The last decade has seen striking progress in our understanding of the epidemiology of schizophrenia. Some traditional beliefs have been confirmed, but others have been swept away, while recent data have implicated new risk factors for the disorder and have changed the way we conceptualize it.

### Descriptive epidemiology

#### Lifetime prevalence

Schizophrenia affects just under 1% of the population at some point in their life. Perhaps the most comprehensive study to demonstrate this comes from Finland; Perala et al estimated lifetime prevalence, according to DSM-IV criteria, at 0.87% for schizophrenia, and 0.32% for schizoaffective disorder.

#### Incidence

For many years the curious view held sway that the incidence of schizophrenia was constant both geographically and temporally. However, we now know that this is not so. A systematic review showed that rates for the incidence of schizophrenia ranged from 7.7 to 43.0 per 100,000, a fivefold difference. There are fewer data concerning long-term trends, but it has been demonstrated that the operationally defined incidence of schizophrenia in South London doubled between 1965 and 1997.

#### Age of onset

Kirkbride et al assessed the incidence of psychosis in three English cities as part of the large AESOP (Aetiology and Ethnicity of Schizophrenia and Other...
Translational research

Psychoses) study. Figure 1 shows the age-specific incidence rates for psychosis as a whole and for the main diagnostic types. It can be seen (Figure 1c) that the peak incidence for schizophrenia in males was between 20 and 24 years, but 29 to 32 years in females; the latter showed a flatter curve with more cases presenting in later life. Thus, the AESOP study confirms previous evidence of an earlier age of schizophrenia onset in males. One of the most detailed studies of gender differences investigated 477 first-contact cases with schizophrenia including those presenting in later life. Though the mean age of onset was therefore later, males still had an earlier mean onset of illness than females (31.2 vs 41.1 years). Castle et al also showed that while the incidence was relatively equal in the two sexes for mild schizophrenia, as the diagnostic criteria were narrowed so there emerged an excess of males. Other studies confirm that narrowly defined schizophrenia tends to be more common (risk ratio 1.4:1), and the illness tends to be more severe, in men. The earlier age of onset in men has been attributed to the male brain’s greater susceptibility to neurodevelopmental disorders, while the excess in women in the postmenopausal period could be secondary to loss of the antidopaminergic action of estrogens.

Mortality

People with schizophrenia have, on average, a shorter life than the rest of the population. McGrath et al, who carried out a systematic review of mortality studies, reported that the standardized mortality ratio (SMR) was 2.6, with suicide and cardiovascular disease the major contributors. Sadly, they found that the SMR has been rising over recent decades.

Risk factors

Risk factors for schizophrenia may be crudely divided into biological and social.

Biological risks

Genetics

The most widely replicated risk factor for schizophrenia is a family history of the disorder in a first-degree relative. Twin and adoption studies have shown that this is largely due to genetic factors rather than family environment. Assuming a model in which genes and

Figure 1. Incidence of psychosis in the AESOP Study.
Reproduced from ref 7: Kirkbride JB, Fearon P, Morgan C, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center Aesop study. Arch Gen Psychiatry. 2006;63:250-258. Copyright © 2006 American Medical Association

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environmental factors act additively, the heritability of schizophrenia can be calculated to be between 66% and 83%. Current thinking implicates a large number of common genes of very small effect plus rarer variants such as copy number variations. However, as genetics is discussed in detail elsewhere in this issue, we will not consider this topic further here.

Parental age

In recent years, there has been a renewed interest in Edward Hare’s observation that advanced paternal age is a risk factor for schizophrenia in the offspring. Malaspina et al collected paternal birth data for 638 individuals with schizophrenia in Israel and reported that the risk rose from 1/141 among those whose fathers were less than 25 years at their birth to 1/47 for those whose fathers were 50 to 54 years (Figure 2).

| Paternal age (y) | Incidence rate per 1,000 |
|------------------|-------------------------|
| 1/141            | 25-29                   |
| 1/121            | 30-34                   |
| 1/99             | 35-39                   |
| 1/85             | 40-44                   |
| 1/80             | 45-49                   |
| 1/68             | 50-54                   |

Figure 2. Incidence of schizophrenia by paternal age. Reproduced from ref 18: Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry. 2001;58:361-367. Copyright © 2001 American Medical Association

Pre- and perinatal events

Obstetric complications

Numerous studies have reported an excess of pregnancy and birth complications, collectively termed “obstetric complications” (OCs) in schizophrenic patients. Cannon et al conducted a meta-analysis of population-based studies examining the relationship between OCs and later development of psychosis. They found significant associations with schizophrenia for ten individual complications, which they grouped into three categories: (i) complications of pregnancy (bleeding, pre-eclampsia, diabetes, rhesus compatibility); (ii) abnormal fetal growth and development (low birth weight, congenital malformations, small head circumference); (iii) complications of delivery (asphyxia, uterine atony, emergency cesarean section).

Season of birth

One of the most consistently replicated epidemiological features of schizophrenia is the small but significant excess of winter-spring births found in the Northern hemisphere (about 7% to 10%); patterns in the Southern hemisphere are less clear. Various theories have been put forward to explain this stubborn association; the most widely accepted postulates a teratogenic agent, or dietary deficiency, which impairs fetal brain development. Considerable effort has been put into establishing whether the winter-spring birth excess could be due to exposure to influenza during fetal life but the results remain inconsistent. It has been found that the offspring exposed to prenatal maternal genital and reproductive infections were five times more likely to develop schizophrenia spectrum disorders than those who were not. Prenatal exposure to toxoplasmosis and to herpes simplex type 2 have also been blamed. In utero exposure to maternal malnutrition, maternal diabetes, smoking, and rhesus incompatibility have also been considered. As yet none of these exposures to infectious or noninfectious agents can be taken as proven.

Hearing impairment increases the risk for psychosis. The underlying mechanism could be sensory deprivation or social isolation and defeat but hearing impairment and psychosis may be due to a common cause such as exposure to prenatal infections such as rubella.
Drug abuse

Stimulants

The capacity of psychostimulants to produce psychotic symptoms is well known. Since the 1990s, methamphetamine abuse and the consequent psychosis has spread from Japan, Thailand, and Taiwan to California, and then eastwards across the USA. Both amphetamine and methamphetamine produce a picture almost identical to that of paranoid schizophrenia.

Cannabis

Recently much more attention has been paid to the relationship between cannabis and psychosis. Initially it was widely believed that schizophrenic patients took cannabis as “self-treatment” either to alleviate negative or affective symptoms, or to counteract the dysphoric side effects of antipsychotics. However, acute ingestion of cannabis or its active ingredient tetrahydrocannabinol (THC) was found to precipitate acute psychotic episodes in experimental studies, and continuing use of cannabis is known to exacerbate existing psychotic illness. Andreasson et al followed up 45,570 conscripts into the Swedish army; those who abused cannabis at 18 years were more likely to be admitted to hospital with schizophrenia over the next decade and a half. There was a dose-response relationship such that the more cannabis consumed the greater was the likelihood of schizophrenia.

Social risk

For the last quarter of the 20th century, etiological research interest in social factors in psychosis was virtually absent. However, from the late 1990s evidence has grown that social factors play an important role in the aetiology of schizophrenia.

Urban residence

Schizophrenia is over-represented in the most deprived sections of the population. In 1939 it was reported that there were higher admission rates for schizophrenia in the poorer central areas of Chicago compared with the suburbs. This pattern was consistently confirmed in other large cities in the USA and Europe, most recently in Ireland.

| Country in which the study was conducted | Study design | Number of participants (adjusted risk) | Follow-up | Odds ratio (95% CI) |
|------------------------------------------|-------------|----------------------------------------|-----------|--------------------|
| United States (Tien & Anthony, 1990)     | Population based | 4494 | NA | 2.4 (1.2-7.1) |
| Sweden (Andreasson et al, 1987; Zammit et al, 2002) | Conscript cohort | 50 053 | 15 years | 2.3 (1.0-5.3) |
| | | | 27 years | 3.1 (1.7-5.5) |
| The Netherlands (NEMESIS) (van Os et al, 2002) | Population based | 4045 | 3 years | 2.8 (1.2-6.5) |
| Israel (Weiser, Knobler, Noy, & Kaplan, 2002) | Population based | 9724 | 4-15 years | 2.0 (1.3-3.1) |
| New Zealand (Dunedin) (Arseneault et al, 2002) | Birth cohort | 1034 | 15 years | 3.1 (0.7-13.3) |
| New Zealand (Christchurch) (Fergusson et al, 2003) | Birth cohort | 1265 | 3 years | 1.8 (1.2-2.6) |
| The Netherlands (Ferdinand et al, 2005) | Population based | 1580 | 14 years | 2.8 (1.8-4.4) |
| Germany (EDSP) (Henquet et al, 2005) | Population based | 2437 | 4 years | 1.7 (1.1-1.5) |
| United Kingdom (Wiles et al, 2006) | Population based | 8580 | 18 months | 1.5 (0.5-3.9) |
| Greece (Stefanis et al 2004) | Birth Cohort | 3500 | NA | 4.3 (1.0-17.9) |
| Australia (McGrath et al, 2010) | Birth Cohort | 3800 | 21 years | 2.2 (1.1-4.5) |

Table I. Epidemiological studies examining cannabis use and risk of psychosis.
For many years, this was widely believed to result from preschizophrenic individuals drifting into the deprived inner cities. However, studies from Sweden and the Netherlands have shown that the incidence of schizophrenia is greater among those born or brought up in urban areas.\textsuperscript{67,68} Pedersen and Mortensen demonstrated that in Denmark, the larger the town and the longer the individual has lived in a town, the greater the risk.\textsuperscript{69} The AESOP study, discussed above, demonstrated that the incidence of schizophrenia in South London was double that in Nottingham and Bristol,\textsuperscript{7} and that even within South London there were wide variations in the rates;\textsuperscript{70} the highest rates were found in the areas with least social cohesion;\textsuperscript{69} this last finding echoes the original findings of Faris and Dunham who suggested that social isolation in socially disorganized parts of the city could increase the risk of schizophrenia.\textsuperscript{62}

**Migration**

An increased risk of schizophrenia has been demonstrated among Surinamese migrants in the Netherlands,\textsuperscript{71} African refugees in Sweden,\textsuperscript{72} Greek migrants to Belgium,\textsuperscript{73} and Scandinavian migrants to Denmark.\textsuperscript{74} A systematic review confirmed a high incidence of schizophrenia among many migrants and ethnic minority groups, and especially black migrants to European countries.\textsuperscript{4} The AESOP study confirmed that all ethnic minority groups in England are at increased risk for schizophrenia, but that African-Caribbeans and black Africans show an especially high risk with a ninefold and sixfold increase in the incidence respectively compared with white Britons.\textsuperscript{75} Many previous studies in the UK have reported similar findings.\textsuperscript{76-82} This excess is not a consequence of misdiagnosis.\textsuperscript{83-85} Furthermore, African-Caribbeans do not show an increased risk of psychosis in the West Indies,\textsuperscript{86-88} indicating that genes alone cannot explain the findings. Hutchinson et al showed that among the siblings of Caribbean patients in the UK, the risk was much lower in those sibs mostly living in the West Indies compared with those mostly living in the UK.\textsuperscript{89} This implies some environmental factor operating in the UK but not in the West Indies. Boydell et al demonstrated that as the proportion of non-white ethnic minorities in a given neighbourhood in London decreases, the incidence of schizophrenia in this minority increases.\textsuperscript{59} The finding was subsequently replicated in the Netherlands, and suggests an ameliorating effect of social support or of decreased exposure to adversities such as racial discrimination, in areas with relatively high proportions of ethnic minorities.\textsuperscript{90}

**Childhood adversity**

**Parental loss or separation**

It has been noted that permanent separation from, or death of, one or both parents was associated with a more than threefold increased risk of schizophrenia (but not bipolar disorder).\textsuperscript{92} Similarly, it was observed in the AESOP study that psychotic cases were three times more likely than controls to have experienced a long-term separation from one or both parents and to have had a parent die before the age of 16.\textsuperscript{93}

**Child abuse**

Of course, parental separation and loss are associated with a range of adverse early experiences, including family conflict, socioeconomic disadvantage, and neglect and abuse.\textsuperscript{94} Evidence is emerging that childhood physical abuse may increase risk of later psychosis, but whether childhood sexual abuse is particularly culpable is contentious.\textsuperscript{95}

**Bullying**

The association between bullying and severe mental health problems, including self-harm, violent behavior, and psychotic symptoms has attracted recent attention.\textsuperscript{96} In one study, the risk of psychotic symptoms was increased twofold among victims of bullying at ages 8 and/or 10 years, independent of other prior psychopathology, family adversity, or child’s IQ, and was stronger for chronic or severe victimization.\textsuperscript{97}

**Adult adversity**

**Life events**

Many studies have reported an excess of stressful life events before relapse of schizophrenic illness.\textsuperscript{98-101} The smaller number of studies of first-episode psychosis have also shown an increased rate of life events prior to the onset of illness.\textsuperscript{102} There is some evidence that intrusive
life events such as assaults and victimization are especially likely to precede psychosis.

**Social isolation**

Those with long-standing psychotic disorders experience very high rates of unemployment, more often live alone, and fail to establish long-term relationships, the consequence being social isolation and exclusion. Marwaha and Johnson, reviewing studies of first-episode psychosis, noted rates of employment at >40%; other studies report similar findings. Furthermore, in a study using Danish national data, it was found that, compared with controls, those who subsequently developed schizophrenia were more frequently unemployed and living alone for as long as 19 years before first hospital admission. Morgan et al compared the prevalence of a number of indicators of adult social disadvantage and isolation in first-episode psychotic cases and controls in the AESOP study. All current and long-term indicators (eg, unemployment, living alone, social housing) were associated with an increased odds of psychosis.

It is uncertain whether the association between social disadvantage and psychosis is a consequence of the developing disorder itself, or a contributory cause of the illness. Possibly urban living may impact on risk by isolating individuals, a process compounded for those whose social development is disrupted by frequent moves, leading to a loss of potentially protective factors, such as social supports. In line with such reasoning, the number of changes of school during adolescence has been associated with an increased risk of psychosis in Denmark.

**Recent conceptual developments**

**Psychotic symptoms in the general population**

Schizophrenia was originally conceived as a disease (or diseases) qualitatively different from the normal state. However, minor psychotic symptoms are reported by a surprising number of people in the general population. Furthermore, the factors associated with these minor psychotic symptoms are the same as those associated with risk for schizophrenia; youth, male sex, poor education, unemployment, membership of an ethnic minority, and cannabis use. Thus, migrant groups with high rates of schizophrenia, such as African-Caribbean people living in the UK, also show higher rates of minor psychosis-like phenomena. Many medical disorders such as hypertension or anemia are considered as occupying the extreme end of a continuum; a disease threshold is imposed (eg, a diastolic BP of 90 mm Hg) at a point beyond which intervention is beneficial. Such a continuum view means that it is useful not only to study individuals with the established disease, but also to examine what factors propel individuals along the continuum towards the threshold. Thus, the NEMESIS follow-up study in the Netherlands demonstrated that individuals from the general population who report childhood abuse are at increased risk of developing both minor psychotic symptoms and psychotic disorder.

**Gene-environment interaction**

Research has begun to focus on the possibility of gene-environmental interaction whereby genes influence risk of disorder only in the presence of a particular environmental factor or vice versa. One report suggested an interaction between obstetric complications and several genes involved in hypoxia, while it has been suggested that cannabis may increase the risk of psychosis, particularly in those with the val/val genotype at the COMT locus. Neither of these reports have yet been replicated.

We noted earlier that heritability estimates for schizophrenia range up to 83%. However, it may be that such calculations from twin studies inflate the apparent role of genes since gene x common environment interactions are subsumed in the heritability figure. The fact that many of the environmental risk factors that operate upon schizophrenia are common to both twins in a pair (eg, urban living, migration) could be one reason for the relative failure of molecular genetics to identify susceptibility genes of large effect for the condition.

**Integrating epidemiology with pathogenesis—do all roads lead to dopamine?**

In summary, the epidemiological evidence suggests that schizophrenia is a multifactorial disorder in which genes interact with each other and with environmental factors to push individuals over a threshold into expression of the disorder. The environmental risk factors operate at various stages of life but until till now there has been...
little attempt to relate them to what we know of pathogenesis. This is unfortunate since in many medical disorders, epidemiology is integrated with etiology and pathogenesis; for example, the risk factors for myocardial infarction are known to facilitate the development of atheroma in the coronary arteries. Such integration has not yet happened in schizophrenia research. However, there is much evidence that dysregulation of striatal dopamine is the final common pathway underlying positive psychotic symptoms. One unifying view is therefore that ultimately all risk factors for schizophrenia impact on the dopamine system. Such a view is schematically portrayed in Figure 3. Here, dopamine dysregulation appears as the final step in a complex developmental cascade that starts early in life and ends with the onset of full-blown psychosis. Thus stimulant drugs are known to increase synaptic dopamine while animal studies show that isolation rearing is associated with an increase in basal dopamine levels. There is much evidence that stress is associated with hyperactivity of the HPA axis, and in turn high cortisol is known to impact on the dopamine system.

**Conclusion**

The two major theories of schizophrenia, the neurodevelopmental and the dopamine hypotheses, have hitherto been largely distinct and indeed independent of much of the epidemiological evidence concerning risk factors for the condition. However, these theories are now beginning to be integrated through the growing evidence that the major developmental risk factors for schizophrenia appear to act by facilitating dopamine dysregulation; this latter appears to be the final common pathway underlying psychosis. The challenge is now to delineate the exact chain of pathogenic mechanisms which connect such risk factors to dopamine dysregulation.

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**Figure 3.** Developmental cascade towards schizophrenia. CNV, copy number variant; HPA, hypothalamic-pituitary-adrenal
La epidemiología de la esquizofrenia: reemplazar el dogma con el conocimiento

Se han realizado importantes avances en nuestra comprensión acerca de la epidemiología de la esquizofrenia. Actualmente se sabe que el trastorno es más común y grave entre los hombres jóvenes y que la incidencia varía geográfica y temporalmente. Se han aclarado los factores de riesgo; los riesgos biológicos incluyen una historia familiar de la enfermedad, avanzada edad paterna, complicaciones obstétricas y abuso de drogas como los estimulantes y el cannabis. Además, la investigación reciente también ha identificado factores de riesgo sociales como el haber nacido y haberse criado en una ciudad, la migración y ciertos tipos de adversidad infantil como el abuso físico y el bullying, al igual que el aislamiento social y situaciones adversas en la vida adulta. La investigación actual está orientada hacia los síntomas psicóticos menores en la población general, la interacción genes-ambiente y cómo los factores de riesgo impactan en la patogénesis; considerando que quizás todos los factores de riesgo finalmente impactan en la dopamina estriatal como la vía final común.

Épidémiologie de la schizophrénie: remplacer le dogme par la connaissance

Notre compréhension de l’épidémiologie de la schizophrénie a fait d’énormes progrès. Nous savons maintenant que la maladie est plus courante et plus sévère chez les hommes jeunes et que l’incidence de la maladie varie géographiquement et chronologiquement. Les facteurs de risque ont été identifiés; les risques biologiques comprennent des antécédents familiaux de la maladie, un âge paternel élevé, des complications obstétriques et la consommation excessive de drogues comme les stimulants et le cannabis. De plus, la recherche récente a également identifié des facteurs de risque sociaux comme le fait d’être né et d’avoir été élevé dans une ville, l’immigration et certains types d’enfance malheureuse comme la maltraitance physique et les brimades, ainsi que l’isolation sociale et les événements négatifs au cours de la vie adulte. La recherche actuelle se concentre sur la signification de symptômes psychotiques mineurs dans la population générale, l’interaction gène-environnement et la façon dont les facteurs de risque influent sur la pathogénèse; tous les facteurs de risque agissent peut-être en fin de compte sur la dopamine striatale, qui serait la voie finale commune.

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