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Clinical outcomes among individuals with a first episode psychosis attending Butabika National Mental Referral Hospital in Uganda: a longitudinal cohort study. A study protocol for a longitudinal cohort study

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ABSTRACT

Introduction Psychotic disorders significantly contribute to high morbidity and mortality. In high-income countries, the predictors of mortality, relapse and barriers to care among patients with first episode psychoses (FEP) have been studied as a means of tailoring interventions to improve patient outcomes. However, little has been done to document relapse rates and their predictors in patients with FEP in low resourced, high disease burdened sub-Saharan Africa.

Objective We shall estimate the rates of relapse of psychotic symptoms and the factors that predict them in patients with FEP over 4 years.

Methods and analysis We will assemble a cohort of patients with an FEP seen at the Butabika National Mental Referral Hospital in Kampala over a 4-year period. Participants will be adults (≥18 years old), who have received a diagnosis of a psychosis according to the Mini International Neuropsychiatric Instrument (M.I.N.I.), with a demonstrable resolution of active symptoms following the use of antipsychotic medications, and deemed clinically stable for a discharge by the healthcare practitioner. All participants will be required to provide written informed consent. Trained research assistants will collect Demographic and clinical parameters, age of onset of symptoms, diagnostic data using the M.I.N.I., physical examination data, symptom severity, level of social and occupational functioning and household income, during the 4-year study period. We will conduct a verbal audit in the event of loss of life. We shall perform survival analysis using the Aalen-Johansen estimator, and describe the population characteristics by demographics, social and economic strata using simple proportions.

Ethics and dissemination All participants will provide written informed consent. Ethical approvals for the study have been obtained from the Makerere University School of Medicine Research and Ethics Committee and the Uganda National Council for Science and Technology. Findings will be published in peer reviewed journals

Strengths and limitations of this study

- This study will be among the first to examine relapse rates of psychosis among individuals with a first episode psychoses (FEP) in Uganda.
- This study will be among the first to examine the predictors of relapse rates of psychosis among individuals with an FEP in Uganda.
- Findings from this study will provide us with the building blocks for future intervention studies in the field of psychosis.
- Our sample size may limit us from examining multiple predictors to relapse among individuals with a psychosis.
- Our short duration of follow-up may limit us from answering questions about long-term predictors of relapse.

INTRODUCTION

Psychotic disorders are a significant contributor of years lived with disability the world over, sub-Saharan Africa (SSA) inclusive.[1–3] Psychotic disorders have been shown to predict poor quality of life,[4 5] increased healthcare costs[6 7] and higher mortality mainly due to suicide, accidents and comorbid infectious diseases.[8–10] Moreover existing literature indicates that psychotic disorders are significantly associated with poor quality of life,[4 5] and increased healthcare costs.[6 7] Individuals with psychoses are more likely to suffer from non-psychotic mental illnesses comorbidity including depression, anxiety and substance misuse disorders,[11–13] often referred to as common mental disorders (CMD), as well as other non-communicable diseases, such as diabetes mellitus, hypertension and dyslipidemias.[14–16]

In high-income countries (HIC), a number of longitudinal assessments of patient-centred outcomes have been conducted to identify predictors of mortality, relapse and barriers to care among patients with first episode psychoses (FEP).[17–19] The majority of interventions that target improvement in patient outcomes (improvement in medication adherence, stigma reduction and relapse prevention)[20 21] draw their evidence from studies that documented the predictors of outcomes in patients with FEP. A couple of follow-up studies documenting predictors of relapse, and clinical outcomes in patients with FEP have been conducted in SSA.[22 23] Moreover, a number of studies indicate that the presentation of psychoses among individuals of African ancestry is heterogeneous in nature.[24–29] The heterogeneous presentation of psychoses in part lead to differences in its incidence, as well as shortages of efficacious treatment options. More work is needed to generate data about the predictors of relapse in SSA—findings from these studies will be critical in designing relapse prevention interventions for individuals with FEP in resource constrained SSA.

Relapse prevention interventions for individuals with an FEP already exist, especially in HIC. However, a number of reasons make the generalisation, and (or) extrapolation of relapse prevention techniques from HIC to SSA inappropriate. First, there is wide variation in the operational definition for first episode psychosis[30]—definitions that could be based on the time of onset of disease or presentation of patients to the health facilities. Second, prognosis of FEP and relapse rates have been shown to differ between HIC and low-income and middle-income countries[22 31]—differences in the level of social support have been sighted as some of the reasons.[32] Also, the metabolism of psychotropic medications may vary, in part due to genetic and gender differences[33–35]—variations that are likely to impact on the response (efficacy) to psychotropic medications, and ultimately rates of relapse. Furthermore, variations in the clinical or symptom presentation, conceptualisation of psychoses, as well as disease severity in some ethnic groups across multiple populations in the world[25 36–39] may dictate the type of treatment that patients receive.[40] Studies that document relapse rates in SSA are urgently needed in order for relapse prevention studies to be designed for these specific populations.

Objectives

a. The primary objective of the study will be to estimate the cumulative rates of relapse (proportion) of a clinical relapse of psychotic symptoms in patients with FEP. The primary outcome will be a clinical relapse defined as (1) re-admission to a hospital after a clinical assessment by a healthcare worker who deems the patient to be severely ill requiring admission to the hospital (2) score ≥20 on the Young Mania Rating Scale (YMRS)[41] or register an increase of 25% in Positive and Negative Symptoms of Schizophrenia Scale (PANSS)[42] score from the last measurement.
b. The secondary objective will be to determine the factors that may predict clinical relapse in patients with FEP who showed initial clinical response to antipsychotic treatment while under admission in hospital. Based on the previous literature,[43–45] we hypothesise that poor adherence to antipsychotic medications (measured using the Medication Adherence Rating Scale (MARS)) for psychosis[46] will be the main predictor of relapse in the study population.

Study outcomes

a. The primary outcome will be a clinical relapse (defined above, clinical acumen or by use of rating scales).
b. The secondary outcome will be all cause mortality (assessed using the verbal WHO autopsy scale).

METHODS

Study setting and design

We are assembling a cohort of patients with an FEP seen at the Butabika National Mental Referral Hospital in Kampala. Butabika National Mental Referral Hospital is a 600-bed hospital located 13 km east of Kampala city (the capital city of Uganda with a population of 3.5 million) The hospital has three acute admission wards, three convalescent wards (housing patients with less acute symptoms and ready for discharge), one male and one female sick ward (where individuals with physical illnesses are admitted), an alcohol and drug unit, a child and adolescent unit and a private wing. It has a medical out-patient that provides a service to HIV/AIDS patients, a dental clinic and a general out-patients clinic. The out-patient clinics operates week days from 9:00 to 17:00, and at a minimum. Each of the units (in-patient and out-patient) is run by team of psychiatrists, medical officers, psychiatric clinical officers, psychiatric nurses, clinical psychologists and psychiatric social workers.

Patients will be enrolled starting May 2020 and will be followed for 4 years. Participants will have been initially assessed as part of the Neuro-Psychiatric Genetics of African Populations-Psychosis (Neuro-GAP) study.[47] Neuro-GAP is a multicentre study, being conducted in Uganda (at five sites: Butabika, Gulu, Naguru, Arua and Mbarara Hospitals), Ethiopia, Kenya and South Africa. While the Neuro-GAP study is cross-sectional in nature, we shall follow only participants with an FEP who meet our eligibility criteria (see below). Participants will be enrolled and followed until occurrence of the outcomes (relapse) or death within the 4-year study period. It is estimated that approximately 1000 participants will be recruited for the Neuro-GAP study over the 4-year period. Individuals with an FEP constitute about 20%–30% of study participants recruited in the Neuro-GAP project—these are the individuals from whom we will identify participants for recruitment (criteria below).

Eligibility criteria

Inclusion criteria

We shall enrol adults (≥18 years old), who have received a diagnosis of a psychosis operationally defined as any of: (1) brief psychotic episode; (2) schizophrenia, or schizophrenia spectrum disorder; or (3) bipolar affective disorders diagnosed according to the Mini International Neuropsychiatric Instrument (M.I.N.I.) version 7.0.2.[48] Participants will be considered to have an FEP if they have (a) experienced psychotic symptoms for the very first time in their lives, (b) experienced psychotic symptoms before, but are accessing psychiatric care (antipsychotic medications) for the very first time in their lives at the study site or (c) if already on antipsychotics or used antipsychotic medications for no longer than 6 weeks.[30] Participants need to have demonstrable resolution of active symptoms following the use of antipsychotic medications, and deemed clinically stable for a discharge by the attending healthcare practitioner. Participants need to live within a 21 km radius from the hospital.

Exclusion criteria

Individuals who present with an FEP, but with a substance use disorder as a primary disorder will be excluded.

Study procedure

Identification and consent: Healthcare workers in the different wards and out-patient departments of Butabika Hospital will be informed about the study. Trained research assistants (RA) shall liaise with the clinicians to identify potential participants for recruitment at the time of admission to the wards. RA's will then assess participants who are due for discharge (patients with a clinical response to medications) for possible enrolment, and provide them with information about the study. Patients who access care at the out-patient clinic (who may not be admitted) but are eligible will also be approached by the RA for enrolment. The RA's will invite potential participants to take part in the study, and obtain written informed consent. During the consenting process, the purpose of the study will be described further, the procedures will be explained and the benefits of taking part in the study will be outlined. On demonstrating understanding and being given a chance to ask questions, the potential participant will then provide a witnessed, signed or thumb print consent.

We will administer the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC)[49] instrument to assess whether the participants have understood the consent process. The UBACC will be translated into Luganda, the commonly spoken local language at the study site. The UBACC is a 10-item scale comprises three factors that evaluate understanding, appreciation and reasoning. It has been used in the Ugandan setting for the Neuro-GAP project, although it is yet to be culturally adapted for use in these settings. A score of less than 14.5 on three separate occasions indicates that the participant has not understood what the study is all about. Such participants will not be recruited, but will be given a chance to return at a later date for recruitment (within a week). We will record the number of participants who fail the UBACC at baseline and cannot be recruited and those who do so after being invited a week later. We will ask participants to provide us with their demographic information (age, gender and education level) and examine whether there are significant differences between participants who are able to consent and those who are not. Participation in this study is completely voluntary. The patient has the right to withdraw at any time during the study, including at follow-up. We will document the reasons for withdrawal. Each interview is anticipated to last a minimum of 120 min—there will be 2–3 breaks at 40-min intervals in between the interviews.

Sample size and power calculation

a. For the first objective (proportion of participants who will relapse), we used the Leslie–Kish Formula[50] to calculate the sample size for cross sectional studies measuring proportions as the outcome variable. We assume that 25% of recruited participants will relapse within the 2–3-year study period. Substituting the figures in the Leslie–Kish Formula (SD of 1.96, and a precision of 5%) yields a sample size of 244 participants. Assuming a 10%–20% loss to follow-up of participants, the adjusted sample size will be 292 participants. Our sample size will provide us with enough power (80%) to detect clinically meaningful differences—a score >20 on the YMRS and an increase of 25% of the PANSS score from baseline between the two groups (those who relapse and those who do not), and identify predictors of a relapse.
b. For the second objective of examining the predictors of relapse, using a conservative prevalence estimate for a major predictor, medication non-adherence as 40% in a population of patients with Schizophrenia,[43–45] with 211 patients we should able to estimate hazard ratios as high as 2.0 or greater within 2 years with an estimated relapse rate of 25% per year. Thus, our sample size of 292 participants should be adequate to answer both objectives.

Study measurements

Trained RA will administer the following standardised questionnaires to all participants. All study questionnaires will be translated into Luganda, the commonly spoken local language at the study site.

1. Demographic and clinical parameters: (a) We will document the age, gender, physical address, contact information, marital and employment status, education level, date/month/year of onset

of current illness. We will document whether the participant lives within a catchment area of ministry of health supported village health team (VHT) member; we will separately contact the VHT and get their details. We will also request for information from the next of kin for future contact in the event of a loss to follow-up. (b) We will document the age of onset of symptoms, duration of illness before accessing hospital care (acute if it is within 6 months of onset and chronic if it is more than 2 years), whether the participant has received prior treatment for the psychosis (traditional or faith healers), whether or not the patient had a say in the choice of antipsychotics that was prescribed to them.

2. We will administer the UBACC[49] to assess participant's capacity to provide informed consent.
3. The M.I.N.I. 7.0.2[48] psychosis, depression, bipolar affective disorders, substance use disorder, Post-Traumatic Stress Disorder (PTSD) and generalised anxiety modules will be used to confirm the presence of a psychoses, and other CMD. The M.I.N.I. has been used in multiple Ugandan study settings including the Neuro-GAP project, although it is yet to be validated for use in these settings
4. Physical examination for weight and height to calculate the body mass index (a proxy indicator for obesity), a blood pressure measurement to assess for hypertension and a random blood sugar level (assessed using a glucometre) as a screen for diabetes mellitus.
5. Symptom severity assessed using the YMRS or PANSS. Both the YMRS and PANSS have been used in Ugandan study settings, although it is yet to be validated for use in these settings.
6. The presence of medication side effects will be assessed using the modified version of the Glasgow Antipsychotic Side Scale.
7. The WHO Disability Assessment Schedule Version 2 (WHODAS 2.0) will be used to assess the level of social and occupational functioning of participants. There are limited data about the use of the WHODAS in Ugandan populations.
8. The level of household income and health care expenditures will be assessed using the Uganda Bureau of Statistics surveillance guidelines.
9. Clinical relapse as operationally defined by (a) participant being re-admitted to hospital, (b) participant scoring ≥20 on the YMRS[41] or an increase of 25% in PANSS[42] scores from the last measurement. The YMRS and PANSS will also be used to rate severity of bipolar affective disorders and schizophrenia spectrum disorders, respectively, and document a relapse of symptoms.
10. Adherence to antipsychotics will be measured using the MARS for psychosis.[46]
11. We will document mortality from any causes in the participants using the WHO verbal autopsy scale.

Instrument	Baseline	Follow-up
Demographic parameters	Yes	No
University of California, San Diego Brief Assessment of Capacity to Consent	Yes	No
Mini International Neuropsychiatric Instrument	Yes	Yes
Physical exam	Yes	Yes
Symptom severity using the Young Mania Rating Scale /Positive and Negative Symptoms of Schizophrenia Scale	Yes	Yes
Glasgow Antipsychotic Side Scale	Yes	Yes
WHO Disability Assessment Schedule V.2	Yes	Yes
House hold income	Yes	Yes
Clinical relapse	No	Yes
Medication adherence using the Medication Adherence Rating Scale Medication adherence using the MARS	No	Yes
WHO audit to assess all course mortality	No	Yes

Pilot data collection

We will conduct a pilot of data collection among 10 participants, and use semi-structured questionnaires to document clarity of study questionnaires, barriers to implementation and ways of circumventing the barriers. We will then make appropriate changes to the study protocol and submit an amendment to the Instituitonal Review Board (IRB) before commencement of the study if need be.

Participant's follow-up: We shall collect the same data as at baseline from participants at month 3 then every 6 months. In the event, the participant accesses healthcare and we are not aware, we will review their medical records and abstract information collected during the course of routine care (where they exist). However, all attempts will be made to collect data directly from the participants at all times. Relapse will be defined as any one of: (a) a re-admission of participants to the hospital often based on clinical signs, (b) a score >20 on the YMRS for individuals with Bipolar affective disorders at follow-up and[41 51] (c) a 25% increase in the total score of the PANSS from baseline in participants with Schizophrenia at follow-up.

Medical record review

There is a possibility that participants will return to access care at the facility and be missed by the RA. They could also be admitted to the facility due to other health complications. We will review participant's medical charts and abstract information about any admission to the hospital, duration of stay, laboratory parameters and any other recorded complications.

Adverse event reporting during participant follow-up

We anticipate that this project will have minimal adverse events that are directly related to the study. However, in the event, we observe any adverse events as a result of the use of prescribed medications during clinical care or loss of privacy/confidentiality, then we will report it promptly to the relevant regulatory bodies per requirement. Confidentiality could be broken in the event that the RA gets information related to the following: (a) participant is suicidal, (b) participant threatens to commit a homicide and (c) participants report a sexual abuse to themselves or other parties. The RA will immediately inform the Principal Investigator (PI) about such, and appropriate action will be taken including reporting such cases to the administration of Butabika Hospital.

Potential risks

There is a potential risk of developing severe psychological distress during the interviews as a result of answering questions that are deemed private by the participant. RA will be trained to identify any of such distress, and the interview will be terminated. Participants may be asked to continue with the interview only if they feel like doing so. Such adversities will be reported to the PI and School of Medicine Research and Ethics Committee (SOMREC). There is also a risk of having information about participants made available in the public domain. We will guard against this by having all identifying information of the patients locked away in file cabinets and password locked computers. The risk to loss of information is minimal.

Benefits

There are no direct monetary benefits to be gained by the individuals. However, participants will receive regular assessments for their symptoms every 6 months for 4 years. The scientific community will be able to get information about the predictors of relapse.

Community tracing

In the event, a participant has not appeared for a clinic visit on their scheduled clinic appointment, we will contact them or their appointed person through telephone. If neither the patient nor the contact person can be reached by phone 3 months from the last date of their scheduled appointment, we will make active attempts to trace the participant at their residence by liaising with the VHT based in the same location. In the event, the participant cannot be traced at their place of residence, we will consider them as a potential loss to follow-up. There exists a number of VHT members who provide care to non-mental health clients. We will use their knowledge about the village to identify individuals in the cohort.

Data analysis plans

Descriptive analysis

We shall describe the population characteristics by demographics, social and economic strata using simple proportions. Then, we shall perform survival analysis using the Aalen-Johansen estimator where death prior to the outcome will be considered a competing risk. For outcome '(a)', we shall describe relapse rates at 1 and 4 years. We shall describe the survival time to relapse for all participants categorising by psychoses, that is, schizophrenia, schizophrenia spectrum disorders or bipolar affective disorders, considering death as a competing risk. For outcome '(b)', we also estimate the predictors of relapse rates using generalised linear equation estimates

Explanatory analyses

We shall use proportional hazard regression to estimate hazard ratios for a clinical relapse (operationally defined above). For this, we shall use proportional hazards regression to estimate the hazard ratios for relapse overall. We shall use directed acyclic graphs to define models for evaluation of predictors of relapse. If the power permits, we shall estimate this for each disorder as well. We will document the total length of follow-up period during which a subject is (1) adherent to antipsychotic medication, (2) in a state of complete remission (defined as having less than the baseline PANSS score at recruitment, and <20 on YMRS) for half the time they are being followed up, (3) in partial remission (no reduction in scores from baseline) and (4) in a psychotic episode (scores on the PANNS and YMRS increase after discharge and never return to baseline). In cases where we have informative censoring, we shall use inverse probability weights from a sample of tracked participants to estimate the outcome.

Public and patient involvement

During the pilot phase of the project, we will engage with patients and document any barriers to implementation of the study procedures. Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION PLANS

Ethical considerations

We will have a two-layered consent process. (1) Trained RAs will read the consent form to the participant and (2) then administer the UBACC to ensure that participants have fully understood the rationale for conducting the study and that they are participating well aware of their rights as participants. Only participants who score ≥10 will be enrolled. Ethical approvals for the study has been obtained from the Makerere University School of Medicine Research and Ethics Committee (#REC-REF 2019-033) and the Uganda National Council for Science and Technology (UNCST HS2638).

A number of ethical considerations are worth pointing out. Beyond the distress that may l be experienced by participants, this will be a minimal risk study. To minimise the risk of loss of privacy and confidentiality, only the investigators will have access to the study records and test results and the link between personal identifying information and study data. No individual identities will be used in any reports or publications associated with

the data from this study. All softcopies of the data will be stored in password locked computers. Hard copies of the questionnaires will be stored in locked file cabinets at the study offices in Butabika National Referral Hospital.

Dissemination plans

A manuscript will be prepared from these findings and submitted to peer-reviewed journal for publication. Findings will also be presented at local and international conferences. We will hold a dissemination workshop and provide results to the patients who have participated in the pilot phase as well as other stakeholders to whom these findings are important in shaping policy and practice.

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REFERENCES

1 Whiteford HA, Degenhardt L, Rehm J, *et al*. Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study 2010. *Lancet* 2013;382:1575–86.
2 Rössler W, Salize HJ, van Os J, *et al*. Size of burden of schizophrenia and psychotic disorders. *Eur Neuropsychopharmacol* 2005;15:399–409.
3 Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. *Eur Arch Psychiatry Clin Neurosci* 2000;250:274–85.
4 Saarni SI, Viertiö S, Perälä J, *et al*. Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders. *Br J Psychiatry* 2010;197:386–94.
5 Michalak EE, Yatham LN, Lam RW. Quality of life in bipolar disorder: a review of the literature. *Health Qual Life Outcomes* 2005;3:72.
6 Laidi C, Prigent A, Plas A, *et al*. Factors associated with direct health care costs in schizophrenia: results from the FACE-SZ French dataset. *Eur Neuropsychopharmacol* 2018;28:24–36.
7 Frey S. The economic burden of schizophrenia in Germany: a population-based retrospective cohort study using genetic matching. *Eur Psychiatry* 2014;29:479–89.
8 Teferra S, Shibre T, Fekadu A, *et al*. Five-year mortality in a cohort of people with schizophrenia in Ethiopia. *BMC Psychiatry* 2011;11:165.
9 Fekadu A, Medhin G, Kebede D, *et al*. Excess mortality in severe mental illness: 10-year population-based cohort study in rural Ethiopia. *Br J Psychiatry* 2015;206:289–96.
10 Simon GE, Stewart C, Yarborough BJ, *et al*. Mortality rates after the first diagnosis of psychotic disorder in adolescents and young adults. *JAMA Psychiatry* 2018;75:254.
11 Kiran C, Chaudhury S. Prevalence of comorbid anxiety disorders in schizophrenia. *Ind Psychiatry J* 2016;25:35–40.
12 Buckley PF, Miller BJ, Lehrer DS, *et al*. Psychiatric comorbidities and schizophrenia. *Schizophr Bull* 2009;35:383–402.
13 Hartz SM, Pato CN, Medeiros H, *et al*. Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry* 2014;71:248–0.
14 Ward M, Druss B. The epidemiology of diabetes in psychotic disorders. *Lancet Psychiatry* 2015;2:431–51.
15 Annamalai A, Kosir U, Tek C. Prevalence of obesity and diabetes in patients with schizophrenia. *World J Diabetes* 2017;8:390–6.
16 Patel V, Chatterji S. Integrating mental health in care for noncommunicable diseases: an imperative for Person-Centered care. *Health Aff* 2015;34:1498–505.
17 Heilbronner U, Samara M, Leucht S, *et al*. The longitudinal course of schizophrenia across the lifespan: clinical, cognitive, and neurobiological aspects. *Harv Rev Psychiatry* 2016;24:118–28.
18 Harrow M, Sands JR, Silverstein ML, *et al*. Course and outcome for schizophrenia versus other psychotic patients: a longitudinal study. *Schizophr Bull* 1997;23:287–303.
19 Jääskeläinen E, Haapea M, Rautio N, *et al*. Twenty years of schizophrenia research in the Northern Finland birth cohort 1966: a systematic review. *Schizophr Res Treatment* 2015;2015:1–12.
20 Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. *Cochrane Database Syst Rev* 2011:CD002831.
21 Hastrup LH, Kronborg C, Bertelsen M, *et al*. Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). *Br J Psychiatry* 2013;202:35–41.
22 Fikreyesus M, Soboka M, Feyissa GT. Psychotic relapse and associated factors among patients attending health services in Southwest Ethiopia: a cross-sectional study. *BMC Psychiatry* 2016;16:354.
23 Alem A, Kebede D, Fekadu A, *et al*. Clinical course and outcome of schizophrenia in a predominantly treatment-naive cohort in rural Ethiopia. *Schizophr Bull* 2009;35:646–54.
24 McGrath J. Dissecting the heterogeneity of schizophrenia outcomes. *Schizophr Bull* 2008;34:247–8.
25 Cohen A, Padmavati R, Hibben M, *et al*. Concepts of madness in diverse settings: a qualitative study from the INTREPID project. *BMC Psychiatry* 2016;16:388.
26 Jongsma HE, Gayer-Anderson C, Lasalvia A, *et al*. Treated incidence of psychotic disorders in the multinational EU-GEI study. *JAMA Psychiatry* 2018;75:36.
27 Jablensky A, Sartorius N, Ernberg G, *et al*. Schizophrenia: manifestations, incidence and course in different cultures. A world Health organization ten-country study. *Psychol Med Monogr Suppl* 1992;20:1–97.
28 Goldner EM, Hsu L, Waraich P, *et al*. Prevalence and incidence studies of schizophrenic disorders: a systematic review of the literature. *Can J Psychiatry* 2002;47:833–43.
29 Saha S, Chant D, Welham J, *et al*. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005;2:e141.
30 Breitborde NJK, Srihari VH, Woods SW. Review of the operational definition for first-episode psychosis. *Early Interv Psychiatry* 2009;3:259–65.
31 Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med* 2006;36:1349–62.
32 Burns JK. The social determinants of schizophrenia: an African journey in social epidemiology. *Public Health Rev* 2012;34.
33 Brandl EJ, Kennedy JL, Müller DJ. Pharmacogenetics of antipsychotics. *Can J Psychiatry* 2014;59:76–88.
34 Pouget JG, Shams TA, Tiwari AK, *et al*. Pharmacogenetics and outcome with antipsychotic drugs. *Dialogues Clin Neurosci* 2014;16:555–66.
35 Kraal AZ, Ward KM, Ellingrod VL. Sex differences in antipsychotic related metabolic functioning in schizophrenia spectrum disorders. *Psychopharmacol Bull* 2017;47:8–21.

36 van der Ven E, Bourque F, Joober R, *et al*. Comparing the clinical presentation of first-episode psychosis across different migrant and ethnic minority groups in Montreal, Quebec. *Can J Psychiatry* 2012;57:300–8.
37 Brekke JS, Barrio C. Cross-ethnic symptom differences in schizophrenia: the influence of culture and minority status. *Schizophr Bull* 1997;23:305–16.
38 Njenga F. The concept of mental disorder: an African perspective. *World Psychiatry* 2007;6:166–7.
39 Teuton J, Bentall R, Dowrick C. Conceptualizing psychosis in Uganda: the perspective of Indigenous and religious healers. *Transcult Psychiatry* 2007;44:79–114.
40 Morgan C, Hibben M, Esan O, *et al*. Searching for psychosis: INTREPID (1): systems for detecting untreated and first-episode cases of psychosis in diverse settings. *Soc Psychiatry Psychiatr Epidemiol* 2015;50:879–93.
41 Young RC, Biggs JT, Ziegler VE, *et al*. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978;133:429–35.
42 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–76.
43 Gilbert PL, Harris MJ, McAdams LA, *et al*. Neuroleptic withdrawal in schizophrenic patients. A review of the literature. *Arch Gen Psychiatry* 1995;52:173–88.
44 Robinson D, Woerner MG, Alvir JM, *et al*. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999;56:241–7.
45 Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. *BMC Psychiatry* 2008;8:32.
46 Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new medication adherence rating scale (MARS) for the psychoses. *Schizophr Res* 2000;42:241–7.
47 Stevenson A, Akena D, Stroud RE, *et al*. Neuropsychiatric genetics of African Populations-Psychosis (NeuroGAP-Psychosis): a case-control study protocol and GWAS in Ethiopia, Kenya, South Africa and Uganda. *BMJ Open* 2019;9:e025469.
48 Sheehan DV, Lecrubier Y, Sheehan KH, *et al*. The Mini-International neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;59(Suppl 20):22–3.
49 Jeste DV, Palmer BW, Appelbaum PS, *et al*. A new brief instrument for assessing decisional capacity for clinical research. *Arch Gen Psychiatry* 2007;64:966–74.
50 Kish L. *Survey sampling*. New York: John Wiley and Sons Inc, 1965.
51 Lukasiewicz M, Gerard S, Besnard A, *et al*. Young mania rating scale: how to interpret the numbers? determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort. *Int J Methods Psychiatr Res* 2013;22:46–58.