CHAPTER 2

EPIDEMIOLOGY

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This chapter reviews the epidemiology of schizophrenia, covering rates across different settings and over time, and particularly populations that appear to be at high risk. We consider gender differences in schizophrenia, as well as late-onset schizophrenia. We also cover risk factors, both genetic and environmental, and attempt to integrate findings in those domains. Finally, we turn to the longitudinal course of schizophrenia and describe factors that may impact upon outcomes for people with this disorder. But first, we ask how common schizophrenia is.

HOW COMMON IS SCHIZOPHRENIA?

Studies that have attempted to determine rates of schizophrenia are bedevilled by a number of methodological problems that include the following:

- *Definition of illness.* There is still no truly valid definition of the disease entity we call schizophrenia. Indeed, definitions have changed over time, dependent upon the prevailing view of what constitutes this putative disorder, and this can have profound implications for estimates of rates. For example, different duration criteria (anything from 2 weeks to 6 months of symptoms) and age cutoffs (anything from age 40 years to no age limit) result in differential proportions of potential cases being excluded from epidemiological samples.
- *The failure to use valid diagnostic interview schedules.* Many early studies simply applied clinical or "best-guess" diagnoses, with an inevitable lack of consistency across raters. More modern studies have tended to use diagnostic interview schedules or applied operational definitions to case record material. Some such schedules produce diagnoses that correlate well with operational definitions, for example, the Structured Clinical Interview for DSM (SCID), which generates *Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnoses, and the Diagnostic Interview for Psychoses (DIP; Castle et

al., 2006), which generates, among others, International Classification of Diseases (ICD) and DSM diagnoses. However, others, such as the lay interviewer–administered Diagnostic Interview Schedule (DIS; Robins, Helzer, Croughan, & Ratcliff, 1981) used in the U.S. Epidemiologic Catchment Area (ECA) study (Regier et al., 1984), tends to overdiagnose schizophrenia, producing higher rates than those found in studies using clinician-rated scales.

- *Different methods of case ascertainment.* Many studies have relied solely on inpatient admission data, but this approach undoubtedly misses some cases. Case registers that record all contacts with psychiatric services are a better reflection of true rates, though in some settings a proportion of cases seek help from agencies other than mental health services. To address this problem in its two incidence studies of schizophrenia in a number of countries across the globe, the World Health Organization (WHO) attempted to ascertain all persons with schizophrenia in contact with any treating agency, including traditional healers where appropriate (Jablensky et al., 1992). General population sampling is another approach (mostly for prevalence studies), but this is expensive and the low rates of schizophrenia in the general population require that a very large sample be screened. Using clinicians for this task is not feasible, and lay interviewers, even if trained in the use of structured interview schedules, tend to be inaccurate in case ascertainment (as discussed earlier).

Despite these problems, a number of more recent studies have sufficient rigor to give us a good sense of prevalence and incidence rates of schizophrenia across diverse settings.

Prevalence

Prevalence refers to the number of cases of schizophrenia is a given population at a particular point in time (point prevalence) or over a stipulated period (period prevalence). Because it is a relatively rare disease, but one that tends to be chronic, prevalence studies are generally easier to perform than incidence studies (see below) requiring less ascertainment time to accumulate sufficient numbers of cases for meaningful analysis. However, methodological issues remain, notably those that have to do with sampling frames: In a general population sample, for example, the relatively few cases found would require screening of very large samples to detect any sizable number of schizophrenia cases. Also, the validated brief screening instruments that have been created tend to lose their positive predictive power in samples with low proportions of cases.

An example of a population-based study is the ECA study (Regier et al., 1984), which used lay interviewers to assess cases of mental illness across five sites in the United States. The aggregated point prevalence estimate for schizophrenia was 7.0 per 1,000 population at risk; lifetime risk was 15.0. However, as already mentioned, there were concerns about the validity of diagnosis in this study, suggesting an overestimation of cases.

Another approach is to use an enriched sample, which is likely to contain a higher proportion of cases, enhancing the efficacy of screening instruments. An example is the Australian National Survey of Low Prevalence (Psychotic) Disorders (Jablensky et al., 2000), which ascertained treated cases of psychosis across four geographical catchments with a total population of some 1,000,000. Supplementary estimates were made of patients solely in contact with either their family doctors or a private psychiatrist, as well as those out of contact with services altogether. Point prevalence rates ranged from 3.1 to 5.9 per 1,000.

This finding of relatively little variation in rates across different settings has been largely upheld by other studies. Suggestions that rates were particularly high in Western

Ireland and Yugoslavia have largely been put down to methodological issues, such as inclusion criteria used. However, it does seem that certain settings do have markedly higher rates of schizophrenia. This might be due to a high aggregation of highly genetic cases in inbred communities (e.g., northern Sweden), or drift into urban areas (and perhaps a "toxic" effect of growing up in big cities), leading to higher rates in more urbanized settings. There is also evidence of higher rates in areas with high proportions of migrants or of those ethnic minorities found to be at heightened risk of schizophrenia (see below).

Incidence

Incidence refers to the number of new cases with the onset of the disorder over a certain time period. Landmark incidence studies were conducted by the WHO in a range of developed and developing countries (Jablensky et al., 1992). Case ascertainment was rigorous (discussed earlier), and diagnoses were made according to the CATEGO algorithm linked to the Present State Examination (PSE; Wing, Cooper, & Sartorius, 1974). Rates ranged from 1.6 per 10,000 population at risk (ages 15–54 years) in Honolulu, to 4.2 in a rural Indian site. When a stricter definition of schizophrenia was applied (so-called S+ under CATEGO), rates varied far less, with the lowest being 0.7 (in Denmark) and the highest 1.4 (in Nottingham, United Kingdom). In a recent review of the world literature that included 55 studies, the distribution of rates was much broader, with some studies with higher rates skewing the distribution. The median rate was 15.2 per 100,000, and the central 80% of rates ranged from 7.7 to 43.0 per 100,000. This suggests greater variability in rates than might usually be assumed.

Variations in rates can be influenced (though not entirely accounted for) by a number of the methodological considerations we addressed earlier. One issue is definition of illness. The extent of variation in rates consequent to vagaries of illness definition has been shown clearly in the Camberwell Register First Episode Study (Castle, Wessely, Van Os, & Murray, 1998), where all patients who used psychiatric services in a defined area of southeast London were rediagnosed according to a range of diagnostic criteria. Use of broad ICD-9 criteria (akin to a clinical diagnoses of schizophrenia or related disorders) gave a rate of 19.2 per 100,000 population per year for males, and 17.6 for females; more stringent DSM-III criteria produced rates of 13.9 for males and 6.3 for females; and the rates using very stringent Feighner criteria were 14.8 and 6.0 for males and females, respectively.

These data also point to the fact that males are more vulnerable to schizophrenia than females, and that this difference is more marked when more stringent criteria are applied. This has been confirmed in an analysis of data from 55 studies from around the globe that showed a median male:female risk ratio of 1.4. It is also clear that males with schizophrenia tend to have an onset of illness later than their female counterparts. This, along with the findings of poorer premorbid adjustment and premorbid IQ, and overall worse outcome for males with schizophrenia, has led to the conclusion that males might be differentially susceptible to a severe early-onset form of the illness consequent to neurodevelopemental deviance. Another consideration has been the potential ameliorating effect of endogenous estrogens in females with schizophrenia, leading to a more benign outcome, but also leaving women at risk for a later onset, menopause-related surge in incidence of schizophrenia.

In the controversy about whether the rates of schizophrenia have been declining over the last few decades, studies supporting such a notion are generally from developed countries and have relied on treated incidence statistics, which might be biased expressly by changes over time in treatment service provision models. Furthermore, studies using case registers in a defined setting (e.g., the previously discussed Camberwell Register), have

not generally found any decline in rates: indeed, in Camberwell, the rates rose over the two decades from the mid-1980s, in part at least due to an influx of African Caribbeans, who are at a high risk for developing the disorder (see below).

Immigrants and Ethnic Minorities

The literature is replete with evidence to support immigrants' particularly high risk of developing schizophrenia. Most consistently this has been shown for African Caribbean migrants to the United Kingdom. A number of studies using different methodologies and different sets of diagnostic criteria have found that both first-generation migrants and their offspring are at higher risk of developing schizophrenia than native-born white inhabitants.

A recent meta-analysis (Cantor-Graae & Selten, 2005) of 18 studies of migrants from a number of different ethnic backgrounds (one from Australia, and the others from the United Kingdom, the Netherlands, Denmark, and Sweden) yielded a mean weighted relative risk for first-generation migrants (40 effect sizes) of 2.7 (95% confidence interval [CI], 2.3–3.2). For second-generation migrants, the mean relative risk was 4.5 (95% CI, 1.5–13.1). Diagnostic issues did not explain these differences, an important consideration given that some authors have suggested that immigrants are particularly vulnerable to brief psychotic episodes that do not meet stringent criteria for schizophrenia.

There was, however, a positive association between risk of schizophrenia and lower socioeconomic status of region of birth (i.e., those immigrants from developing countries had higher rates than those from developed countries). There was also a significant association with skin color, in that immigrants from countries with a majority of black inhabitants had a relative risk of schizophrenia of 4.8 (95% CI, 3.7–6.2), clearly higher than all migrants combined. The elevated relative risk was found for both males and females.

Thus, it seems clear that migrants have a higher risk of developing schizophrenia than native-born individuals in their own or their adoptive countries. The offspring of migrants also appear to be at heightened risk, though there is more spread in those results. The reasons for this increased vulnerability are complex and may encompass differential migration of vulnerable individuals, and/or biological–social risk factors in the adopted countries. For example, researchers have found an association between rates of schizophrenia and the perception of discrimination in the adopted country.

IS THERE A LATE-ONSET FORM OF SCHIZOPHRENIA?

Kraepelin's original view of dementia praecox was of an early-onset disorder (all individuals under age 40 years, and most under age 25). More recently, DSM-III stipulated that onset of the disorder could not occur after age 45, but this constraint was scrapped in later revisions of the criteria. The European tradition has tended to "allow" an onset of schizophrenia at any age, and there is good evidence for a late "peak" in onsets, predominantly among women, after the age of 60. This group of individuals has been labeled variably "late paraphrenia" and "paraphrenia" (in ICD-9), and most recently "late-onset schizophrenia-like psychosis" (by the International Late-Onset Schizophrenia Working Group). The features are usually of florid and well systematized delusional systems; mostly of a persecutory nature; and auditory, visual, olfactory, and somatic hallucinations in the absence of formal thought disorder or negative symptoms.

What remains somewhat controversial is whether late-onset cases represent the same disease entity, or whether alternative etiological processes are occurring. Some of the risk

factors associated with early-onset disorder (see below) are not common in late-onset cases, but a family history of psychosis still bestows an elevated risk (albeit less than that in younger patients). Some researchers have suggested etiological links with mood disorders, and there is good epidemiological and clinical evidence that increased risk is associated with poor premorbid social (but not occupational) adjustment, premorbid paranoid and schizoid personality traits, uncorrected sensory impairment (visual and auditory), and social isolation.

RISK FACTORS

The genetic contribution to schizophrenia is well-documented in tables of morbid risk of the disease for relatives of affected probands, as outlined elsewhere (Glatt, Chapter 6) in this volume. The morbid risk in the monozygotic twin of a proband is estimated to be 48% compared to 1% for the general population. However, transmission within families does not follow a simple Mendelian pattern, and it is likely that schizophrenia is caused by many genes of small effect in combination with stochastic factors, as well as environmental risk factors, that exert their impact independently or interactively with genetic risk.

Although no major environmental risk factor has been definitively demonstrated, a number have been proposed. Unfortunately, at this stage, none of the putative risk factors are specific to schizophrenia or meet all the epidemiological criteria for causality proposed by Mervyn Susser, including strength of association; specificity of cause and of effect; consistency in replicability and in survivability; predictive performance; and theoretical, factual, biological, and statistical coherence.

Obstetric Complications and the Neurodevelopmental Hypothesis of Schizophrenia

There is good evidence that neurodevelopmental deviance contributes to the pathophysiology of schizophrenia. Neuropathological evidence for a neurodevelopmental basis to schizophrenia includes the following:

- Ventricular enlargement already present at the time of onset of symptoms.
- An absence of gliosis in postmortem brain tissue.
- Evidence for cytoarchitectural abnormalities, including neuronal disarray.
- Neuronal malpositioning (possibly as a result of aberrant neuronal migration).

Other evidence for the neurodevelopmental hypothesis comes from elevated levels of minor physical anomalies and abnormal dermatoglyphics in persons with schizophrenia, indicative of neuronal disruption *in utero*. In addition, developmental delays and other motor, social, and cognitive deficits in childhood, apparent well before illness onset, are also important pointers. Further evidence is to be found in the increased risk of pregnancy, birth, and neonatal complications in persons who later develop the disorder, with estimates ranging from a two- to a seven-fold increased risk depending on the study design and the manner in which obstetric complications have been operationalized.

Specific complications that have been significantly associated with later onset of schizophrenia include the following:

- Measures of fetal growth retardation, including measures of small-for-gestational-age births and reduced head circumference.

- Intrauterine infections such as influenza, Coxsackie B, rubella, and toxoplasmosis.
- Malnutrition (specifically, exposure to famine in the northern Netherlands in the winter of 1944–1945 following German blockade of the region).
- Nutritional deficiencies, such as hypovitaminosis D.
- Placentation abnormalities.
- Rhesus factor (RH) incompatibility.

Increasingly, however, researchers are developing more sophisticated frameworks for identifying homogeneous, etiologically plausible obstetric insults, and positive associations have been observed for preeclampsia, fetal distress, low Apgar scores, as well as composite markers of neonatal hypoxic encephalopathy, birth asphyxia, and other hypoxic–ischemic complications. In addition, there is less reliance on crudely summated, generalized scales to measure obstetric complications, and one of the most refined scales currently in use, the McNeil–Sjöström Scale, takes into account the biological plausibility of the obstetric insult, including its potential effect on the developing central nervous system, its severity, and its timing in pregnancy.

The period of greatest vulnerability appears to be the second trimester *in utero,* when one would expect more subtle sequelae to adverse exposures, with consequences for neuronal migration, glial–neuronal interactions, and resultant cortical connectivity. By contrast, there is less evidence of gross organogenic and structural abnormalities in the brain that one might find following first trimester insult, whereas the absence of gliosis provides limited evidence that the impact of exposure was prior to the third trimester. Nonetheless, critical development of the brain is still taking place in the first few years of life and the impact of insults at later stages of development should not be underestimated. The impact is not limited to physical insults, and rearing environment and childhood stressors have also been associated with later schizophrenia.

Season of Birth

Interest in the seasonality of births of individuals who develop schizophrenia has persisted since the results of the first systematic study of the association between season of birth and schizophrenia, published in 1929, showing an excess of winter births among Swiss inpatients. A comprehensive review of the literature in 1997 uncovered over 250 studies of seasonality of births in schizophrenia and affective psychoses. Studies of birth seasonality in the northern hemisphere have consistently shown a winter–spring excess of 5–8% in schizophrenia. The findings in southern hemisphere studies have not been as consistent and, where positive, have tended to show smaller effect sizes. Correlations have been found between season of birth and parameters including sociodemographic factors, family history, and obstetric complications; and between season of birth and specific subtypes, symptoms, and signs in schizophrenia. Explanatory models for seasonal variation in births in schizophrenia cover the following:

- Genetic factors.
- Obstetric complications, particularly those that impact the developing central nervous system, some of which may be environmentally determined (e.g., exposure to viral and bacterial agents).
- External environmental factors, such as variation in light and external toxins, including cigarette smoke, nutritional deficiencies, temperature, and other climatic effects.
- Different procreational habits in the parents of high-risk children.

There is no strong evidence for age-incidence and age-prevalence effects in the findings.

Paternal Age

Recent studies have found an association between schizophrenia and paternal, but not maternal, age, with older fathers more likely to have children who later develop the disorder. This association persists even after researchers control for potential confounders. The association is stronger in nonfamilial cases of schizophrenia, and there appears to be a dose-dependent effect with increasing paternal age. It is suggested that sporadic de novo mutations in male germ cells, which increase with increasing age, may be modifying the expression of the paternal gene.

Urbanicity and Other Social Risk Factors

Urbanicity (generally constructed as urban dwelling but sometimes operationalized as urban birth) is associated with schizophrenia. For the most part, researchers have concentrated on two potential mechanisms underlying this association. On the one hand, the breeder (or causation) hypothesis proposes that urban environments contribute to causation of psychosis through increased exposure to infections, toxins, poverty, stress, and the like. On the other hand, the urban drift (or selection) hypothesis maintains that the increase is due to the drift of affected persons into urban centers. These mechanisms are not mutually exclusive, and both may underlie the association between urbanicity and schizophrenia. There is some evidence that the causation hypothesis may be exerting a stronger impact than the selection hypothesis, and more recent studies suggest that the effect may be genetically mediated.

In utero exposure to maternal stressors (e.g., maternal exposure to the 5-day invasion of the Netherlands in 1940; death of a spouse during the pregnancy period; unwanted pregnancy) has been implicated in schizophrenia. Childhood stressors, such as separation from a parent, death of a parent through suicide, and sexual abuse in childhood, have also been reported as independent risk factors for schizophrenia. It has been proposed that the increased risk of schizophrenia in immigrants (2.7 times higher than in the general population) may be a result of broader social risk factors related to social isolation (discussed previously) or "social defeat."

Burden of Disease, Morbidity, and Mortality

Schizophrenia is one of the top 10 causes of years lived with disability (YLD) worldwide for all ages, and is one of the leading causes of disability adjusted life years (DALY) for 15- to 44-year-olds. A major Australian national survey of the prevalence of schizophrenia and the other psychoses revealed a disturbing picture of disability and reduced quality of life for affected persons. Persons with schizophrenia were more likely than the general population not to have completed secondary education (56.1%) and to be currently unemployed, broadly defined to include formal employment, study, and home duties (77.5%), with a very large proportion (90.6%) reliant on welfare benefits as their main source of income. Over half of the schizophrenia sample (55.5%) reported a chronic course of illness, with 33.1% experiencing a significant clinical deterioration over time. Another one-third of the total (36.9%) described a remittent pattern of illness. Levels of disability and impairment across the entire range of variables assessed were high. Overall, 52.9% of the interviewed sample with schizophrenia experienced serious or major dys-

function in social or occupational functioning, including dysfunction in capacity for self-care (35.3%), participation in daily household activities (50.0%), and ability to socialize (61.2%) and to maintain intimate relationships (48.4%).

The physical health of people with schizophrenia is poor, and detection and treatment rates in this group are notoriously low. Lifestyle factors (poor nutrition, lack of exercise, and high rates of smoking and nonmedical use of drugs) underlie myriad poor health outcomes. In addition, use of antipsychotic medications is associated with an increased risk of a range of conditions, including diabetes and the metabolic syndrome. Smoking, in particular, is a likely contributory factor for the spectrum of morbidity and mortality outcomes related to cardiovascular and cerebrovascular disease.

An excess of HIV and hepatitis, diseases associated with substance abuse, has also been found and is not unexpected given the high levels of drug and alcohol comorbidity in this group. One surprising finding, in view of the high rates of smoking among persons with schizophrenia, has been the reported reduction in cancer incidence and mortality in this population. Some recent studies have not found this association, although one Danish study using national registers confirmed the findings for tobacco-related cancers, including lung cancer, in males but not females. It is posited that age cohort effects may explain some of the inconsistencies and that one may expect to find increased incidence of cancer in younger cohorts who are more likely to be exposed to smoking risks than older, institutionalized cohorts. Although it has been suggested that the reduction in non-smoking-related cancers found in some studies may be due to the protective action of neuroleptic medication, the evidence is not conclusive.

Overall mortality from both natural and unnatural causes is increased in schizophrenia when standardized by sex and age group. The excess in natural causes of mortality covers the range of conditions including cardiovascular disease, cerebrovascular disease, respiratory disease, digestive disease, and genitourinary disease. Moreover, there is compelling evidence from population-based register linkage studies that persons with schizophrenia are underdiagnosed and undertreated for ischemic heart disease but overrepresented in mortality statistics for ischemic heart disease. However, the single largest cause of excessive mortality in schizophrenia is suicide, with suicide rates elevated above not only population rates but also rates for other psychiatric disorders. The risk of suicide is significantly increased in the first year after discharge following inpatient admission, but especially in the first few weeks after discharge.

Marital Status, Fertility, and Fecundity

Social isolation in schizophrenia is pervasive. It is therefore not surprising that, compared to the general population, persons with schizophrenia are less likely to marry or to enter into long-term conjugal relationships. They are also less likely to have children, and if they do have children, they have fewer children. In the Australian National Prevalence Survey across a catchment of 1.1 million persons ages 18–64, a large proportion of the study sample with schizophrenia was single, separated, divorced, or widowed (72.7%). Only a small proportion had children (27.1%). The findings were different for men and women, with women more likely than men to be in long-term relationships and to be parents.

Data from epidemiological studies on fertility and fecundity in schizophrenia challenge researchers to explain why schizophrenia persists, with incidence rates relatively stable over time and place, despite the reported reduction in "reproductive fitness" in persons with the disorder. Some of the hypotheses put forward include the following:

- That low rates of fertility and fecundity in women with schizophrenia are offset by high rates in men with schizophrenia.
- That fertility and fecundity are increased among unaffected family members, who pass on the unexpressed genetic liability.
- That unaffected family members benefit from evolutionary physiological advantages, such as resistance to infection or injury.
- That an increase over time in environmental causal factors, such as obstetric complications, compensates for a reduction over the same time in genetic risk.

However, the supporting evidence for any of these theories is poor, with inconsistent findings and little resolution of the contradictions that arise. Furthermore, it has been proposed that in a model of schizophrenia that includes multiple genes and latent carriers, the impact of lowered reproductive fitness leading to loss of susceptibility alleles would be negligible.

LONGITUDINAL COURSE

The Kraepelinian notion that schizophrenia (actually dementia precox, a severe early-onset subtype of schizophrenia as we know it today) was a disease with an inevitably poor outcome has been challenged by more recent longitudinal studies.

Problems with research in this area include the following:

- *Differences in sample selection.* For example, including only long-term hospitalized cases, inevitably biasing toward a poor outcome.
- *Incomplete ascertainment of cases.* It would be expected that patients lost to follow-up would more likely be those with a good outcome, who no longer required active treatment.
- *Varying duration of follow-up.* Most decline in psychosocial functioning occurs in the first 5 years of the illness and later flattens out or even shows some degree of improvement.
- *Lack of consistency in defining outcome, with various parameters being considered.* For example, symptom alleviation (mostly positive symptoms), social outcome, occupational outcome, "quality of life," and service utilization.

Factors robustly associated with a poorer longitudinal illness course include being male, early onset of illness, poor premorbid social and occupational adjustment, low premorbid IQ, a predominance of negative symptoms, and a lack of affective symptoms. It has been argued that this reflects a particular subtype of schizophrenia consequent to neurodevelopmental deviance (discussed earlier).

A number of other factors serve to perpetuate a poor outcome. These include delayed, suboptimal, or intermittent treatment with antipsychotic medication and ongoing illicit substance use. There is also a strong association between poor outcome and a family environment characterized by so-called high expressed emotion (EE). High EE is a construct that encompasses critical comments, hostility, and/or overinvolvement of family members with nominally more than 72 hours per week of face-to-face contact with the individual. Clinical interventions have been shown to be effective in reducing EE in family members and enhancing outcomes for patients.

KEY POINTS

- Schizophrenia appears in all known human societies at a rate of around 0.5%, though there is variation according to definition of illness and geographical setting.
- Immigrants are at higher risk of developing schizophrenia, as are ethnic minorities.
- Schizophrenia is largely a disorder of young adulthood (expressly in males), but it can manifest for the first time even very late in life.
- The most powerful know risk factor for schizophrenia is genetic, but a number of environmental factors, expressly those afflicting early neurodevelopment, also serve to increase the risk of developing the disorder.
- Social risk factors for schizophrenia include urban birth and upbringing, and being an ethnic migrant.
- Schizophrenia often has a chronic longitudinal course, expressly if the onset of the illness is early in life, insidious in onset, and dominated by negative symptoms.
- Substance abuse is common among people with schizophrenia and is associated with a worse longitudinal course of illness.
- Schizophrenia is often associated with significant psychosocial disability, relationship problems, isolation, and lack of gainful employment.
- People with schizophrenia are at high risk for certain medical problems, including cardiovascular risk factors, that are often underdiagnosed and undertreated, leading to increased mortality.

REFERENCES AND RECOMMENDED READINGS

Brown, S. (1997). Excess mortality of schizophrenia. *British Journal of Psychiatry, 171,* 502–508.

Cantor-Graae, E., & Selten, J.-P. (2005). Schizophrenia and migration: A meta-analysis and review. *American Journal of Psychiatry, 162,* 12–24.

Castle, D. J., Jablensky, A., McGrath, J., Carr, V., Morgan, V., Waterreus, A., et al. (2006). The diagnostic Interview for Psychoses (DIP): Development, reliability and applications. *Psychological Medicine, 36,* 69–80.

Castle, D. J., & Murray, R. M. (1993). The epidemiology of late onset schizophrenia. *Schizophrenia Bulletin, 19,* 691–700.

Castle, D. J., Wessely, S., Der, G., & Murray, R. M. (1991). The incidence of operationally defined schizophrenia in Camberwell, 1965–1984. *British Journal of Psychiatry, 159,* 790–794.

Castle, D. J., Wessely, S., & Murray, R. M. (1993). Sex and schizophrenia: Effects of diagnostic stringency, and associations with premorbid variables. *British Journal of Psychiatry, 162,* 658–664.

Castle, D. J., Wessely, S., Van Os, J., & Murray, R. M. (1998). *Psychosis in the inner city: The Camberwell First Episode Study.* Hove, UK: Psychology Press.

Eaton, W. W. (1991). Update of the epidemiology of schizophrenia. *Epidemiologic Reviews, 13,* 320–328.

Jablensky, A. V., & Kalaydjieva, L. V. (2003). Genetic epidemiology of schizophrenia: Phenotypes, risk factors, and reproductive behavior. *American Journal of Psychiatry, 160,* 425–429.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., & Cooper, J. E. (1992). Schizophrenia: Manifestations, incidence, and course in different cultures: A World Health Organization ten-country study. *Psychological Medicine Monograph Supplement 20,* 1–97.

Jablensky, A., McGrath, J., Herrman, H., Castle, D., Gureje, O., Morgan, V., et al. (2000). Psychotic disorders in urban areas: An overview of the methods and findings of the Study on Low Prevalence Disorders, National Survey of Mental Health and Well-Being 1996–1998. *Australian and New Zealand Journal of Psychiatry, 34,* 221–236.

Jones, P., & Cannon, M. (1998). The new epidemiology of schizophrenia. *Psychiatric Clinics of North America, 21,* 1–25.

McGrath, J. J. (2005). Myths and plain truths about schizophrenia epidemiology—the NAPE lecture 2004. *Acta Psychiatrica Scandinavica, 111,* 4–11.

Morgan, V. A., Mitchell, P. B., & Jablensky, A. V. (2005). The epidemiology of bipolar disorder: Sociodemographic, disability and service utilization data from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Bipolar Disorder, 7,* 326–337.

Murray, J. L., & Lopez, A. D. (Eds). (1996). *The global burden of disease.* Geneva: World Health Organization, Harvard School of Public Health, and World Bank.

Regier, D. A., Myers, J. K., Kramer, M., Robins, L. N., Blazer, D. G., Hough, R. L., et al. (1984). The NIMH Epidemiologic Catchment Area Program: Historical context, major objectives, and population characteristics. *Archives of General Psychiatry, 41,* 934–941.

Robins, L. N., Helzer, J. E., Croughan, J., & Ratcliff, K. (1981). The National Institute of Mental Health Diagnostic Interview Schedule. *Archives of General Psychiatry, 38,* 381–389.

Torrey, E. F., Miller, J., Rawlings, R., & Yolken, R. (1997). Seasonality of births in schizophrenia and bipolar disorder: A review of the literature. *Schizophrenia Research, 28,* 1–38.

Van Os, J., & Marcelis, M. (1998). The ecogenetics of schizophrenia: A review. *Schizophrenia Research, 32,* 127–135.

Wing, J. K., Cooper, J. E., & Sartorius, N. (1974). *The measurement and classification of psychiatric symptoms.* Cambridge, UK: Cambridge University Press.