

Received:
27 September 2018
Revised:
11 December 2018
Accepted:
20 February 2019

Cite as: Derege Kebede,
Abebaw Fekadu,
Teshome Shibre Kelkile,
Girmay Medhin,
Charlotte Hanlon,
Rosie Mayston,
Atalay Alem. The 10-year
functional outcome of
schizophrenia in Butajira,
Ethiopia.
Heliyon 5 (2019) e01272.
doi: [10.1016/j.heliyon.2019.e01272](https://doi.org/10.1016/j.heliyon.2019.e01272)



The 10-year functional outcome of schizophrenia in Butajira, Ethiopia

Derege Kebede^{a,*}, Abebaw Fekadu^{b,f,g}, Teshome Shibre Kelkile^c, Girmay Medhin^d,
Charlotte Hanlon^{b,e}, Rosie Mayston^e, Atalay Alem^b

^a Department of Preventive Medicine, School of Public Health, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

^b Department of Psychiatry, School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

^c Department of Psychiatry, Horizon Health Network, Fredericton, NB, Canada

^d Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia

^e Centre for Global Mental Health, Health Service, and Population Research Department, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, UK

^f Centre for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

^g Department of Global Health & Infection, Brighton and Sussex Medical School, Brighton, UK

* Corresponding author.

E-mail address: deregekebede@yahoo.com (D. Kebede).

Abstract

Background: Long-term functional schizophrenia outcomes are not well characterized in low-income environments because of the rarity of prospective studies.

Objectives: To assess and describe long-term schizophrenia's functional outcomes and potential outcome predictors.

Methods: Following a baseline assessment, 316 people with schizophrenia were studied for 10 years, on average. Of the total, 79 were incident cases: cases with onset of the illness occurring two years or less from entry into the study. SF-36 scores of physical and social functioning were used to assess functional

outcomes. Linear mixed models were employed to evaluate the association of functioning with potential predictors.

Results: Social and physical functioning scores regarding the cohort were lower than the population's norm for most of the follow-up period. Incident cases had better function than prevalent cases. Fifteen percent of incident and 30% of prevalent cases had reduced social functioning for at least six years. Declining symptom severity during the follow-up period was significantly associated with improvement in social functioning. When baseline functioning was controlled for, the long-term trend in functionality was not associated with demographic or illness characteristics (age and speed of onset, duration of illness and neuroleptic use at entry, substance use, and medication adherence).

Conclusion: Long-term physical and social functioning of the population with schizophrenia were significantly lower than the population norm. A significant proportion of the cohort had lower functioning for the long-term. Functioning was not associated with demographic or illness characteristics of the study population.

Keywords: Psychiatry, Clinical psychology, Epidemiology, Public health

1. Introduction

The field of mental health services has experienced a shift from its previous emphasis to reduce symptoms through a treatment focused approach to taking into consideration both the functioning and well-being of the patient (Brazier et al., 2014). Follow-up studies of schizophrenia have often focused on clinical outcomes, with less consideration of functional outcomes (Feeny et al., 2013). In those studies that examined functional outcomes the measuring instruments used were not generic and or they lack data on population norms, and thus comparison of the disability of schizophrenia to the general population or other illness was not possible.

Prospective population-based studies of course and outcome of schizophrenia are scarce in low and middle-income countries. Of these, studies focusing on physical and social functioning are even rarer (Ran et al., 2017; Esan et al., 2012; Novick et al., 2012; Gureje and Cohen, 2011; Thara et al., 1994; Ohaeri, 1993). We have earlier reported on short-term functional outcomes, and long-term clinical course and outcome of schizophrenia in Butajira, a rural community in Ethiopia (Shibre et al., 2014; Alem et al., 2009; Kebede et al., 2004a).

The unique features of the study were that cases were recruited from the community instead of clinics, and over three-quarters of these were neuroleptic naïve at entry. Also, we used the Medical Outcomes Short Form (SF-36) instrument a generic functional assessment instrument that enables comparison with the population norm or other illnesses. Because of the availability of published local general population norms

the SF-36 (Kebede et al., 2004b), we were able to compare the physical and social functioning of the people with schizophrenia to the general population of Butajira.

In this paper, we describe the long-term social and physical functional outcome of people with schizophrenia that were followed for an average of 10 years. We also present the results of comparisons of functioning between our cohort with general population of Butajira. Also, we have evaluated several potential socio-demographic and clinical predictors of physical and social functioning in schizophrenia.

2. Methods

Details concerning case identification methods for Butajira's cohort have been previously reported (Shibre et al., 2014; Shibre et al., 2002; Kebede et al., 2003; Alem et al., 2009) and are as follows:

Butajira is a predominantly rural district, located in central Ethiopia and found approximately 132 km from the capital, Addis Ababa. Primary occupations in this area include farming, as well as small businesses which are located in town.

Participants were enrolled into the study between March 1998 and May 2001, following a two-stage method. Throughout the initial stage, 68,378 adults, aged 15–49 years (out of the total district population of the age group of 83,282) were interviewed via home surveys which used the Composite International Diagnostic Interview (CIDI 2.1) (Sartorius and Janca, 1996; Ustün et al., 1997). The key informant method was used to identify and recruit additional participants (Shibre et al., 2002). Participants found positive during this stage were given a diagnostic assessment using Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1) (Sartorius and Janca, 1996; Ustün et al., 1997). Following SCAN interviews, 359 persons confirmed to have schizophrenia (APA, 1994; World Health Organization, 1994), were placed in the cohort of which, 46 cases with incomplete income data were excluded. This gave a total of 316 cases, of which 79 were incident cases: cases with onset of the illness occurring two years or less from entry into the study (Fig. 1). The study also identified 345 people with bipolar disorders and 215 with major depression. The relatively small number of cases of major depression is because the screening process focused on identifying those people with major depression with psychotic features.

All participants were provided with access to basic psychiatric treatment, primarily via first-generation antipsychotics such as haloperidol, chlorpromazine, thioridazine and fluphenazine decanoate, as well as tricyclic antidepressants such as amitriptyline or imipramine. These are commonly used in psychiatric clinics throughout the country. Doses of antipsychotic medications and chlorpromazine doses equivalent to the antipsychotic medications were provided at between 25 mg and 300 mg/day.

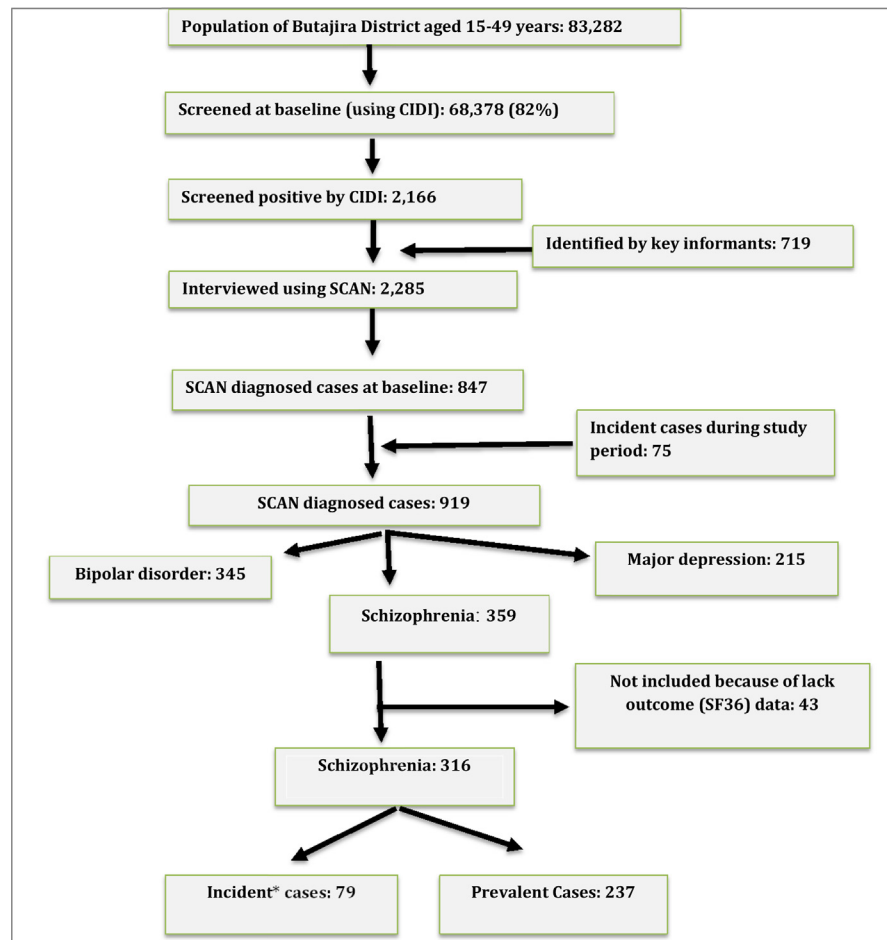


Fig. 1. Flow diagram of the follow-up study of people with schizophrenia in Butajira, Ethiopia. *Incident cases with onset of illness two years or less at entry to the study.

The primary outcomes that were evaluated yielded annual SF-36 scores on physical and social functions: PF and SF. Follow-up measurements of clinical and functional characteristics continued on a monthly basis in the Butajira psychiatric clinic, as well as two additional outreach clinics established due to the research project.

The SF-36 scores were used to quantify functional outcomes. The SF-36 is often used to measure functional outcomes regarding that of physical and mental illnesses, and has proven to be effective in measuring functioning, as well as health-related quality of life (Brazier et al., 1992). The instrument continuously demonstrated appropriate internal consistency and stability, as well as concurrent validity in patients with schizophrenia (Tunis et al., 1999; Russo et al., 1998). The Amharic version used here also demonstrated reliability and validity in assessing Butajira's general population (Kebede et al., 2004b). The SF-36 instrument provides 36 items yielding eight domains when scored. The initial domain includes physical functioning, which provides an assessment of limitations to physical activities, such as walking and climbing. Social functioning domain includes two items and examines impacts on physical and

emotional health related to regular social activities. We used these two (PF and SF) domains to assess physical and social functioning because they directly assess daily functions (Ware, 1993). Higher SF-36 scores represent higher function capabilities.

Clinical course, as well as outcome data were collected via the Longitudinal Interval Follow-up Evaluation (LIFE) chart (Keller et al., 1987). The LIFE chart is a questionnaire able to summarize longitudinal data. Four psychiatrists were trained for four days to administer and address the LIFE chart. Primary rating policies regarding the LIFE chart include the Psychiatric Status Rating (PSR). The PSR is a six-point symptom rating severity. A one rating indicates the absence of symptoms. In contrast, a six rating is consistent with significant or severe symptoms. Utilizing all available information, the PSR provided reports from cases and families of those experiencing the condition, monthly clinical records, annual symptomatic and functional ratings, psychiatric nurse reports, and finally project outreach reports provided by workers who held monthly contacts with patients and their families. When participants were unable to attend the required psychiatric clinic for a final assessment, raters visited participants at home with their permission. Two senior psychiatrists well-versed with the LIFE chart supervised ratings.

The Statistical Package for Social Sciences (SPSS version 19) and A SAS-based SF-36 scoring algorithm were used to analyze data. When comparing cohort SF-36 scores to the general population, published SF-36 values of Butajira's general population were reviewed and used (Kebede et al., 2004b). In order to evaluate potential outcome predictors linear mixed models on SPSS were used. Baseline values of outcomes were included in the models to adjust for baseline differences in scores. Models for each outcome were assessed, which were the yearly scores of PF and SF and PSR. The following predictors were evaluated as predictors using the nine categorical variables: age, sex, literacy, marital status, urban-rural residence, substance use, speed of onset, neuroleptic use at baseline, and medication adherence. Seven continuous variables, those being baseline PF, SF and PSR scores, follow-up PSR scores, age of onset, duration of illness at baseline, and duration of follow-up were also used. We fitted multivariate random mixed linear models to evaluate long-term outcome (Twisk, 2003).

2.1. Ethical considerations

Addis Ababa University's Research and Publication Office approved the study. All subjects or caregivers provided consent. Free health care, including medications, were available to all participants throughout the follow-up.

3. Results

A total of 316 people with schizophrenia that were identified at baseline and with complete data on functional outcome were used in the analysis (Fig. 1), 79 of which

were incident cases with the onset of illness two years or less at on entry to the study. Males accounted for 83% of cases in both the incident and prevalent cases (Table 1). About three-quarters of the cohort were not married, living in rural areas. The average age of incident cases (26 years) was lower than that of prevalent cases (32 years). However, the average years of education were similar in the two groups (about three years). At baseline, 75% of incident and 88% of prevalent cases had no

Table 1. Baseline characteristics of people with schizophrenia in the Butajira follow-up study, Ethiopia.

		Incident Cases ^a		Prevalent Cases		All Cases	
		Number	Percent	Number	Percent	Number	Percent
Sex	Female	13	16.5	41	17.3	54	17.1
	Male	66	83.5	196	82.7	262	82.9
Marital status	Married	19	24.4	67	29.0	86	27.8
	Others	59	75.6	164	71.0	223	72.2
Residence	Urban	22	27.8	53	22.4	75	23.7
	Rural	57	72.2	184	77.6	241	76.3
Speed of onset	Acute ^b	45	66.2	117	60.0	162	61.6
	Insidious	23	33.8	78	40.0	101	38.4
History of treatment	None	54	74.0	178	88.6	232	84.7
	Other	19	26.0	23	11.4	42	15.3
Substance use	No	60	75.9	144	60.8	204	64.6
	Yes	19	24.1	93	39.2	112	35.4
Medication adherence	≤75%	49	62.0	144	60.8	193	61.1
	>75%	30	38.0	93	39.2	123	38.9
Total ^c		79	100.0	237	100.0	316	100.0
		Mean	Standard Error (SE)	Mean	SE	Mean	SE
Age	Years	26.0	.8	32.2	.5	30.6	.5
Education	Years	3.6	.5	2.8	.3	3.0	.2
Age of onset	Years	24.9	.8	23.3	.5	23.7	.4
Follow-up duration	Years	10.0	.3	10.6	.2	10.5	.2
Duration of illness at entry to study	Years	1.4	.3	9.8	.6	7.6	.5
Baseline physical functioning score ^d	Scale: 1-100	69.1	2.5	58.4	1.6	61.0	1.4
Baseline social functioning score ^d	Scale: 1-100	48.7	2.8	40.4	1.3	42.5	1.2
Baseline symptom severity score ^e	Scale: 1-6	5.2	.1	4.9	.1	4.9	.1

^a Incident cases are those with the onset of illness two years or less on entry to the study.

^b Acute = onset within three months or less.

^c Missing values not shown-sub-totals may vary.

^d Higher mean score values indicate higher functioning.

^e Higher mean score values indicate more severe symptoms.

history of neuroleptic treatment, and baseline social function score was higher in the incident (48.7) compared to prevalent cases (40.4). Both incident and prevalent cases were followed for ten years.

There was a progressive increase in the SF-36 social functioning (SF) scores (i.e., the trend of improvement) during the period, but this was not as marked for physical functioning (Fig. 2). The level of improvement in social and physical function was higher in incident than prevalent cases. However, the scores for both were significantly lower than that of the population means for most of the follow-up period, as shown by the non-overlap of the 95% confidence limits of the mean values between the study and the general population.

Percentages of follow-up time in reduced functional states are shown in Fig. 3. Three-quarters of the cohort had reduced functioning for at least two years, and 15–30% for at least six years. A higher percentage of prevalent cases had reduced functioning (i.e., physical and social functioning lower than the population norm) for a longer period compared to incident cases. For example, 15% of incident and 30% of prevalent cases had reduced social functioning for at least six years. The corresponding figures for physical function were 11% and 27%, respectively.

The association between the yearly improvement of social and physical functioning, and course of illness on the one hand and demographic and clinical factors on the other were evaluated using multivariate random mixed linear model (Table 2). Baseline social functioning was significantly associated with improving trend of social functioning throughout the follow-up study ($P < 0.001$). Improvements in social functioning were significantly associated with declining PSR scores (i.e., symptom severity) throughout the follow-up study in prevalent cases ($P < 0.001$), but was not evident in incident cases. Onset age, onset speed, duration of illness at recruitment,

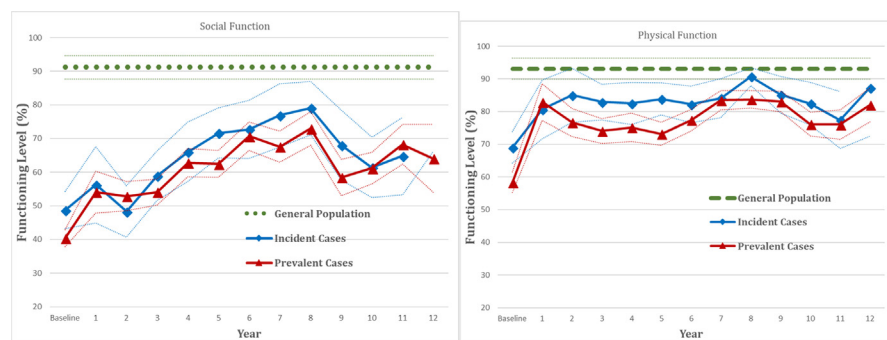


Fig. 2. Yearly trend in mean functioning level (%) of people with schizophrenia* compared to the general population norm, Butajira, Ethiopia (the fine dotted lines represent 95% confidence limits). * Incident cases ($n = 79$) are those with the onset of illness two years or less on entry to the study. The rest were categorized as prevalent cases ($n = 237$); Short Form Medical Outcome (SF-36) physical and social function scores were used as outcome measures. SF-36 score mean values are given on a scale of 1–100. Higher mean values indicate higher functioning.

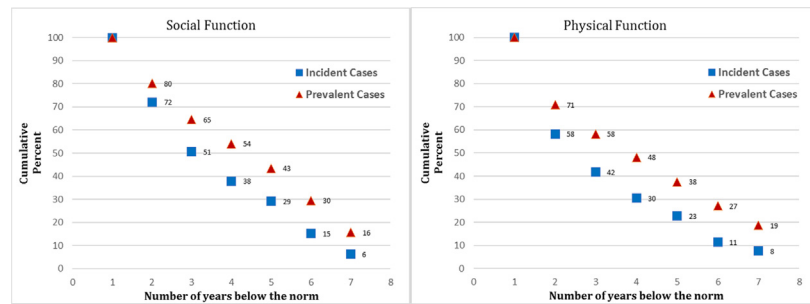


Fig. 3. Length of time in which people with schizophrenia had reduced *social and physical functioning**, Butajira, Ethiopia. * As compared with the population norm. For example: about a third (29%) of the incident and close to half (43%) of prevalent cases had reduced social functioning for five years or more. Incident cases are those with the onset of illness two years or less on entry to the study.

history of neuroleptic treatment before recruitment, and substance use (alcohol, tobacco, and khat¹), and medication adherence were not associated with social functioning. Similarly, age, sex, rural residency, education, and marital statuses were not related to social functioning.

The baseline level of PF scores (Table 3) was significantly associated with improving trend of physical functioning during the follow-up period in both incident and prevalent cases ($P < 0.001$). Improvement to physical functioning was not significantly associated with declining PSR scores during the follow-up period. Age of onset, onset speed, illness duration at recruitment, history of use of neuroleptic treatment before recruitment, substance use, and medication adherence were not associated with physical functioning. Age, sex, rural residence, education, and marital status were not associated with improvement in physical functioning.

4. Discussion

Our results show that physical and social functioning of the study population with schizophrenia were lower than the population norm for most of the follow-up time, although functioning improved with time. Declining symptom severity during the follow-up period were associated with improvements to social functioning when baseline functioning was controlled for. Demographic or illness characteristics (age and speed of onset, illness duration, neuroleptic use at entry, substance use, and medication adherence) were not associated with the long-term trend in functionality or clinical course.

¹ Khat is a flowering plant (*Catha edulis*), the leaves of which are chewed for their stimulant and appetite-suppressing effect. The leaves contain cathinone, which is an amphetamine-like molecule.

Table 2. Factors associated with a yearly trend in improvement of the social functioning of people with schizophrenia followed for an average of 10 years in Butajira, Ethiopia.

		Incident Cases ^a				Prevalent Cases				All Cases			
		β^b	95% confidence interval		P	β^b	95% confidence interval		P	β^b	95% confidence interval		P
			Lower	Upper			Lower	Upper			Lower	Upper	
Age	Years	-.05	-.2	.1	ns	.01	-.05	.1	ns	.00002	-.1	.1	ns
Sex	Female	1.2	-1.1	3.5	ns	-.2	-1.4	1.0	ns	.1	-.9	1.2	ns
	Male	Ref				Ref				Ref			
Residence	Urban	1.1	-1.0	3.3	ns	.1	-1.0	1.2	ns	.3	-.6	1.3	ns
	Other	Ref				Ref				Ref			
Education	Years	.03	-1.4	1.4	ns	.02	-.1	.2	ns	.1	-.1	.2	ns
	Other	Ref				Ref				Ref			
Marital status	Married	.003	-2.5	2.5	ns	-.4	-1.5	.7	ns	-.3	-1.4	.7	ns
	Other	Ref				Ref				Ref			
Age of onset	Years	-1.0	-2.1	.2	ns	.02	-.1	.1	ns	.01	-.1	.1	ns
Speed of onset	Acute	1.1	-1.0	3.2	ns	.2	-.8	1.3	ns	.2	-.7	1.1	ns
	Insidious	Ref				Ref				Ref			
Duration of illness at entry	Years	-.1	-.7	.5	ns	.01	-.1	.1	ns	.01	-.1	.1	ns
Neuroleptic use at entry	No	-1.8	-3.9	.3	ns	-.5	-2.0	1.0	ns	-.8	-2.0	.4	ns
	Yes	Ref				Ref				Ref			
Substance use	No	-.7	-2.8	1.5	ns	.04	-1.0	1.0	ns	-.1	-.9	.8	ns
	Yes	Ref				Ref				Ref			
Medication adherence	≤75%	.2	-1.8	2.1	ns	.8	-.2	1.7	ns	.7	-.2	1.5	ns
	>75%	Ref				Ref				Ref			
Yearly severity of illness score	1-6	-.4	-1.1	.2	ns	-.4	-.7	-.04	ns	-.4	-.7	-.1	ns
Baseline social function score	1-100	.5	.3	.6	<.001	.4	.3	.5	<.001	.5	.4	.5	<.001
Time	Years	1.5	.5	2.5	.005	1.2	.6	1.7	<.001	1.3	.8	1.7	<.001
Intercept	1-100	60.0	54.9	65.1	<.001	56.1	53.5	58.6	<.001	56.9	54.6	59.2	<.001

^a Incident cases are those with the onset of illness two years or less on recruitment to the study.

^b Yearly mean follow-up scores on the Short Form Medical Outcome (SF-36) social function scores were used as outcome measures. Coefficients, *B*, obtained from a random coefficient model adjusted for age, sex, baseline SF36 scores, and longitudinal Psychiatric Status Rating (PSR) scores, and follow-up duration. A positive coefficient, *B*, indicates a trend of improvement in functioning. ns = not significant.

Table 3. Factors associated with a yearly trend in improvement of the physical functioning of people with schizophrenia followed for an average of 10 years in Butajira, Ethiopia.

		Incident Cases ^a			Prevalent Cases			All Cases					
		β^b	95% confidence interval		P	β^b	95% confidence interval		P	β^b	95% confidence interval		P
			Lower	Upper			Lower	Upper			Lower	Upper	
Age	Years	.1	.0	.2	ns	.02	-.02	.1	ns	.03	-.01	.1	ns
Sex	Female	-.1	-1.4	1.3	ns	.8	-.03	1.6	ns	.6	-.1	1.3	ns
	Male	Ref				Ref				Ref			
Residence	Urban	-.4	-1.6	.8	ns	-.7	-1.4	.1	ns	-.6	-1.3	.0	ns
	Other	Ref				Ref				Ref			
Education	Years	-.01	-.2	.1	ns	-.1	-.2	.04	ns	-.04	-.1	.04	ns
	Other	Ref				Ref				Ref			
Marital status	Married	.6	-.9	2.1	ns	-.1	-.9	.6	ns	.02	-.7	.7	ns
	Other	Ref				Ref				Ref			
Age of onset	Years	-.2	-.9	.4	ns	-.1	-.1	.01	ns	-.04	-.1	.01	ns
Speed of onset	Acute	-.1	-1.3	1.1	ns	-.3	-1.1	.4	ns	-.3	-.9	.3	ns
	Insidious	Ref				Ref				Ref			
Duration of illness at entry	Years	.3	-.2	.9	ns	.03	-.01	.1	ns	.03	-.01	.1	ns
Neuroleptic use at entry	No	-.3	-1.6	.9	ns	.9	-.2	2.0	ns	.5	-.3	1.4	ns
	Yes	Ref				Ref				Ref			
Substance use	No	.5	-.8	1.7	ns	.1	-.6	.8	ns	.2	-.4	.8	ns
	Yes	Ref				Ref				Ref			
Medication adherence	≤75%	.6	-.5	1.7	ns	-.1	-.7	.6	ns	.04	-.5	.6	ns
	>75%	Ref				Ref				Ref			
Yearly severity of illness score	1–6	-.1	-.4	.3	ns	.04	-.2	.3	ns	.01	-.2	.2	ns
Baseline physical function score	1–100	.4	.4	.5	.000	.5	.4	.5	.000	.5	.4	.5	.000
Time	Years	.02	-.7	.7	ns	.4	-.03	.8	Ns	.3	-.03	.7	ns
Intercept	1–100	83.6	80.2	86.9	.000	75.7	73.7	77.7	73.3	77.4	75.6	79.1	.000

^aIncident cases are those with the onset of illness two years or less on recruitment to the study.

^bYearly follow-up scores on the Short Form Medical Outcome (SF-36) physical function scores were used as outcome measures. Coefficients, *B*, obtained from a random coefficient model adjusted for age, sex, baseline SF36 scores, and longitudinal Psychiatric Status Rating (PSR) scores, and follow-up duration. A positive coefficient, *B*, indicates a trend of improvement in functioning. ns = not significant.

The findings are unlikely a result of bias or confounders; precautions were taken to avoid methodological pitfalls. We included all people with schizophrenia from a defined community instead of institutional-based enrolment, and over 85% of the people with schizophrenia were neuroleptically naïve at baseline. We stratified incident in addition to prevalent cases and controlled for duration of illness in a multivariate model to limit selection bias (Revier et al., 2015). We used accepted diagnostic classification schemes and data collection tools that have been evaluated for reliability (Alem et al., 2004; Kebede et al., 2004b; Fekadu et al., 2000; Rashid et al., 1996). Clinical diagnoses and course of illness were assessed longitudinally using standardized methods. We were able to compare functional outcomes of the study population to that of the general population and used suitable multivariate models to address possible confounders when evaluating predictors of functional and clinical outcomes.

Due to schizophrenia's ability to be disabling, baseline functioning levels are expected to be lower in those with schizophrenia compared to the general population. Although this gap diminished, it persisted after the follow up, indicating high levels of residual disability due to the illness. We have shown that a substantial percentage of people with schizophrenia had continued to be in a state of reduced functioning during follow-up. Thus, although on average improvement was seen, a significant percentage of cases had a chronic unrelenting course of illness as was described in the literature (Jääskeläinen et al., 2013; Newman et al., 2012; Haro et al., 2008; Cohen et al., 2008; Patel et al., 2006). We are not aware of other studies of schizophrenia that had attempted a comparison of functioning in cases and the general population.

Our finding of low levels of physical and social functioning at baseline was to be expected since most of the people with schizophrenia had no history of neuroleptic use before joining the study. In addition, improvement in social functioning during follow-up was expected as all cases were treated by typical neuroleptics. Other studies have also reported functional recovery during the first five years after recovery (Robinson et al., 2004). On the other hand, it is possible that our finding may under-estimate the actual functioning level of the people with schizophrenia. This is because long-standing cases may express relative satisfaction with their condition due to adaptation to their condition over time and because they usually compare themselves to their peer group with similar impairments instead of the general population (Priebe, 2007; Habtamu et al., 2017).

Longitudinal symptom severity level was associated with social functioning in our study. Several studies reviewed by Jarcaz et al., (2015) have also shown similar results. When symptom severity is controlled for in the mixed random model, physical and social functioning were not associated with socio-demographic separations or characteristics. This is in accord with our earlier report on the short

term of schizophrenia (Kebede et al., 2005) and other studies (Kua et al., 2003). However, this is not in accord with follow-up studies conducted in developed, as well as developing countries (Rangaswamy and Greeshma, 2012; Bromet et al., 1995; Jablensky et al., 1992). Systematic reviews (van der Werf et al., 2014) have shown gender as an important predictor at different stages of life, although our study did not show this. This could be differences in methods between our and other studies. Very few of such studies adjusted for covariates using appropriate multivariate models for repeated measurements as we did. The associations observed in those other studies were thus not shown to be independent of each other or to other relevant clinical factors, particularly differences in baseline functioning and longitudinal illness severity.

Both duration of illness and neuroleptic naivety were found to not be associated with trends of physical and social functioning in the current study. Illness duration throughout the study might correspond to the duration of untreated psychoses (DUP); the majority of cases had no history of treatment with a neuroleptic medication at baseline. DUP showed an association with poor outcomes in some studies in both developed and developing countries (Penttila et al., 2014; Norman and Malla, 2001). However, its significance has been disputed as it may be the result of confounding (Verdoux et al., 2001). Substance use was not significantly associated with functioning in our study, although some studies had shown such an association as reviewed by Holla and Thirthalli (2015). However, the reviewers had stated that substance use and outcome in schizophrenia had not been well studied. Treatment adherence was also not associated with functionality. Our findings of non-significant association between substance use and treatment adherence with functionality could be due to type II error as the size of group was relatively small.

The study did have limitations. The possibility of errors due to misclassification of age as a proportion of participants could not state their actual age, which necessitated using major historical events in an effort to estimate age. Thus, any accuracy regarding related variables including age of onset and illness duration may be affected. The LIFE Chart and PSR scores were used to measure clinical severity. It is not clear how this method compares with standard scales for psychopathology such as PANSS (Suzuki, 2011). Our assessments of functional outcome were completed cross-sectionally and annually. It was assumed assessments would reflect an accurate pattern of outcomes throughout the 12 months before the assessment. While this is common practice, we cannot ascertain whether people with schizophrenia had a stable course of illness throughout the duration of the intervening period between annual assessments. Symptomatic and functionality assessment were based on information obtained from both the patients and care-givers.

In conclusion, our study shows a significant gap in physical and social functioning between the study and the general population that persisted with the follow-up, albeit with the diminishing of the gap with time. Baseline functioning levels and course of illness were associated with long-term functioning. When adjustments were made, socio-demographics and additional clinical factors were not associated with trends in physical and social functioning. Long-term follow-up studies of 20–30 years are rare in developing countries and have not been conducted throughout sub-Saharan Africa. Further, follow up of the people with schizophrenia in Butajira is recommended to describe longer-term illness course and functional outcomes.

Declarations

Author contribution statement

Derege Kebede: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Abebaw Fekadu, Teshome Shibre Kelkile, Girmay Medhin: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Charlotte Hanlon, Rosie Mayston: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Atalay Alem: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Funding statement

This work was supported by The Stanley Medical Research Institute (SMRI).

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

All study participants and involved staffs are acknowledged for their support and effort.

References

- Alem, A., Kebede, D., Shibre, T., Negash, A., Deyassa, N., 2004. Comparison of computer assisted SCAN diagnoses and clinical diagnoses of major mental disorders in Butajira, Rural Ethiopia. *Ethiop. Med. J.* 42 (2), 137–143.
- Alem, A., Kebede, D., Fekadu, A., et al., 2009. Clinical course and outcome of schizophrenia in a predominantly treatment-naive cohort in rural Ethiopia. *Schizophr. Bull.* 35 (3), 646–654. Epub 2008 Apr 29.
- APA American Psychiatric Association, 1994. *Diagnostic and Statistical Manual of Mental Disorders*, fourth ed. American Psychiatric Association, Washington, DC.
- Brazier, J.E., Harper, N., Jones, N.M.B., O’Cathain, Thomas, K.J., Usherwood, T., Westlake, L., 1992. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 305, 160–164.
- Brazier, J., Connell, J., Papaioannou, D., Mukuria, C., Mulhern, B., Peasgood, T., et al., 2014. A systematic review, psychometric analysis and qualitative assessment of generic preference-based measures of health in mental health populations and the estimation of mapping functions from widely used specific measures. *Health Technol. Assess.* 18 (34).
- Bromet, E.J., Dew, M., Eaton, W., 1995. Epidemiology of psychosis with special reference to schizophrenia. In: Tsuang, M.T., Tohen, M., Zahner, G.E.P. (Eds.), *Textbook in Psychiatric Epidemiology*. Wiley-Liss, Inc., New York, pp. 283–300.
- Cohen, A., Patel, V., Thara, R., Gureje, O., 2008. Questioning an axiom: better prognosis for schizophrenia in the developing world? *Schizophr. Bull.* 34 (2), 229–244.
- Esan, O.B., Ojagbemi, A., Gureje, O., 2012. Epidemiology of schizophrenia—an update with a focus on developing countries. *Int. Rev. Psychiatr.* 24 (5), 387–392.
- Feeny, D.H., Eckstrom, E., Whitlock, E.P., Perdue, L.A., 2013. *A Primer for Systematic Reviewers on the Measurement of Functional Status and Health-Related Quality of Life in Older Adults* (Prepared by the Kaiser Permanente Research Affiliates Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 13-EHC128-EF. Agency for Healthcare Research and Quality, Rockville, MD.
- Fekadu, A., Kebede, D., Alem, A., Shibre, T., 2000. Use of psychiatric rating instruments in Ethiopia. *Ethiop. Med. J.* 38 (3), 191–203.
- Gureje, O., Cohen, A., 2011. Differential outcome of schizophrenia: where we are and where we would like to be. *Br. J. Psychiatry* 199 (3), 173–175.

Habtamu, K., Alem, A., Medhin, G., Fekadu, A., Dewey, M., Prince, M., Hanlon, C., 2017. Validation of the world health organization disability assessment schedule in people with severe mental disorders in rural Ethiopia. *Health Qual. Life Outcomes* 15 (1), 64. Apr 5.

Haro, J.M., Novick, D., Suarez, D., Ochoa, S., Roca, M., 2008. Predictors of the course of illness in outpatients with schizophrenia: a prospective three year study. *Prog. Neuro Psychopharmacol. Biol. Psychiatr.* 32, 1287–1292.

Holla, B., Thirthalli, J., 2015. Course and outcome of schizophrenia in Asian countries: review of research in the past three decades *Asian. J. Psychiatr.* 14, 3–12.

Jääskeläinen, E., Juola, P., Hirvonen, N., McGrath, J., Saha, S., Isohanni, M., Veijola, J., Miettunen, J., 2013. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr. Bull.* 39 (6), 1296–1306.

Jablensky, A., Sartorius, N., Ernberg, G., et al., 1992. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol. Med. Monogr. Suppl.* 20, 1–97.

Jaracz, K., Gorna, K., Kiejda, J., Grabowska-Fudal, B., Jaracz, J., Suwalska, A., Rybakowski, J.K., 2015. Psychosocial functioning in relation to symptomatic remission: a longitudinal study of first episode schizophrenia. *Eur. Psychiatr.* 30, 907–913.

Kebede, D., Alem, A., Shibre, T., et al., 2003. Onset and clinical course of schizophrenia in Butajira-Ethiopia—a community-based study. *Soc. Psychiatr. Psychiatr. Epidemiol.* 38 (11), 625–631.

Kebede, D., Alem, A., Shibre, T., et al., 2004a. The sociodemographic correlates of schizophrenia in Butajira, rural Ethiopia. *Schizophr. Res.* 69 (2–3), 133–141.

Kebede, D., Alem, A., Shibre, T., Negash, A., Deyassa, N., Beyero, T., 2004b. Health-related quality of life (SF-36) survey in Butajira, rural Ethiopia: normative data and evaluation of reliability and validity. *Ethiop. Med. J.* 42 (4), 289–297.

Kebede, D., Alem, A., Shibre, T., et al., 2005. Short-term symptomatic and functional outcomes of schizophrenia in Butajira, Ethiopia. *Schizophr. Res.* 78 (2–3), 171–185.

Keller, M.B., Lavori, P.W., Friedman, B., et al., 1987. The longitudinal interval follow-up evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. *Arch. Gen. Psychiatr.* 44 (6), 540–548.

Kua, J., Wong, K.E., Kua, E.H., Tsoi, W.F., 2003. A 20-year followup study on schizophrenia in Singapore. *Acta Psychiatr. Scand.* 108 (2), 118–125.

- Newman, S.C., Bland, R.C., Thompson A, H., 2012. Long-term course and outcome in schizophrenia: a 34-year follow-up study in Alberta. *Can. Psychol. Med.* 42, 2137–2143.
- Norman, R.M., Malla, A.K., 2001. Duration of untreated psychosis: a critical examination of the concept and its importance. *Psychol. Med.* 31 (3), 381–400.
- Novick, D., Haro, J.M., Hong, J., et al., 2012. Regional differences in treatment response and three year course of schizophrenia across the world. *J. Psychiatr. Res.* 46 (7), 856–864.
- Ohaeri, J.U., 1993. Long-term outcome of treated schizophrenia in a Nigerian cohort. Retrospective analysis of 7-year follow-ups. *J. Nerv. Ment. Dis.* 181 (8), 514–516.
- Patel, V., Cohen, A., Thara, R., Gurege, O., 2006. Is the outcome of schizophrenia really better in developing countries? *Rev. Psiquiatr.* 28 (2), 149–152.
- Penttila, M., Jaaskelainen, E., Hirvonen, N., Isohanni, M., Miettunen, J., 2014. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br. J. Psychiatry* 205, 88–94.
- Priebe, S., 2007. Social outcomes in schizophrenia. *Br. J. Psychiatry* 191 (suppl 50), s15–s20.
- Ran, M.S., Yang, L.H., Liu, Y.J., Huang, D., Mao, W.J., Lin, F.R., Li, J., Chan, C.L., 2017. The family economic status and outcome of people with schizophrenia in Xinjin, Chengdu, China: 14-year follow-up study. *Int J Soc Psychiatr.* 63 (3), 203–211. May.
- Rangaswamy, T., Greeshma, M., 2012. Course and outcome of schizophrenia. *Int. Rev. Psychiatr.* 24 (5), 417–422. October.
- Rashid, E., Kebede, D., Alem, A., 1996. Evaluation of an Amharic version of the composite international diagnostic interview (CIDI) in Ethiopia. *Ethiop. J. Health Dev.* 10, 69–77.
- Revier, C.J., Reininghaus, U., Dutta, R., et al., 2015. Ten-Year outcomes of first-episode psychoses in the MRC ÆSOP-10 study. *J. Nerv. Ment. Dis.* 203, 379–386.
- Robinson, D.G., Woerner, M.G., McMeniman, M., Mendelowitz, A., Bilder, R.M., 2004. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatr.* 161 (3), 473–479. Mar.
- Russo, J., Trujillo, C.A., Wingerson, D., Decker, K., Ries, R., Wetzler, H., Roy-Byrne, P., 1998. The MOS 36-item short form health survey: reliability,

validity, and preliminary findings in schizophrenic outpatients. *Med. Care* 36, 752–756.

Sartorius, N., Janca, A., 1996. Psychiatric assessment instruments developed by the world health organization. *Soc. Psychiatr. Psychiatr. Epidemiol.* 31 (2), 55–69.

Shibre, T., Kebede, D., Alem, A., et al., 2002. An evaluation of two screening methods to identify cases with schizophrenia and affective disorders in a community survey in rural Ethiopia. *Int. J. Soc. Psychiatry* 48 (3), 200–208.

Shibre, T., Hanlon, C., Medhin, G., et al., 2014. Suicide and suicide attempts in people with severe mental disorders in Butajira, Ethiopia: 10 year follow-up of a population-based cohort. *BMC Psychiatry* 14 (150), 1–12.

Suzuki, T., 2011 Feb 15. Which rating scales are regarded as ‘the standard’ in clinical trials for schizophrenia? A critical review. *Psychopharmacol. Bull.* 44 (1), 18–31.

Thara, R., Henrietta, M., Joseph, A., et al., 1994. Ten-year course of schizophrenia—the Madras longitudinal study. *Acta Psychiatr. Scand.* 90 (5), 329–336.

Tunis, S.L., Croghan, T.W., Heilman, D.K., Johnstone, B.M., Obenchain, R.L., 1999. Reliability, validity, and application of the medical outcomes study 36-item short-form health survey (SF-36) in schizophrenic patients treated with olanzapine versus haloperidol. *Med. Care* 37 (7), 678–691.

Twisk, J.W.R., 2003. *Applied Longitudinal Data Analysis for Epidemiology. A Practical Guide.* Cambridge University Press, pp. 77–100.

Ustün, B., Compton, W., Mager, D., Babor, T., et al., 1997. WHO study on the reliability and validity of alcohol and drug use disorder instruments: overview of methods and results. *Drug Alcohol Depend.* 47 (3), 161–169.

van der Werf, M., Hanssen, M., Kohler, S., Verkaaik, M., Verhey, F.R., , RISE Investigators, van Winkel, R., van Os, J., Allardyce, J., 2014. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. *Psychol. Med.* 44, 9–16.

Verdoux, H., Liraud, F., Bergey, C., Assens, F., Abalan, F., van Os, J., 2001. Is the association between duration of untreated psychosis and outcome confounded? A two year follow-up study of first-admitted patients. *Schizophr. Res.* 49, 231–241.

Ware, J.E., 1993. *SF-36 Health Survey: Manual and Interpretation Guide.* The Health Institute, New England Medical Centre, Boston.

World Health Organization, 1994. *International Statistical Classification of Diseases and Related Health Problems (ICD).* WHO, Geneva.