Published in final edited form as:
Psychiatr Clin North Am. 2007 September ; 30(3): 323–338. doi:10.1016/j.psc.2007.04.007.

Epidemiology of Schizophrenia: Review of Findings and Myths

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Abstract

By describing patterns of disease distribution within populations, identifying risk factors, and finding associations, epidemiological studies have contributed to our current understanding of schizophrenia. Advanced paternal age and the association with auto-immune diseases are some of the newly described epidemiological finding in schizophrenia epidemiology, shaping our current definition of schizophrenia. Though early intervention strategies have gained momentum, primary prevention of schizophrenia still seems a very distant aspiration. In this article we review the major epidemiological features of schizophrenia, with particular attention to the recent advances using population-based data. We also discuss some pervasive myths in schizophrenia epidemiology, such as the universal distribution and the gender equality myths. Review of the available evidence shows that schizophrenia does not distribute itself equally across cultures and countries, and the disease is more prevalent among males.

Introduction

The epidemiology of schizophrenia has progressed from descriptive accounts to a surge in analytic epidemiologic findings over the last two decades. This article reviews the epidemiology of schizophrenia, concentrating on results which are most credible methodologically and consistent across studies, focusing particularly on the most recent developments. We also provide comments about some misconceptions regarding schizophrenia epidemiology, specifically pointing to widespread misinterpretation 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 schizophrenia is the proportion of the population at a point in time that has the disorder. The point prevalence of schizophrenia is about five per thousand in the population. The estimate depends on the age distribution of the population– if persons too

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young to be at risk are included in the denominator, for example, the estimates will be lower. Table 1 presents findings from areas in which credible estimates of both prevalence and incidence are available. The range in prevalence in Table 1 is from 2.7/1000 to 8.3/1000, and this range would not be much affected if several dozen other studies, available from prior reviews, were included [1]. Lifetime prevalence has been estimated by surveys with examinations by medically trained persons, with resulting estimates not too different from those shown in Table 11.

Incidence

The incidence of schizophrenia is about 0.20/1000/year. The incidences presented are all estimated for one 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 much affected if several dozens of 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 is usually more than ten times the annual incidence, indicating the chronic nature of the disorder.

There is considerable variation in incidence rates around the world, as shown in Figure 1. The dark bars represent the WHO study of incidence, which reveal a smaller variation, presumably due to the standardization of method [4]. The conclusion of that study suggested to some that there was little or no variation in schizophrenia around the world, which would make schizophrenia a very unusual disease indeed. Figure 1 shows variation greater than one order of magnitude, from a low estimate in Vancouver of .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, where males tend to have a younger onset [7]. The peak incidence for males and females is in the decade 15–24. The peak for young adults is more marked for males, and the females have a second peak in the years 55–64. Evidence suggests that males have higher lifetime risk of schizophrenia, which is born out in two meta-analysis addressing that issue, showing that males have about 30%–40% higher lifetime risk of developing schizophrenia [8, 9].

Analytical epidemiology: Natural History and Risk Factors

Natural History

Onset—The onset of schizophrenia is varied. In the classic long-term follow-up study of Ciompi, about 50% had an acute onset, and 50% a long prodrome. The intensive study of prodrome by Hafner and colleagues [10] suggests onset of negative symptoms tends to occur about five 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 a variety of signs, symptoms, conditions, and behaviors are associated with raised risk for schizophrenia, but none with such strength or uniqueness as to be useful in prediction. Earlier work on high risk (HR) groups has shown that offspring of schizophrenic parents were more likely to have a lower IQ, poor attention skills, thought disorder-like symptoms, poor social adjustment, and psychiatric symptoms as compared to the offspring of controls [10–12]. Although several concerns have been raised regarding the generalizability of HR findings to non- familial forms of schizophrenia, recent longitudinal studies conducted in the United Kingdom, Sweden, Finland, and New Zealand have provided

evidence that individuals with schizophrenia differ from their peers even in early childhood, in a variety of developmental markers, such as the age of attaining developmental milestones [13–15], levels of cognitive functioning [16, 17], educational achievement [13, 18–20], neurological and motor development [21–23], social competence [19, 24], and psychological disturbances [24].:More recent evidence also suggest the association between low IQ is specific to schizophrenia as it was not found in bipolar disorder [25]. It is noteworthy that there seems to be no common causal paths which link these developmental markers with schizophrenia [26]. Indeed, individuals who later develop schizophrenia or related disorders may have already experienced a general or pan-developmental impairment early as in their childhood. Prospectively collected data from the 1972–73 birth cohort in New Zealand, showed that [20] schizophrenic subjects may have suffered a significant deficit in neuromotor, language, and cognitive development in the first decade of their lives. The compelling evidence linking an array of childhood developmental abnormalities and schizophrenia is echoing with the hypothesis that schizophrenia is a neurodevelopmental disorder, for which causes may be traced to a defect in the early brain development [27–30].

Course—The symptomatic course of schizophrenia is varied. In Ciompi's classic study, about half 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 which are not strictly prospective, such as the study by Ciompi, can be deceptive, because there is a tendency to focus on a residue of chronic cases, making the disorder appear more chronic than it actually is. Figure 2 shows data on time to rehospitalization for a cohort of patients with schizophrenia 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 that subgroup of the cohort with ten hospitalizations, more than 90% are rehospitalized within three years following the tenth episode. While it could be that the occurrence of episodes are reinforcing the illness, (so-called "schubweis (stepwise)" process), or that hospitalization itself is damaging [31], it seems more likely the cohort is sorting itself into those with tendency for more versus less chronicity of disorder. This process may lead clinicians and others to overestimate the chronicity of the disorder, since they see individuals in the bottom curve of Figure 2 about fifteen times as often as individuals in the top curve (Cohen and Cohen 1984). For this reason, the natural history of schizophrenia is best studied with cohorts of first onsets [32].

Outcome—Predictors of outcome for schizophrenia remain elusive, for the most part. In a review of thirteen prospective studies of course in first onset cohorts, negative symptoms predicted poor outcome in four studies, and gradual onset, typical of negative symptoms as noted above, predicted poor outcome in several studies [32]. 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 WHO study on this issue (1979), with the right most columns extracted by us from the publication of Leff and colleagues [33]. Those in developing countries are less likely to have been chronically psychotic over the period of follow-up, and more likely to have no residual symptoms after five years, than those in the developed countries. This result remains to be explained. It could be that individuals meeting criteria for schizophrenia in developing countries include a subset destined for better prognosis because of the risk factor structure in those countries—more deaths of compromised fetuses, for example; or a cause connected to good prognosis, such as a parasite which is rare in developed countries. 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 who can share the burden of care for persons with schizophrenia.

The course of schizophrenia, from early prodrome through to later outcome, is influenced by social variables, including socioeconomic position and marital status [34]. The individual who eventually is diagnosed with schizophrenia is more likely to be single than others, even as many as 20 years prior to diagnosis, where the relative odds is about 4. The relative odds of being single, as compared to those never diagnosed with 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 of formation of marriages. Likewise, the individual who eventually is diagnosed with schizophrenia is more likely to be unemployed than others, many years earlier than the first diagnosis of schizophrenia, and many years afterward. Although there is a long literature on the relationship of low socioeconomic position to risk for schizophrenia [35, 36], it seems likely that the association is due to the effects of insidious onset on the ability of the individual to compete in the job market. Recent studies from Scandinavia suggest that, if anything, the parents of persons with schizophrenia are likely to come from a higher, not lower, social position [37].

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. Below are presented risk factors which have found at least in several credible studies and in which it is fairly clear that the risk factor has been present prior to the onset of schizophrenia.

Season of Birth—For a long time it has been known that individuals with schizophrenia are more likely to be born in the winter, and the results have been reported from the samples in 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 [38, 39]. One possible explanation is that the mother is passing through the second trimester of her pregnancy in the height of the flu season, and that infections during that period raise 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 via the interaction with genetic vulnerability [40].

Birth complications—The finding regarding season of birth suggests that something about pregnancy and birth might be awry in individuals who later develop schizophrenia. There have been case-control studies available for decades on this issue, but the generally positive findings were clouded by the possibility that the mother's recall was biased. In the last fifteen years there have been many studies reporting a relative odds of about two for those with one or another sort of birth complication, and several meta-analyses on this topic exist [41–43]. 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, preeclampsia); 2) abnormal fetal growth and development: (low birthweight, 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 epidemiological perspective to include a combination of disciplines and approaches. The complications variously suggest as a possible cause malnutrition [44], extreme prematurity, and hypoxia or ischemia [30, 45–47].

Parental age—The role of advanced parental age in relation to a higher risk of schizophrenia was first proposed in the mid-20th century, and has gained extensive scientific attention in recent years. Based upon the family background data of 1000 patients in the Ontario hospital, Canada, Gregory [48] reported that parents of patients with schizophrenia were, on average, 2–3 years older than those of the general population. However, subsequent investigations showed inconsistent findings [49, 50], and it was argued that observed maternal age-associated higher risk in schizophrenia might be largely confounded by raised paternal age [49, 51]. Recently, several population-based epidemiological studies in Demark, Israel, Sweden, and the United States have provided stronger evidence as to the role of paternal age in schizophrenia [9, 52–56]. 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% CI: 1.60–5.47) in the group aged 55 or above in comparison with the age of 20–24. Additionally, once paternal age is statistically adjusted, maternal age no longer is a significant predictor of schizophrenia. The evidence from one nested case-control study indicates that the paternal age-related excess in the risk of schizophrenia is generally greater in females [55]. In addition, current population-based cohort research tends to support that advancing paternal age-related increased risk of schizophrenia only appears significant among those without family history, indicating the possibility of accumulation of de novo mutations in paternal sperm [57]]

Infections and the immune system—A series of ecologic studies suggest that persons whose mothers were in their second trimester of pregnancy during a flu epidemic have higher risk for schizophrenia {Munk-Jorgensen, 2001 #72; Mednick, 1988 #69; Brown, 2002 #9; Brown, 2004 #153}. Infection during pregnancy as a risk factor is consistent with the neurodevelopmental theory of schizophrenia [28, 58]. Later studies, which are more convincing, include individual assessment of infection, either via comparison of antibodies in adults with schizophrenia versus normal individuals [59], 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 with antibodies to Toxoplasmosis Gondii have higher prevalence of schizophrenia [60]. One study suggests a relative risk of 5.2 for individuals with documented infection by the rubella virus during fetal development [61]. Another prospective study found higher risk for psychosis in individuals whose mothers had higher levels of antibodies to herpes simplex virus [62]. A study in Brazil compared individuals who had meningitis during the 1971–1974 epidemic, with their sibs who did not have meningitis, and found that that the prevalence of psychosis, and schizophrenia specifically, was five times higher in those who had meningitis. The finding is intriguing because the average age of infection with meningitis was 26 months, i.e., much later than prenatal infection [63]. 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 with schizophrenia have unusual resistance or susceptibility to autoimmune diseases. Studies have consistently shown that individuals with schizophrenia are somehow less likely to have rheumatoid arthritis [64]. While it could be that medications for schizophrenia are protective for rheumatoid arthritis in some unknown way, some of the studies were conducted prior to the era in which neuroleptic medications were available. It could be that other physiologic consequences of schizophrenia are protective, or it could be that a single gene raises risk for the one disorder and protects for the other. A single small study suggests that mothers of individuals with schizophrenia have lower risk for rheumatoid arthritis, but it's size and quality are not convincing [65]. It is intriguing, in this regard, that case control studies have shown that persons taking non-steroidal anti-inflammatory medications, which primarily treat arthritis, may be protected from dementia [66, 67].

Other autoimmune disorders have been linked to schizophrenia, including thyroid disorders [68], type 1 diabetes [69], and celiac disease [70]. Currently the evidence is strongest for thyroid disorders and celiac disease. In a study from the Danish population registers, persons whose parents had celiac disease were three times as likely to later be diagnosed with 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 increasing risk of autoimmune response. It is also possible that gluten proteins are broken down into psychoactive peptides [71].

The results linking schizophrenia to autoimmune disease are paralleled by the clinical and laboratory study of autoimmune processes in schizophrenia. There are apparently abnormalities of the immune system in schizophrenia, but it is not clear whether these are causal or a consequence of schizophrenia or its treatment [72]. It is possible that a single weakness in the immune system in those with schizophrenia explains both the data on infections and the results on autoimmune disorders, but this remains to be proven [73]. Meanwhile, there are ongoing clinical trials of anti-inflammatory [74] and antibiotic [75] agents for schizophrenia.

Ethnicity—Ethnic status is a relatively easy to identify characteristic of an individual which 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 ten times higher than those in the general population [76]. Since immigrant groups who do not have black skin do not have higher rates, and since the second generation is affected, it is unlikely to be the stresses of immigration. Since rates in the countries of origin are not elevated it is unlikely to be a genetic difference between races. The cause appears to be the psychological 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 [77, 78].

Cannabis Use—There are numerous case control studies showing that persons with schizophrenia are more likely to have taken, or be using, cannabis [79]. Recently there have been prospective studies in Sweden, the Netherlands, New Zealand, and Israel, showing higher risk ranging from 2 to as high as 25 [80–83]. It could be that individuals in the premorbid phase of schizophrenia are 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 [84–89].

Urban residence—In the 1930's Faris and Dunham showed that, while 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 (1939), with decreasing rates as one moves outward into zones of transition, working class, and family. This finding, and other similar findings [90], were interpreted as due to the selection into the city of individuals who would develop schizophrenia. But later studies from Europe were strictly prospective, with the cohort defined in late adolescence, well prior to onset [91], or even at birth [92]. The relative risk is about 2–4 times higher for those born in urban areas. The difficulty is identifying the plausible biological 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 to leave the family of origin and define a new life plan [77], differences in birth practices, such as breastfeeding [93], crowding which might permit spread of infections [94], discussed below, differences in the manner in which animals are, or are not, brought into the household [95] and a host of other factors [96].

Myths in schizophrenia epidemiology

In recent years reviews have yield a reconsideration of some widely cited, but poorly supported by evidence, aspects of schizophrenia epidemiology [97]. 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 [97]. It is puzzling that these two interrelated beliefs are usually cited as evidence for a biological origin of the disease, when most diseases in medicine do vary across cultures, countries, and gender.

As seen in Table 1 and Figure 1 this paper, 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, with a range of 7.7 to 43 [8]. Regarding the male to female rate ratio, a review of available data from 31 studies, estimate the median rate to be 1.4:1 [97]. Regarding the gender ratio in schizophrenia, two independent meta-analyses, with some overlap in study sampling, have shown increased risk for men in schizophrenia [8, 9].

Discussion

What has been accomplished over the last several decades, and what are prospects for future progress? Even as late as one-quarter century ago, the epidemiology of schizophrenia was nearly a blank page. There was even argumentation about the value of the concept itself. The only risk factors which seemed strong and consistent were the conditions of lower social class life, and the family history of schizophrenia. Since that time, 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 above. In general, the risk factors have been considered in the context of theories of how schizophrenia might actually be developing in the psychological and physiological 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 et al 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 are born in urban areas than the proportion with parents who have schizophrenia—the situation of relative versus population-attributable risk (Mortensen et al. 1999). 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, in which the high risk is not simply due to 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 where it may be ethically feasible to approach the individual, identify the risk, and begin efforts to protect them from the catastrophic effects of the first episode of schizophrenia. Studies such as these have begun, albeit very cautiously (McGorry et al. 1996; Tsuang et al. 1999; Woods et al. 2003). 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.

Acknowledgments

Supported by NIMH Grant #53188

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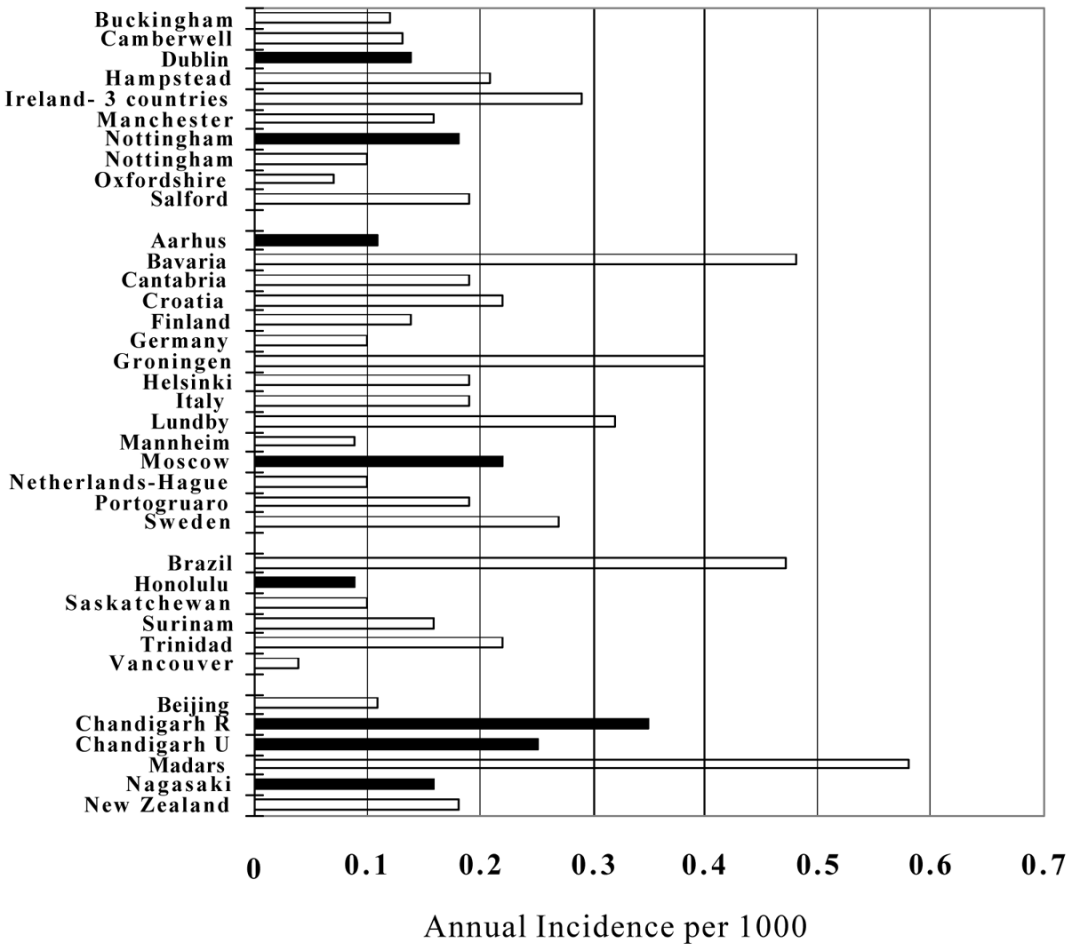

FIGURE 1. Incidence of Schizophrenia in Selected Studies published after 1985

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.

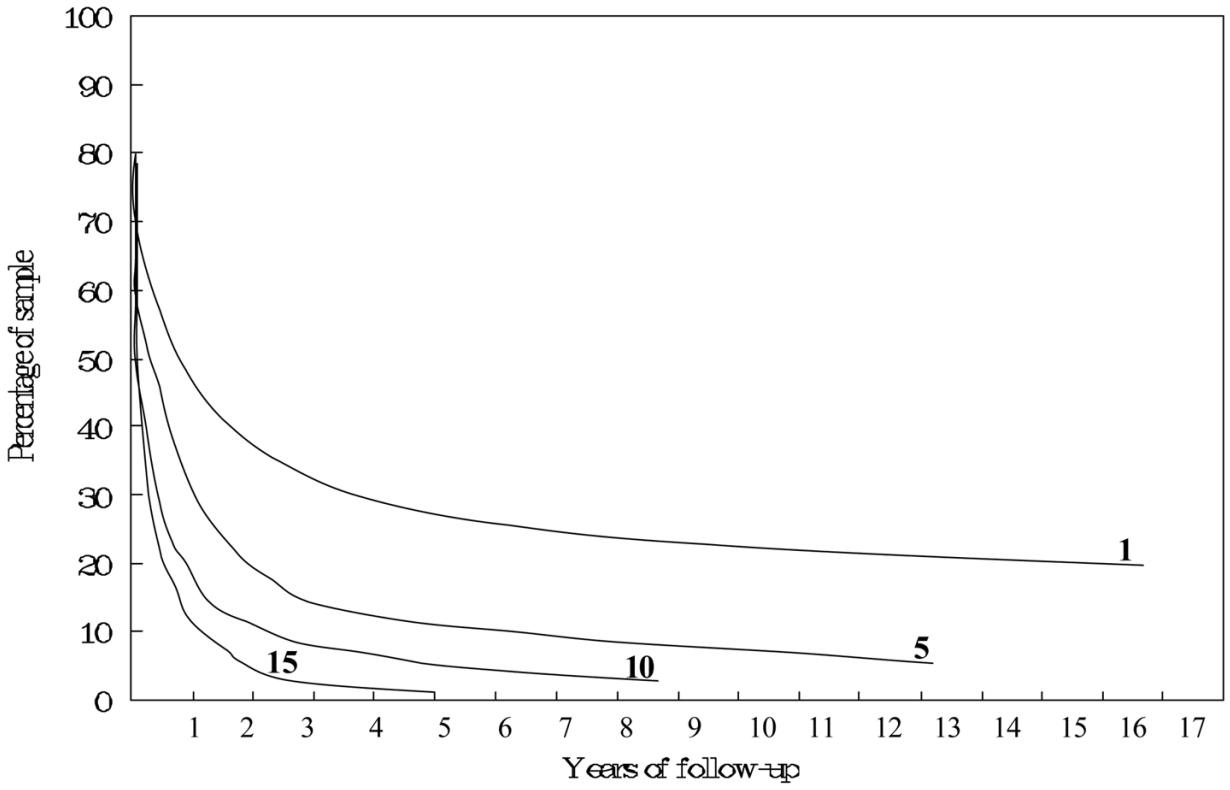

FIGURE 2. Community survival in schizophrenia (1, 5, 10, and, 15 represent the number of hospital discharges)

Source: Mortensen and Eaton (1994).

TABLE 1

Prevalence and incidence of Schizophrenia per 1000 population.

Area	Date	Author	Age	Prevalence		Incidence
				Type	Rate	
Denmark	1977	Nielsen	15 +	Lifetime	2.7	
	1972	Munk-Jorgensen	All	Annual		0.12
Baltimore, Maryland, USA	1963	Wing	All	One 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	WHO	15–54	Annual		0.22
Portogruaro, Italy	1982–9	de Salvia et al.			2.7	
	1989	de Salvia et al.		Annual		0.19
Hampstead, England	1991–5	Jeffreys et al.			5.1	
	1991–5	McNaught et al.		Annual		0.21

Selected from reviews by Eaton (1985, 1991), with additions of Jeffreys et al. (1997), McNaught et al. (1997), and de Salvia et al. (2000).

TABLE 2

WHO Followup of Schizophrenia.

Developed Countries	**Sample size**	**Percent with no symptoms**	**Percent with chronic psychosis**
London, England	50	6	40
Aarhus, Denmark	64	5	14
Moscow, Russia	66	17	21
Washington, D.C., USA	65	6	23
	51	3	23
Developing countries			
Agra, India	73	42	10
Cali, Colombia	91	11	21
Ibadan, Nigeria	68	34	10

Source: Leff et al. (1992).