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Epidemiology of schizophrenia – An update with a focus on developing countries

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Abstract
Developments over the past few decades in analytical epidemiological research in schizophrenia have challenged some long-held views about the disorder. For example, the conventional view that schizophrenia may have a favourable outcome in developing countries is currently being challenged by emerging empirical data. However, quality research from developing countries is still relatively scarce. In this article we review some major epidemiological findings of schizophrenia with a focus on data from the developing world and within the context of the methodological issues and challenges associated with such studies.

Introduction

Understanding the epidemiology of a disorder is crucial not only to describing the occurrence and aetiology of the disorder, but also for providing sign posts for care, health service planning, and a basis for developing, prioritizing, and evaluating interventions. The measurement of health and disease is fundamental to the practice of epidemiology because it uses a range of health measures to characterize and determine the health status of a population. These measures include incidence, prevalence, mortality rates, and natural history of diseases, their outcomes and the risk factors associated with the diseases, among other measures.

As noted by several commentators, the epidemiology of schizophrenia is characterized by a multiplicity of variations (Kirkbride et al., 2006; McGrath et al., 2004; Saha et al., 2005, 2008). These variations have important relevance for clinical care, health service planning and public health. While the variations according to genetic risk (Gottesman & Gould, 2003; O'Donovan et al., 2009; Sullivan et al., 2003), family history of mental illness (Cardno et al., 1999; Mortensen et al., 1999, 2010), and reduced incidence with advancing age (Hafner et al., 1993; Malaspina et al., 2001) are well established, variations by season of birth (Schwartz, 2011), exposure to infections during pregnancy (Boksa, 2008), Rhesus factor incompatibility (Hollister et al., 1996), maternal starvation during pregnancy (Malaspina et al., 2008), migrant status (Cantor-Graae & Selten, 2005; Coid et al., 2008), urban/rural birth or residence, place of upbringing (Mortensen et al., 1999), minority status (Cantor-Graae & Selten, 2005; Coid et al., 2008) and economic status of country (Saha et al., 2005) continue to generate controversies (McGrath, 2006).

Particularly important is the relationship between the variation and the economic/development status of a country. Countries have been classified by major international organizations such as the World Bank, the World Health Organization (WHO), the International Monetary Fund (IMF) into different categories based on several factors. In 2010, the World Bank classified countries according to the 2008 Gross National Income (GNI) per capita (GNI per capita is the dollar value of a country's final income in a year, divided by its population). The four groups are low income, lower middle income, upper middle income, and high income. The low income and middle income economies are sometimes referred to as developing economies/countries (as in this paper). A country's GNI per capita is linked to the health status of its inhabitants and the quality of research that emanates from it. Conducting research on the epidemiology of schizophrenia and other psychiatric disorders in developing economies/countries is associated with numerous challenges which may

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impact on the validity of the findings from such studies. Limitation of resources has meant that not many studies from these countries have investigated the epidemiology of major psychiatric disorders, and when they do, the focus has often been on relatively small clinical rather than large community samples (Alem & Kebede, 2003). A consequence of the resource limitation is the gross under-representation of research from the developing world in the international psychiatric literature (Patel & Sumathipala, 2001; Saha et al., 2006). Apart from issues related to resource constraints, conducting valid psychiatric research in developing countries is more complicated than in developed countries because many existing ascertainment tools for mental disorders have been developed in western cultures and their direct translation into local languages often results in questionable validity indices of such instruments.

In this review we focus on the epidemiology of schizophrenia with a particular attention to data from developing countries. The review examines incidence, prevalence and the outcome of the disorder within the context of the methodological issues and challenges associated with such studies.

What is schizophrenia?

Schizophrenia is characterized by a diverse array of symptoms affecting emotion, affect, behaviour, perception, thought, speech, motor activity. No specific symptom is found in every case but some symptoms are more characteristic than others. Symptoms include abnormal experiences such as hallucinations, which are commonly auditory or visual but could occur in other sensory modalities, and delusions, which are commonly persecutory but could also be grandiose, nihilistic or bizarre. In general, features of the disorder characterized by a distortion of thinking or of perception or by disorganized behaviour or speech are regarded as positive symptoms. On the other hand, those that are indicative of a loss of functions such as bluntness or flatness of affect, poverty of thought and speech, social withdrawal and loss of motivation are regarded as negative symptoms. Other symptoms may affect behaviour, speech, cognition as well as motor and coordination problems such as excitement, retardation and posturing.

Diagnosis is often made on the basis of criteria specifications in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) by the American Psychiatric Association or the *International Classification of Diseases*, 10th edition (ICD-10) by the WHO. Other than difference in the specification for duration of symptoms to meet the requirement for diagnosis, 6 months for DSM-IV and 1 month for ICD-10, both classification systems share substantial similarities in requiring the presence of symptoms from a list that includes delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, and negative symptoms of affective flattening, alogia, or avolition. In general, the diagnosis of schizophrenia requires considerable clinical skills because there are no pathognomonic signs or symptoms and no physical of laboratory tests provide useful hints of diagnosis.

Prevalence

Prevalence estimates vary according to the temporal criteria used (i.e. point-prevalence period-prevalence, or lifetime prevalence). Such estimates are more useful in the study of the burden of chronic diseases than incidence estimates. Point prevalence refers to the proportion of the population with a disease on a specified day; period prevalence refers to the proportion with the disease during a particular time frame (e.g. 3, or 6, or 12 months), while the lifetime refers to the proportion that ever had the disease at any time during their life. Several factors influence the prevalence of a disease. These include the incidence of the disease, duration of the disease, differential mortality, migration pattern, improved diagnostic facilities, and case fatality rate associated with the condition.

As reported in several reviews, there is variability in the prevalence of schizophrenia (Saha et al., 2005; Torrey, 1987). In a systematic review by Saha et al. (2005) which included 1,721 prevalence estimates from 188 studies and 46 countries, the median and respective 10–90% quantiles for the point prevalence, period prevalence and lifetime prevalence estimates were 4.6 (1.9–10.0), 3.3 (1.3–8.2) and 4.0 (1.6–12.1) per 1,000 individuals, respectively. In the same review, analysis based on economic status of sites which included 19 estimates from the least developed countries and 96 estimates from developed countries showed that the mean prevalence and 10–90% quintile in developing countries was 1.64 (0.22–6.46) per 1,000 individuals. The mean prevalence estimate from less developed countries was significantly lower than the estimate from developed countries which was 7.67 (1.54–12.00) per 1,000 individuals. However, the authors urged for caution in the interpretation of the results because the use of a single economic variable to assess a complex and multidimensional concept may be rather crude (Saha et al., 2005). Several other studies from developing countries show a wide range of variability in case finding, diagnosis and results. For example in the Dominican Republic a high prevalence of 8.5 per 1,000 was found using a computerized case register compiled with a portable MS-DOS computer

and augmented by key informant interviews to determine the prevalence of psychotic disorders (Kay, 1990). In Botswana a 1-year prevalence of schizophrenia amongst individuals aged 15 years or older living in six villages in a remote area of Botswana yielded a prevalence estimate of schizophrenia of 5.3 per 1,000 using ICD-9 criteria, and 4.3 per 1,000 using DSM-III. All cases were diagnosed independently by two psychiatrists (Ben-Tovim & Cushnie, 1986). In Ethiopia, weighted lifetime and 1-month prevalence of schizophrenia were 4 and 3 per 1,000 individuals, respectively, using an Amharic version of the Composite International Diagnostic Interview (CIDI) to collect data from a random community sample of 1,420 individuals (Kebede & Alem, 1999). However, a similar study among the Borana semi-nomadic people in southern Ethiopia that included 1,854 people found no case of schizophrenia. The interviews in the Borana study were conducted by trained high school graduates using the Oromiffa version of the CIDI (Beyero et al., 2004). In order to further explore this finding (of no cases of schizophrenia) and also investigate how serious mental disorder was conceptualized in that cultural setting, the investigators changed the methodology by combining structured interviews with key informant interviews. They also conducted focus group discussions with key members of the Borana pastoralist community. Subsequently, focus group participants were used as key informants to identify cases with possible psychotic disorder, based on their conceptualization. Cases identified by key informants were interviewed by a trained psychiatrist using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) to confirm presence of disorder. Using this approach, participants were able to identify eight individuals with schizophrenia which was confirmed by SCAN interviews (Shibre et al., 2010).

In Thailand a prevalence of 8.8 per 1,000 was reported in a community mental health survey that was supplemented by a count of hospital admissions. Other studies on the prevalence of schizophrenia from developing countries and the corresponding results per 1,000 population at risk include those from Taiwan (2.1) (Rin & Lin, 1962), Iran (2.1) (Bash & Bash-Liechti, 1969), India (2.6) (Dube & Kumar, 1972) Indonesia (1.4) (Salan, 1992), and Kosrae 6.8 (Waldo, 1999). It should be noted that in these estimates there were differences in the profile of the populations studied and the methodology used to generate the estimates (Jablensky, 2000). For example, while the study in Indonesia used a two-stage survey, with key informant interviews, the investigators in the Kosrae study combined key informants and clinic records with some interviews.

Incidence

The incidence of a disease represents the rate of occurrence of new cases arising during a given period in a particular population. Incidence, which unlike prevalence is a rate, is more useful in examining changes in disease risk in different populations over time. Incidence is better than prevalence estimates at examining causal relationships. For this reason, incidence is useful in the development of effective prevention and early intervention. While studies to determine the prevalence of schizophrenia are relatively cheap and require fewer subjects, studies that examine incidence are very costly, time-consuming and could be complicated by loss to follow-up. As such, valid incident studies are less common than prevalence studies in developing countries. To estimate the incidence of a disorder, the use of retrospective data analyses is common in many developing countries since many lack adequate vital-event registration system. This, however, is subject to recall bias, especially since many of the populace are not literate. Despite the aforementioned challenges, there are some research findings about the occurrence of schizophrenia from developing countries that have contributed to our understanding of the disorder.

A systematic review of the incidence of schizophrenia which included data from 161 studies drawn from 33 countries spanning 35 years and which generated 1,458 rates placed the median value (10–90% quintile) of the incidence of schizophrenia at 15.2 per (7.7–43.0) per 100,000 (McGrath et al., 2004). Another study based on analyses of 167 discrete incidence rates from 52 studies, in which countries were divided into three categories according to per capita gross national product (GNP) showed that the median (and 10–90% quantiles) incidence rates per 100,000 individuals for developing countries was 20.0 (0.4–35.0) (Saha et al., 2006) . There was no significant difference between this median incidence and that derived for developed countries (16.0 (8.0–48.0)). However, in this study, the rates from developing countries were generated from four studies compared to 42 studies from the developed countries, thus confirming the paucity of information on the incidence of schizophrenia from the developing world. While Saha et al. (2006) found no significant difference in incidence rates between developing and developed countries, the WHO 10-country study found significant differences between the incident rates for the 'broad' diagnostic category of schizophrenia in the different centres (Jablensky et al., 1992). Based on 'broad' diagnostic criteria, the incidence of broadly defined schizophrenia was highest in India.

Outcome

One issue that has generated a lot of debate in the epidemiology of schizophrenia is the finding of a better course and outcome in patients with schizophrenia from developing countries when compared to those of patients from developed countries. Several studies and reviews suggest that the course and outcome is considerably more favourable in patients from developing countries (Bhugra, 2005; Hopper & Wanderling, 2000; Jablensky et al., 1992; Messias et al., 2007; Sartorius et al., 1977, 1986). However, emerging evidence from some developing countries has started to challenge this long held view (Cohen et al., 2008). One such is a study of the 5-year clinical course and outcome of schizophrenia in Ethiopia (Teferra et al., 2012). The findings from this study showed that the 5-year outcome was unfavourable for a large proportion of the patients. At least 45% of the participants were continuously symptomatic over the period. This unfavourable outcome was consistent with an earlier short-term (2-year) outcome in the same cohort. In another study (Alem et al., 2009) in Ethiopia the investigators followed up the participants for a mean duration of 3.4 years and found that about a third (30.8%) of cases were continuously ill while most of the remaining members of the cohort experienced an episodic course. Only 5.7% of the cases attained a near-continuous complete remission, and in the final year of follow-up over half of the cases (54%) were in psychotic episode. Even worse outcomes have been reported in other studies. For example, also in Ethiopia Kebede et al. (2003) reported that of the 321 cases of schizophrenia in a follow-up study, over 80% had negative symptoms and over 67% reported continuous course of the illness.

Several studies have attempted to explain the differential outcome in earlier reports between developed and developing countries that suggested a better outcome in the latter. Hopper and Wanderling (2000) examined six sources of bias in the WHO collaborative project, the International Study of Schizophrenia (ISoS): differences in follow-up, arbitrary grouping of centres, diagnostic ambiguities, selective outcome measures, gender, and age. The authors concluded that none of these potential confounders explained the differences in course and outcome between developing and developed countries. Also, Bresnahan et al. (2003) have suggested that the most common explanations for the differential outcome could fall into four categories: family relationships, informal economics, community cohesion, and segregation of the mentally ill. The authors were of the opinion that developing countries better serve those with schizophrenia than developed countries and that the contrasting experiences of developed and developing countries with respect to schizophrenia may be interpreted as providing evidence for socio-environmental influences on this disorder. Furthermore, in a review by Messias et al. (2007), the authors noted that subjects in the WHO follow-up study from developing countries were less likely to have been chronically psychotic over the period of follow-up and more likely to have no residual symptoms after 5 years than those from developed countries. The authors suggested that "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" (Messias et al. 2007. p. 325).

A possible explanation for the differential outcome may be the effect of misclassification of cases of acute and transient psychotic disorders (ATPD) as schizophrenia in the cohort from developing countries in the WHO international study on schizophrenia. As suggested by Messias et al. (2007), ATPD is a subset of non-affective psychotic disorder destined for better outcome. Though clinically similar to schizophrenia in presentation, they have been shown to generally have a good outcome (Marneros et al., 2003; Pillmann & Marneros, 2005; Singh et al., 2004) and are also relatively more common in developing countries. The incidence of ATPD in developing countries has been shown to be up to 10-fold the incidence in industrialized countries (Susser & Wanderling, 1994) . For ATPDs, the ICD states 'complete recovery usually occurs within a few months, often within a few weeks or even days.' In the WHO collaborative study on determinants of outcome of severe mental disorders, the screening inclusion criteria (Sartorius et al., 1986) accommodated cases of ATPD while the exclusion criteria did not exclude ATPDs. It could be argued that the same criteria were used both in developed as well as developing countries. However, the 10-fold difference in the epidemiology between developing and developed countries could make a significant difference between outcome in the two groups. Sartorius et al. (1986) showed that 49% of the patients in developing countries had an acute onset compared with 26% from developed countries. The reverse was true for cases with slow onset; 43% were from developed countries and 27% from developing countries. This may also suggest that the cases with acute onset had substantial representation in the cohort from developing countries, especially since according to the authors, the type of onset (i.e. acute, subacute and gradual) and the setting (developing versus developed) were the most important predictors of several dimensions of course and outcome in the study (Jablensky et al., 1992). Apart from the aforementioned issues, one of the case finding/screening

criteria in the WHO study required that the cohort had made a first contact with any 'helping agency' because of problems suggesting the presence of a psychotic disorder. While it may be common for people in developing countries to seek help on account of positive psychotic symptoms such as hallucination and delusions, it is unlikely that family members would seek help for negative symptoms. This means that cases that might have a poorer outcome would have been excluded from the cohort. Furthermore, in the IPSS study, catatonia was diagnosed in 10% of cases in developing countries compared with less than 1% in developed countries (Bhugra, 2005). It is becoming increasingly clear that catatonia is more commonly a consequence of mood disorders than of schizophrenia (Pommepuy & Januel, 2002).

As recently noted by Gureje (Gureje & Cohen, 2011) outcome of schizophrenia remains a topic of interest not just because the prognosis of a disorder is an important clinical issue for patients, providers and caregivers, but also because in psychiatry the course and outcome of psychopathology remain important parameters for their delineation into disorder categories in existing classifications. In regard to the likelihood that the course and outcome of schizophrenia are affected by the developmental status of the country of residence of those affected, there is still a considerable gap in our knowledge.

Conclusion

Schizophrenia is one of the most serious disorders affecting humans. Our knowledge of the epidemiology of disorder has improved substantially in the past few decades, with evidence suggesting that some previously held views about its epidemiology were not exactly accurate. Still, there remain important gaps in the literature, especially in developing countries. These can only be filled with more population-based studies using widely accepted and validated ascertainment tools. Knowledge of the epidemiology of the disorder, especially when derived from diverse groups with differences in exposure to putative risk factors, may help throw light on the etiology of the disorder and provide insight to possible preventive measures.

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