



Short-term symptomatic and functional outcomes of schizophrenia in Butajira, Ethiopia

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Abstract

Background: Prospective outcome studies based on a community sample of mostly neuroleptic naive cases of schizophrenia are uncommon.

Objectives: To describe short-term symptomatic and functional outcomes of schizophrenia, and potential predictors of outcome.

Methods: After a baseline assessment, 63 incident and 208 prevalent cases of schizophrenia were followed by a yearly clinical assessment for an average of 2.5 (range 1–4) years. Scores of negative symptoms and positive symptoms were used as indicators of symptomatic outcomes. SF-36 scores of physical and social functioning, and role limitation due to mental health problems were used as indicators of functional outcomes. Several variables were evaluated as potential predictors of outcome in random coefficient models.

Results: Functioning and other measures of health related quality of life were significantly diminished in cases as compared to the general population of the area at baseline and follow up. Of the socio-demographic and clinical factors evaluated, only lower negative and positive symptom scores were significantly associated with improvements in functioning. The level of functioning observed in cases from Butajira was lower than that reported for cases from developed countries.

Conclusions: Our findings are not in accord with other outcome studies that have reported better functional outcome for cases of schizophrenia from developing countries.

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Keywords: Schizophrenia; Psychosis; Outcome; Functioning; Disability

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1. Introduction

There is a large scientific literature characterizing the course and outcome of schizophrenia in developed countries (Eaton, 1995; Hegarty et al., 1994). The WHO international multi-center studies reported that the outcome of schizophrenia was generally better in developing than developed countries (Jablensky et al., 1992; Leff et al., 1992). Independent of the WHO multi-center studies, several developing-country investigators (mainly from India) have also reported better outcome for schizophrenia (Institute of Medicine, 2001). There have been expressions of concern on whether these samples are representative of developing countries in general (Hopper and Wanderling, 2000). This concern is particularly pertinent to Africa where no prospective outcome studies have been reported except for Nigeria (Obembe et al., 1995; Ohaeri, 1993). It is evident that additional outcome studies are needed from other developing countries.

A person's functioning and disability is conceived as a dynamic interaction between health conditions (e.g. disorders) and contextual factors (e.g. the social environment) in ICIDH-2: WHO's international classification of functioning and disability (WHO, 1999). Describing the degree of functioning or disability by comparing the functional outcome of individuals with schizophrenia to that of the local general population, using generic (instead of disease-specific) measures is one way of adjusting for these contextual factors. The importance of such case-population comparisons has also been stressed (Westermeyer and Harrow, 1988), although very few studies from developed countries (Nasrallah et al., 2004; Pukrop et al., 2003; Tunis et al., 1999; Russo et al., 1998), and none from developing countries, have reported such comparisons. Instead most investigators have used the judgment of a rater(s), to describe and ascertain if a case's overall functioning is commensurate with that expected of an 'average' person with a similar socio-demographic characteristics to adjust for contextual factors (Hegarty et al., 1994; Jablensky et al., 1992). Because of the subjective nature of such a judgment, it may limit the validity of comparisons of functional outcomes across different groups and populations.

Several studies in the developed world have shown associations, albeit inconsistently, between symptomatic and functional outcome of schizophrenia; socio-

demographic characteristics such as sex, marital status, urban–rural residence, and socio-economic status; and illness characteristics such as age of onset, duration of untreated psychoses, and neuroleptic treatment (Bromet et al., 1995; Westermeyer and Harrow, 1988). The presence and severity of negative and positive symptoms have also been associated with functional outcomes (Ho et al., 1998). The associations of these factors to symptomatic and functional outcome in developing countries is not well known as very few studies have evaluated these associations after adjusting for potential confounders.

We have earlier reported baseline results of a study from rural Ethiopia that identified and recruited cases of schizophrenia (90% of whom were neuroleptic naive at baseline) to describe course and outcome (Kebede et al., 2004b; Kebede et al., 2003). We identified 321 cases and followed 84% of this cohort for an average of 2.5 (range 1–4) years by yearly clinical assessments. Moreover, because of the availability of published local general population norms for the Medical Outcomes Short Form SF-36 (Kebede et al., 2004a), we were able to compare functioning and other measures of health related quality of life in cases and the general population of Butajira and to additionally compare the results to similar reports from industrialized countries. We also evaluated several potential socio-demographic and clinical predictors of outcome in our study cohort.

2. Methods

The details of the methods that were followed have been described elsewhere (Kebede et al., 2004b; Kebede et al., 2003). We initially conducted a door-to-door survey of the entire district adult (ages 15–49 years) population. We completed the baseline survey in May 2001, by interviewing 68,378 individuals out of the estimated 83,282 population (aged 15–49 years) in the area. The average non-response rate was more in rural areas (18.7%) than in the town (13.6%). Being out of the district on a business trip, accounted for 65% of the non-response.

The psychoses and affective disorder modules of the Composite International Diagnostic Interview (CIDI) were used for the interviews and as a screening instrument to identify all potential cases of psychoses,

bipolar disorder and major depression. In addition, key informants (KI) were used to identify individuals with probable major mental illnesses. The performance of the CIDI and KI methods in identifying cases with schizophrenia and affective disorders has been reported earlier (Shibre et al., 2002).

In the second stage those cases that tested positive for psychoses and affective disorders on the CIDI and those identified by key informants underwent evaluation by physicians using the Amharic version of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) (Wing, 1996; Wing et al., 1989). A total of 2159 individuals were identified as probable cases of schizophrenia or affective disorders by the CIDI interview. Of these, 1738 (80.5%) volunteered for the SCAN interview. The key informants identified a total of 719 probable cases of major mental disorder. Of these, 547 (76.1%) subsequently underwent evaluation by the SCAN. A total of 2285 SCAN interviews were undertaken (79% of the total 2878 potential cases identified both by the CIDI interview and key informants). Out of all SCAN interviewed persons, 321 were diagnosed as having schizophrenia, 315 cases as having bipolar disorders and 212 cases as having major depression according to ICD-10 criteria. The present study focused on individuals with schizophrenia who met the following inclusion criteria: (a) age between 15 and 49 years; (b) residence for at least 6 months in the area; and (c) evidence of the presence of schizophrenia (ICD-10 designation: F20) after a comprehensive assessment using the SCAN.

At baseline and yearly follow-ups symptom ratings were assessed by physicians using the Scale for Assessment of Negative Symptoms (SANS) and Scale for Assessment of Positive Symptom (SAPS) (Andreasen, 1982). Psychiatric nurses trained in its use administered the SF-36 (Ware, 1993). Cases were scheduled for yearly follow-up evaluations after the baseline assessment, using the same instruments, although the actual times cases were evaluated varied. Following the baseline assessment of all 271 cases, 41 (15.1%) cases had four yearly follow up assessments, 87 (32.1%) cases had three, 79 (29.2%) cases had two, and 64 (23.6%) cases had only one follow up assessment.

We used SANS and SAPS scores to quantify symptomatic outcomes. Negative symptom scores were computed as the sum of alogia, anhedonia/asociality, avolition, affective, attention deficit global ratings in

the SANS and the maximum score was 25. Positive symptom dimensions were defined as the sum of delusions, hallucination, bizarre behavior, positive formal thought disorder, and inappropriate affect global ratings of the SAPS and the maximum score was 25.

SF-36 scores were used to quantify outcomes related to functionality, disability and health-related quality of life. The SF-36 is widely used for measuring outcomes of both physical and mental illnesses and has been shown to validly measure functioning and health related quality of life (Brazier et al., 1992). The instrument has also demonstrated good internal consistency, stability, and concurrent validity in cases of schizophrenia (Tunis et al., 1999; Russo et al., 1998). The Amharic version that was used in this study has also demonstrated good reliability and validity in the general population of Butajira (Kebede et al., 2004a). The SF-36 instrument includes 36 items that yield 8 domains (or scales) when scored. The first domain is physical functioning (PF, 10 items), which assesses limitations in physical activities, such as walking and climbing. The role-physical (RP, 4 items) and the role-emotional (RE, 3 items) domains measure problems with work and other daily activities as a result of physical and emotional problems, respectively. Bodily pain (BP, 2 items) assesses limitations due to pain, whereas vitality (VT, 4 items) measures energy and tiredness. The social functioning domain (SF, 2 items) examines the effect of physical and emotional health on normal social activities, and the mental health domain (MH, 5 items) assess happiness, nervousness and depression. The general health perception domain (GH, 5 items) evaluates personal health and the expectation of changes in health. Subscales of the SF-36, such as mental health, vitality, and general health perception, assess the patient's subjective sense of well-being and depression rather than disability. In contrast, rating of role performance (RP, RE, SF, and PF) assess daily functioning directly (Ware, 1993). Higher SF-36 scores represent higher levels of function.

For the comparison of the SF-36 scores of cases to those of the general population, published normative SF-36 values of the general Butajira population were used (Kebede et al., 2004a). We have also compared our results to published SF-36 score differentials between cases and normative values in developed countries. A systematic review of the published liter-

ature was conducted to identify studies of schizophrenia that studied health related quality of life using the SF-36. We searched Medline for articles published before December 2004 (all languages) using the search terms SF-36, schizophrenia and psychoses. We screened all articles retrieved from the search ($n=24$) and included all those that stated PF, RP, SF and RE values in their papers ($n=7$). Baseline values were used for comparison to local general population normative values. The cross-sectional data of these studies come from 39 cases of schizophrenia from Seattle, US (Russo et al., 1998); from 143 cases of schizophrenia from Pittsburgh, USA (Strassnig et al., 2003); from 369 cases of schizophrenia (at baseline) from a multi-center study in USA (Nasrallah et al., 2004); from 91 cases of schizophrenia hospital admissions from Cologne and Munich in Germany (Pukrop et al., 2003); from 109 cases of schizophrenia (at baseline) from Madrid, Spain (Bobes et al., 1999); from 65 cases of schizophrenia (at baseline) from Australia and New Zealand (Gureje et al., 2003); and, from 1155 cases of schizophrenia (at baseline) from US, Canada and UK that participated in a multi-center trial (Tunis et al., 1999); All these cases were on atypical neuroleptic medication and were a mix of recent and long-standing cases when they were assessed. Except for the study from Germany, which had its own internal control, normative SF-36 values of the general populations of the USA (Ware, 1993), Spain (Alonso, 1998), and Australia (Butterworth and Crosier, 2004) were used for comparison.

We conducted a stratified analysis and presented the results of our study separately for 63 recent-onset (cases with onset of recognizable illness within the last 2 years prior to recruitment into the study) and for 208 long-standing cases (duration of illness between 3 and 30 years), to describe the outcome in two different stages of illness, and to also limit the selection bias that could arise from the use of varying proportions of chronic cases (Bromet et al., 1995; Westermeyer and Harrow, 1988). We chose 2 years as a cut-off point not only to define a group of incident cases as close to their onset of illness as possible, but also to assemble a sufficient number to conduct multivariate analysis (Rothman, 1986). To estimate the proportion of follow-up time under neuroleptic treatments, we used data from clinical face-sheets filled by psychiatric nurses every month when patients came for their treatments.

A SAS-based SF-36 scoring algorithm (Ware, 1993) supplied by the developers of the instrument was used to calculate individual scores. SPSS-PC (version 11) was used for both univariate, bivariate and multivariate analyses. We used ANOVA to compare mean differences in SANS, SAPS and SF-36 scores, and Chi square test for trend to evaluate trends

Table 1
Sociodemographic, illness and follow-up characteristics of the study population of cases of schizophrenia in Butajira, Ethiopia 2004

Characteristics	Recent onset cases*	Long-standing cases	All cases
Duration of illness, year [mean (min, max)]	1.1 (0, 2)	9.7 (3, 30)	7.6 (0, 30)
Years of follow-up [mean (min, max)]	2.4 (1, 4)	2.5 (1, 5)	2.5 (1, 4)
Total (at baseline)	75 (100.0)	246 (100.0)	321 (100.0)
Total followed (used for analyses)	63 (84.0)	208 (84.5)	271 (84.4)
Profile of missing follow-up or outcome data	12 (100.0)	38 (100.0)	50 (100.0)
Deceased	2 (16.7)	13 (34.2)	15 (30.0)
Moved out of area	3 (25.0)	8 (21.1)	11 (22.0)
Refusals	2 (16.7)	4 (10.5)	6 (12.0)
Unable to locate	3 (25.0)	7 (18.4)	10 (20.0)
Missing baseline outcome data	2 (16.7)	6 (15.8)	8 (16.0)
Sex			
Male	51 (81.0)	169 (81.3)	220 (81.2)
Female	12 (19.0)	39 (18.8)	51 (18.8)
Marital status			
Married	16 (25.4)	62 (29.8)	78 (28.8)
Other	47 (74.6)	146 (70.2)	193 (71.2)
Residence			
Urban/semi-urban	16 (25.4)	47 (22.6)	63 (23.2)
Rural	47 (74.6)	161 (77.4)	208 (76.8)
Age [mean (SE)]	24.6 (0.7)	32.7 (0.5)	30.8 (0.5)
Years of education [mean (SE)]	3.4 (0.5)	2.7 (0.2)	2.9 (0.2)
Age of onset of illness [mean (SE)]	23.5 (0.7)	23.0 (0.5)	23.2 (0.4)
History of neuroleptic treatment at baseline			
No	53 (84.1)	187 (89.9)	240 (88.6)
Yes	10 (5.9)	21 (10.1)	31 (11.4)
Percent of follow up time on treatment [mean (SE)]	29.3 (3.9)	27.5 (2.0)	27.7 (1.7)

*Recent onset cases=cases with onset of recognizable illness within the last two years prior to recruitment into the study; long-standing cases are the remaining cases.

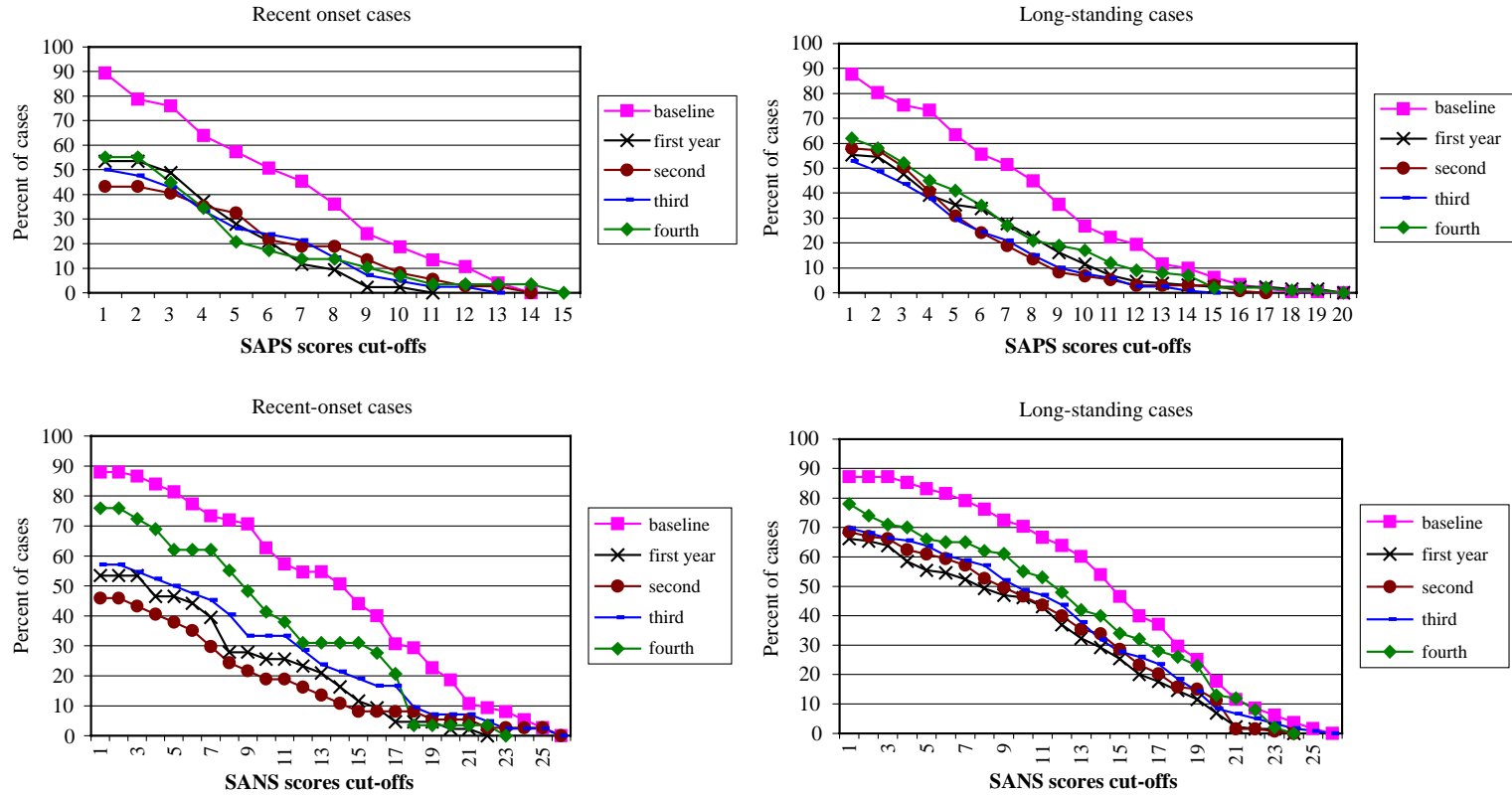


Fig. 1. Distribution of cases of schizophrenia by cut-off scores on the Scale of Positive Symptoms (SAPS) and the Scale for Negative Symptoms (SANS), Butajira Ethiopia, 2004. Higher scores represent higher levels of symptoms. For recent onset cases for example, the cumulative percent of cases who scored 5 or more (i.e. worse) on SAPS at baseline and subsequent years were: 51%, 21%, 22%, 24%, and 17%, respectively.

Table 2

Factors associated with improvements in symptomatic outcomes (positive^a and negative^b symptom scores) among recent^c and long-standing cases of schizophrenia followed for an average of 2.5 (range 1–4) years, Butajira, Ethiopia 2004

Characteristics	Positive symptoms						Negative symptoms									
	Recent onset			Long-standing			Recent onset			Long-standing						
	<i>B</i> ^d	95% confidence interval		<i>B</i>	95% confidence interval		<i>B</i>	95% confidence interval		<i>B</i>	95% confidence interval		<i>p</i>			
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper				
Age (years)	0	-0.1	0.1		-0.1	-0.2	0		0.1	-0.1	0.4		-0.1	-0.2	0	
Sex: male vs female	-2.4	-3.8	-0.9	0.001	-0.5	-1.4	0.5		-4.2	-7.0	-1.4	0.004	-0.6	-2.2	1.0	
Residence: urban vs rural	0	-1.5	1.5		0	-1.0	0.9		-5.0	-7.9	-2.2	0.001	-0.7	-2.3	0.9	
Marital status: married vs other	0	-1.5	1.6		1.2	0.4	2.1	0.005	0.9	-2.1	3.8		2.8	1.2	4.4	0.001
Education (years)	0.1	-0.1	0.3		0	-0.1	0.1		0.6	0.3	0.1	0.001	0.1	-0.1	0.3	
Age of onset (years)	0	-0.1	0.2		-0.1	-0.1	0		0.1	-0.1	0.4		0	-0.1	0.1	
Duration of illness (years)	-0.6	-1.2	0.1		-0.1	-0.1	0		-0.1	-1.3	1.1		-0.1	-0.2	0	
History of neuroleptic treatment at baseline: No vs yes	0	-0.1	0.1		0	-0.1	0.1		0	-0.1	0.1		0	-0.1	0.1	
Percent of follow-up time under treatment	1.1	-0.2	2.3		-0.6	-1.4	0.3		0.7	-1.6	3.1		-0.8	-2.3	0.6	
Time (follow up)	0	-0.5	0.5		0	-0.3	0.4		-0.6	-1.5	0.3		-0.7	-1.3	-0.1	0.01
Baseline symptom score	1.0	0.9	1.2	0.001	0.9	0.8	1.0	0.001	0.8	0.6	1.0	0.001	0.6	0.5	0.7	0.001

^a Baseline and yearly follow up mean scores on the Scale for Positive Symptoms were used as outcome measures.

^b Baseline and yearly follow up mean scores on the Scale for Negative Symptoms were used as outcome measures.

^c Recent onset cases=cases with onset of recognizable illness within the last two years prior to recruitment into the study. Long-standing cases are all others.

^d Coefficients obtained from a random coefficient model with all of the above listed variables included. Age, age of onset of illness and duration of illness were entered separately to avoid problems of co-linearity.

in proportions. To evaluate potential predictors of outcome we employed linear random coefficient models. These have the advantage of using all available data by tolerating missing data. They also allow covariate adjustments, including adjustment for baseline severity levels and unequally spaced time intervals of follow-up (Hennen, 2003; Twisk, 2003).

We fitted models for each of the six outcomes evaluated (actual score change-from-baseline at each yearly assessments for SANS and SAPS scores, and SF-36 scores: PF, SF, and RE) and fitted them as dependent variables. As independent variables, the following were evaluated using the models: four binary variables (sex, marital status, urban–rural residence, history of neuroleptic treatment); and six time-independent continuous variables (age, years of education, age of onset of illness, percent of follow up time under treatment, duration of illness, and the relevant baseline SANS, SAPS, or SF-36 score); and three time-dependent continuous variables (duration of follow-up, and [for functional outcomes only] yearly values of negative and positive symptoms scores). Maximum likelihood estimations were used to fit the random coefficient models to the data, and unstructured correlation matrices were assumed.

The review committees of both the Department of Community Health and the Faculty of Medicine, Addis Ababa University, approved the study. All study subjects were interviewed after informed consent was obtained. The study has made possible the establishment of a mental health service in the district. Cases identified were offered psychiatric treatment (oral and injectable neuroleptic medications) as appropriate, free of charge and this has continued until the present.

3. Results

A total of 271 (84%) cases were available for this follow-up analysis. Over 80% of cases were male, 77% were from rural areas, and they had a mean age of 31 years and 3 years of education. Of the 50 cases that were not included in the analyses, 15 died before having their follow up assessment. Another 18 who died but who had follow up assessments were included in the analysis. (The issue of mortality and schizophrenia will be explored in another paper). Twenty one cases were not available for follow up because of change of address, and 6 refused

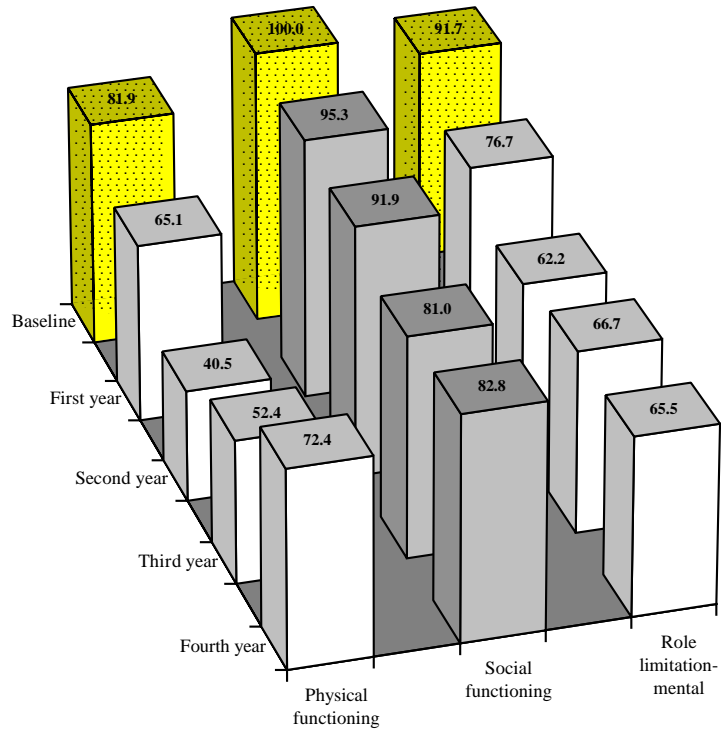
Table 3
SF-36 mean values (and standard deviation) of recent onset* and long-standing cases of schizophrenia and the general population of Butajira, Ethiopia 2004

SF-36 dimensions	Recent onset cases					Long-standing cases					General population (n = 1990)
	Baseline (n = 63)	1st year (n = 43)	2nd year (n = 37)	3rd year (n = 42)	4th year (n = 29)	Baseline (n = 208)	1st year (n = 129)	2nd year (n = 130)	3rd year (n = 119)	4th year (n = 101)	
Physical functioning	67.5 (27.0)	81.0 (67.5)	86.5 (81.0)	78.2 (86.5)	79.1 (78.2)	69.1 (34.8)	73.0 (69.1)	73.0 (73.0)	70.4 (73.0)	72.7 (70.4)	93.1 (15.7)
Role limitations—physical	44.0 (77.2)	59.3 (44.0)	75.7 (59.3)	61.9 (75.7)	65.5 (61.9)	51.7 (71.3)	50.0 (51.7)	56.2 (50.0)	49.6 (56.2)	51.5 (49.6)	89.8 (28.6)
Bodily pain	49.8 (59.0)	76.6 (49.8)	86.1 (76.6)	77.6 (86.1)	88.0 (77.6)	59.8 (51.8)	65.8 (59.8)	77.6 (65.8)	76.3 (77.6)	79.0 (76.3)	88.9 (21.0)
General health	29.9 (72.1)	50.1 (29.9)	54.9 (50.1)	53.8 (54.9)	56.4 (53.8)	31.5 (70.0)	46.1 (31.5)	44.3 (46.1)	50.1 (44.3)	53.4 (50.1)	72.2 (20.2)
Vitality	40.8 (46.6)	54.9 (40.8)	59.1 (54.9)	53.2 (59.1)	51.0 (53.2)	43.0 (43.1)	51.7 (43.0)	49.6 (51.7)	49.2 (49.6)	49.5 (49.2)	60.0 (5.7)
Social functioning	32.9 (50.6)	52.0 (32.9)	56.1 (52.0)	59.8 (56.1)	58.2 (59.8)	36.2 (47.9)	47.2 (36.2)	50.9 (47.2)	54.9 (50.9)	56.4 (54.9)	91.2 (17.2)
Role limitations—mental	12.2 (49.5)	25.6 (12.2)	37.8 (25.6)	33.3 (37.8)	34.5 (33.3)	14.3 (47.3)	16.8 (14.3)	20.0 (16.8)	27.2 (20.0)	28.1 (27.2)	92.4 (24.3)
Mental health	45.4 (26.5)	63.7 (45.4)	65.0 (63.7)	61.6 (65.0)	59.7 (61.6)	52.1 (20.1)	61.3 (52.1)	64.5 (61.3)	61.6 (64.5)	60.1 (61.6)	71.0 (9.9)

Higher mean value indicate higher functioning. All mean SF-36 dimensional scores values of cases were significantly lower than the general population values ($p < 0.01$).

* Recent onset cases=cases with onset of recognizable illness within the last two years prior to recruitment into the study. Long-standing cases are all others.

Recent onset cases



Long-standing cases

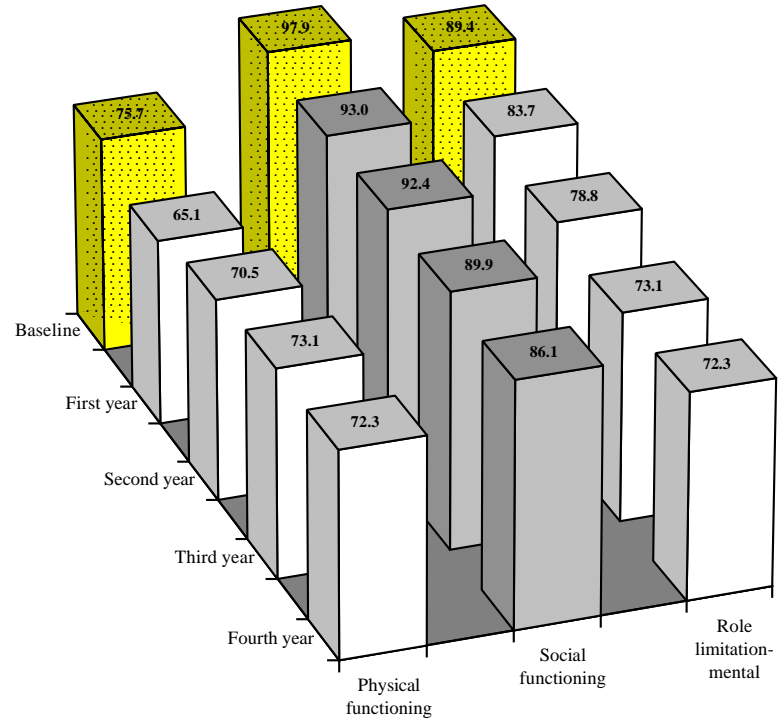


Fig. 2. Percent of schizophrenia cases with individual SF-36 scores below the general population values (i.e. poor functioning) at baseline and at subsequent years of follow up, Butajira, Ethiopia 2004. Numbers on bar indicate percent. For both groups the trend of improvement from baseline is statistically significant for all functional dimensions (p for trend < 0.01).

Table 4

Factors associated with improvements in functional outcomes (physical and social functioning* and role limitations due to mental problems**) among cases of schizophrenia followed for an average of 2.5 years, Butajira, Ethiopia 2004

Characteristics	Physical functioning						Social functioning						Role limitations due to mental health problems											
	Recent-onset [†]			Long-standing			Recent-onset			Long-standing			Recent-onset			Long-standing								
	B [§]	95% CI		p	B	95% CI		p	B	95% CI		p	B	95% CI		p	B	95% CI		p				
		Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper					
Age (years)	-1.2	-5.2	2.8	-0.3	-0.7	0.1		-5.1	-8.9	0.0		0.0	-0.4	0.4		-1.2	-2.9	0.4	0.1	-0.4	0.7			
Sex: male vs female	-0.5	-10.1	9.0	4.3	-1.6	10.3		7.3	-1.6	16.2		-2.0	-7.7	3.7		1.9	-18.4	22.2	-8.3	-18.7	2.1			
Residence: urban vs rural	-4.9	-14.8	5.0	2.5	-3.4	8.5		-3.0	-12.0	6.0		4.1	-1.6	9.7		6.2	-14.3	26.7	5.5	-5.0	15.9			
Marital status: married vs other	-4.3	-14.0	5.4	-1.6	-7.0	3.8		0.1	-9.6	9.7		0.7	-4.7	6.0		-3.2	-25.3	19.0	-3.5	-13.2	6.1			
Education (years)	1.3	0	2.5	0.5	-0.2	1.2		0.6	-0.6	1.7		0.2	-0.4	0.9		2.4	-0.2	5.1	0.8	-0.5	2.0			
Age of onset (years)	-0.4	-1.1	0.3	-0.1	-0.5	0.3		-0.5	-1.2	0.2		-0.3	-0.7	0.1		-0.9	-2.5	0.8	-0.2	-0.8	0.5			
Duration of illness (years)	-0.9	-5.0	3.2	-0.3	-0.7	0.1		-5.0	-8.9	0		0	-0.4	0.4		-7.8	-16.5	0.9	0.4	-0.3	1.0			
SAPS score	-1.2	-1.8	-0.5	0.001	-0.6	-1.2	0.0	0.04	-2.2	-3.2	-1.1	0.001	-0.9	-1.4	-0.4	0.001	-2.3	-4.3	-0.3	0.03	-1.4	-2.4	-0.4	0.006
SANS score	-1.2	-1.6	-0.8	0.001	-1.1	-1.4	-0.8	0.001	-1.4	-1.9	-0.8	0.001	-0.8	-1.1	-0.5	0.001	-1.3	-2.3	-0.4	0.01	-0.6	-1.1	0	
History of neuroleptic treatment at baseline: No vs yes	0.2	0	0.3		0	-0.1	0.1		0.1	0.0	0.2		0	-0.1	0.1		0.1	-0.2	0.3	-0.1	-0.2	0		
Percent of follow-up time under treatment	4.0	-4.7	12.7		0.3	-5.0	5.7		-0.9	-9.0	7.2		-1.5	-6.7	3.8		7.1	-10.9	25.0	-3.0	-12.6	6.7		
Time (follow up)	-0.9	-2.8	0.9		0.0	-1.9	1.9		4.7	1.6	7.8	0.004	4.0	2.4	5.6	0.000	6.4	0.8	12.1	0.03	5.2	1.9	8.5	0.002
Baseline SF-36 score	-0.9	-1.1	-0.8	0.001	-0.9	-0.9	-0.8	0.001	-0.9	-1.1	-0.7	0.001	-0.8	-0.9	-0.7	0.001	-1.1	-1.4	-0.8	0.001	-0.8	-0.9	-0.7	0.001

*Baseline and yearly follow up mean scores of the Physical Functioning (PF), and Social Functioning (SF) dimension of the SF-36 were used as outcome measures. **Baseline and yearly follow up mean scores of the Role-Emotional (RE) dimension of the SF-36 were used as outcome measure. This dimension measures the degree of limitation/restriction of personal, familial and social functions due to mental problems. [†] Recent onset cases=cases with onset of recognizable illness within the last two years prior to recruitment into the study. Long standing cases are all others; [§] Coefficients obtained from a random coefficient model with all of the above listed variables included. Age, age of onset of illness and duration of illness were entered separately to avoid problems of co-linearity. 95% CI=95% Confidence interval.

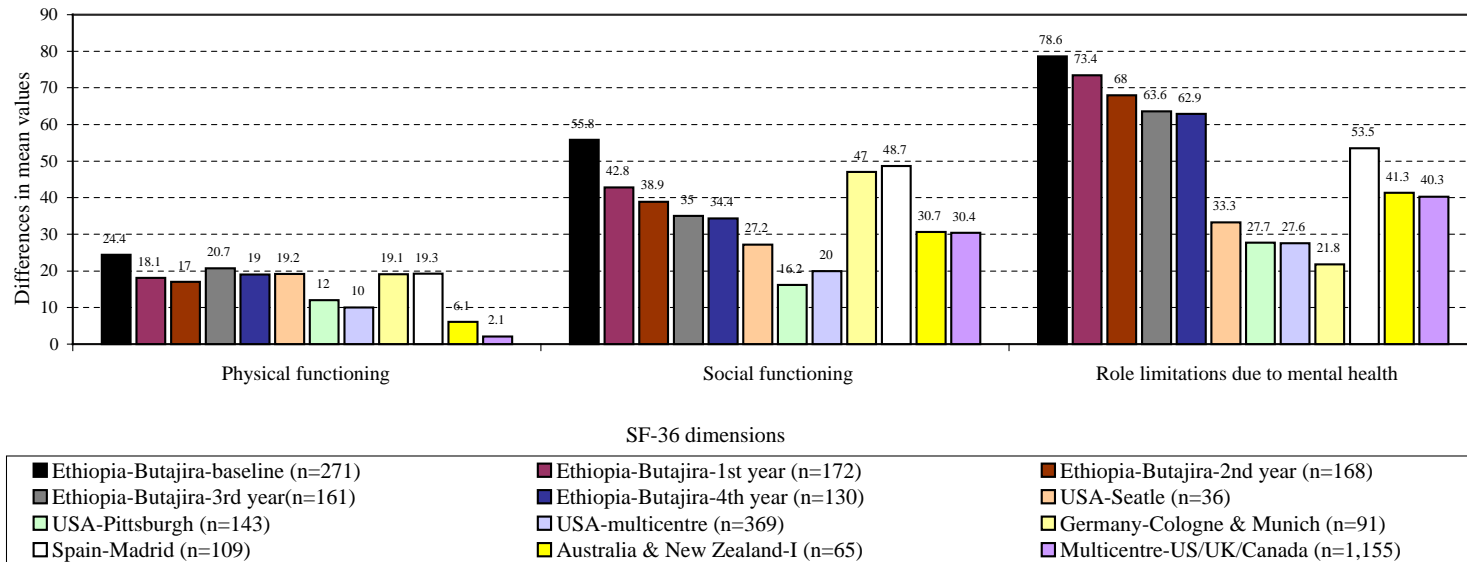


Fig. 3. SF-36 score mean difference between cases of schizophrenia and respective normative populations: Butajira and industrialized countries. Higher mean differences, i.e. higher bar height, indicate lower functioning. See text for sources of international data.

(Table 1). No statistically significant differences were noted in the distribution of male sex, mean age, married, urban residence, neuroleptic naivety, mean age of onset, mean percent of follow up time on neuroleptic treatment, or mean duration of illness in the 50 cases not included in the follow-up analyses, when compared to the 271 cases for whom complete data were available.

The distribution of cases by SAPS and SANS score cut-off levels is shown in Fig. 1. Eleven percent scored zero on the SAPS at baseline, compared to 47%, 57%, 50%, and 45% at the 1st, 2nd, 3rd, and 4th years, respectively. The proportion of cases scoring zero on the SANS was 12% at baseline but between 24% and 54% during subsequent years. Likewise, the proportion of cases with SANS scores of 5 or more decreased on subsequent follow-ups (range: 35–62%) compared to the baseline (77.3%). The distribution of follow-up scores was uniformly lower than that of baseline for both SANS and SAPS scores. This pattern was similar for both recent-onset and long-standing cases. The difference between baseline and yearly mean SAPS and SANS scores was significantly different for both recent-onset and long-standing cases ($p < 0.001$).

In recent-onset cases (Table 2) the magnitude of improvement of SAPS scores from baseline was significantly associated with female sex ($p = 0.001$). None of the other variables were associated with the improvement in scores. Among long-standing cases being married was significantly associated with improvement in SAPS scores. The magnitude of SANS scores was also significantly associated with sex, with higher level of improvement in females compared to males ($p < 0.004$). Urban residence and education were also significantly associated with improvement in SANS scores ($p = 0.001$). In long-standing cases, married individuals had higher improvements in scores than non-married individuals ($p = 0.001$).

All baseline and follow-up SF-36 mean dimensional scores of the cases were lower than the mean scores of the general population of Butajira for both recent-onset and long-standing cases (Table 3). These differences were statistically significant ($p < 0.01$) for all dimensions. Follow-up mean SF-36 scores (i.e. functioning and other measures of health related quality of life) were also significantly different from baseline values for all dimensions in recent-onset cases ($p < 0.01$). In long-standing cases, except for physical functioning and role limitation due to physical health, all dimensions were statistically significant ($p < 0.01$).

The proportions of cases that had individual SF-36 scores of functioning below the mean general population values (i.e. those with poor functioning) are shown on Fig. 2. Among recent-onset cases, more than 90% of cases had baseline SF and RE scores less than the mean of the general population. For all SF-36 dimensions of functioning a linear trend of a

decreasing proportion of cases from baseline is seen in both recent-onset and long-standing cases (p for trend < 0.01).

The associations of socio-demographic and clinical variables with functional outcomes are explored in Table 4. Among recent-onset and long-standing cases, SANS and SAPS scores were inversely associated with improvements in physical and social functioning ($p = 0.001$) and role limitations due to mental health problems ($p < 0.05$). Age, sex, marital status, urban–rural residence, education, neuroleptic use before or after baseline, age of onset, and duration of illness were not significantly associated with improvement in functioning when SANS and SAPS scores were included in the multivariate model.

The case vs. normative population mean SF-36 differences for cases from Butajira are shown side by side with other published mean differences from developed countries in Fig. 3. For the SF-36 measure of role restriction due to mental health (RE) the level of difference-from-normative value (i.e., the level of poor functioning) of cases from Butajira is higher than levels from developed countries. Physical and social functioning levels were comparable to those from Germany and Spain, but were lower than the rest of the industrialized countries.

4. Discussion

Our results show a high level of positive and negative symptoms and poor functioning or disability in the cases at baseline, although there were significant improvements over time. These improvements were associated with a number of socio-demographic and clinical characteristics of the cases.

Our findings are unlikely to be due to bias or confounders. We have taken precautions to avoid the methodological limitations of several prospective course and outcome studies (Eaton, 1995; Westermeyer and Harrow, 1988): (a) we have stratified by incident (recent-onset) and prevalent (long-standing) cohorts to limit selection bias; (b) instead of using care-seeking or institution-based (i.e. non-representative) sample of cases, we have recruited all cases from a defined community, (c) over 90% of the cases were neuroleptic naive at baseline (Kebede et al., 2003); (d) we have employed acceptable diagnostic classification methods to identify cases and used structured, standardized, widely accepted data collection tools to measure both outcomes and potential predictors (the reliability of the local versions of these instruments have also been assessed and reported (Alem et al.,

2004; Fekadu et al., 2000; Rashid et al., 1996); (e) we were able to follow and verify the outcome of over 84% of cases assessed at baseline; (f) 75% the cases were clinically assessed twice or more after baseline; (g) we have compared outcome characteristics of the cases to the general population of the area; and, (h) we used appropriate multivariate techniques to adjust for potential confounders in evaluating predictors of course and outcome.

Our finding of high levels of negative and positive symptoms of the cases at baseline was to be expected, since 90% of the cases were neuroleptic naïve (Kebede et al., 2003). Our finding of significant improvement in positive symptoms from the baseline was also expected as all cases were offered typical neuroleptics, the efficacy of which is well established (Adams et al., 2001; Wyatt, 1991). Moreover, the improvements in negative symptoms in our sample were not as marked as that for positive symptoms, probably because patients were offered only typical neuroleptics (Malla et al., 1999). ‘Atypical’ neuroleptics are not yet widely available in Ethiopia.

The findings of a significant association between female sex and improvements in positive symptoms, and the association of female sex, rural residence, and higher years of education with improvements in negative symptoms, are in agreement with other outcome studies in both developed and developing countries (Jablensky et al., 1992; Bromet et al., 1995). Among long-standing cases, being married was also associated (inversely) with negative symptoms, although it is difficult to assess the importance of this association because the sample did not consist of incident cases.

An important distinction exists between the subjective report of symptoms, such as feeling down hearted, and indicators of disability, such as how well one functions socially and at work. Subscales of the SF-36, such as MH, VT and GH perception, assess a patient’s subjective sense of well-being and depression rather than disability. In contrast, scores of PF, RP, SF and RE assess daily functioning directly (Ware and Sherbourne, 1992). Thus markedly diminished SF-36 scores of general health, vitality, mental health, correspond with the findings of high positive and negative symptoms in the same cases. Because schizophrenia is a disabling disease, it is expected that the level of functioning, especially physical functioning (PF), social functioning (SF), and personal, familial and social

role limitations due to mental health (RE), will be diminished in cases as compared to the general population of the area. However, the magnitude of the difference, even after the years of follow up, was substantial indicating a high level of residual disability in both the recent-onset and long-standing cases.

Even though the level of disability at baseline was high for the Butajira cases, there was a significant trend in functional improvement with follow-up, although this was not as marked as improvements in positive symptoms. A number of other investigators have also noted that improvements in functioning are not as marked as improvements in positive symptoms (Robinson et al., 2004; Westermeyer and Harrow, 1988). The effect of typical neuroleptics on positive symptoms could also improve the subjective feelings of well-being or functionality, although their limited effect on negative symptoms and their side effects may impact negatively on functionality (Lambert and Naber, 2004). Moreover, other forms of rehabilitative interventions may be required to further improve functioning in cases (Institute of Medicine, 2001).

Our study also shows that improvements in functioning are inversely associated with the magnitude of negative and positive symptoms. The association between negative symptoms and lower functioning could be due to measurement overlap. The anhedonia–asociality and the avolition–apathy ratings on SANS also assess occupational functioning and other familial and social role limitations, which are also assessed by the SF-36 (Ho et al., 1998). On the other hand, the disabling effects of positive symptoms on work and other social functioning are well known (Ho et al., 1998). When SANS and SAPS scores were taken into account in a multivariate model socio-demographic and clinical factors were not associated with functional outcomes. Although some of these factors were reportedly associated with functional outcomes in other reports, very few studies controlled for symptom levels in multivariate models in evaluating the associations (Eaton, 1995; Westermeyer and Harrow, 1988).

Duration of illness in our sample may correspond to duration of untreated psychoses (DUP), as 85% or more of our cases were neuroleptic naïve at baseline. DUP has been shown to be associated with poor outcome in a number of studies in both developed (Norman and Malla, 2001) and developing countries (Tirupati et al., 2004), although the latter study did not

adjust for potential confounders in a multivariate model. DUP's significance in developed countries has also been contested on the grounds that it may be a result of confounding (Verdoux et al., 2001). Both DUP and neuroleptic naivety were not associated with poor outcome in the present study. The probable major reasons for delay in seeking treatment in Butajira were the unavailability of mental health service in the area prior to the start of the present study, stigma (Shibre et al., 2001), limited awareness on the need for neuroleptic treatment or the lack of resources to go to the nearest mental health facility (located in the capital city 135 km away).

Marital status was shown to be an independent predictor of outcome in major studies in both developed and developing country settings (Padmavathi et al., 1998; Jablensky et al., 1992). Our finding of no association between marital status and functional outcomes was thus not expected, although a recent study from Singapore also reported a similar finding to ours (Kua et al., 2003). Being married may be an indicator of increased family support and enhanced treatment compliance. If such is the case, our inclusion in the multivariate model of an indicator of treatment compliance may have attenuated the marital status and outcome association. Very few developing country studies have adjusted for treatment compliance (Padmavathi et al., 1998; Jablensky et al., 1992).

We have also shown that the differences between cases and the general population in scores of functionality, and thus levels of disability, in Butajira were equal or higher than those of developed countries. The lower functioning of our cases could be due to the lack of treatment, as all cases in the developed countries were on atypical neuroleptics, while our cases were only offered typical neuroleptics. Other factors could also explain these results. The incident-prevalent ratio of cases may vary between the various studies reported. Moreover, for cases participating in the three clinical trials (Nasrallah et al., 2004; Gureje et al., 2003; Tunis et al., 1999), it is possible that cases with milder course or outcome were over-sampled. It is difficult to quantify the relative contributions of these factors in explaining our findings. However, it is unlikely that only methodological reasons account for our findings, as the level of functioning of cases in Butajira was lower than (or comparable to) cases in all of the developed countries

assessed. Thus, our findings are not in accord with the WHO's cross-country studies (Jablensky et al., 1992; Leff et al., 1992), or other studies (Institute of Medicine, 2001; Ohaeri, 1993) that have reported better functioning of cases from developing countries.

There are limitations to the study. One possible source of error is misclassification of age in this predominantly rural and illiterate population where a proportion of the cases did not know their age. In some cases we had to use major historical events to estimate the age of participants. This problem could also affect the accuracy of related variables such as age of onset and duration of illness. This problem would be less problematic in recent-onset cases compared to long-standing cases. In any case, the resultant misclassification is likely to be random and thus would probably tend to diminish the model coefficients to the null value (Rothman, 1986). Thus, our reported estimates could be regarded as conservative. We have not also used psychiatrists for the collection of data on clinical outcomes. This was not feasible in our situation where there are only 10 psychiatrists for a country of 75 million (Alem, 2001). However, the physicians employed in the study had several years of experience working in a psychiatric hospital, were trained on the SCAN and other clinical instruments, and their reports were evaluated by a senior psychiatrist trained in Manchester, UK (one of the authors: AA). Our outcome assessments were done cross-sectionally at yearly intervals, and assumed that those assessments would truly reflect the outcome pattern during the entire 12 months prior to the assessment. Although, this is a method that has been followed by almost all outcome studies reported in the literature albeit with varying degree of success (an der Heiden and Hafner, 2000), we cannot ascertain if our cases had a stable course of illness during the intervening period between the yearly follow up assessments. Pattern of treatment use was assessed based on information gathered from cases or informants only and was not corroborated by laboratory investigations.

In conclusion, our study shows that: (i) the level of positive and negative symptoms was high at baseline and follow up, and that there were significant improvements in both positive and negative symptoms from the baseline, although the change in negative symptoms was less marked; (ii) female sex was associated with improvement in positive symptoms,

while female sex, rural residence, and education were significantly associated with improvement of negative symptoms; (iii) functioning and other measures of health related quality of life of cases were significantly lower than for the general population of the area, both at baseline and follow up, although there were significant improvements in these measures over time; (iv) of the socio-demographic and clinical factors evaluated in a multivariate model, only lower negative and positive symptom scores were significantly associated with improvements in functioning; and, (v) the level of functioning of cases in the present study is lower than reports from developed countries.

Further follow up of these cases is recommended to describe medium- and long-term outcomes. International comparison of outcomes of schizophrenia would be more informative if studies from both developing and developed countries described and reported the difference in functioning between their cases and the general populations.

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