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Questioning an Axiom: Better Prognosis for Schizophrenia in the Developing World?

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Introduction: **That schizophrenia has a better course and outcome in developing countries has become an axiom in international psychiatry. This is based primarily on a series of cross-national studies by the World Health Organization (WHO). However, increasing evidence from other research indicates a far more complex picture.** ***Methods:*** **Literature review and tabulation of data from 23 longitudinal studies of schizophrenia outcomes in 11 low- and middle-income countries.** ***Results:*** **We reviewed the evidence about the following domains: clinical outcomes and patterns of course, disability and social outcomes (marital and occupational status, in particular), and untreated samples and duration of untreated psychosis. Outcomes varied across the studies and the evidence suggests a need to reexamine the conclusions of the WHO studies. Additionally, assessments of outcomes should take excess mortality and suicide into account.** ***Conclusions:*** **It is time to reexamine presumed wisdom about schizophrenia outcomes in low- and middle-income countries.**

Key words: longitudinal studies/cross-cultural psychiatry/schizophrenia

Introduction

That schizophrenia has a better course and outcome in countries of the developing world has become an axiom in international psychiatry.[1–5] This belief emerges from a long history of cross-national research,[6–9] with the most often cited evidence coming from 3 studies by World Health Organization (WHO): the International Pilot Study of Schizophrenia,[10] the Determinants of Outcome of Severe Mental Disorder (DOSMeD),[11] and the International Study of Schizophrenia (ISoS).[12] These studies have been cited as "arguably the greatest achievements in psychiatric epidemiology,"[13] and their results as constituting "the single most important" finding in cross-cultural psychiatry.[14] No doubt the recent publication of the final ISoS report[15] will bolster convictions in the "better prognosis" hypothesis and may lead to the conclusion that further examination of the question is not necessary. This would be unfortunate given increasing evidence, which presents a far more complex picture. In this review of research conducted independently of the WHO studies, we examine clinical outcomes and patterns of course, disability and social outcomes, and mortality and suicide in people with schizophrenia living in low- and middle-income countries. We also consider evidence about the role of families, gender effects, and the implications of evidence concerning persons with schizophrenia who have not received biomedical treatment.

Methods

To locate research on schizophrenia outcomes in developing countries, we conducted searches of PubMed and PsycInfo using the following keywords: schizophrenia, psychosis, outcome, and developing countries. This strategy identified only a limited number of studies, and we came to rely on a combination of keyword and author searches, as well as tracking down references cited in research reports, a strategy similar to the one used by Bromet et al.[16] Inclusion criteria were research site in a low- or middle-income country (as defined by the World Bank[17]), minimum of 1-year follow-up (either prospective or retrospective), and English language. We did not use the developing/developed country variable because it is difficult to operationalize.[18,19]

Following this strategy, we found published reports from 23 research projects on schizophrenia outcomes in 11 low- and middle-income countries (Brazil, Bulgaria, China, Colombia, Ethiopia, India, Indonesia, Jamaica, Nigeria, South Africa, and Trinidad—see tables 1 and 2), a greater diversity of sociocultural environments than represented in ISoS. The identified studies were prospective and retrospective, had follow-up periods

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Table 1. Prospective Studies of Schizophrenia Outcomes in Low-Income Countries

Site	Follow-up (y)	Sample Type	Baseline (*N*)	Lost to Follow-up (%)	Mortality (%)	Follow-up (%)
São Paulo, Brazil[37,38,52,64]	2	Hospital	124	11.3	5.6	83.1
Sichuan, China[29,51,61,81]	10[a]	Community	510	7.8	19.2	72.9
Butajira, Ethiopia[32,33,42]	1–4	Community	321	15.6	10.3	84.4[b]
Chandigarh, India[27]	4.5–6+	Clinic	174	35.1	7.5	57.5
Chandigarh, India[28,82]	1.5–2.5	Clinic	112	16.1	2.7	81.2
Multisite study, India[22,25,83]	2	Clinic	386	11.9	4.4	83.7
Multisite study, India[22,26,84]	5	Clinic	386	NA	NA[c]	74.4
MLS,[d] India[21,30,31,44,45,85,86]	10	Clinic	90	5.6	10.0	84.4
MLS, India[20]	20	First episode Clinic	90	14.4	17.8	67.8
Chennai,[e] India[36,43,46]	1	First episode Community	49	0.0	0.0	100.0
Rural Karnataka, India[41]	1.5	Community	100	1.0	6.0	93.0
Bali, Indonesia[23,54]	11[f]	Hospital	59	1.7	20.3	78.0
Jamaica[39,87]	1	Community	317	2.8	0.9	96.2
Ilesa, Nigeria[53]	2.1–3.2	First episode Hospital	116	11.2	7.8	81.0
Cape Town, South Africa[47]	2	Hospital	57	15.8	NA	84.2
Trinidad[88]	1	First episode Community	46	6.5	NA	93.5
WHO studies		First episode				
Sofia, Bulgaria[15]	16	First episode	60	5.0	3.0	91.7[g]
China[15]	12	First episode	89	12.4	22.5	65.2
Cali, Colombia[15]	26	Clinic	101	16.8	11.9	71.3
Agra, India[15]	26	Clinic	140	25.7	30.7	43.6
Chandigarh (rural), India[15]	15	First episode	54	13.0	18.5	68.5
Chandigarh (urban), India[15]	15	First episode	155	39.4	9.0	51.6
Ibadan, Nigeria[11]	2	First episode	142	31.0	NA	69.0

Note: MLS, Madras Longitudinal Study; NA, not applicable.
[a]Outcomes based on 2-y follow-up of untreated subjects, mortality based on 10-y follow-up.
[b]Eighteen cases who had died were included in follow-up analyses.
[c]By year 5, 12 subjects (3.1%) had committed suicide.
[d]Results from this study included in International Study of Schizophrenia.
[e]Survey identified 265 persons with schizophrenia. Of these, 75 had never received treatment. Of this subsample, 49 accepted treatment and were followed-up.
[f]Five-year retrospective study served as baseline.
[g]Forty percent of subjects included were not interviewed. Follow-up assessments were based on medical records.

ranging from 1 to 20 years, included prevalent and first-episode cases, and drew samples from a variety of settings (outpatient clinics, hospital samples, and communities). Twelve of the studies followed 100 or more subjects. Rates of attrition (not due to mortality) were generally low to moderate in most of the prospective studies.

The heterogeneity in types of samples, follow-up periods, and outcome measures made it impossible to conduct meta-analyses. Our results are based on a reading of the research reports, tabulations of the available data, and interpretations of the evidence. To provide a basis for comparison, we have included data from the following ISoS sites—Bulgaria, China, India (Agra, urban Chandigarh, and rural Chandigarh), and Colombia. To represent WHO research in Nigeria, we include data on 2-year outcomes in the DOSMeD site in Ibadan.[11] Even though the Madras Longitudinal Study (MLS)[20,21] was included in ISoS, we have listed it as a separate study because it was conducted independently of the WHO research. Data for MLS are taken from reports in journals and not from the ISoS publication. Madras is the former name for Chennai. Hong Kong was excluded because it is classified by the World Bank as a high-income country.[17]

Three studies, the Indian Multisite Study,[22] the MLS, and the one in Bali, Indonesia,[23,24] have published results from different follow-up periods. To provide as much detail as possible about these cohorts, data from each follow-up period are presented separately in the tables. It should also be noted that the MLS cohort was originally part of the Multisite Study, and that the research in Indonesia began as a 5-year retrospective study and then prospectively followed the cohort for another 6 years. Therefore, data about the same subjects are sometimes presented in more than one place in each of the tables.

Table 2. Retrospective Studies of Schizophrenia Outcomes in Low-Income Countries

Site	Follow-up (y)	Sample	Baseline (*N*)	Lost to Follow-up (%)	Mortality (%)	Follow-up (%)
Bali, Indonesia[24,89]	5	Hospital	59	1.7	11.9	86.4
Lagos, Nigeria[90]	2	Hospital	23	NA	NA	NA
Ibadan, Nigeria[63]	7–26	Hospital	142	NA	NA	NA
Abeokuta, Nigeria[35]	13	Clinic	140	14.3	NA	85.7

Note: NA, not applicable.

Results

Clinical Outcomes and Patterns of Course

Tables 3 and 4 summarize the evidence on clinical outcomes and patterns of course. Most notable is the wide variation across studies. First, the proportion of individuals who experience chronic pattern of course ranges from 4.5% (over 5 years) in the Multisite Study in India[22,25,26] to 51.7% (over 12 years) in the ISoS China sites.[15] Second, there is variation in the proportion of individuals who are assessed as suffering from severe or chronic psychotic symptoms at follow-up: from a low of 0.0% or 5.0% in the ISoS Chandigarh rural and urban sites, respectively, to 29.2% in the ISoS China sites,[15] to more than 30% in 2 earlier studies in Chandigarh.[27,28] At 2-year follow-up, 77.9% of the cohort in rural China were assessed as experiencing either ''continued marked symptoms'' or ''further deterioration of illness.[29] Third, impressions of patterns of course may change over time. This is apparent in 2 Indian studies. At 2-year follow-up, the overall patterns of course for subjects in the Multisite Study[22] were Best (45.2% complete recovery or no relapses), Intermediate (44.3% $\geq$1 relapses with complete or incomplete remission), and Worst (10.5% chronic psychosis). By 5-year follow-up, the proportion of subjects categorized as having Best pattern of course had fallen to 28.2%, and the proportion in the Worst category had fallen to 4.5%. In contrast, the proportion of subjects categorized as having an Intermediate pattern of course had increased to 67.2%. In other words, over time, some subjects in the Best category experienced relapses and some subjects in the Worst category experienced improvement. At the end of the Multisite Study, the Madras cohort continued to be followed in the MLS.[20,21,30] At 10-year follow-up, the cohort displayed a continued shift of more subjects into the Intermediate category: Best, 17.1%; Intermediate, 76.3; Worst, 6.6%. At 20-year follow-up, 16.4% of subjects were evenly divided into the Best and Worst categories, while the proportion in the Intermediate category had increased to 83.6%. Thus, although relatively few individuals experienced chronic symptoms, over time the majority experienced relapse.

Disability and Social Outcomes

Tables 5 and 6 summarize the evidence on disability and social functioning. Once again, there is wide variation. In India and Indonesia disability and social outcomes tend to be good, while those in China, Brazil, and Ethiopia tend to be poor.

Variation Is Also Found in Two Specific Domains: Marriage and Employment

In high income countries, persons with schizophrenia have been found to have low rates of marriage. As a consequence, there is often an implicit assumption that high rates of marriage among persons with schizophrenia is an indicator of sociocultural environments that promote better course and outcome.[31] Table 7 summarizes the data we found about marital status. If one looks at the category ''ever married,'' most rates are relatively high: Ethiopia (70.0%),[32–34] Nigeria (60.8%[35]), Indonesia (63.0% at 11-year follow-up[23]), and Chennai, India (60.9%[36]and 69.7%[30]). However, rates of marriage at times of assessment were well below those for the respective general populations (table 7). Furthermore, separation and divorce were fairly common for subjects in a number of cohorts—Brazil (15.4%),[37,38] Ethiopia ($\approx$17.9),[32,33] and Chennai (39.6%)[36]—and much higher than those of general populations. A retrospective study in Nigeria[35] found that 27.5% of the sample had experienced marital breakup while 39.2% had never been married. Regarding men, a large majority (66.1%) had never married. Gureje and Bamidele[35] note, ''The finding that less than 40% of the male sample with a mean current age of about 36 years had ever married is indicative of severe social disability.'' At the same time, 42.6% of ''ever married'' women had experienced divorce or separation, a rate about 16 times greater than that of the general population.

Employment status is also considered an important measure of disability in schizophrenia,[39] and the extent to which societies offer opportunities for gainful employment, and thus, social reintegration is thought to be associated with course and outcome.[40] Table 8 summarizes data on employment and household work. Even within India, the

Table 3. Clinical Outcomes or Patterns of Course, Prospective Studies

Site	Psychiatric Assessment	Follow-up (y)	• Clinical Outcomes ○ Patterns of Course (%)
Jamaica[39]	PSE	1	○ 13: 1-y relapse rate
Trinidad[88]	PSE	1	• 19.6: Poor outcome[a]
Chennai,[b] India[43,46]	PSE PHSS	1	• 28.6: Complete recovery without relapse or exacerbation
Rural Karnataka, India[41]	PANSS	1.5	• Much improved[c]
São Paulo, Brazil[64]	PSE	2	• 23.8: Symptom free • 60.2: ≥1 psychotic symptom
Sichuan,[d] China[29]	PSE	2	• 22.1: Complete/partial remission • 71.6: Continued marked symptoms • 6.3: Further deterioration of illness
	GPIS		○ 8.3: Relapse rate per year
Multisite study, India[22,25,26]	PSE PPHS	2	○ 45.2: Complete recovery or no relapses, residual symptoms ○ 44.3: ≥1 relapses with complete or incomplete remissions ○ 10.5: Chronic psychosis
Chandigarh, India[28]	PSE	1.5–2.5	• 37.4: No/minimal psychotic symptoms • 28.6: Mild/moderate psychotic symptoms • 34.1: Chronic psychosis
Ilesa, Nigeria[53]	PSE BPRS	2.1–3.2	• 45.7: No current mental disorder • 36.2: Active/residual schizophrenia • 18.1: Other/Dead
Butajira, Ethiopia[33]	SANS SAPS	1–4	• 45-50: No positive symptoms during follow-up[e] • 24-54: No negative symptoms during follow-up[f]
Chandigarh, India[27]	NA	4.5–6+	○ 45: No psychotic symptoms, some nonpsychotic symptoms ○ 23: Relapses with remission ○ 32: Chronic psychosis
Multisite study, India[22,25,26]	PSE PPHS	5	○ 28.2: Complete recovery or no relapses, residual symptoms ○ 67.2: ≥1 relapses with complete or incomplete remissions ○ 4.5: Chronic psychosis
MLS, India[20,21,30]	PSE PPHS	10	○ 17.1: Complete recovery or no relapses, residual symptoms ○ 76.3: ≥1 relapses with complete or incomplete remissions ○ 6.6: Chronic psychosis
Bali, Indonesia[23]	DSM-IV-TR	11[g]	• 23.9: In remission[h] • 19.6: In partial remission
MLS, India[20]	PSE PPHS	20	○ 8.2: Complete recovery or no relapses, residual symptoms ○ 83.6: ≥1 relapses with complete or incomplete remissions ○ 8.2: Chronic psychosis
WHO studies			
Sofia, Bulgaria[15]	GAF-S	16	Last 2 y ○ 38.2: No psychotic symptoms ○ 12.7: Episodic ○ 45.5: Continuous psychotic symptoms ○ 3.6: Not classified
	BSPSS		16-y course[i] ○ 41.8: Continuous psychotic symptoms ○ 54.5: Episodic ○ 3.6: Not classified
China (ISoS)[15]	GAF-S	12	Previous month • 48.2: None or mild symptoms • 29.2: Severe symptoms
	BSPSS		Last 2 y ○ 34.5: No psychotic episodes ○ 6.9: Episodic ○ 51.7: Continuously psychotic

Table 3. Continued

Site	Psychiatric Assessment	Follow-up (y)	• Clinical Outcomes ○ Patterns of Course (%)
Cali, Colombia (ISoS)[15]	GAF-S	26	Previous month • 31: None or minimal symptoms • 20: Mild symptoms • 20: Moderate symptoms • 30: Serious symptoms 26-y course ○ 48.6: Episodic[j] ○ 18.1: ≥1 relapses with complete or incomplete remissions ○ 33.3: Continuous psychosis
Agra, India (ISoS)[15]	GAF-S	25	Previous month • 56.4 (men): none or mild symptoms • 77.3 (women): none or mild symptoms
	BSPSS		Last 2 y • 77.0: Recovered • 11.5: Severe symptoms ○ 32.1: Asymptomatic for 21–25 y ○ 14.8: Asymptomatic for 6–20 y ○ 13.1: Asymptomatic for <5 y ○ 41.0: Symptomatic for entire period
Chandigarh (rural), India (ISoS)[15]	GAF-S	15	Previous month • 61: Recovered • 16: Moderate symptoms • 24: Mild symptoms
	BSPSS		Course previous 2 y[k] ○ 71: No psychotic episodes ○ 8: Episodic ○ 8: Continuously psychotic
Chandigarh (urban), India (ISoS)[15]	GAF-S	15	Previous month • 66: Recovered • 18: Mild symptoms • 11: Moderate symptoms • 5: Severe symptoms
	BSPSS		Course previous 2 y[l] ○ 64: No psychotic episodes ○ 9: Episodic ○ 19: Continuously psychotic
Ibadan, Nigeria[11]		2	2-y course • 81.7: Complete remission • 15.3: Incomplete remission • 2.0: Unremitting psychosis • 1.0: Unknown

Note: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; PSE, Present State Examination; PHSS, Psychiatric History and Sociodemographic Schedule; PANSS, Positive and Negative Symptom Scale; GPIS, General Psychiatric Interview Schedule; PPHS, Psychiatric and Personal History Schedule; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms; MLS, Madras Longitudinal Study; ISoS, International Study of Schizophrenia; GAF-S, Global Assessment of Functioning-Symptomatology; BSPSS, Bleuler Severity of Psychotic Symptoms Scale.
[a]Continuation of initial psychotic episode, suicide, or recurrence of psychotic symptoms after being symptom free for at least 3 mo.
[b]Untreated at baseline.
[c]PANSS total score of 38.85.
[d]Outcomes based on 95 subjects who did not receive treatment during follow-up.
[e]Significant reduction between baseline and follow-up ($P < .001$).
[f]Significant reduction between baseline and follow-up ($P < .001$).
[g]Five-year retrospective study served as baseline.
[h]PANSS total score of 74.50 (moderately ill); all PANSS scores unchanged from baseline at 5 y.
[i]No subjects were free of psychotic symptoms throughout the entire period.
[j]Only 4.2% had a single episode.
[k]No information on the other 13% of sample.
[l]No information on the other 8% of sample.

Table 4. Clinical Outcomes or Patterns of Course, Retrospective Studies

Site	Psychiatric Assessment	Follow-up (y)	• Clinical Outcomes ○ Patterns of Course (%)
Bali, Indonesia[24,89] Ibadan, Nigeria[63]	PANSS PSE SANS	5 7–26	• 77.00: Total score (moderately ill[91]) • 50.7: No psychotic symptoms • 23.9: Persistent neurotic symptoms or drug reactions[a] • 25.4: Chronic psychosis or $\geq$3 relapses

Note: PANSS, Positive and Negative Symptom Scale; PSE, Present State Examination; SANS, Scale for Assessment of Negative Symptoms.
[a]Also includes reports of negative social behavior from relatives or employer.

variation is striking: in rural Karnataka, only 13% of the sample had regular employment,[41] whereas in the Multisite Study more than 80% of the sample was employed in some capacity.[22,25,26] In Brazil, more than 50% of the sample had either no occupation or were not working because they were receiving a sickness benefit.[38] Rates of unemployment were similar in Indonesia (41.3%)[23] and Ethiopia (45.3%).[42]

Most research in India has found that a high proportion of persons with schizophrenia are either employed or engaged in household work, and several studies have assessed how well subjects were performing these tasks. The work by Srinivasan and Thara[43,44] is especially informative. First, occupational status was assessed annually for 10 years. Second, outcomes for men and women were considered separately because of their distinct occupational domains—employment and household work, respectively. Third, criteria were established (time in occupation and level of performance) for categorizing outcomes. At year 10, 52.5% and 47.5% of men were classified as having good or poor employment outcomes, respectively. This presents a different impression than the data on whether men had been employed during the previous year, which ranged between 63% and 73% during the follow-up period.[43] Two-thirds of women were rated as having good home-making functioning. However, it is difficult to determine the extent to which functional abilities were required to perform assigned household tasks (cooking, washing clothes and utensils, household maintenance, caring for children, and others in the household) because other women in the household generally helped with these tasks.

Lack of Biomedical Treatment

Several studies conducted research among persons who had not received biomedical treatment. This is of particular interest because the ''better prognosis'' hypothesis implies that the ''natural'' course of schizophrenia will be relatively benign in the developing world.[29]

A community survey in rural China identified 510 persons who had a current diagnosis or history of schizophrenia.[29] Of these, 30.6% had never received treatments of any kind, while 5.9% were receiving regular antipsychotic medication, 42.7% had histories of hospitalization and/or irregular treatment, and 20.8% had received traditional Chinese treatments. At baseline, lack of treatment of any kind and duration of untreated psychosis (DUP) greater than a year were associated with poor clinical status. At 2-year follow-up, the 95 subjects who had gone without treatment were, on average, assessed as having poor clinical status.

In rural Ethiopia, a community survey identified 321 persons with schizophrenia of whom 88.8% had never received treatment with antipsychotic medication. Although data are not presented by Kebede et al.,[42] one might reasonably conjecture that the baseline high rate of continuous course of illness (67.2%) among subjects was, at least in part, the result of lack of treatment. At 1- to 4-year follow-ups, subjects displayed a significant improvement in positive symptoms, a result attributed to the antipsychotic medication that was offered free of charge to all subjects.[33]

A community survey in Chennai, India, identified a cohort of 261 persons with a diagnosis of schizophrenia, of whom 28.7% had never received treatment even though they lived within 10 km of 4 public general hospitals with psychiatric units and 1 large mental hospital.[36] Compared with those who had received treatment, those in the untreated group were, on average, older and more likely to be unemployed, illiterate, and living in an extended family. Clinically, the untreated group was more likely to be symptomatic and suffering from severe global disability. Free treatment was offered to those in the untreated group and 49 accepted.[45] At 1-year follow-up, 69.4% of these subjects continued in poor clinical status, an outcome that was found to be associated with DUP.[46] DUP was also found to be a predictor of outcome in South Africa.[47,48]

In rural Karnataka, Murthy et al.[41] identified 100 persons with schizophrenia who had not received antipsychotic treatment in the previous 6 months. Scores on severity of symptoms, levels of disability, and extent of

Table 5. Disability and Social Outcomes, Prospective Studies

Site	Functional Assessment	Follow-up (y)	Follow-up Status (%)
Chennai, India[43]	WHO/DAS	1	• 73.4: Moderate to severe global disability[a] • 34.7: No impairment in social functioning • 51.0: No impairment in occupational functioning
Rural Karnataka, India[41]	WHO/DAS II	1.5	Overall disability • Significant reduction ($P = <.001$) from baseline
São Paulo, Brazil[64]	WHO/DAS	2	Social functioning • 54.3: Social withdrawal[b] • 37.2: Self-care[c] • 52.2: Interest and information[d]
Sichuan, China[29]	SDSS	2	Social functioning • 20.9: Mildly impaired • 10.9: Moderately impaired • 68.2: Seriously impaired
Multisite study, India [22,25,26]	PPHS PSE	2	Social interaction • 33.7: No impairment • 53.6: Some impairment • 12.7: Severe impairment
Ilesa, Nigeria[53]	NA	2.1–3.2	Social relationships • 43.6: Satisfactory • 23.4: Moderate problems • 22.3: Severe problems • 10.6: NA
Butajira, Ethiopia[33,42]	SF-36	1–4	• Functional status generally poorer in Butajira than in industrialized countries[e]
Multisite study, India[22,25,26]	PPHS PSE	5	Social interaction • 25.8: No impairment • 52.6: Some impairment • 21.6: Severe impairment
Bali, Indonesia[23]	ESAS	11[f]	• 39.1: Self-supportive • 13.0: Semi self-supportive • 15.2: Socially adjusted to family or community • 32.6: Maladjusted
Madras Longitudinal Study, India[20]	GAF	20	GAF functioning • 73.8: None or some difficulty in social and occupational domains
WHO studies			
Sofia, Bulgaria[15]	GAF-D	16	GAF-D • 32.7: No or minimal social disability • 36.4: Poor functioning
	DAS		DAS • 32.7: No or minimal disability • 36.4: Poor social functioning
China (ISoS)[15]	GAF-D	12	• 32.8: Good social functioning • 39.6: Serious impairment in social functioning[g]
Cali, Colombia (ISoS)[15]	GAF-D	26	GAF-D • 45.8: No or minimal social disability • 27.8: Mild social disability • 23.6: Moderate social disability • 2.8: Severe social disability
	DAS		DAS • 52.3: Good to excellent social functioning • 9.0: Poor social functioning • 0.0: Severe social functioning

Table 5. Continued

Site	Functional Assessment	Follow-up (y)	Follow-up Status (%)
Agra, India (ISoS)[15]	GAF-D	25	GAF-D • 48.7: Better functioning—men • 81.8: Better functioning—women
	DAS		DAS • 60.0: Good to excellent adjustment • 19.0: Fairly good functioning • 21.0: NA
Chandigarh (rural), India (ISoS)[15]	GAF-D	15	• 71: Good to excellent social functioning • 5: Serious impairment in social functioning
Chandigarh (urban), India (ISoS)[15]	GAF-D	15	• 63: Good to excellent social functioning • 14: Serious impairment in social functioning
Ibadan, Nigeria[11]	NA	2	% of follow-up social functioning unimpaired • 65.6: 76–100 • 15.6: 46–75 • 7.3: 16–45 • 11.5: 0–15

Note: GAF-D, Global Assessment of Functioning-Disability; WHO/DAS, World Health Organization Disability Assessment Scale; SDSS, Social Disability Screening Schedule; PPHS, Psychiatric and Personal History Schedule; PSE, Present State Examination; SF-36, Medical Outcomes Study Short Form; PPHS, Psychiatric and Personal History Schedule; PSE, Present State Examination; ESAS, Eguma's Social Adjustment Scale; GAF, Global Assessment of Functioning; ISoS, International Study of Schizophrenia.
[a]At baseline, 98.7% of subjects assessed as having severe global disability.
[b]At baseline, 74.3%.
[c]At baseline, 55.7%.
[d]At baseline, 68.2%.
[e]Comparisons of mean differences in social and physical functioning and role limitations between subjects and general population. At baseline, 7% were homeless.
[f]Five-year retrospective study served as baseline.
[g]Tendency for men to have higher levels of social functioning than women (GAF-D, 62.9 vs 58.3 for men and women, respectively).

family burden were all high at baseline. Following 18 months of treatment with antipsychotic medication and psychosocial care, the cohort displayed, on average, significant improvements in all domains.

In sum, these findings suggest that good outcomes cannot be assumed for untreated schizophrenia in low- and middle-income countries and that treatment does make a significant difference.

Mortality and Suicide

Throughout the world, persons with schizophrenia have rates of mortality that are significantly higher than general populations.[49] That this is the case in low- and middle-income countries is suggested by the crude mortality data in table 2. In long-term studies ($\geq$10 years), mortality rates range from 9.0% to 30.7% in the ISoS sites (urban Chandigarh and Agra, respectively) and from 10.0% to 19.2% and 20.3% in other research sites (Chennai, Bali, Indonesia, and rural China, respectively). It is likely that the reported mortality rates are underestimates given the lack of information about subjects lost to follow-up.

Crude mortality rates do not indicate how persons with schizophrenia compare to general populations. Standardized mortality ratios (SMRs) provide that measure. Wherever SMRs are available, there is little question that persons with schizophrenia in low- and middle-income countries have elevated rates of mortality.[49,50] The research by Ran et al.[51] is particularly revealing because of its large sample size (510), low rate of attrition (7.8%), and long-term follow-up (10 years). The SMR for the cohort was 4.0; the rate among men (4.9) was higher than it was among women (3.3). Suicide and death by accident accounted for much of the elevated SMR, but not all of it: the SMR for natural causes was 2.6. SMRs for men in the São Paulo, Brazil cohort,[52] were (4.5), but those for women were nearly seven times as high (25.5).

Other studies offer information about the context in which high rates of mortality occur. Of 9 known deaths in a Nigerian cohort, 5 took place while subjects were "in traditional healers' establishments" while 2 other subjects "had been beaten to death by night guards who had found them wandering."[53] In Indonesia, of the 11 subjects who died of natural causes, only 2 were receiving medical treatment at the time of their deaths.[54] The average age of death in this cohort, 33.3 years, was strikingly similar to that in the MLS, 34.2 years.[20] In contrast, life expectancies for general populations in Indonesia and India are approximately 65 and 61 years, respectively.

Table 6. Disability Outcomes, Retrospective Studies

Site	Functional Assessment	Follow-up (y)	Follow-up Status (%)
Bali, Indonesia[23,24,89]	ESAS	5[a]	• 34.8: Self-supportive • 19.6: Semi self-supportive • 30.4: Socially adjusted to family or community • 15.2: Maladjusted
Ibadan, Nigeria[63]	NA	7–26	• Women deteriorated rapidly in social domains (employment, marriage, and education) after first episode • Men tended to be ''better adjusted at home''
Abeokuta, Nigeria[35]	GSDS	13	Social Outcome[b] • 22: Unimpaired • 19: Some impairment • 23: Moderate impairment • 36: Severe impairment

Note: ESAS, Eguma's Social Adjustment Scale; GSDS, Gronigen Social Disability Scale.
[a]Based on scores of 46 subjects remaining in sample at 11-y follow-up.
[b]More women than men had impaired social outcomes ($P = .03$).

Table 9 summarizes the information that is available about suicide. The studies in rural China,[51] Brazil,[52] the MLS,[20,21] and Bulgaria[15] suggest that rates of suicide are comparable to, if not higher than, the lifetime rates (4.9%–5.6%) reported by Palmer et al.[55] In contrast, there were no reported suicides in the 1-year studies in Chennai,[46] Rural Karnataka,[41] and the 11-year study in Indonesia.[23,24,54] In general, data on suicide must be viewed with caution. For example, the reported rate of suicide in the MLS (7.8%) may have been an underestimate: ''Because postmortem examinations were not done, it was not possible to determine the actual cause of death in some cases.''[20]

The Role of Families

There is a long history to the notion that the better course and outcome of schizophrenia in low- and middle-income countries is attributable to relatively high levels of family support and tolerance.[9,15] This view has been maintained despite a paucity of evidence.[56,57] The research literature reviewed here provides evidence that, at the very least, should make us question past assumptions. For example, the Indian family has been noted as being especially supportive of members with schizophrenia.[58,59] We do not doubt this view, but do believe it may be an overgeneralization. While it is true that over the course of 20 years, the great majority of subjects in the MLS lived with their natal or marital families,[20,21] research also offers insights about the nature of subjects' family relationships. At the same time that families supported mentally ill members and did not abandon or push them into homelessness, unemployed men with schizophrenia were subjected to ''rejection and harsh criticism.''[44] Other evidence from Chennai suggests that living in an extended family is a risk factor for not being brought to care, even when living in close proximity to facilities that offer treatment free of charge.[43] Finally, ethnographic research in Chennai with a group of separated and divorced women with schizophrenia (but not part of any outcome study) found that their lives were marked by ''hostility from family members.''[60]

Evidence from other countries adds still more complexity. Whereas less than 2% of ISoS subjects experienced homelessness in the 2 years prior to follow-up (an admitted underestimate),[15] higher rates of homelessness were found among samples in rural areas of China[61] and Ethiopia[42] (8% and 7%, respectively). In a 13-year retrospective study, Gureje and Bamidele[35] were surprised, ''given the traditional family structure in Nigeria,'' that 4% of subjects were homeless or experiencing housing instability. They speculated, ''In a setting where there are no public support services for the mentally ill, it is likely that the traditionally supportive family networks break down with prolonged illness.'' Evidence from rural China also belies the notion of universal family tolerance and support of members with schizophrenia in that ''insufficient family care or maltreatment'' was associated with poor clinical status.[48]

In sum, the research literature suggests that we must not make broad assumptions about the nature of family support for persons with schizophrenia. Support certainly exists, but it may be mixed with conflict or even breakdown in the absence of supports for the families themselves.

Gender

It is generally accepted that women with schizophrenia experience better outcomes than men.[62] Although, gender

Table 7. Marital Status

Site	Marital Status • Baseline ○ Follow-up (%)	National Rates[92]
São Paulo, Brazil[37,38]	• 16.9: Married • 65.3: Single • 15.4: Separated/divorced • 2.4: Widowed	1980, urban, 15+ y 56.2: Married 35.5: Single 2.9: Separated/divorced 5.3: Widowed
Sichuan, China[29]	• 41.7: With partner • 58.3: No partner	1995, rural, 15+ y 72.8: Married 20.1: Single 0.6: Separated/divorced 6.5: Widowed
Butajira, Ethiopia[32,33]	• 30.0: Married[a] • 52.1: Never married • 17.9: Separated/divorced/widowed	2000, total, 15+ y 57.3: Married[b] 34.3: Single 6.3: Divorced 2.0: Widowed
India		
Madras Longitudinal Study[20,31]	10 y ○ 69.7: Ever married[c] ○ 31.3: Never married 20 y ○ 73.7: Married ○ 26.3: Single	1999, total, 15+ y 69.5: Married 22.0: Single 1.0: Separated/divorced 7.5: Widowed
Chennai[36,43]	• 60.9: Ever married[d] • 39.6: Ever divorced/separated ○ 67.3: Poor marital statuse	
Rural Karnataka[41]	• ≈50[f]	
Bali, Indonesia[23,24]	5 y ○ 51.0: Married ○ 49.0: Single 11 y ○ 63.0: Ever married[g]	1997, total, 15–49 y 69.7: Married 25.3: Single 2.5: Separated/divorced 2.5: Widowed
Nigeria		
Ilesa[53]	○ 16.0: Married, satisfactory ○ 7.4: Married, problems ○ 16.0: Complete breakdown of marriage ○ 51.1: NA ○ 9.6: Dead	1991, total, 15–79 y 62.4: Married 30.5: Single 2.6: Separated/divorced 4.5: Widowed
Abeokuta[35]	• 28.3: Married[h] • 27.5: Separated/divorced • 39.2: Never married • 5.0: Widowed	
Ibadan[11]	• 44.4%: Single • 48.5%: Married/cohabitating • 5.8%: Divorced/separated/widowed • 1.2%: Other/not known	

[a]At follow-up, 28.8% of sample were married.
[b]Includes consensual union.
[c]By 10-y follow-up, 9 marriages (6 women, 3 men) had ended in divorce.
[d]Of 261 subjects at baseline (4 subjects no information).
[e]Of those, 49 subjects untreated at baseline and followed-up.
[f]"A little over half…were currently married."
[g]One divorced and 1 widowed.
[h]Men (66.1%: never married, 14.3%: married, 17.9%: separated/divorced, 1.8%: widowed); Women (15.6%: never married, 40.6%: married, 35.9%: separated/divorced, 7.8%: widowed).

Table 8. Employment Status

Site	Employment Status • Baseline (No Information at Follow-up) ○ Follow-up (%)
São Paulo, Brazil[38]	• 19.3: Working regularly • 7.3: Some activity • 10.5: Housewife • 10.5: Retired • 11.3: Sickness benefit • 41.1: No occupation
Sichuan, China[29]	• 32.1: Full-time farm work • 45.5: Part-time farm or household work • 22.4: No work
Butajira, Ethiopia[42]	• 50.3: Full-time work • 4.4: Domestic work • 45.3: Unemployed
India	
Chandigarh[28]	○ 39.6: Working/no impairment ○ 16.5: Working/some impairment ○ 44.0: Not working
Multisite study[22,25,26]	2 y ○ 40.2: Working/no impairment ○ 42.2: Working/some impairment ○ 17.6: Not working
Multisite study[22,25,26]	5 y ○ 39.0: Working/no impairment ○ 43.2: Working/some impairment[a] ○ 17.8: Not working
MLS[44,45]	10 y Men ○ 52.5: Good occupational outcome[b] ○ 47.5: Poor occupational outcome[c] Women ○ 66.7: Good home-making function[d] ○ 33.3: Poor home-making function[e]
MLS[20]	20 y Men ○ 76: Employed[f] Women ○ 75: Housewives or unmarried living with parents ○ 25: Employed[g]
Chennai[43]	○ 51.0: No impairment in job/housework function[h]
Rural Karnataka[41]	• 13: Regular employment
Bali, Indonesia[23]	11 y ○ 37.0: Employed full time ○ 21.7: Employed part time ○ 41.3: Unemployed
Jamaica[39]	○ 43: "Gainful employment" during follow-up
Nigeria	
Ilesa[53]	○ 36.2: Working ○ 52.3: Not working ○ 9.6: Sead
Lagos[90]	○ 56.6: Maintained employment
Abeokuta[35]	○ 51.7: Little or no disruption in occupation ○ 25: Significant work disruptions[i] ○ 13: Totally incapacitated
Trinidad[88]	• 23.9: Employed • 34.8: unemployed • 41.3: No information
WHO studies	
Sofia, Bulgaria[15]	Past 2 y • 45.3: Some paid employment • 13.1: Full-time household work
China[15]	Past 2 y • 27.6: Some paid employment[j] • 34.5: Household work • 41.4: Retired[k]
Cali, Colombia[15]	• 68: Employed[l] • 18: Full-time household work • 14: NA
Agra, India[15]	• 44.3: Employed[m] • 34.4: Household activities • 4.9: Retired • 9.8: Unemployed • 6.6: NA
Chandigarh (rural), India[15]	Past 2 y • 45: Some paid employment[n] • 58: Full-time household work
Chandigarh (urban), India[15]	Past 2 y • 64: Some paid employment[o] • 28: Fulltime household work

Note: MLS, Madras Longitudinal Study,
[a]In general, men's employment was "erratic and irregular consequent to the illness."
[b]No change or improvement in employment or income status during follow-up.
[c]Deterioration in employment or income status during follow-up.
[d]Performed regular housework $\geq$50% of follow-up.
[e]Performed regular housework $\leq$50% of follow-up.
[f]Half full-time, others part-time or in family business. Of those employed, two-thirds had minimal or no impairment in work.
[g]Mostly intermittent employment.
[h]Seven subjects (14.3% of sample) unemployed at inclusion gained employment during follow-up.
[i]In all, 4.6% of men and 51.5% of women were rated as having poor occupational outcomes.
[J]About two-thirds of these subjects had worked for 12 mo or more.
[k]A small proportion of this category included in other categories.
[l]Of these, 59% were employed full-time during previous 2 y.
[m]In rural areas of Agra, employment was "in routine, rustic jobs—such as taking cattle to graze and feed—tasks which family members judged them to be performing well."
[n]Of these, 37% were employed for the entire 2 y.
[o]Of these, 54% were employed for the entire 2 y.

Table 9. Suicide

Site	Years	Suicide %
São Paulo, Brazil[52]	2	4.3
Sichuan, China[51]	10	4.2
Butajira, Ethiopia[33]	1–4	NA
India		
Multisite study[22,25]	2	2.1
	5	3.1
Madras Longitudinal Study[20,21]	10	5.6
	20	7.8
Chennai[46]	1	0.0
Rural Karnataka[41]	1.5	0.0
Bali, Indonesia[23,24,54]	11	0.0
ISoS[15]		
Sofia, Bulgaria	16	3.6
Beijing, China	12	2.2
Cali, Colombia	26	1.0
Agra, India	25	2.9
Chandigarh, urban, India	15	2.6
Jamaica[39]	1	0.0
Ilesa, Nigeria[53]	2.1–3.2	0.9

Note: ISoS, International Study of Schizophrenia.

effects were not explored consistently in the research we reviewed, some observations are possible. In India, several studies found that course and outcome is better for women.[15,21,26,30] However, that was not the case everywhere. Men tended to have better outcomes in Colombia.[15] In the ISoS China study,[15] there were few gender differences, but women tended to do better in the study by Ran et al.[29] in rural China. In Nigeria, women seemed more likely to suffer from continuous psychosis and were particularly prone to relapse.[63]

Outcomes in social domains also displayed gender effects. In Nigeria, women tended to fare worse than men, while women in Ethiopia tended to show greater improvement in functioning during follow-up.[33] In ISoS, men in China also tended to have higher levels of social functioning. This was in contrast to Agra where 81.8% of women were rated as having "better functioning at follow-up," a rate more than 1.5 times that of men.[15]

The most striking gender effect was in Ethiopia where a community survey found a 5:1 male to female ratio in the prevalence of schizophrenia.[33] Whether this reflects an exceptional case of gender differences in frequency, excess mortality, or that women with schizophrenia are being kept extremely isolated requires further investigation.

Conclusions

During the past 30 years, international psychiatry has embraced the notion that the course and outcome of schizophrenia is better in so-called "developing" countries.[2–5,13,14] We believe our review of 23 studies in 11 low- and middle-income countries—a much greater range of sociocultural environments than in ISoS—provides enough evidence to justify a reexamination of this axiom.

First, there appears to be great variation in clinical outcomes and patterns of course. Whereas, some studies in India strongly support the "better prognosis" hypothesis,[15,20,21] outcomes do not appear to be nearly as positive in Brazil[64] and China.[29] Additionally, limited evidence suggests that gender effects vary cross-nationally.

Second, similar patterns are found in the domains of disability and social functioning: good in most studies in India[15,20,21] and Indonesia,[23] but poorer in Nigeria,[35,53] and much poorer in a cohort of untreated persons in Chennai, India.[43] Social functioning by gender also varied: in the MLS, women had high levels,[26,45] while in Nigeria women fared poorly.[35,63] Outcomes in occupational and marital status also varied. A more important point, however, is that status in these 2 domains must be interpreted in the context of sociocultural norms and assessed, at least to some degree, qualitatively. Viewed from this perspective, the data in table 7 suggest that rates of marriage for people with schizophrenia are relatively low and rates of divorce/separation are high.

With regard to occupational status, "the crude distinction between 'employment' and 'unemployment'"[39] is uninformative because the role of work in shaping the course and outcome of schizophrenia has not been explored adequately.[56] For example, what are the effects on outcome of farm work in rural Ethiopia[42] or China?[29] Did jobs "in the unorganized/informal sector [as] street vend[ors], shops assistants, and domestic help" impel good outcomes in the MLS?[44]

Furthermore, assessment of social functioning is, in general, "fraught with problems"[27] given variation in sociocultural environments, norms, and attitudes.[3] Unfortunately, neither the research reviewed above nor the WHO studies provide the evidence that allows us to evaluate the quality of family and social interactions, the nature of employment, and the meaning of marriage for the subjects in the various studies. Ethnographic methods are needed to gain a better understanding of the social functioning of persons with schizophrenia in a range of sociocultural environments.[18,19]

Third, the WHO studies have led "to the ironic observation that abundance cripples" and that "scarcity" and "collaborative social world[s]" are responsible for better outcomes.[56] Yet, our review of the research suggests a different conclusion: wherever it is found, lack of care is associated with relatively poor outcomes and that accessing care is associated with improved outcomes. Because the individuals in many of the studies were receiving care at leading academic psychiatric facilities, one might even say that their relatively good clinical, occupational, and social outcomes reflected the effects of quality care as much as, if not more than, the effects of sociocultural environments. Thus, the favorable outcomes that have been found by some studies cannot be assumed

to be representative of outcomes in low- and middle-income countries where the majority of persons with schizophrenia have little or no access to care.

Fourth, the evidence about excess mortality must not be ignored. We agree with Ran et al.[51]: "It may be premature to suggest that there is a better prognosis for schizophrenia in [developing] countries if withdrawals or attrition due to death…are not included in follow-up analyses."

Fifth, further research into the role of families is necessary. Although expressed emotion studies are informative about the nature of family interactions, such research provides little understanding of the processes that for example, lead Indian families to keep members with schizophrenia out of care, or that bring about the breakdown of family support for subjects in Nigeria, or that force homelessness upon some persons with schizophrenia in China. Surveys of public attitudes in Nigeria[65,66] and Ethiopia,[67] as well as qualitative and survey research with families in India[60,68–70] suggest high levels of stigma about mental illness. These negative attitudes, at least in Africa, are believed to result in families abandoning mentally ill members.[71] Appalling conditions in psychiatric facilities in Asia[72–74] also raise questions about whether presumed tolerance translates into better outcomes.

Sixth, variability in outcomes is evident in high-income countries, too. Reviews of long-term studies[16,75,76] show variability from study to study, and ISoS[15] shows variability in outcomes across high-income countries. One analysis of DOSMeD data[77] indicates that 2-year outcomes in Prague and Nottingham were similar to those in India, while outcomes in Cali were close to those in high-income countries. Given this variation, we need to find a better framework for comparing schizophrenia outcomes in different sociocultural environments.

Seventh, the evidence provided by this review suggests that the sampling methods utilized in the WHO studies may have resulted in overly optimistic perceptions of course and outcome in low- and middle-income countries. Except for the China ISoS site, sampling in all the WHO studies relied on a variety of help-seeking agencies to identify potential subjects.[10,11,15] However, community surveys in rural China,[29] India,[36,43,46] Indonesia,[78] and Ethiopia have shown that large proportions of persons with schizophrenia (between about 25% and almost 90%) never receive biomedical treatments. Furthermore, outcomes in these samples, whether or not subjects received treatment following inclusion in the studies, tended to be poor. Therefore, there is the possibility that case-finding methods which focus exclusively on help-seeking agencies will miss large proportions of seriously ill, poor prognosis individuals.

This review has 2 main limitations. First, our strategy to identify studies—searches of bibliographic databases and locating references cited in journal articles—may not have been comprehensive, and it is possible that we did not find all the studies that met our criteria. It is also possible that reliance on English language articles excluded a number of reports about other outcome studies. Nevertheless, because this was a narrative review and not a meta-analysis, we do not believe these potential shortcomings would have substantially influenced our conclusions. Second, a more serious limitation is the possibility that apparent variations in course and outcome were the function of methodological heterogeneity among the studies. We do not believe this was the case because the methods and instruments used in the studies were generally consistent with each other.

In conclusion, we suggest it is time to revisit the hypothesis that the course and outcome of schizophrenia is better in low- and middle-income countries. Although a host of sociocultural factors have been cited as contributing to variation in the course and outcome of schizophrenia—eg, family support and styles of interaction, industrialization, and urbanization[4]—there is little direct evidence, and what exists provides little help in unpacking the "black box" of culture.[79] Clinical, epidemiological, and ethnographic research are required to better understand how neuropsychiatric processes and social worlds interact to shape the lives of persons with schizophrenia in low- and middle-income countries.

The questions in need of investigation include:

- Of the prevalent cases in each catchment area, how many are receiving psychiatric care? How many are receiving alternative forms of treatment? How many are receiving no care at all?
- What are the biomedical and other treatment effects on outcome? How do variations in treatment influence variations in outcomes within and across research sites?
- What are the clinical outcomes in terms of positive and negative symptomatology of incident and prevalent cases?
- How might employment and nonpaid occupations influence or be influenced by clinical factors?
- What is the quality of family life (natal and marital) of persons with schizophrenia and how does this influence (or is influenced by) outcome?
- What are the pathways to care (biomedical and traditional) and what are the clinical and sociocultural factors associated with help-seeking decisions?
- What are the circumstances that lead to suicidality and excess mortality among persons with schizophrenia?

The knowledge that will come from answering these and other questions is important for at least 3 reasons. First, identifying the processes that promote good prognosis will inform the care and treatment of persons with schizophrenia wherever they live. Second, accurate information about the realities of the day-to-day lives of persons with schizophrenia in low- and middle-income countries will inform advocacy efforts to: (a) close the

enormous gap between the numbers of people in need of care and the small number who actually receive it[80]; and (b) provide greater supports for families. Finally, globalization is bringing about enormous sociocultural and socioeconomic changes to the societies of low- and middle-income countries. In turn, these changes will, inevitably, transform the nature of families and the communities in which they live, the epidemiological profile of nations and regions, and the services provided by health systems. No doubt, globalization will have significant consequences for the lives of persons with schizophrenia. To prevent or at least limit the potential harm that may result, it is essential that we have detailed understandings about how sociocultural and psychiatric processes interact. For these reasons, it would make sense to put aside presumed wisdom and reexamine the question of the prognosis of schizophrenia in low- and middle-income countries.

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