

Schizophrenia & Psychotic Disorders: Current epidemiological highlights

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Introduction

We all know that much of what we learned at medical school was wrong with the same being the case for today's CPD. The difficulty is sifting those facts that are correct from those we need to update. One area where there have been many advances over recent decades is in the epidemiology of schizophrenia and related psychotic disorders where textbooks still on the library shelves are quite wrong in suggesting that there is little to interest the eager student: around 1% of people in the world have schizophrenia, it occurs equally in men and women with no geographical variation, and is of unknown aetiology. This dead-hand of schizophrenia epidemiology has been removed by recent research that reveals a rich landscape of variation and variability that gives clues to causation, can guide service development and even, perhaps, prevention. This article, based on a longer piece by Jablensky and colleagues (1) replacing the out of date library stocks, sets out some of that evidence and why the subject is so intriguing. This is a set of epidemiological highlights.

Schizophrenia represents a uniquely challenging disease to study. While the syndrome of schizophrenia is clearly a manifestation of a brain in trouble, something that can be mimicked or even induced by drugs and gross brain lesions, it remains quintessentially a clinical syndrome depending critically on self-reported subjective experience. The underlying structural and functional pathology is likely to be several orders of magnitude more subtle than brain disorders that we call neurological, caused in the main by dead or dysfunctional cells. Current views of schizophrenia pathology (that may, of course, be wrong) concentrate on the synapse, and the creation and maintenance of neural networks at long- and short-range. Relatively minor perturbations may lead to the mental experiences we call schizophrenia that are vastly remote from an abnormally transcribed protein or synaptic inefficiency that may be at their heart. This means that schizophrenia is perhaps the most ultimately complex disorder, where genetic effects are subtle and affect neural networks that, themselves, help create the environment, including the stressfulness and meaning of life events that undoubtedly play a part in causation. The brain and its genes are not simply passive targets of the environment like the heart or the liver; they actually create much of our environment that we experience in the psychological domain.

Thus, there is as yet no objective diagnostic test or validated biological marker for schizophrenia that could provide a secure anchor for epidemiological field research and we have to rely on purely clinical definitions that undoubtedly lead to error, being imprecise and overlapping with features of other more basic biological problems. This will change. It is likely that the schizophrenia syndrome may arise from many disparate underlying problems; only last year have we seen reports of cases of first episode psychosis, clinically indistinguishable from others, that were caused by auto-antibodies to NMDA receptors; treatment was not by antipsychotic drugs but by plasmaphoresis (Zandi et al., 2010) (2). It is likely that other such causes will be found, including those that emanate from the psychological domain in terms of stress, and that the old idea that schizophrenia is a "functional" psychosis will be consigned to the dustbin. Biomarkers will come, but are not yet widely available and certainly will not help current attempts to reclassify schizophrenia through the DSM-V and ICD-11 criteria that are, in the author's opinion, premature and futile. The problems of diagnosis are not considered further here but the interested reader is referred to the Jablensky et al (2010) (1) paper for a full discussion.

The current article concentrates on the incidence of schizophrenia and other psychotic disorders in order to show the many factors that appear to determine differences between groups and populations. These differences point to causes and mechanisms, and also have direct clinical applications in terms of everyday practice and service commissioning and planning. The article does not consider genetics in any detail, but acknowledges the ineluctable importance of genes that, in the brain especially, are there to interact with the environment through the proteins and subsequent biological cascade for which they code, a process often triggered by that environment itself.

Basic concepts

Given that we have still to rely on clinical definition, it should be of no surprise that the measurement of the prevalence, incidence and morbid risk of schizophrenia depends critically on (i) the capacity to identify in a given population all affected individuals and (ii) the availability of a diagnostic system which will select “true” cases corresponding to established clinical concepts of the day (until there is a more biologically-based approach). The first prerequisite refers to the sensitivity of the case finding and the second to the specificity of disease category allocation needed to minimise false positive diagnoses. The majority of case finding designs falls into three groups: case detection in clinical populations; population surveys: door-to-door or representative sample surveys; birth cohort studies.

The first of these depends on the service as much as the illness such that case finding for schizophrenia that is restricted to hospital admissions, or even to community services, is liable to be methodologically sub-optimal, particularly for prevalence where the design leads to over-representation of chronic and severe cases. Door-to-door and survey methods have been used for many decades (Brugger; 1931) (3) but are hampered by the fact that schizophrenia is relatively rare. Where a complete census of a population is not feasible (most situations) the sample survey in which a probability sample is drawn and interviewed to establish point or lifetime prevalence is used. The archetypes are the NIMH Epidemiological Catchment Area (ECA) study in which around 20,000 people at five sites in the US were interviewed (Robins & Regier, 1991) (4); the National Comorbidity Survey (Kessler et al., 1994) (5) based on a national probability sample of 5,877 US residents; the Australian National Mental Health Survey (Andrews et al., 2001) (6), in which a national probability sample of 10,641 adults was interviewed; and the UK Office of National Statistics (ONS) surveys comprising over 10,000 adults, younger people having been studied separately in the UK (Jenkins et al., 2003) (7).

The fundamental importance of development

Birth cohort studies produce a “natural” morbidity and mortality life table (Susser & Schwartz, 2006) (8) providing estimates of incidence and prevalence, but are eminently suitable for testing hypotheses about early life risk factors. Their use for psychiatry has revolutionized our views of psychotic disorders by adding a developmental perspective. Recent examples of the search for such developmental precursors of adult schizophrenia using prospectively collected data start with the British 1946 birth cohort of the National Survey of Health and Development, NSHD (N=5 362; Jones et al., 1994) (9); the UK 1958 birth cohort of the National Child Development Study, NCDS (N=15 398; Done et al., 1994) (10); and the North Finland 1966 birth cohort (N=11 017; Jones et al., 1998; Isohanni et al., 1998) (11,12). Samples from two birth cohorts in the US, the National Collaborative Perinatal Project 1959-1966 (N=9 236; Cannon et al., 2002) (13) and the Child Health and Development Study 1960-1967 (N=19 044; Susser et al., 2000) (14) have been drawn on for follow-up studies focusing on prenatal, perinatal and early childhood influences on the development of schizophrenia.

The British 1946 cohort (Jones et al., 1994) (9) covering all births in a week of March 1946 indicated that children who would, as adults, develop schizophrenia showed differences in a range of developmental domains. These included delayed motor milestones in the first two years of life, problems with language acquisition, and cognitive and social development. The disorder had long been thought to have a developmental aspect but this was the first direct, epidemiological evidence from prospective data. The motor findings were replicated and pushed even further back into early life in the North Finland 1986 cohort that includes 12,000 births from the two most northerly provinces of Finland (Oulu and Lapland) due to be born during 1966, the subjects being ascertained in utero.

Isohanni and colleagues (2001) (15) used information on motor development collected when the Finnish cohort members were 12 months old. They divided them into four groups depending on the precocity or rapidity of their integrative development, an example being the age at which they could stand unaided or “toddler”. Figure 1, adapted from their paper, shows that the incidence of schizophrenia when these individuals (here, only boys are shown) grew-up was related to their early life efficiency in wiring-up these motor circuits: before and after adjustment for various alternative explanations, there was an inverse, dose-response relationship between age at learning to walk unaided in the first year of life and risk of schizophrenia later in life. This variation in early CNS wiring is also related to adult cognitive function. Ridler et al. (2006) (16), in the same cohort, later showed using MR brain imaging that the fronto-striatal-cerebellar structural circuits that may determine these temporally remote relationships in the general population are disturbed in schizophrenia. This is part of the burgeoning evidence of disturbed neural connectivity in schizophrenia and points at the underlying neurobiology by which we may, one day, define some or all of the mental illness that we currently call schizophrenia, and at which we may direct new interventions. This is a nice example of work at the interface between epidemiology and neuroscience.

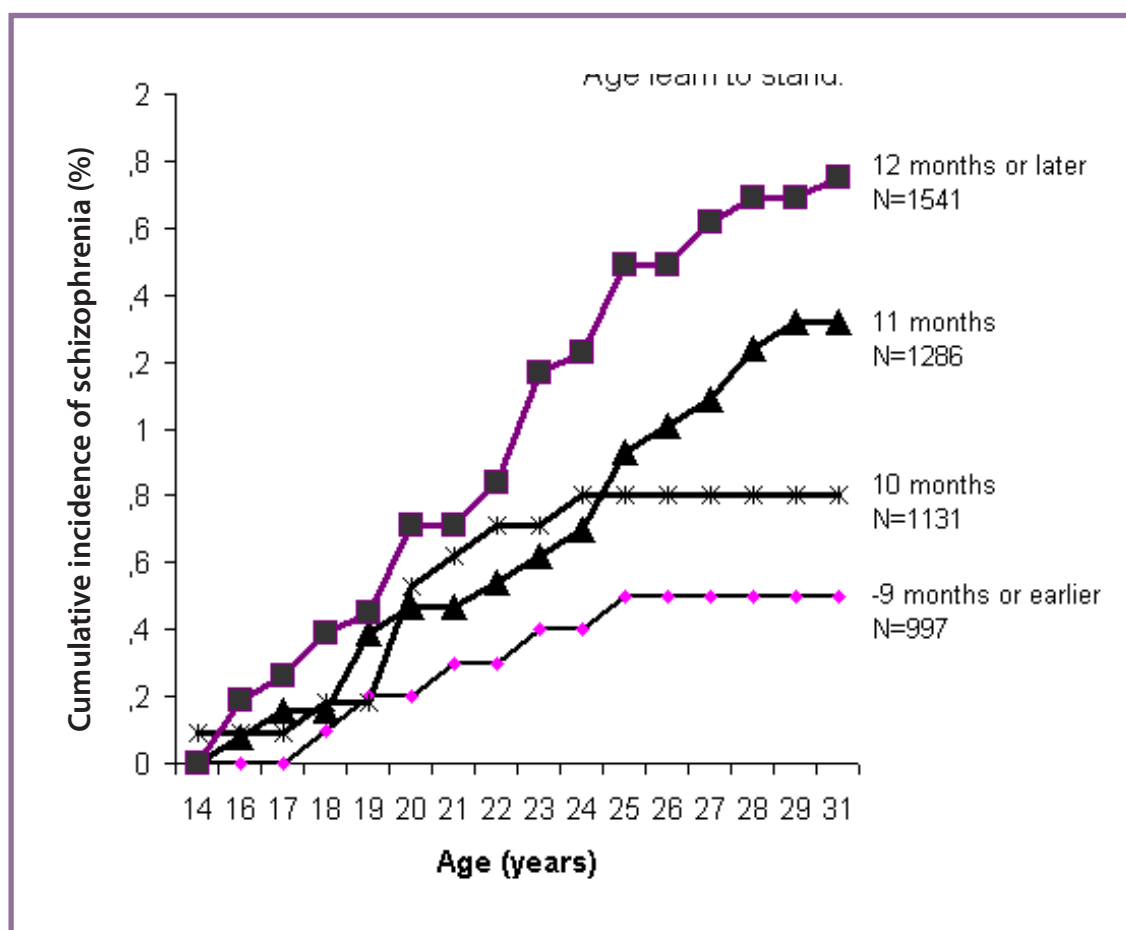


Figure 1 (Adapted from Isohanni et al., 2001)15

Cumulative incidence of schizophrenia in men in the North Finland 1966 birth cohort stratified by the age in months at which they learned to stand unaided. This milestone was ascertained from their mothers at a child health clinic when the boys were one year old; the schizophrenia outcome came from national hospital discharge registers. The later the subjects could stand up without support during their first year of life, the greater their risk of schizophrenia as adults (summarized by the slope of the line)

Elaborations of the birth cohort design that have contributed to this literature include follow-up studies of individuals who had undergone some kind of routine assessment at a specified age, particularly through military conscription. Examples are the Swedish conscript study including 50,087 men given a psychometric examination at entry to the army at age 18-20 during 1969-1970 and followed up through the national psychiatric case register until 1983 (Malmberg et al., 1998) (17) showing the teenage IQ of men who developed schizophrenia was lower than those that didn't; and a similar Israeli study with the same findings based on a pre-conscription cognitive and behavioural assessment during 1985-1991 of 9,724 male adolescents aged 16-17 and a follow-up through the psychiatric case register (Davidson et al., 1999) (18). Follow-up studies of cohorts defined by a particular maternal exposure at a given time have also been crucial. For example, the offspring of pregnant women exposed to acute famine during the 1945 Dutch "hunger winter" (Susser and Lin, 1992) (19) where gestational malnutrition was linked to later schizophrenia; the stress of the 5-day blitzkrieg against Holland in 1940 (van Os & Selten, 1998) (20); radiation in utero due to the Nagasaki A-bomb in 1945 (Imamura et al., 1999) (21); or prenatal rubella (Brown et al., 2001) (22). These are all examples of productive, opportunistic research that showed a range of early life stressors being associated with an increased risk for schizophrenia later in life.

Descriptive epidemiology of Schizophrenia

The descriptive epidemiology of schizophrenia still contains gaps but the contours of the overall picture have been laid down and enable some tentative conclusions. Overall, the textbook figure that 1% of the population suffers from schizophrenia is not too wide of the mark, perhaps a little high, so long as one remembers that this is not a point prevalence, but a life-time risk (ie 1% meets criteria for schizophrenia at some time or another in their life, not right now), and that the figure for any psychotic disorder is rather higher at around 3.1% (Perälä 2007) (23).

The incidence rate of schizophrenia (annual number of emerging new cases in a defined population per unit of individuals at risk, usually 100,000) is of particular interest since its variation is sensitive to the effects of causal and risk factors. One crucial issue for incidence is deciding when a disorder begins, something which is difficult when the onset is sometimes insidious, may be characterised by social change in terms of work, educational or social function, and when very early developmental factors are seen such as developmental delays, cognitive abnormalities and childhood behavioural oddities outlined above.

Table 1 (adapted from Jablensky et al., 2010) (1) provides an overview of selected incidence studies of schizophrenia. The 16 studies published between 1980 and 2007 feature a diversity of methods and incidence estimates ranging from low (10 – 41 per 100,000) to high (62 – 216 per 100,000). Some of the variation across these surveys is likely to be related to the method of ascertainment or diagnostic criteria, but the highest rates have been obtained in populations with special characteristics, such as genetic isolates (Haukka et al. 2001) (24) or areas with high density of migrant groups (Boydell et al. 2003; Kirkbride et al. 2006) (25,26). For comparison, the variation of the incidence rates in the WHO 10-country study (Jablensky et al. 1992) (27) is relatively unaffected by differences in case finding methods and diagnostic assessment, and are fairly close to the mean rates based on 147 studies from 33 countries in the systematic review by McGrath et al. (2004) (28) and, in England, a systematic review of 147 studies by Kirkbride et al., (2011) (29).

Variation in the incidence of schizophrenia over time

There is much conjecture as to whether the incidence of schizophrenia is changing. Descriptions of schizophrenia in the medical literature before the 18th century were rare, leading to speculation that the industrial revolution had some causal influence (Hare, 1983) (30). However, it is likely that during much of the 19th century schizophrenia was rather less conspicuous than it is today because of the much higher prevalence of organic brain diseases such as general paresis from neurosyphilis. While the number of people hospitalised with schizophrenia increased rapidly in the early decades of the 20th century, it remains unclear whether this was due to increased use of the diagnosis, social pressure to institutionalise the mentally ill, or a real rise in incidence. Certainly, there is no good evidence of

changes in incidence during the past few decades of increasing community care (Kirkbride et al., 2009) (31).

Variation in the incidence of schizophrenia according to place – from country to neighbourhood

Evidence suggests that a range of population-related biological and environmental factors may contribute to the onset of schizophrenia and to the maintenance of its incidence and prevalence in populations. Many of the environmental factors are likely to interact with genetic vulnerability at the individual level. Peaks and troughs do exist in the epidemiological landscape of schizophrenia, resulting from likely interactions between genetic variation across human groups, culture, migration and habitat, the social fabric, nutrition and geography. As Jablensky et al., (2010) (1) point out, these sources of variation merit the attention of epidemiologists, social anthropologists and biological researchers alike.

Some populations have either high or very low rates of schizophrenia: these are most likely to be genetic isolates. Very high rates of schizophrenia (2-3 times the national or regional rate) have been reported for population isolates, such as an area in northern Sweden (Böök et al., 1978) (32); and several areas in Finland (Hovatta et al., 1999; Arajärvi et al. 2005) (33,34). Even higher rates have been found on the Palau islands in the Pacific (Myles-Worsley et al. 1999) (35); and in Daghestan, Northern Caucasus (Bulayeva et al. 2005) (36) where the lifetime morbid risk is as high as 5%. The lifetime prevalence of strictly diagnosed schizophrenia in Palau has been estimated at 2.8% in men and 1.2% in women. The common factor accounting for such exceptionally high rates is the founder effect and gene drift over multiple generations of extended pedigrees, resulting in an aggregation of specific haplotypes with limited numbers of pathogenic alleles (Bulayeva et al. 2005) (36). Conversely, evidence suggests that some populations have little schizophrenia, such as the Hutterites in South Dakota (Eaton & Weil 1955; Torrey 1995; Nimgaonkar et al. 2000) (37-39), but the reasons are not clear.

Urban-rural differences in incidence are consistent; rates are higher in more urban areas. The Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) study, a large 3-centre population-based epidemiological study of first episode psychoses in the UK (Kirkbride et al. 2006) (26), identified all cases of schizophrenia and other psychoses, aged 16-64, presenting to services over a two-year period in Southeast London, Nottingham and Bristol – settings which provided a mix of urban, suburban and a few rural environments. The incidence of schizophrenia was two to three times higher in the most urban area (Southeast London) than in the less urban areas. The study also adjusted for alternative explanations for these differences, such as age, sex and ethnicity. This finding confirmed other UK reports of raised rates of schizophrenia in urban areas (Allardyce et al., 2001) (40). The evidence also excluded the notion of “drift” as an explanation, with urban childhood upbringing appearing to confer risk (Lewis et al., 1992; Mortensen et al., 1999) (41,42). This variation in incidence according to neighbourhood characteristics is seen at a more micro-level, within towns and cities, where poorer neighbourhoods have higher incidence than more affluent suburbs. This phenomenon was known in the 1930s, when Faris and Dunham demonstrated higher rates of first admission for schizophrenia in inner city census tracts of Chicago which followed a centripetal gradient towards the city centre (Faris and Dunham, 1939) (43). This striking finding was in direct contrast to the affective psychoses (i.e. bipolar disorder) which followed no such pattern. The same pattern was observed in subsequent research (Pedersen & Mortensen, 2006b; Kirkbride et al., 2007a & b) (44-46).

Age and sex

One of the most robust epidemiological findings about schizophrenia is that the majority of onsets fall within the period of life between 15 to 54 years of age. Neither childhood-onset schizophrenia (onset before age 12), nor late-onset schizophrenia (onset after age 50), present with any clinical features or risk factors that are qualitatively distinct from those characterising schizophrenia arising in young adults (Nicolson & Rapoport, 1999; Brodaty et al., 1999; Palmer et al., 2001) (47-49), with the possible exception of psychotic disorganisation symptoms being more likely to characterise early

onset cases and systematised paranoid delusions being predominant in late onset cases (Häfner et al., 2001) (50). The distribution of age at onset has been described as a continuum where variation is consistent with a model incorporating random genetic and developmental effects and environmental experiences unique to the individual (Kendler et al., 1996) (51). This age at onset distribution confirms that schizophrenia is a disorder intimately connected to the life course and one that can be considered developmental, as evidenced by the early childhood developmental phenomena discussed, above.

Co-morbidity with medical problems and diseases

Physical disease is common among patients with schizophrenia but is rarely diagnosed. Over half of inpatients and between a fifth and a half of outpatients with schizophrenia have been found in different surveys to suffer from concurrent medical illnesses. A diagnosis of schizophrenia is associated with around 15 years of life lost due to increased mortality, much due to cardiovascular disease (Chwastiak & Tek. 2009) (52). The cluster of interrelated characteristics commonly referred to as the metabolic syndrome (central obesity, raised triglycerides, reduced HDL-cholesterol, raised fasting plasma glucose, and hypertension (Alberti et al., 2005) (53) is particularly relevant. Schizophrenia showed a fourfold increased risk of being associated with metabolic syndrome in the Northern Finland 1996 birth cohort study (Saari et al. 2005) (54). Other studies have reported prevalence as high as 36% to 51% in schizophrenia (McEvoy et al., 2005; De Hert et al., 2006; John et al., 2009) (55-57). There is growing evidence that this high prevalence of metabolic syndrome among schizophrenia patients might be explained by interactions between second generation antipsychotic medications, lifestyle factors and an inherent predisposition to diabetes and heart disease associated with the condition itself (Goff et al., 2005; McEvoy et al., 2005) (58,55).

Comorbid substance use

Amphetamine leads to a dose-dependent hyper-dopaminergic state and, in high enough dose, will reliably cause a paranoid psychosis (self-referential, persecutory beliefs); the excess dopamine in the limbic striatum leads to abnormal attribution of salience to everyday phenomena. This is one plank of the dopamine hypothesis of psychosis. On a more prosaic level, substance use disorders are the most commonly reported co-morbid problem among schizophrenia patients and involve alcohol, stimulants, anxiolytics, hallucinogens, antiparkinsonian drugs, as well as tobacco and caffeine; cannabis use is very common and dependence massively under-estimated. In the epidemiologically-principled CAMEO early intervention service covering Cambridgeshire & Peterborough (www.cameo.nhs.uk) substance use among people with first-episode psychosis was twice that of the general population and was more common in men than women. Cannabis abuse was reported in 51% of patients and alcohol abuse in 43%. More than half had used Class A drugs, and 38% reported poly-substance abuse. Age at first use of cannabis, cocaine, ecstasy and amphetamine was significantly associated with age at first psychotic symptom.

In an Australian epidemiological sample of 852 individuals with DSM-III-R diagnosed psychoses (Kavanagh et al. 2004) (59), lifetime repeated use of cannabis (misuse or dependence) was reported by 41% of the participants, followed by amphetamines (18%), LSD (17%), heroin (14%), cocaine (12%), and PCP (10%). Trends in the joint incidence and prevalence of cannabis use and of schizophrenia between 1970 and 2002 in the United Kingdom were used by Hickman et al. (2007) (60) to estimate that the marked increase of cannabis use in younger age groups may result by 2010 in approximately 10% of schizophrenia cases being attributable to cannabis.

Cannabis abuse was a significant predictor of poor two-year outcome in the WHO study and has been shown to precipitate psychotic relapse or exacerbate the symptoms of schizophrenia (Linszen et al., 1994) (61). Heavy cannabis use prior to the manifest onset of psychotic symptoms has been consistently reported. Regardless of the controversy as to whether cannabis use causes schizophrenia in those who would otherwise not have developed it (see Moore et al., 2007) (62), this drug undoubtedly causes great harm through dependence, complicates the management of those users who have schizophrenia and worsens their outcome (Zammit et al., 2008) (63).

Migrant status and ethnicity

The exceptionally high incidence rate of schizophrenia and other psychoses in immigrant or ethnic minority groups in Western Europe is consistently replicated, yet remains controversial and challenging (Bhugra, 2004; Cantor-Graa & Selten, 2005; Singh, 2006) (64-66). One of the earliest investigations of psychoses in immigrant populations was Ødegaard's study of Norwegian migrants to the US living in Minnesota (Ødegaard, 1932) (67). He demonstrated that these immigrants were twice as likely to develop schizophrenia as either native-born Americans or Norwegians in Norway and proposed that selective migration of individuals with hereditary proneness to psychosis could account for the phenomenon.

European interest in the increase in psychoses in immigrant populations followed the influx of economic migrants to the United Kingdom and other Northern European countries since the 1950s. An early study reported increased rates of psychoses in Black Caribbean migrants in the UK, compared with the native-born White British population (Hemsi, 1967) (68). A 4- to 5-fold increased risk for schizophrenia in the Black Caribbean group has since been replicated in a number of population-based studies (Littlewood & Lipsedge, 1981; McGovern & Cope, 1987; Harrison et al., 1988; Castle et al., 1991; Wessely et al., 1991; Harrison et al., 1996; Bhugra et al., 1997; Eaton & Harrison, 2000; Fearon et al., 2006) (69-77). In the largest study of schizophrenia in Asian immigrants to date, the East London First Episode Psychoses (ELFEP) project, incidence rates of schizophrenia were estimated separately for Indian, Pakistani and Bangladeshi migrant groups. After adjustment for age and sex, the latter two ethnic groups, but not the Indian group, were found to have significantly raised rates of schizophrenia compared with the White British. Stratification by sex revealed that the effect was sex-specific, with Pakistani and Bangladeshi women having between 4- and 5-fold increased rates of schizophrenia compared with White British women, while incidence rates in their male counterparts did not differ from those in White British men (Kirkbride et al., 2008b) (78).

Migration itself is a major life event and may place considerable stress upon the individual. This is likely to be compounded by post-migratory experiences including securing housing and employment, developing social relationships and networks and understanding the norms, rules and customs of the host culture. In a general population sample, it has been found that although the prevalence of psychotic symptoms is greater in Black or Ethnic Minority (BME) groups, the risk of outbreak of psychosis may be explained by discrimination and stressful life events (Johns et al., 2004) (79). While the prevalence of stressful life events may be similar across ethnic groups, there is evidence that such events have a greater negative effect in ethnic minorities (Gilvarry et al. 1999; Cooper et al. 2008;) (80,81).

Deprivation, social fragmentation and low social capital at the neighbourhood level may also have pronounced effects for migrants independent of, or interacting with, individual-level experiences, particularly given that migrants predominantly live in urban areas. Three studies, in different settings, have shown that the risk for migrants increases as they live in areas with a smaller proportion of minority residents, especially if the latter have darker skin colour (Boydell et al., 2001; Cantor-Graa & Selten, 2005; Veling et al., 2006b; 2007; Kirkbride et al., 2007b;) (82,65,84,46). Although psychosocial stress is a likely factor affecting migrants, there is at present no plausible mechanism linking such stress selectively to schizophrenia. Unexplored gene-environment interactions, involving various infectious, nutritional or toxic environmental factors, remain a possibility.

Childhood life events may be important in the genesis of psychoses in immigrant groups. In the AESOP study, Morgan et al. (2007) (85) found that the risk for schizophrenia due to parental death or separation was similar for the White British, Black Caribbean and Black African groups. However, such parental separation events were nearly twice as common in the Black Caribbean group, suggesting that this risk factor may have a greater impact in this population. Family disruption is important as it may lead to, or be a marker for, a range of other adverse outcomes such as childhood behaviour disorders, low educational achievement and longer-term socioeconomic problems.

One area of uncertainty regarding migration and psychotic illness is whether the recently migrated communities from Eastern Europe and the ex-Soviet Block that have arrived in the UK over the recent decade will also suffer from high rates of illness. This is currently being addressed by a Cambridge-based study (see www.sepea.org) and is touched upon by a study by Cheng et al., (2011) (86) mentioned below.

Regardless of the causes of the migration phenomenon, it represents a major health need for migrant communities, across generations, for mental health services and perhaps particularly for funding agencies and commissioners. Areas with larger migrant communities need more services. An example of this effect comes, again, from the Cambridgeshire-based early intervention service, www.cameo.nhs.uk, where Cheng and colleagues (2011) (85) used the epidemiologically-principled service design to compare the administrative incidence of first episode psychosis in that mixed urban and highly rural county with figures from two samples from predominately city catchments, the AESOP and ELFEP studies already cited. They showed (Figure 2) that higher crude incidence rates in cities are due in large part to their ethnic and migrant composition. Extrapolation to our region might suggest that urban centres, such as Luton, with large BME communities need more mental health services, and they need to be tailored to the particular needs of the populations they serve.

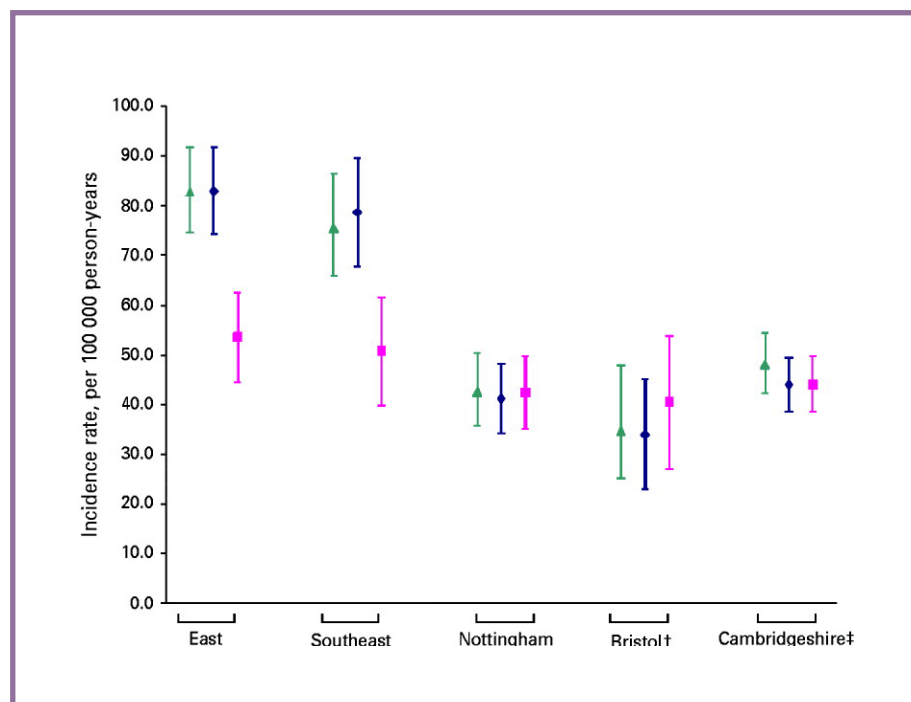


Figure 2 (From Cheng et al., 2011) (86)

Comparison of crude and directly standardized incidence rates in Cambridgeshire and four catchment areas of the AESOP and ELFEP studies (directly standardized to the population (18-34 years) of England estimated in the 2001 Census). Adjustment of the crude incidence rates (green or left hand bar of each triplet) for age and sex differences in the populations made little difference (blue or middle bar) with Cambridgeshire having a lower rate than the cities (although a reduction because Cambridgeshire has a disproportionately high young adult population in the period of risk for schizophrenia). Adjustment for the ethnic make-up of the populations led to much more similar rates (pink or right hand bar in each triplet) suggesting that higher rates in cities are due in large part to factors related to their ethnic mix.

Schizophrenia risk, multiple levels of causation and implications for services

As Jablensky et al. (2010) (1) conclude, the effects of socio-environmental risk factors on the incidence of schizophrenia are complex but important. It is likely that societal level effects interact with individual liability that is determined by both genetic and environmental factors. Genetic factors

have not been covered in the present article; interested readers are directed to the primary article and elsewhere. The risk of psychosis for single persons has been shown to be higher when they live amongst predominately married residents (Van Os et al., 2000) (87). A similar effect regarding the risk of schizophrenia for Black or minority ethnicity individuals have been shown when they reside in predominately white neighbourhoods (Boydell et al., 2001; Kirkbride et al., 2007b; Veling et al., 2008) (82,46,88).

These findings all support the assertion of Faris and Dunham (1939) (43) that social isolation is involved in the genesis of psychotic disorders. The social isolation hypothesis may extend into a broader hypothesis including both the social structure of the neighbourhood and the notion of “social capital” which has been suggested by some (Kirkbride et al., 2008a; Kirkbride et al., 2007b) (89,46), but not all studies (Drukker et al., 2006) (90) as having a buffering or protective effect on the risk of schizophrenia.

Conclusions

We do not yet completely understand the underlying neurobiology of the mental states that we call schizophrenia, but it is likely that the irregularities in the brain's innate connectivity economy are crucially involved. Despite gaps in our understanding (at which future generations will be agape) epidemiological studies based on the crudities of the overt clinical syndrome not only indicate that there is considerable variation across populations, ages and individual experiences, suggesting a variety of potential contributions to causal constellations, but they also shed light on those underlying neurobiological processes, particularly in the developmental domain. The study of diseases in populations using observational epidemiological designs involves taking careful account of the technical limits to the inferences that can be drawn. However, there is little doubt that it has contributed much to our increasing understanding of the enigma that is schizophrenia. It will continue so do to, particularly when combined with genetic and experimental designs. Epidemiology should command service design and, thanks to its progress, the textbook notion that schizophrenia is a disorder of unknown aetiology is simply no longer true.

GP comment

What have I learned from this paper?

1. The risk factors for developing schizophrenia are complex and some may be determined very early, as shown by the relationship between late walking and increased risk of schizophrenia.
2. Genetic influences, culture and migration can all play a role in determining the risk of developing schizophrenia.
3. The lifetime risk of developing symptoms that meet the diagnostic criteria for schizophrenia is just under 1% and the lifetime risk for developing any psychotic disorder is around 3%.

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Table 1 Selected incidence studies of schizophrenia together with two systematic reviews & meta-analyses (Adapted from Jablensky et al., 2010)

Author	Country	Population	Method	Incidence rate per 100,000 population at risk
Historical surveys (published before 1980)				
Ødegaard (1946a)	Norway	Total population (n=14,231)	First admissions 1926-35	24
Helgason (1964)	Iceland	Total population (n=2,388)	First admissions 1966-67	27
Häfner and Reimann (1970)	Germany	City of Mannheim (n=330 000)	Case register	54
Raman and Murphy) (1972)	Mauritius	Total population (n=257 000)	First admissions	24 (Africans) 14 (Indian Hindus) 9 (Indian Moslems)
Lieberman (1974)	Russia	Moscow district (n=248 000)	Follow-back (to onset) of prevalent cases	20 (men) 19 (women)
Eaton et al. (1974)	USA	Maryland state	First admissions	30

<i>Surveys published 1980 – 2007</i>				
Joyce et al. (1987)	New Zealand	Total population	First admissions (1974-1984)	18
Castle et al. (1991)	UK	London (Camberwell)	Case register	25 (ICD-9) 17 (RDC) 8 (DSM-III)
Nicole et al. (1992)	Canada	Area in Quebec (n=338 300)	First admissions	31 (ICD) 9 (DSM-III)
Lin et al. (1989)	Taiwan	3 communities (n=39 024)	Household survey	17
Rajkumar et al. (1993)	India	Area in Chennai (Madras) (n=43 097)	Door-to-door screen and informants (interview)	41
Hickling & Rodgers-Johnson 1995)	Jamaica	Total population (n=2 460 000)	First contact (interview)	24 ('broad' schizophrenia) 21 ('restrictive' schizophrenia)
McNaught et al. (1997)	UK	London health district (n=112 127)	2 censuses, 5 years apart	21 (DSM-IIIR)
Brewin et al. (1997)	UK	Nottingham	2 cohorts of first contacts (1978-80 and 1992-1994)	25; 29 (all psychoses) 14; 9 (ICD-10)
Mahy et al. (1999)	Barbados	Total population (n=262 000)	First contacts	32 ('broad' schizophrenia) 28 ('restrictive' schizophrenia)
Haukka et al. (2001)	Finland	National birth cohorts (1950-1969)	Case register data (ICD-8 and ICD-9)	62 (men) 63 (women)
Svedberg et al. (2001)	Sweden	Stockholm (3 catchment areas)	First admissions (1991-1992)	9 (DSM-IV)
Scully et al. (2002)	Ireland	2 counties (n=104 089)	First contacts 1995-2000 (interview)	35 (DSM-IV)
Boydell et al. (2003)	UK	South-east London (Camberwell)	First contact (records) (1965-1997)	6 -153 (DSM-IIIR)
Kirkbride et al. (2006)	UK ÆSOP study	3 cities	First contact (interview) (1997-1999) DSM-IV diagnoses	216 (London) 82 (Nottingham) 82 (Bristol)
Veling et al. (2006a)	The Netherlands	The Hague (n=518,000)	First contacts (2000-02)	22 (DSM-IV)
Menezes et al. 2007	Brazil	Area in Sao Paulo (n=2,315,000)	First contacts (2002-04)	10 (DSM-IV)

WHO 10-country study (Jablensky et al. 1992)

Denmark	Aarhus	First contacts	18 ('broad' schizophrenia) 7 ('restrictive' schizophrenia)
India	Chandigarh (urban area)	First contacts	35 ('broad' schizophrenia) 9 ('restrictive' schizophrenia)
India	Chandigarh (rural area)	First contacts	42 ('broad' schizophrenia) 11 ('restrictive' schizophrenia)
Ireland	Dublin	First contacts	22 ('broad' schizophrenia) 9 ('restrictive' schizophrenia)
Japan	Nagasaki	First contacts	21 ('broad' schizophrenia) 10 ('restrictive' schizophrenia)
Russia	Moscow	First contacts	28 ('broad' schizophrenia) 2 ('restrictive' schizophrenia)
UK	Nottingham	First contacts	24 ('broad' schizophrenia) 14 ('restrictive' schizophrenia)
USA	Honolulu	First contacts	16 ('broad' schizophrenia) 9 ('restrictive' schizophrenia)

Systematic review (McGrath et al. 2004)

Data from 33 countries	147 studies	Cumulative plots of incidence rates	24 (mean, both sexes) 22 (mean, men) 21 (mean, women)
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Systematic review (Kirkbride et al. 2011)

Data from England	147 studies	Meta-analysis of incidence rates	A little over 30 (all psychotic illness) Around 15 (schizophrenia)
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² Systematic Review of the Incidence and Prevalence of Schizophrenia and Other Psychoses in England
Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, McCrone P, Murray RM & Jones PB. Report for the Department of Health Policy Research Programme March 2011.