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Epidemiology of Schizophrenia: Review of Findings and Myths

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The epidemiology of schizophrenia has progressed from descriptive accounts to a surge in analytic epidemiologic findings over the last 2 decades. This article reviews the epidemiology of schizophrenia, concentrating on the results that are most credible methodologically and consistent across studies and focusing particularly on the most recent developments. The authors also comment on some misconceptions regarding schizophrenia epidemiology, specifically pointing to widespread misinterpretations of evidence regarding the incidence of schizophrenia and the gender ratio of the disease.

DESCRIPTIVE EPIDEMIOLOGY: PREVALENCE AND INCIDENCE OF SCHIZOPHRENIA

Prevalence

The point prevalence of a disease is the proportion of the population that has the disorder at a point in time. The point prevalence of schizophrenia is about 5/1000 in the population. The estimate depends on the age distribution of the population: for example, if persons too young to be at risk are included in the denominator, the estimates will be lower. Table 1 presents findings from areas in which credible estimates of both prevalence and incidence are available. The prevalence in Table 1 ranges from 2.7/1000 to 8.3/1000, and this range would not be affected greatly if several dozen other studies, available from prior reviews, were included [1]. Lifetime prevalence has been estimated by surveys of examinations by medically trained persons; the resulting estimates do not different widely from those shown in Table 1 [1].

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Table 1
Prevalence and incidence of schizophrenia per 1000 population

Area	Date	Author	Age in years	Prevalence		Incidence
				Type	Rate	
Denmark	1977	Nielsen	15 +	Lifetime	2.7	
	1972	Munk-Jorgensen	All	Annual		0.12
Baltimore, Maryland, USA	1963	Wing	All	1 year	7	
	1963	Warthen	All	Annual		0.7
Camberwell, England	1963	Wing	15+	One year	4.4	
	1971	Hailey	All	Annual		0.11
Ireland	1973	Walsh	15+	Point	8.3	
	1986	World Health Organization	15–54	Annual		0.22
Portogruaro, Italy	1982–1989	de Salvia et al			2.7	
	1989	de Salvia et al		Annual		0.19
Hampstead, England	1991–1995	Jeffreys et al			5.1	
	1991–1995	McNaught et al		Annual		0.21

Data from Eaton WW. Epidemiology of schizophrenia. Epidemiol Rev 1985;7:105–26; Eaton WW. Update on the epidemiology of schizophrenia. Epidemiol Rev 1991;13:320–28; with additions from McNaught AS, Jeffreys SE, Harvey CA, et al. The Hampstead Schizophrenia Survey 1991. II: Incidence and migration in inner London. Br J Psychiatry 1997;170:307–11; Jeffreys SE, Harvey CA, McNaught AS, et al. The Hampstead Schizophrenia Survey 1991. I: Prevalence and service use comparisons in an inner London health authority, 1986–1991. Br J Psychiatry 1997;170:301–6; and de Salvia D, Barbato A, Salvo P, et al. Prevalence and incidence of schizophrenic disorders in Portogruaro. An Italian case register study. J Nerv Ment Dis 1993;181(5):275–82.

Incidence

The incidence of schizophrenia is about 0.20/1000/year. The incidences presented are all estimated for 1 year, making the comparison somewhat tighter. The range in annual incidence in Table 1 is from 0.11/1000/year to 0.70/1000/year, and this range would not be affected greatly if several dozen other studies, reviewed elsewhere, were included [2,3]. The presentation of prevalence and incidence figures from the same areas in juxtaposition shows that the point prevalence usually is more than 10 times the annual incidence, indicating the chronic nature of the disorder.

There is considerable variation in incidence rates around the world, as shown in Fig. 1. The dark bars represent the World Health Organization study of incidence, which reveals a smaller variation, presumably resulting from the standardization of method [4]. That study suggested to some that there was little or no variation in schizophrenia around the world, which

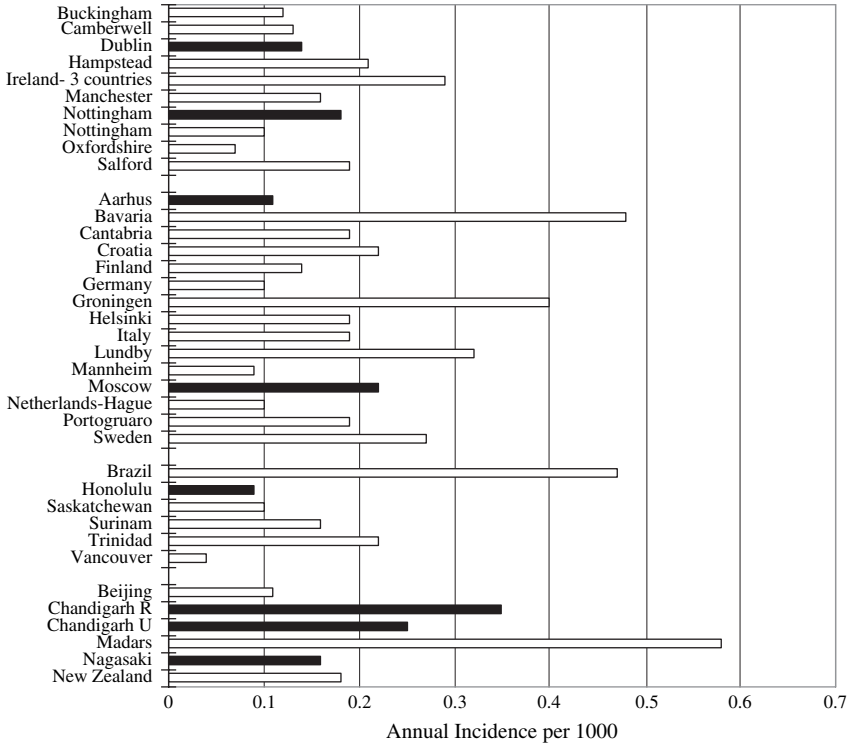

Fig. 1. Incidence of schizophrenia in selected studies published after 1985. Criteria: study focus is the general population of a defined geographic area; diagnosis is made by a psychiatrist; case finding includes inpatient and outpatient services; greater than 25000 person-years of risk in age group studies.

would make schizophrenia a very unusual disease indeed. Fig. 1 shows variation greater than one order of magnitude, from a low estimate in Vancouver of 0.04/1000/year to a high estimate in Madras of 0.58/1000/year. Both the Vancouver [5] and Madras [6] studies were carefully done, and their estimates are credible.

The force of morbidity for schizophrenia peaks in young adulthood. The age of onset varies between men and women, with males tending to have a younger onset [7]. The peak incidence for males and females is in the decade between the ages of 15 and 24 years. The peak for young adults is more marked for males, and women have a second peak in the years between the ages of 55 and 64 years. Evidence suggests that males have higher lifetime risk of schizophrenia; two meta-analysis addressing that issue show that males have about a 30% to 40% higher lifetime risk of developing schizophrenia [8,9].

ANALYTIC EPIDEMIOLOGY: NATURAL HISTORY AND RISK FACTORS

Natural History

Onset

The onset of schizophrenia is varied. In the classic long-term follow-up study by Ciompi [10], about 50% had an acute onset, and 50% had a long prodrome. The intensive study of prodrome by Hafner and colleagues [11] suggests that onset of negative symptoms tends to occur about 5 years before the initial psychotic episode, with onset of positive symptoms much closer to the first hospitalization.

Childhood developmental abnormalities

Many long-term follow-up studies, both retrospective and prospective, suggest that a variety of signs, symptoms, conditions, and behaviors are associated with an increased risk for schizophrenia, but none has adequate strength or uniqueness to be useful in prediction. Earlier work on groups at high-risk has shown that offspring of schizophrenic parents were more likely than the offspring of controls to have a lower IQ, poor attention skills, thought disorder–like symptoms, poor social adjustment, and psychiatric symptoms [11–13]. Although several concerns have been raised regarding the generalizability of high-risk findings to nonfamilial forms of schizophrenia, recent longitudinal studies conducted in the United Kingdom, Sweden, Finland, and New Zealand have provided evidence that individuals who have schizophrenia differ from their peers, even in early childhood, in a variety of developmental markers, such as the age of attaining developmental milestones [14–16], levels of cognitive functioning [17,18], educational achievement [14,19–21], neurologic and motor development [22–24], social competence [20,25], and psychologic disturbances [25]. More recent evidence also suggests the association with low IQ is specific to schizophrenia, because it was not found in bipolar disorder [26]. There seem to be no common causal paths linking these developmental markers with schizophrenia [27]. Indeed, individuals who later develop schizophrenia or related disorders already may have experienced a general or pan-developmental impairment early in their childhood. Prospectively collected data from the 1972–1973 birth cohort in New Zealand showed that schizophrenic subjects may have suffered significant deficits in neuromotor, language, and cognitive development in the first decade of their lives [21]. The compelling evidence linking an array of childhood developmental abnormalities and schizophrenia echoes the hypothesis that schizophrenia is a neurodevelopmental disorder for which causes may be traced to a defect in the early brain development [28–31].

Course

The symptomatic course of schizophrenia is varied. In Ciompi's classic study [10], about half the subjects had an undulating course, with partial or full remissions followed by recurrences, in an unpredictable pattern. About one third had relatively chronic, unremitting course with poor outcome. A small minority in that study had a steady pattern of recovery with good outcome. Follow-up

studies that are not strictly prospective, such as the study by Ciompi [10], can be deceptive, because there is a tendency to focus on a residue of chronic cases, making the disorder seem more chronic than it actually is. Fig. 2 shows data on time to rehospitalization for a cohort of schizophrenic patients in Denmark. The proportion remaining in the community without rehospitalization is shown on the vertical axis, and time is on the horizontal axis. After the initial hospitalization, about 25% are not rehospitalized even after 15 years. For the subgroup of the cohort with 10 hospitalizations, more than 90% are rehospitalized within 3 years following the tenth episode. Although reoccurrence of episodes might reinforce the illness (the so-called "schubweis [stepwise] process"), or hospitalization itself might be damaging [32], it seems more likely the cohort sorts itself into those who have tendency for greater or less chronicity of disorder. This process may lead clinicians and others to overestimate the chronicity of the disorder, because they see individuals in the bottom curve of Fig. 2 about 15 times as often as individuals in the top curve [33]. For this reason, the natural history of schizophrenia is best studied with cohorts of first onsets [34].

Outcome

For the most part, predictors of outcome for schizophrenia remain elusive. In a review of 13 prospective studies of the course of illness in first-onset cohorts, negative symptoms predicted poor outcome in four studies, and gradual onset, typical of negative symptoms as noted previously, predicted poor outcome in several studies [34]. There is variation in the course of schizophrenia around the world, with better prognosis in so-called "developing" countries. Table 2 shows a summary of data from the 1979 World Health Organization study

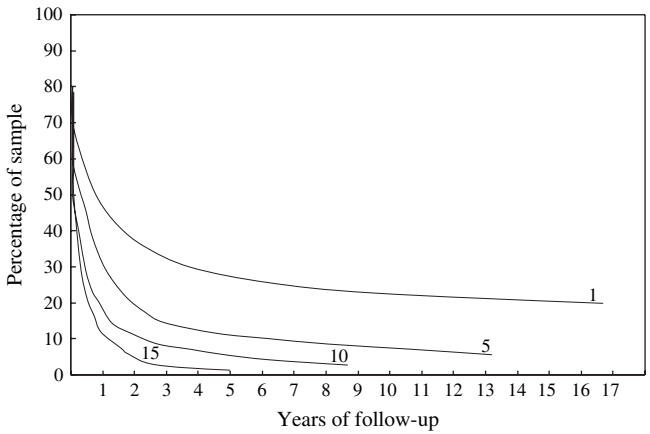

Fig. 2. Community survival in schizophrenia in patients who have had 1, 5, 10, or 15 hospital discharges. *From* Mortensen PB, Eaton WW. Predictors for readmission risk in schizophrenia. Psychol Med 1994;24:223–32; Reprinted with permission from Cambridge University Press.

Table 2
World Health Organization follow-up of schizophrenia

Location	Sample Size	No Symptoms (%)	Chronic Psychosis (%)
Developed countries			
London, England	50	6	40
Aarhus, Denmark	64	5	14
Moscow, Russia	66	17	21
Washington, DC, USA	65	6	23
	51	3	23
Developing countries			
Agra, India	73	42	10
Cali, Colombia	91	11	21
Ibadan, Nigeria	68	34	10

Data from Leff J, Sartorius N, Jablensky A, et al. The International Pilot Study of Schizophrenia: five-year follow-up findings. Psychol Med. 1992;22(1):131–45.

on this issue [35], with the columns at the far right extracted by the authors from the publication of Leff and colleagues [36]. Schizophrenic persons in developing countries are less likely than those in the developed countries to have been chronically psychotic over the period of follow-up and are more likely to have no residual symptoms after 5 years. This result remains to be explained. It could be that schizophrenia in developing countries includes a subset with better prognosis because of the risk factor structure in those areas, such as higher mortality of compromised fetuses. Another interpretation is that the environment of recovery in the developed world is more pernicious, involving harsher economic competition, a greater degree of stigma, and smaller family networks to share the burden of care for persons who have schizophrenia.

The course of schizophrenia, from early prodrome through to later outcome, is influenced by social variables, including socioeconomic position and marital status [37]. Even 20 years before diagnosis, an individual who eventually is diagnosed as having schizophrenia is more likely to be unmarried than other members of his or her age cohort (relative odds, 4). The relative odds of being single, as compared with those never diagnosed as having schizophrenia, peak at the time of admission, at more than 15, and remain high for decades afterward. The effect is greater for males, possibly because their earlier onset occurs during the years when marriages are most likely to be formed. Likewise, the individual who eventually is diagnosed as having schizophrenia is more likely than others in his or her age cohort to be unemployed many years earlier than the first diagnosis of schizophrenia and many years afterward. Although there is extensive literature on the relationship of low socioeconomic position to risk for schizophrenia [38,39], it seems likely that the association results from the effects of the insidious onset on the individual's ability to compete in the job market. Recent studies from Scandinavia suggest that, if anything, the parents of persons who have schizophrenia are likely to come from a higher, not a lower, social position [40].

Risk Factors

The genetics of schizophrenia, including family history as a risk factor, are beyond the scope of a general review on the epidemiology of schizophrenia. This section presents risk factors that have been reported in several credible studies and for which it is fairly clear that the risk factor was present before the onset of schizophrenia.

Season of birth

For a long time it has been known that individuals who have schizophrenia are more likely to be born in the winter, and the results have been reported from the samples in both the Northern and Southern hemispheres. The relative risk is small, on the order of a 10% increase for those born in the winter versus summer, but it has been replicated many times [41,42]. One possible explanation is that the second trimester of pregnancy occurs in the height of the influenza season and that maternal infections during that period raise th risk for schizophrenia in the offspring. Another explanation offered by a recent study suggests that the seasonal effects may increase one's risk of schizophrenia by the interaction with genetic vulnerability [43].

Birth complications

The finding regarding season of birth suggests that something about pregnancy and birth might be awry in individuals who later develop schizophrenia. Case-control studies on this issue have been available for decades, but the generally positive findings were clouded by the possibility that the mother's recall was biased. In the last 15 years many studies have reported a relative odds of about 2 for those with one or another sort of birth complication, and several meta-analyses on this topic exist [44–46]. Later analyses have begun to specify the individual type of birth complication, with the hope of elucidating the causal mechanism. A recent meta-analytic review of this literature categorizes the types of birth complications as (1) complications of pregnancy (bleeding, diabetes, rhesus incompatibility, pre-eclampsia); (2) abnormal fetal growth and development: (low birth weight, congenital malformations, reduced head circumference), and (3) complications of delivery (uterine atony, asphyxia, emergency cesarean section) [22]. The review concludes that the investigations into specific mechanisms need to move now from the epidemiologic perspective to include a combination of disciplines and approaches. The complications variously suggest malnutrition [47], extreme prematurity, and hypoxia or ischemia [30,48–50] as possible causes.

Parental age

The association between advanced parental age and a higher risk of schizophrenia was first proposed in the mid-twentieth century and has gained extensive scientific attention in recent years. Based on the family background data of 1000 patients in hospitals in Ontario, Canada, Gregory [51] reported that parents of patients who had schizophrenia were, on average, 2 to 3 years older than the parents of persons in the patients' age cohort who did not have

schizophrenia . Subsequent investigations showed inconsistent findings [52,53], however, and it was argued that the observed higher risk in schizophrenia associated with older maternal age might be largely confounded by raised paternal age [52,54]. Recently, several population-based epidemiologic studies in Demark, Israel, Sweden, and the United States have provided stronger evidence regarding the role of paternal age in schizophrenia [9,55–59]. A population-based birth cohort study from in Israel found that the relative risk of schizophrenia rose monotonically in each 5-year group of paternal age, with a maximum relative risk of 2.96 (95% confidence interval, 1.60–5.47) in the group aged 55 years or older in comparison with a paternal age of 20 to 24 years. Additionally, once paternal age is statistically adjusted, maternal age is no longer a significant predictor of schizophrenia. The evidence from one nested case-control study indicates that the increased risk for schizophrenia related to paternal age is generally greater in women [58]. In addition, current population-based cohort research suggests that the increased risk of schizophrenia related to advancing paternal age seems significant only among those without a family history of schizophrenia, indicating the possibility that de novo mutations accumulate in sperm [60].

Infections and the immune system

A series of ecologic studies suggests that persons whose mothers were in their second trimester of pregnancy during an influenza epidemic are at higher risk for developing schizophrenia [59,61–63]. Infection during pregnancy as a risk factor is consistent with the neurodevelopmental theory of schizophrenia [29,64]. Later studies, which are more convincing, include individual assessment of infection, either by comparison of antibodies in adults who have schizophrenia and in normal individuals [65], or even more convincing prospective studies in which the infection can be determined to have occurred during the pregnancy. There is consistent evidence that individuals who have antibodies to *Toxoplasmosis gondii* have higher prevalence of schizophrenia [66]. One study suggests a relative risk of 5.2 for individuals with documented infection by the rubella virus during fetal development [67]. Another prospective study found higher risk for psychosis in individuals whose mothers had higher levels of antibodies to Herpes simplex virus [68]. A study in Brazil compared individuals who had meningitis during the 1971 to 1974 epidemic with their siblings who did not have meningitis and found that that the prevalence of psychosis, and specifically schizophrenia, was five times higher in those who had meningitis. The finding is intriguing because the average age of infection with meningitis was 26 months, much later than prenatal infection [69]. If this finding is replicated, it will have important implications for the neurodevelopmental theory of schizophrenia.

Autoimmune diseases

A relatively small but consistent literature indicates that persons who have schizophrenia have unusual resistance or susceptibility to autoimmune diseases. Studies have consistently shown that individuals who have schizophrenia

are somehow less likely to have rheumatoid arthritis [70]. Although medications for schizophrenia may be protective for rheumatoid arthritis in some unknown way, some of the studies were conducted before neuroleptic medications were available. Other physiologic consequences of schizophrenia may be protective, or a single gene may raise the risk for the one disorder and give protection against the other. A single small study suggests that mothers of individuals who have schizophrenia have a lower risk for rheumatoid arthritis, but the study's size and quality are not convincing [71]. It is intriguing, in this regard, that case control studies have shown that persons taking nonsteroidal anti-inflammatory medications, which primarily treat arthritis, may be protected from dementia [72,73].

Other autoimmune disorders have been linked to schizophrenia, including thyroid disorders [74], type 1 diabetes [75], and celiac disease [76]. Currently the evidence is strongest for thyroid disorders and celiac disease. In a study from the Danish population registries, persons whose parents had celiac disease were three times as likely to be diagnosed later as having schizophrenia. Celiac disease is an immune reaction to wheat gluten. One possible explanation is that the increased permeability of the intestine brought about by celiac disease increases the level of antigen exposure, thereby increasing the risk of autoimmune response. It also is possible that gluten proteins are broken down into psychoactive peptides [77].

The results linking schizophrenia to autoimmune disease are paralleled by the clinical and laboratory study of autoimmune processes in schizophrenia. There apparently are abnormalities of the immune system in schizophrenia, but it is not clear whether these are causal or a consequence of schizophrenia or its treatment [78]. It is possible that a single weakness in the immune system in persons who have schizophrenia explains both the data on infections and the results in autoimmune disorders, but this possibility remains to be proven [79]. Meanwhile, there are ongoing clinical trials of anti-inflammatory [80] and antibiotic [81] agents for schizophrenia.

Ethnicity

Ethnic status is a relatively easily identified individual characteristic that indicates a shared history with others. Markers of ethnic status include race, country of origin, and religion. Country of origin has proven to be a consistent risk factor for schizophrenia in the United Kingdom and the Netherlands. In the United Kingdom, those immigrating from Africa or the Caribbean and their second-generation offspring have rates of schizophrenia up to 10 times higher than those in the general population [82]. Because immigrant groups who do not have black skin do not have higher rates, and because the second generation is affected, the stresses of immigration are unlikely to be causative. Because rates in the countries of origin are not elevated, it is unlikely that a genetic difference between races is causative. The cause seems to be the psychologic conditions associated with being black in England or being from Surinam in Holland. It could be discrimination or a more subtle form of difficulty

associated with planning one's life when the future is as uncertain, as it is for racial groups at the structural bottom of society [83,84].

Cannabis use

Numerous case-control studies show that persons who have schizophrenia are more likely to have taken, or be using, cannabis [85]. Recently prospective studies in Sweden, the Netherlands, New Zealand, and Israel have shown that the risk for developing schizophrenia is 2 to 25 times higher in persons who have used cannabis [86–89]. Individuals in the premorbid phase of schizophrenia might be responding to initial, mild symptoms of schizophrenia by using drugs, even though these studies have attempted to control for premorbid conditions. On the other hand, it could be that cannabis precipitates, or even causes, an episode of schizophrenia [90–95].

Urban residence

In the 1930s Faris and Dunham [96] showed that, although the addresses of first admissions for manic depressive illness were distributed more or less randomly throughout Chicago, admissions for schizophrenia tended to come from the center of the city, with rates decreasing as one moves outward into zones of transition, working class, and family neighborhoods. This and other similar findings [97] were interpreted as reflecting the tendency for individuals who would develop schizophrenia to move into the city. Later studies from Europe, however, were strictly prospective, with the cohort defined in late adolescence, well before onset [98], or even at birth [99]. The relative risk of developing schizophrenia is about two to four times higher for those born in urban areas. The difficulty lies in identifying the plausible biologic process associated with urban residence. It could include differences in the physical environment, such as the higher concentration of lead in the soil and air in cities; differences in the cultural environment, such as the expectation that one will leave the family of origin and define a new life plan [83]; differences in birth practices, such as breastfeeding [100]; crowding, which might permit spread of infections [101] as discussed later; differences in the manner in which animals are, or are not, brought into the household [102]; and a host of other factors [103].

MYTHS IN SCHIZOPHRENIA EPIDEMIOLOGY

In recent years reviews have led to a reconsideration of some aspects of schizophrenia epidemiology that are widely cited but poorly supported by evidence [104]. The first is the notion that schizophrenia has universal incidence across cultures and countries. The second is the belief that schizophrenia distributes itself equality in males and females. Taken together these beliefs could be conceptualized as (1) schizophrenia is an equalitarian disorder, and (2) schizophrenia is an exceptional disorder [104]. It is puzzling that these two interrelated beliefs are usually cited as evidence for a biologic origin of the disease, when most diseases in medicine do vary across cultures, countries, and gender.

As seen in Table 1 and Fig. 1, the incidence of schizophrenia varies significantly across countries. Another study found the incidence of schizophrenia

varying significantly, with a median value of 15.2 per 100,000 population and with a range of 7.7 to 43 [8]. A review of available data from 31 studies estimates the median male: female ratio to be 1:4 [104]. Two independent meta-analyses, with some overlap in study sampling, have shown men to be at increased risk of developing schizophrenia [8,9].

DISCUSSION

What has been accomplished over the last several decades, and what are prospects for future progress? Even as late as 25 years ago, the epidemiology of schizophrenia was nearly a blank page. There was even argument about the value of the concept itself. The only risk factors that seemed strong and consistent were lower social class and a family history of schizophrenia. Since then there has been considerable progress delineating a more-or-less consistent picture of the descriptive epidemiology and the natural history of schizophrenia. Research in analytic epidemiology has generated a series of heretofore-unsuspected risk factors, as described previously. In general, the risk factors have been considered in the context of theories about how schizophrenia actually might develop in the psychologic and physiologic life of the individual–even if the linkage is sometimes speculative. These developments are healthy.

In the future there will be concerted efforts to study risk factors in combination. This process has begun already. For example, Mortensen and colleagues [105] have studied the combined effects of season of birth, urbanization of birthplace, and family history of schizophrenia. The combination is informative in evaluating the importance of the risk factors. Although the relative risk for urban birth is much smaller than the risk associated with having a parent who has schizophrenia, the importance of urban birth is greater, because a much larger proportion of the population is born in urban areas than to parents who have schizophrenia–the situation of relative versus population-attributable risk [105]. If the causal path connected to urban birth could be identified, the prospects for prevention would be much stronger.

The combination of risk factors will facilitate prospective studies of high-risk individuals for whom the high risk is not simply the result of family history, as in earlier high-risk studies. Furthermore, combination of risk factors will raise the positive predictive value of the risk formulation to the point that it may be ethically feasible to approach individuals, identify the risk, and begin efforts to protect them from the catastrophic effects of the first episode of schizophrenia. Such studies have begun, albeit very cautiously [106–108]. In general, epidemiologic research has built a strong knowledge base over the past quarter century, and this knowledge base will continue to contribute to public health efforts at prevention of schizophrenia in the coming decades.

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