or Oxford or Peterborough or Plymouth or Portsmouth or Preston or Ripon or Salford or Salisbury or Sheffield or Southampton or st Albans or (Stoke adj2 Trent) or Sunderland

or Truro or Wakefield or Wells or Westminster or Winchester or Wolverhampton or Worcester or York).ti,ab.

19 (Reading or Dudley or Northampton or Luton or Milton Keynes or Walsall or Southend or Huddersfield or Poole or Middlesbrough or Blackpool or Bolton or Ipswich or Telford or West Bromwich or Stockport or Slough or Watford or Rotherham or Eastbourne or Sutton Coldfield or Blackburn or Colchester or Oldham or Crawley or st Helens).ti,ab.

20 (Barking or Dagenham or Barnet or Bexley or Brent or Bromley or Camden or Croydon or Ealing or Enfield or Greenwich or Hackney or Hammersmith or Fulham or Haringey or Harrow or Havering or Hillingdon or Hounslow or Islington or Kensington or Chelsea or Kingston upon Thames or Lambeth or Lewisham or Merton or Newham or Redbridge or Richmond upon Thames or Southwark or Sutton or Tower Hamlets or Waltham Forest or Wandsworth or Westminster or Camberwell).ti,ab.

21 16 or 17 or 18 or 19 or 20

22 9 and 15 and 21

#### PSychINFO

1 schizo\*.ti,ab.

2 (psychotic or psychosis or psychoses).ti,ab.

3 (bipolar adj3 disorder\*).ti,ab.

4 (delusion\* adj3 disorder\*).ti,ab.

5 (dementia adj (praecox or precox)).ti,ab.

6 (((severe or serious or chronic) adj mental adj (illness\* or disorder\*)) or SMI).ti,ab.

7 (mani\* adj3 depressi\*).ti,ab.

8 chronic psychosis/

9 exp psychosis/

10 schizoaffective disorder/

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12 (inciden\* or prevalen\* or epidemiolog\*).ti,ab.

13 ((first\* or 1st\* or hospital\*) adj3 (episode\* or contact\* or admission\* or admit\*)).ti,ab.

14 (case adj3 register\*).ti,ab.

15 case control\*.ti,ab.

16 (prospectiv\* or population\* or communit\* or survey\*).ti,ab.

17 12 or 13 or 14 or 15 or 16

18 (England or United Kingdom or UK or Britain or GB or British or Wales or Scotland or Ireland).ti,ab,lo.

19 (Bath or Birmingham or Bradford or Brighton or Hove or Bristol or Carlisle or Cambridge or Canterbury or Chester or Chichester or Coventry or Derby or Durham or Ely or Exeter or Gloucester or Hereford or Kingston upon Hull or Hull or Lancaster or Leeds or Leicester or Lichfield or Lincoln or Liverpool or London or Manchester or Newcastle upon Tyne or Norwich or Nottingham or Oxford or Peterborough or Plymouth or Portsmouth or Preston or Ripon or Salford or Salisbury or Sheffield or Southampton or st Albans or (Stoke adj2 Trent) or Sunderland or Truro or Wakefield or Wells or Westminster or Winchester or Wolverhampton or Worcester or York).ti,ab,lo.

20 (Reading or Dudley or Northampton or Luton or Milton Keynes or Walsall or Southend or Huddersfield or Poole or Middlesbrough or Blackpool or Bolton or Ipswich or Telford or West Bromwich or Stockport or Slough or Watford or Rotherham or Eastbourne or Sutton Coldfield or Blackburn or Colchester or Oldham or Crawley or st Helens).ti,ab,lo.

21 (Barking or Dagenham or Barnet or Bexley or Brent or Bromley or Camden or Croydon or Ealing or Enfield or Greenwich or Hackney or Hammersmith or Fulham or Haringey or Harrow or Havering or Hillingdon or Hounslow or Islington or Kensington or Chelsea or Kingston upon Thames or Lambeth or Lewisham or Merton or Newham or Redbridge or Richmond upon Thames or Southwark or Sutton or Tower Hamlets or Waltham Forest or Wandsworth or Westminster or Camberwell).ti,ab,lo.

22 18 or 19 or 20 or 21

23 11 and 17 and 22

24 limit 23 to yr="1950 - 2010"

#### EMBASE

1 Schizo\*.ti,ab.

2 (psychotic or psychosis or psychoses).ti,ab.

3 (bipolar adj3 disorder\*).ti,ab.

4 (delusion\* adj3 disorder\*).ti,ab.

5 (dementia adj (praecox or precoc)).ti,ab.

6 (((severe or serious or chronic) adj mental adj (illness\* or disorder\*)) or SMI).ti,ab.

- 7 (mani\* adj3 depressi\*).ti,ab.
- 8 affective psychosis/ or exp mania/ or schizoaffective psychosis/
- 9 exp psychosis/
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- 11 (inciden\* or prevalen\* or epidemiolog\*).ti,ab.
- 12 ((first\* or 1st\* or hospital\*) adj3 (episode\* or contact\* or admission\* or admit\*)).ti,ab.
- 13 (case adj3 register\*).ti,ab.
- 14 case control\*.ti,ab.
- 15 (prospectiv\* or population\* or communit\* or survey\*).ti,ab.
- 16 11 or 12 or 13 or 14 or 15
- 17 exp United Kingdom/
- 18 (England or United Kingdom or UK or Britain or GB or British or Wales or Scotland or Ireland).ti,ab.
- 19 (Bath or Birmingham or Bradford or Brighton or Hove or Bristol or Carlisle or Cambridge or Canterbury or Chester or Chichester or Coventry or Derby or Durham or Ely or Exeter or Gloucester or Hereford or Kingston upon Hull or Hull or Lancaster or Leeds or Leicester or Lichfield or Lincoln or Liverpool or London or Manchester or Newcastle upon Tyne or Norwich or Nottingham or Oxford or Peterborough or Plymouth or Portsmouth or Preston or Ripon or Salford or Salisbury or Sheffield or Southampton or st Albans or (Stoke adj2 Trent) or Sunderland or Truro or Wakefield or Wells or Westminster or Winchester or Wolverhampton or Worcester or York).ti,ab.
- 20 (Reading or Dudley or Northampton or Luton or Milton Keynes or Walsall or Southend or Huddersfield or Poole or Middlesbrough or Blackpool or Bolton or Ipswich or Telford or West Bromwich or Stockport or Slough or Watford or Rotherham or Eastbourne or Sutton Coldfield or Blackburn or Colchester or Oldham or Crawley or st Helens).ti,ab.
- 21 (Barking or Dagenham or Barnet or Bexley or Brent or Bromley or Camden or Croydon or Ealing or Enfield or Greenwich or Hackney or Hammersmith or Fulham or Haringey or Harrow or Havering or Hillingdon or Hounslow or Islington or Kensington or Chelsea or Kingston upon Thames or Lambeth or Lewisham or Merton or Newham or Redbridge or Richmond upon Thames or Southwark or Sutton or Tower Hamlets or Waltham Forest or Wandsworth or Westminster or Camberwell).ti,ab.
- 22 17 or 18 or 19 or 20 or 21

23 10 and 16 and 22

CINAHL

1. Schizo\*.ti,ab
2. (psychotic OR psychosis OR psychoses).ti,ab
3. (bipolar adj3 disorder\*).ti,ab
4. (delusion\* adj3 disorder\*).ti,ab
5. (("dementia praecox") OR ("dementia precox")).ti,ab
6. ("severe mental illness\*" OR "severe mental disorder\*" OR "serious mental illness\*" OR "serious mental disorder\*" OR "chronic mental illness\*" OR "chronic mental disorder\*" OR SMI).ti,ab
7. (mani\* adj3 depressi\*).ti,ab
8. PSYCHOTIC DISORDERS/ OR AFFECTIVE DISORDERS, PSYCHOTIC/ OR BIPOLAR DISORDER/ OR PSYCHOSES, SUBSTANCE-INDUCED/ OR PSYCHOSES, ALCOHOLIC/ OR SCHIZOPHRENIA/ OR SCHIZOPHRENIA, CHILDHOOD/ OR PARANOID DISORDERS/
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. (inciden\* OR prevalen\* OR epidemiolog\*).ti,ab
11. (("first\* episode\*" OR "first\* contact\*" OR "first\* admission\*" OR "first\* admit\*" OR "1st\* episode\*" OR "1st\* contact\*" OR "1st\* admission\*" OR "1st\* admit\*" OR "hospital\* episode\*" OR "hospital\* contact\*" OR "hospital\* admission\*" OR "hospital admit\*")).ti,ab.
12. (case adj3 register\*).ti,ab
13. "case control\*".ti,ab
14. (prospectiv\* OR population\* OR communit\* OR survey\*).ti,ab
15. 10 OR 11 OR 12 OR 13 OR 14
16. exp UNITED KINGDOM/
17. (England OR "united kingdom" OR UK OR Britian OR GB OR British OR Wales OR Scotland OR Ireland).ti,ab
18. (Bath OR Birmingham OR Bradford OR Brighton OR Hove OR Bristol OR Carlisle OR Cambridge OR Canterbury OR Chester OR Chichester OR Coventry OR Derby OR Durham OR Ely OR Exeter OR Gloucester OR Hereford OR "Kingston upon Hull" OR Hull OR Lancaster OR Leeds OR Leicester OR Lichfield OR Lincoln OR Liverpool OR London OR Manchester OR "Newcastle upon Tyne " OR Norwich OR Nottingham OR Oxford OR Peterborough OR Plymouth OR

Portsmouth OR Preston OR Ripon OR Salford OR Salisbury OR Sheffield OR Southampton OR "st Albans" OR "Stoke on Trent" OR "Stoke upon Trent" OR Sunderland OR Truro OR Wakefield OR Wells OR Westminster OR Winchester OR Wolverhampton OR Worcester OR York).ti,ab

19. (Reading OR Dudley OR Northampton OR Luton OR "Milton Keynes" OR Walsall OR Southend OR Huddersfield OR Poole OR Middlesbrough OR Blackpool OR Bolton OR Ipswich OR Telford OR "West Bromwich" OR Stockport OR Slough OR Watford OR Rotherham OR Eastbourne OR "Sutton Coldfield" OR Blackburn OR Colchester OR Oldham OR Crawley OR "st Helens").ti,ab

20. (Barking OR Dagenham OR Barnet OR Bexley OR Brent OR Bromley OR Camden OR Croydon OR Ealing OR Enfield OR Greenwich OR Hackney OR Hammersmith OR Fulham OR Haringey OR Harrow OR Havering OR Hillingdon OR Hounslow OR Islington OR Kensington OR Chelsea OR "Kingston upon Thames" OR Lambeth OR Lewisham OR Merton OR Newham OR Redbridge OR "Richmond upon Thames" OR Southwark OR Sutton OR "Tower Hamlets" OR "Waltham Forest" OR Wandsworth OR Westminster OR Camberwell).ti,ab

21. 16 OR 17 OR 18 OR 19 OR 20

22. 9 AND 15 AND 21

## **APPENDIX III – DIAGNOSTIC ALGORITHM**

We developed an algorithm to apply the diagnostic hierarchy we used in this review (Figure 3.1) to the diagnostic classifications used in the original citations we identified. The algorithm was developed by an experienced academic psychiatrist (PBJ) and independently verified by the research team. The algorithm is too large to be provided in the main body or appendix of this report, but will be available as a supplemental file in an online repository (subject to agreement with the Funders). Presently this data is available, on request, from the authors.

## APPENDIX IV – DETAILS OF ANALYSES CONDUCTED IN THIS REVIEW

The analysis matrix below gives details of all the analyses conducted for this review. While relevant rates were identified and analysed, it was beyond the scope of this report to present data on every possible permutation from the [citation matrix](#) (Figure 3.1). In the main body of this report we included results from selected analyses. Data from all other analyses will be subject to ongoing research. This review process marks the beginning of an updatable review to provide rich meta-analytical data for the future.

This matrix records citations providing potentially relevant data to each analysis considered in this review. Using the citation matrix (marked on the left hand side, below), we applied analysis filters to our study level variables to identify citations providing potentially relevant data. These citation and study IDs are recorded on the right hand side of the analysis matrix. Citation IDs were colour-coded according to whether the data should be included in that analysis. Study IDs were colour-coded according to whether the citation provided:

### *Included citations [green Citation ID]*

- Unique data from a single study (“unique” data) [light green Study ID]
- A core publication for data relevant to that analysis, but other citations had also reported similar or identical rates from the same study [dark green Study ID]
- Data as part of a set of citations publishing unique data from a single study setting. This could occur in rare instances where the “study” was a catchment area such as the Camberwell Case Register, but where rates from each citation were deemed to be independent. [blue Study ID]

### *Excluded citations [red or orange Citation ID]*

- Duplicate publication of data included by a “core” citation. Data considered as “satellite” data [red Study ID]



- Citations identified during citation filtering as potentially providing data for a given analysis, but upon further inspection, no relevant rate data was published [orange Study ID]<sup>xvi</sup>

Planned analyses where no relevant citations were identified by our systematic review are highlighted in grey.

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<sup>xvi</sup>This arose due to the way we set up our filters in our study-level database, not because of any misreporting by the original authors. For example if a study reported separate rates of schizophrenia for men and women, but only reported the *overall* incidence of bipolar disorder, this study would show up in our filtering process as providing rates of bipolar disorder for men and women, even though it did not. Only upon inspection of rate-level data would we determine that did not contain any relevant data for the analysis of rates of bipolar disorder for men and women.

### **Analysis Matrix**

Available online ([www.psychiatry.cam.ac.uk/epicentre/review](http://www.psychiatry.cam.ac.uk/epicentre/review)) as too big to be provided in the content of this report, subject to agreement with the funding body.

## APPENDIX V – FINAL SAMPLE OF CITATIONS IDENTIFIED IN REVIEW

Note, the citations below are listed according to their citation ID number for this review. Study numbers are shown in brackets (see Appendix VI for list of studies). Where a decimal point is included in the study number *i.e.* S6.14, this denotes the citation included data from more than one distinct studies (*i.e.* S6 and S14).

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*Addendum:*

- Coid JW, Kirkbride JB, Barker D, et al. "Raised incidence rates of all psychoses among migrant groups: Findings from the East London first episode psychosis study": Erratum. *Archives of General Psychiatry*. Feb 2009 2009;66(2):161.
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- C148 [S70].** Hare E.H. Mental illness and social condition in Bristol. *Journal of Mental Sciences*.102:349-357.



## APPENDIX VI – STUDY INDEX

Study Code	Acronym <sup>†</sup>	Full title/Author (PI) name <sup>‡</sup>
S1	-	Agius (PI)
S2	-	Camberwell Psychiatric Case Register
S3	-	Salford Psychiatric Case Register
S4	IPSS	International Pilot Survey of Schizophrenia
S5	-	Bhugra (PI)
S6	DOSMD	Determinants of Outcome of Severe Mental Disorder
S7	MHE	Mental Health Enquiry
S8	ELFEP	East London First Episode Psychoses study
S9	PACE	Population-adjusted Clinical Epidemiology study
S10	ORLS	Oxford Record Linkage Study
S11	ÆSOP	Aetiology and Ethnicity in Schizophrenia and Other Psychoses study
S12	-	Gater (PI)
S13	-	Harrison G (PI)
S14	SIN	Schizophrenia in Nottingham
S15	-	Hampstead Schizophrenia Survey
S16	EMPIRIC	Ethnic Minority Psychiatric Illness Rates in the Community
S17	-	King (PI)
S18	PRiSM	PRiSM Psychosis Study
S19	-	Prince – Study I (PI)
S20	-	Buckinghamshire Study
S21	-	Van Os (PI)
S22	-	General Registrar's Office dataset
S23	-	Second British National Survey of Psychiatric Morbidity
S24	-	Birmingham (PI)
S25	-	Brooke (PI)
S26	-	British National Survey of Psychiatric Morbidity
S27	-	Carpenter (PI)
S28	-	Commander – Study I (PI)
S29	-	De Alarcon (PI)
S30	-	Dean (PI)

Study Code	Acronym <sup>†</sup>	Full title/Author (PI) name <sup>‡</sup>
S31	NCDS	National Child Development Study (1958 British Birth Cohort)
S32	-	Gilchrist (PI)
S33	-	Gould (PI)
S34	-	Gunn (PI)
S35	-	Harris (PI)
S36	-	Camden Schizophrenia Survey
S37	-	Hemsi (PI)
S38	-	Hitch (PI)
S39	NSHD	National Survey of Health and Development (1946 British Birth Cohort)
S40	-	Kai (PI)
S41	-	Kendell (PI)
S42	-	Littlewood (PI)
S43	-	MacPherson (PI)
S44	-	Haden (PI)
S45	-	McGovern (PI)
S46	GPRD	General Practice Research Database
S47	-	Fourth National Survey of Ethnic Minorities
S48	-	Ring (PI)
S49	-	Rowlands (PI)
S50	-	National Confidential Inquiry into Suicide and Homicide by People with Mental Illness
S51	-	Shaw (PI)
S52	-	Singh (PI)
S53	-	Soomro (PI)
S54	-	Taylor (PI)
S55	-	Thomas (PI)
S56	-	Turner (PI)
S57	-	Watts (PI)
S58	-	Commander - Study II (PI)
S59	-	Congdon (PI)
S60	-	Gibbons (PI)
S61	-	Giggs (PI)

Study Code	Acronym <sup>†</sup>	Full title/Author (PI) name <sup>‡</sup>
S62	-	Harrison J (PI)
S63	-	Hemphill (PI)
S64	-	Survey of Psychiatric Morbidity among Prisoners in England and Wales
S65	LEO	Lambeth Early Onset study
S66	APMS	Adult Psychiatric Morbidity in England
S67	-	McCullagh (PI)
S68	-	Prince – Study II (PI)
S69	-	Jones S (PI)
S70	-	Hare EH (PI)

<sup>†</sup>Where reported

<sup>‡</sup>Either official title of study as published or name of lead/author PI where no study title given

## APPENDIX VII – PSYCHOMETRIC PROPERTIES OF STUDY QUALITY MEASURE USED IN THIS STUDY

The seven variables we identified to provide information on the quality of studies included in this systematic review were chosen by consensus by the authorship panel. Based on considerable experience in conducting, assessing and reporting epidemiological research in psychotic disorders, our view was that these binary variables (see Section 3.4.4) would sum to provide an accurate “score” of quality. However, we recognised that this study quality score was also somewhat arbitrary and may therefore not necessarily have psychometric validity. To assess this possibility, we conducted some initial Rasch models on six of these variables (“leakage score” has been initially omitted because of some missing data, but this will subsequently be included). Rasch modelling confirmed that the sum score of these quality indicators provided a satisfactory representation of the data from each variable (see output below). We note that while the study quality variable has some psychometric validity, the separate issue of whether what is *reported* and what is actually *conducted* by a study are two potentially different constructs. However, following expert advice (Prof. John McGrath) in this area, we made the assumption that a failure to report an aspect of study quality reflected the absence of conduct of that particular marker. Further, it could be argued that failure to report a positive study quality marker was, of itself, a proxy marker for the quality of the conduct of the study.

### Psychometric scaling of the study quality criteria (six binary variables) using a Rasch model in Stata

The quality criteria were:

- |                                    |        |
|------------------------------------|--------|
| 1. Defined catchment               | (var1) |
| 2. Accurate denominator            | (var2) |
| 3. Population-based case finding   | (var3) |
| 4. Standardised research diagnosis | (var4) |
| 5. Blinding to demographic vars    | (var5) |
| 6. Inclusion criteria              | (var6) |

Descriptive statistics for each criteria (tabulation of 0= criteria not met, 1 = met) for var1-var6 (defined above)

-> tabulation of var1

var1	Freq.	Percent	Cum.
-----+-----			
0	8	6.56	6.56
1	114	93.44	100.00
-----+-----			
Total	122	100.00	

-> tabulation of var2

var2	Freq.	Percent	Cum.
-----+-----			
0	36	29.75	29.75
1	85	70.25	100.00
-----+-----			
Total	121	100.00	

-> tabulation of var3

var3	Freq.	Percent	Cum.
-----+-----			
0	57	47.11	47.11
1	64	52.89	100.00
-----+-----			
Total	121	100.00	

-> tabulation of var4

var4	Freq.	Percent	Cum.
-----+-----			
0	59	48.76	48.76
1	62	51.24	100.00
-----+-----			
Total	121	100.00	

-> tabulation of var5

var5	Freq.	Percent	Cum.
-----+-----			
0	102	84.30	84.30
1	19	15.70	100.00
-----+-----			
Total	121	100.00	

-> tabulation of var6

var6	Freq.	Percent	Cum.
0	46	38.02	38.02
1	75	61.98	100.00
Total	121	100.00	

### Psychometric model to establish interval (Rasch) scale for sum score

Item level and overall model tests using Stata *raschtest* command (conditional maximum likelihood estimation). This analysis justifies the sum score of the criteria met as a sufficient statistic for the summary of study quality. Also a mapping between sum score and an interval metric is provided (for use in meta-regression analyses with interval quality score as a covariate).

```
. raschtest var1-var6, id(id)
Estimation method: Conditional maximum likelihood (CML)
Number of items: 6
Number of groups: 7 (5 of them are used to compute the statistics of test)
Number of individuals: 122
Number of individuals with missing values: 1 (removed)
Number of individuals with nul or perfect score: 20
Conditional log-likelihood: -115.1203
Log-likelihood: -198.5348
```

*Significance tests for item level and model misfit, and standardized item fit.*

Difficulty			Standardized					
Items	parameters	std Err.	Rlc	df	p-value	Outfit	Infit	U
-----								
var1	-3.30309	0.63340	0.877	4	0.9278	-1.240	-0.377	-0.317
var2	-0.56598	0.33999	2.053	4	0.7261	1.024	1.120	1.508
var3	0.65635	0.34961	6.861	4	0.1434	0.152	-1.075	0.219
var4	0.78004	0.35230	6.175	4	0.1865	-1.696	-1.167	-1.685
var5	3.91214	0.56982	5.365	4	0.2519	-0.361	0.012	0.396
var6*	0.00000	.	2.493	4	0.6459	-0.147	0.715	0.331
-----								
Rlc test		Rlc=	22.456	20	0.3163			
Andersen LR test		Z=	22.954	20	0.2911			

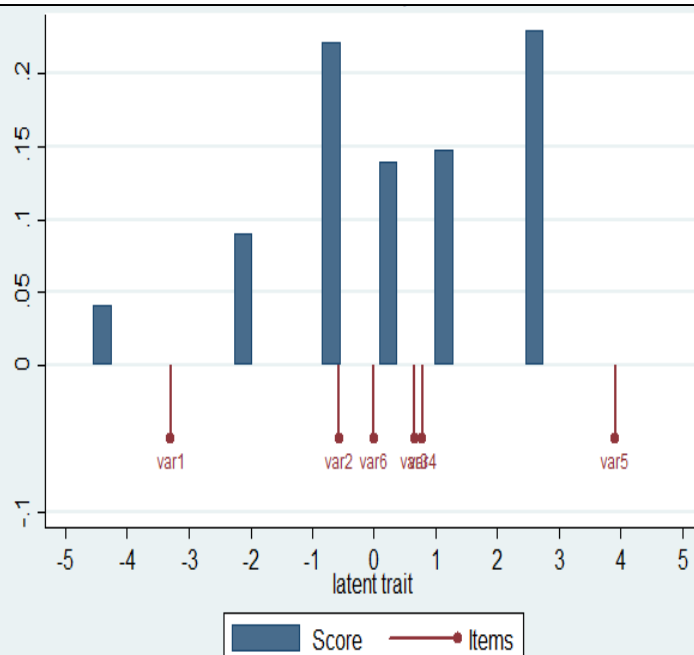
*Conversion between sum score and interval score, with score frequencies*

Simple			
Sum	<b>Interval</b>		
Score	<b>score</b>	std Err.	Frequency

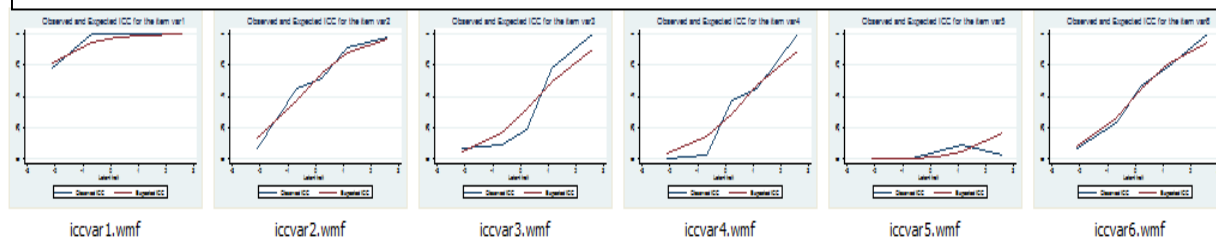
0	-4.402	2.075	5
1	-2.120	1.378	11
2	-0.691	1.078	27
3	0.227	1.008	17
4	1.138	1.079	18
5	2.599	1.410	28
6	5.006	2.107	15

Below, we show the location of the items and the quality score (latent trait) values, under the Rasch model, where both items and studies lie on the same continuum.

This plot relates the quality criteria (items 1 through 6 displayed in red as x-axis locations var1-var6, alongside a frequency distribution of the sum scores for the quality score, located at the x-axis value where the study qualities are located.



Also plotted are panels showing the fit of the model to the data (for each item, displayed from left to right as var1 to var6 in consecutive panels). These show a strong correspondence; i.e. the blue lines are close to the red lines, for the most part.



**APPENDIX VIII – PRISMA CHECKLIST**

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3+Methods Section (4-11)
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online material 1 [ON1]
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, 10-11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	10



Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Meta-regressions (10-11)
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11 & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1 & ON2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1, Figures 2 & 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-22
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-22
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-22
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	22-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	30-33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24-29
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	34

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

4, 10, 11, 14, 20, 22-25, 28, 30, 31, 37, 46, 49-64, 78, 79, 88-93, 97-104, 106-113, 117, 118, 121, 170, 189, 193, 212, 216, 233-318

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