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Doctoral Dissertation

INTERNATIONAL DIFFERENCES IN RESPONSE, REMISSION AND COURSE OF SCHIZOPHRENIA

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Ab imo pectore

A mis padres,
que me enseñaron con el ejemplo
el valor del conocimiento
desde una edad muy temprana

Para Gabriela,
que siempre me ha apoyado en los momentos difíciles
y ha dado amor y alegría a mi vida

A Lucas,
cuyo amor por el conocimiento compruebo cada día
y que me ha dado la inmensa felicidad de la paternidad

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1 PRESENTATION

This doctoral dissertation explores international differences in the course of schizophrenia using information provided by the rich dataset gathered by the Schizophrenia Health Outcomes (SOHO) study during the first half of the last decade. SOHO, like other important observational and pragmatic clinical trials conducted recently in the field of the antipsychotic treatment of schizophrenia (CATIE, EUFEST, etc.), has provided important and much needed comparative outcomes data in patients taking antipsychotic medications. SOHO provides information across a wide range of treatment outcomes, most notably in the areas of effectiveness, tolerability, social functioning and health service use. However, what sets the data from SOHO apart from the aforementioned trials is that it allows analysis of data from regions of the world that are usually under-represented in the research literature, such as North Africa, the Middle East and Latin America. This notable feature has provided the right framework for development of comparative regional studies of the many variables gathered during the study.

I had the opportunity to become familiar with the data from the worldwide-SOHO study (W-SOHO) because I was the main project manager for the study and was responsible for overseeing recruitment, quality control, and data dissemination, which was exploited through numerous publications in major psychiatric journals. As part of the data dissemination process, several members of the study advisory council and investigators in general requested and obtained access to the study dataset to investigate research hypotheses of their interest that were not generated by the study sponsor. Importantly, several of these projects led to the development of doctoral dissertations, most notably at Cambridge and Maastricht Universities.

In my case, and similar to the examples listed above, I requested and was granted unrestricted access to the W-SOHO database to test several research hypotheses that were not related to the original objectives of the study sponsor. Briefly, my purpose was to use the newer findings from the W-SOHO study to test the current validity of the international differences in the course of schizophrenia presented in the now classic studies by Jablensky and co-workers. More specifically, I wanted to determine whether the differences in treatment outcomes and prognosis between regions with

different levels of development found by Jablensky et al. were still present 30 years after the WHO studies were conducted.

After completing this research project, I believe that the information presented in this dissertation allows me to outline an accurate description of the course of schizophrenia across the world. The final objective of this dissertation is to provide useful information that helps to develop and implement clinical approaches and mental health policy strategies which, in turn, would help to improve the mental health of the population irrespective of the level of development of the home country.

2 SUMMARY

Objectives: The overall objectives of this dissertation are to describe the course of patients with schizophrenia during three years of follow-up and to study differences between regions across the world that have different levels of development.

The specific objectives of this dissertation are:

- To describe the frequency of treatment response in outpatients with schizophrenia in different regions of the world
- To analyse the demographic (age, gender, marital status) and clinical factors (age of onset, time since onset, severity of disease, functioning) associated with response
- To describe the frequency of clinical and functional remission in outpatients with schizophrenia in different regions of the world
- To analyse the demographic (age, gender, marital status) and clinical factors (age of onset, time since onset, severity of disease, functioning) associated with clinical and functional remission

Methods: Data from the Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO) study was used to determine the frequency of response, symptomatic and functional remission, and to describe the course of disease in outpatients with schizophrenia in different regions of the world. The W-SOHO study was a 3-year, prospective, observational study that included over 17,000 outpatients with schizophrenia from 37 countries classified into six regions (Northern Europe, Southern Europe, Latin America, East Asia, Central & Eastern Europe, North Africa & Middle East). Cox proportional-hazards regression was employed to assess the factors associated with response and remission. Multinomial logistic regression was used to assess the correlates of disease course.

Results: The study found that approximately two-thirds of the patients (66.4%) achieved response during the 3-year follow-up. Response rates varied across regions, and were highest in North Africa & Middle East (84.6%) and Latin America (78.6%) and were lowest in Southern Europe (62.1%) and East Asia (60.9%). The study also found that 66.1% of patients achieved clinical remission during the 3-year follow-up (range: 60.1% in North Europe to 84.4% in East Asia) and 25.4% achieved functional remission

(range: 17.8% in North Africa and Middle East to 35.0% in North Europe). Regional differences were not explained by participants' clinical characteristics. Baseline social functioning, being female and previously untreated were consistent predictors of remission across regions. In addition, there were significant differences between regions in the proportion of patients experiencing continuous remission, remission plus relapse, and a persistent symptomatic course, and between the regions in the duration of remission. Overall, Latin America, East Asia, and North Africa & Middle East had more favourable outcomes because they had the largest proportion of people who achieved continuous remission, the longest time in remission and had the lowest percentage with a persistent symptomatic course. Having good social functioning at baseline was consistently associated with better clinical outcome. These results seem to indicate that patients from Latin America, East Asia, North Africa & Middle East may have a more favourable disease course than patients from European nations.

Conclusions: Clinical outcomes of schizophrenia seem to be worse in Europe compared with other regions of the world. However, functional remission follows a different pattern.

3 INTRODUCTION

3.1. Prognostic factors in schizophrenia

Prognostic factors are variables that are present early in the disease process (usually at or before the first episode) and affect long-term outcomes. There is an overlap between risk factors and prognostic factors, although not all risk factors are prognostic of outcome.

In 1998, the World Health Organization [1] stated that the following factors were prognostic for poor outcome in schizophrenia:

- Presence of the negative syndrome
- Poor pre-morbid adjustment
- Male gender
- Younger age at onset
- Insidious onset
- Longer interval from onset to treatment
- Absence of any clear precipitating events

In contrast, the following factors were proposed as prognostic for a good outcome in schizophrenia:

- Female gender
- Older age at onset
- Good pre-morbid social functioning
- Acute presentation
- Florid positive symptoms (e.g. hallucinations, delusions, grossly disordered thinking)

In this section I report a snapshot of factors prognostic of outcome for schizophrenia taken from representative references published in the last 10 years. Most research was conducted in first-episode patients. I have focused on papers reporting outcomes of patients in epidemiological samples and have not reviewed the vast amount of studies of antipsychotic treatment reporting predictors of outcome in schizophrenia, because the outcomes can be influenced by the experimental conditions.

3.1.1. Age at onset

An individual's age at the onset of psychotic symptoms is a prognostic indicator for outcome in schizophrenia; the younger the individual is at the onset of positive psychotic symptoms, the poorer the outcome tends to be.

A younger age at illness onset was associated with cognitive deterioration [2–4], increased severity of functional disabilities [5], an insecure attachment style in male schizophrenia inpatients [6], homelessness [7], more severe negative symptoms [3], and living in an institution [8].

In the study by González-Blanche et al. [9], older age at illness onset was associated with functional recovery. Among patients followed for up to 16 years, better outcome was associated with older age on admission [10].

3.1.2. Gender

Schizophrenia seems to affect equal numbers of men and women, but the onset is often later in women than in men; men typically present in their late teenage years or early 20s, whereas women generally present in their late 20s or early 30s [11]. It is generally accepted that, compared with men, schizophrenia in women has a milder course and better prognosis [1, 12, 13]. Among patients followed for up to 16 years, better outcome was associated with being female [10]. Häfner [14] reported that illness onset and the symptom-related course of schizophrenia showed no gender differences if age was not taken into account. Prior to the menopause in women, illness onset was delayed and the severity of illness was reduced by oestrogen. As a result, the age distribution of onset and severity of first-episode illness in young men and post-menopausal women differed from the normal.

Häfner [14] proposed that the poorer social course of schizophrenia in men compared with premenopausal women was accounted for by the lower level of social development in men at illness onset which subsequently impaired further development. Another study reported that the only significant predictors of 5-year social outcome were social development at psychosis onset and the socially adverse illness behaviour of young men [15]. It was proposed that the influence of traditional predictors (age, gender, chronic/acute type of onset, and symptomatology) was mediated by these two variables assessed at the end of the prodromal stage.

Male gender independently predicted cognitive deterioration, and it was suggested that males might have a higher susceptibility than females for cognitive deterioration in first-episode schizophrenia [2]. Differences in social functioning and organizational ability between adolescent males and females with schizophrenia led to differences in hospital admissions and stays; males with poorer social functioning and organizational ability prior to first admission experienced more admissions and longer stays [16]. Antipsychotic noncompliance was associated with homelessness in men but not in women [7].

A study of brain function (global connectivity) in male and female patients with schizophrenia reported that among first-episode patients, the speed of global connectivity was faster in females, suggesting greater adaptive capacity [13]. However, in chronic illness, the reduction in global functional connectivity was greater in females than males, suggesting that additional breakdowns in brain network connectivity may develop in females with illness chronicity.

Evidence for differences between men and women in the course of schizophrenia is conflicting, possibly because similar measures may have different predictive values depending on the stage of illness [17].

3.1.3. Onset of illness

In the review of schizophrenia studies conducted by Bromet et al. [18], an insidious onset of schizophrenia was a predictor of poorer outcome, and Harrow and Jobe [19] identified no acute onset as a poor prognostic factor in schizophrenia outcome. Morgan and colleagues [20] classified mode of onset as sudden (<1 week), acute (<1 month) or insidious (>1 month), and found that an insidious mode of onset was independently associated with a substantially longer duration of untreated psychosis (DUP) compared with an acute onset. An insidious mode of onset was also associated with a substantially longer DUP compared with an acute onset by Compton et al. [21].

3.1.4. Family history

A family history of schizophrenia predicted a poorer outcome [18, 22]. In the meta-analysis conducted by Esterberg et al. [23], family history had a small but significant impact on age-at-onset and on negative symptoms. Sex differences in age-at-onset were not observed in individuals with a family history of schizophrenia, making age-at-onset in females similar to that in males. A positive family history was also associated with poorer intellectual functioning and less reduction in symptoms at 2- and 3-year follow-up together with a greater likelihood of abnormal electroencephalogram (EEG) findings [24].

3.1.5. Perinatal factors (obstetric, infectious and immunological)

While a variety of perinatal insults (e.g. the mother is malnourished or has viral illnesses or infections during pregnancy, obstetric complications or delayed early development) have been proposed as risk factors for schizophrenia in later life [25–27], these risk factors are not necessarily prognostic for poor outcome. Jääskeläinen et al. [28], for example, reported that while delayed psychomotor development in children was a marker of increased risk of the development of schizophrenia, it was not a predictor of more severe illness outcome.

3.1.6. Positive and negative symptoms

A number of studies reported that negative symptoms were associated with poor outcomes:

- The severity of negative symptoms was a predictor of poorer outcome in the review of schizophrenia studies conducted by Bromet et al. [18]. In addition, Ho et al. [29] reported that severe negative symptoms at the time of first hospitalization predicted poorer outcome at 2 years in terms of occupational impairment, financial dependence on others, impaired relationships with friends, impaired ability to enjoy recreational activities, and global assessment of functioning
- The presence of negative symptoms was associated with relapse [30], and employment outcomes [5]
- Higher negative symptom severity was associated with a lower likelihood of achieving recovery [31]
- Fewer negative symptoms at first presentation predicted a better outcome (in psychopathology and general functioning) [9, 32]

While the presence of positive symptoms was proposed as being indicative of a good prognosis [1], findings relating to positive symptoms and outcomes are mixed. Ho et al. [29] suggested that this might be because while many of the patients studied were in acute exacerbations, they may have been in different phases of the disease.

- In the 20-year follow-up study conducted by Harrow and Jobe [33], the persistence of positive symptoms (delusions) after the acute phase predicted a lower likelihood of future global recovery, particularly work disability. It was suggested that internal factors, such as good pre-morbid developmental achievements, reduced the probability of chronic delusional activity in schizophrenia
- The presence of severe positive symptoms (but not negative symptoms) was associated with homelessness [7]
- Siegel et al. [17] reported that a higher level of positive symptoms at intake was associated with a longer duration of hospitalization, increased overall symptoms, decreased ability to meet basic needs, and decreased quality of work later in life. Lower levels of positive, negative, and depressive symptoms at intake predict a higher overall level of function at follow-up [17]

Siegel et al. [17] reported that lower levels of symptoms generally (lower levels of positive, negative and depressive symptoms at intake) predicted a higher overall level of function at follow-up, and Levine et al. [34] reported that higher baseline symptoms predicted a poor response to treatment. Higher baseline clinical severity was associated with a reduced likelihood of achieving remission [35].

A lower level of disorganized thinking was associated with functional recovery [9].

3.1.7. Duration of untreated psychosis

The duration of untreated psychosis (DUP) – the interval between onset of a psychosis and administration of the first pharmacological treatment for schizophrenia – has been increasingly investigated over the past 10 years as a predictor of outcome in schizophrenia.

Most of the evidence indicates that a prolonged DUP may be viewed as a negative prognostic factor, and that the longer that psychosis remains untreated, the worse is the outcome [36].

- In the review of schizophrenia studies conducted by Bromet et al. [18], DUP was a predictor of poorer outcome, and other studies have reported that a DUP ≥1 year was associated with poorer outcome [22, 37]
- Melle et al. [38] and Amminger et al. [2] reported an association between DUP and the severity of positive, negative and cognitive symptoms
- Jeppesen et al. [39] reported longer DUP to be independently associated with more psychotic symptoms at entry, 1-year and 2-year follow-up
- Marshall et al. [40] reported that patients with a long DUP were significantly less likely to achieve remission
- Gunduz-Bruce [41] reported that DUP was specifically associated with time to response to treatment for delusions but not hallucinations
- Bottlender et al. [37] reported that the impact of the duration of DUP on outcome was independent of the mode of onset, the age at first admission, and gender
- Morgan and colleagues [20] reported that a longer DUP was associated with unemployment
- Dell'Osso and Altamuro [36] warned that negative symptoms might be underestimated and inadequately considered within DUP

Shorter DUP was associated with better outcomes.

- A meta-analysis [42] and a systemic review [40] reported that a shorter DUP was associated with better outcomes in terms of a greater response to antipsychotic treatment, symptom response, functioning, and quality of life
- Whitty et al. [32] reported that a shorter DUP predicted a better outcome (in psychopathology and general functioning) after 4 years
- Shorter DUP predicted full recovery (remission of positive and negative symptoms plus adequate social/vocational functioning) in the study by Robinson et al. [43]

Three elements that distinguish early intervention in schizophrenia from standard care have been proposed and are being investigated; early detection, phase-specific treatment, and the use of early intervention teams [36]. Preliminary findings suggest that outcomes are better with early interventions that reduce DUP [38, 44].

3.1.8. Suicide attempt at the time of admission

Suicide attempts at the onset of schizophrenia were reported to be a risk factor for future suicide [45, 46]. Greater education levels were associated with an increased risk of suicide, possibly due to greater insight concerning the implications of the disease [45].

3.1.9. Insight

In the study by Saravanan et al. [47], insight at baseline did not predict remission or better global functioning, but patients whose insight improved relatively early on in treatment had the better outcomes. Higher levels of insight at baseline were significantly associated with lower levels of schizophrenia symptoms at follow-up [48]. Greater insight was found to be an independent predictor of lower readmission and relapse over 18 months [49]. In their systematic review of studies of the impact of insight on outcome, Lincoln et al. [50] reported that most studies supported the assumption that insight is associated with adherence during the treatment phase, but the association with long-term adherence remained unclear.

3.1.10. Treatment adherence

Compliance with treatment emerged as the most important predictor of outcome in the study of first-episode patients conducted by Bachmann et al. [22]. Adherence with medication was associated with achieving recovery [31]. Lack of treatment compliance was associated with relapse [30, 51, 52], hospitalization [52, 53], suicide [52], and persistence of psychotic symptoms [53]. Moreover, the lower the level of compliance, the greater was the risk of hospitalization [54]. Antipsychotic noncompliance was associated with homelessness in men but not in women [7].

Samalin et al. [51] proposed that adherence in schizophrenia is a complex phenomenon that is related to many factors, including:

- Patient-related factors – poor insight, cognitive impairment and comorbidity [51]
- Treatment-related factors – antipsychotic efficacy and tolerability [51]
- Environmental factors – the degree of social support available [51]
- Clinician-related factors – the therapeutic alliance between patients and healthcare professionals [51, 55, 56]

The strongest predictor of adherence was adherence in the month before baseline assessment [52]. Other baseline predictors of adherence included initial treatment for schizophrenia and greater social activities. Baseline predictors of non-adherence were alcohol dependence and substance abuse in the previous month, hospitalization in the previous 6 months, independent housing and the presence of hostility.

Some schizophrenia patients, however, may not need to continue long-term antipsychotics. In their 15-year follow-up of patients taking and not taking antipsychotics, Harrow and Jobe [19] commented that, in contrast to randomised controlled trials (RCTs) where there was an increased risk of relapse when stopping antipsychotic treatment, there was a subset of patients who stopped taking antipsychotics and who did not immediately relapse and who experienced periods of recovery and good functioning. Among schizophrenia patients not receiving antipsychotics, a trend towards better functioning over a 15-year period was associated with more internal resources and positive attitudes about themselves (including better pre-morbid developmental achievements, favourable personality and attitudinal approaches, less vulnerability, and greater resilience) [19].

3.1.11. Life stress prior to onset

Having no precipitating stress at the first episode is a poor prognostic factor [19].

Sexual abuse in childhood is associated with hallucinations, but not delusions, thought disorder or negative symptoms [57, 58]. Sexual abuse both during childhood and adulthood was associated with hallucinations, delusions, and thought disorder [57]. Physical abuse was associated with positive psychotic symptoms [58].

3.1.12. Neurobiological markers

A number of neurobiological markers were found to be prognostic of outcome in schizophrenia:

- More cerebral asymmetry was associated with full recovery and adequate social/vocational functioning [43]
- Progressive ventricular enlargement was associated with poor outcome [59]
- Progressive decrement in frontal lobe white matter volume and enlargement in frontal lobe cerebrospinal fluid volume were associated with greater negative symptom severity [60]
- Reductions in frontal lobe grey and white matter volumes correlated with poorer executive functioning [60]
- A larger pituitary volume predicted less improvement in overall and positive psychotic symptoms, and a poorer response to treatment by week 12 [61]
- An abnormal baseline EEG predicted poorer outcome at 3 years in terms of persistence of both positive and negative symptoms as well as anxiety and depression [62]

- Higher levels of both tonic (skin conductance level, nonspecific skin conductance response rate) and phasic (number of skin conductance orienting responses) activity were associated with more negative symptoms and with a combination of poorer social and occupational outcome at 1-year follow-up [63]. It was suggested that these findings indicated that high levels of arousal and over-reactivity to the environment may interfere with efficient cognitive processing in schizophrenia, contributing to poor outcome, and that negative symptoms might partially serve as a means of coping with over-arousal
- Dopaminergic D2 receptor (D2R) density and pre-morbid adjustment scores were associated with poor prognosis [64]. An increased D2R density was only present in the group of schizophrenia patients with longer and, therefore, poorer pre-morbid adaptation

3.1.13. Comorbid conditions: depression, alcohol dependence, substance dependence

Conley [65] reported that individuals with schizophrenia and concurrent depressive symptoms had poorer long-term functional outcomes, including greater use of relapse-related mental health services, violence or suicidality, substance use problems, poorer life satisfaction, quality of life, mental functioning, family relationships, and medication adherence.

A lifetime diagnosis of alcohol dependence predicted a poorer response to antipsychotic medication over the first 12 weeks of treatment [66]. Baseline alcohol dependence was a predictor of non-adherence [52].

A diagnosis of lifetime substance use disorder predicted the presence of more positive symptoms, fewer negative symptoms, a longer duration of untreated psychosis, and a poorer response to antipsychotic medication over the first 12 weeks of treatment [66]. Substance abuse was associated with homelessness [7]. Substance abuse in the previous month was a predictor of non-adherence [52]. Drug misuse was also associated with unemployment [67].

A diagnosis of lifetime cannabis use disorder predicted a lower age of schizophrenia onset [66]. In their review of cannabis use, D'Souza et al. [68] reported that cannabis use can exacerbate symptoms in patients with schizophrenia, as well as trigger relapse, and have negative consequences on the course of the illness.

3.1.14. Pre-morbid functioning (general)

A number of studies reported that pre-morbid functioning was a predictor of later levels of functioning [17, 18, 69]. Poor pre-morbid functioning was associated with more severe negative symptoms especially at the onset of the illness [70], more negative symptoms and increased positive symptoms [71], more severe

neuropsychological impairments [72], a poorer response to treatment [73], and relapse [30]. Good pre-morbid functioning was associated with a better response to treatment [73], and pre-morbid functioning and higher cognitive scores predicted a good response to treatment (symptom improvement) over 2 years [34]. Scales that assess pre-morbid functioning in schizophrenia are available [74].

3.1.15. Social functioning

Better pre-morbid social adjustment was associated with functional recovery [9] and lower negative symptoms after 1 year of treatment [75]. Social functioning at study entry (including being socially active) was associated with achieving recovery [31]. Among schizophrenia patients not receiving antipsychotics and with positive personality characteristics, a trend towards better functioning over a 15-year period was associated with more internal resources and positive attitudes about themselves (including better pre-morbid developmental achievements, favourable personality and attitudinal approaches, less vulnerability, and greater resilience) [19]. Social functioning (indicated by the presence of a social network) was reported to be predictive of outcome in schizophrenia [69].

Poorer pre-morbid social adaptation was associated with more negative symptoms and smaller social networks at entry and 1-year follow-up [39]. Poorer social functioning and organizational ability prior to first admission in adolescents were associated with more days per year in hospital for male (but not female) schizophrenia patients [16].

It was proposed [14, 15] that the poorer social course of schizophrenia in men compared with premenopausal women was accounted for by men's lower level of social development at illness onset and subsequent impaired further development, and that the influence of the traditional predictors (age, gender, chronic/acute type of onset, and symptomatology) was mediated by these two variables assessed at the end of the prodromal stage.

An insecure attachment style was associated with symptoms and duration of hospitalization in male schizophrenia inpatients [6].

3.1.16. Marital status

Harrow and Jobe [19] identified being unmarried as a poor prognostic factor in schizophrenia outcome. A long-term study reported that being married was associated with better outcome [10].

3.1.17. Housing status

In a long-term study (up to 16 years), higher pre-morbid autonomy in living arrangements was associated with better outcome [10].

3.1.18. Educational history

Educational level was reported to be predictive of outcome in schizophrenia [69].

Whitty et al. [32] reported that more years spent in education were predictive of a better outcome (in psychopathology and general functioning) after 4 years. In the study by González-Blanche et al. [9], more years of education was associated with functional recovery. Education was reported to be a significant predictor of employment outcomes by Tsang et al. [5]. In the study by Norman et al. [75], better academic pre-morbid adjustment was correlated with lower negative symptoms after 1 year of treatment. Marwaha et al. [67] reported a higher level of education to be associated with employed status.

Jeppesen et al. [39] reported poorer pre-morbid school adaptation to be independently associated with poor vocational outcome at 1-year and 2-year follow-up.

Siegel et al. [17] reported that level of education affected later level of function; although first-episode patients showed a positive association between level of education and future quantity of work, this relationship was not apparent for previously treated patients, suggesting that the benefit of education for working that is found for first-episode patients is lost as the illness progresses.

Among patients who attempted suicide at the onset of the disease, however, higher education levels were associated with an increased risk of future suicide, possibly due to greater insight of the implications of the disease [45].

3.1.19. Occupational functioning

Girón & Gómez-Beneyto [30] reported that unemployment was associated with relapse.

In the systematic review conducted by Tsang et al. [5], cognitive functioning was the most significant predictor of employment outcomes. Other significant predictors included education, negative symptoms, social support and skills, age, work history (previous history of successful employment), and multidisciplinary team rehabilitation to restore community functioning and well-being. Gasquet et al. [35] reported that paid employment was associated with achieving remission. Marwaha et al. [67] reported a higher level of education and living with family to be associated with employed status, and more severe non-psychotic symptoms to be associated with unemployed status. Jeppesen et al. [39] reported poorer pre-morbid school adaptation to be independently associated with poor vocational outcome at 1-year and 2-year follow-up. In the 20-year follow-up study conducted by Harrow and Jobe [33], internal factors, such as good pre-morbid developmental achievements, reduced the probability of chronic positive symptoms (delusional activity) and associated reduction in work disability and global dysfunction in schizophrenia. Morgan and colleagues [20] reported that a longer DUP was associated with unemployment.

3.1.20. Cognitive functioning

Cognitive functioning was the most significant predictor of employment outcome in the systematic review of studies conducted by Tsang et al. [5].

The magnitude of relative impairment in digit symbol performance (a measure of processing speed/cognitive function) at the first psychotic episode was a prognostic factor for poor early outcome with respect to the development or persistence of negative symptoms [76]. In the meta-analysis of longitudinal studies of cognitive function in schizophrenia conducted by Szöke et al. [77], many schizophrenia patients experienced cognitive deterioration; this did not necessarily deteriorate further over time, but could improve, probably due to practice in testing rather than reversal of the dysfunction. Performance in semantic verbal fluency, however, remained stable over time.

Better cognitive functioning at stabilization was associated with full recovery, adequate social/vocational functioning, and symptom remission [43]. In females, better pre-morbid intellectual functioning was associated with better outcomes. Among adolescent females with schizophrenia (but not males), the higher the pre-morbid level of intellectual functioning the fewer the days per year in hospital [16].

Higher pre-morbid IQ independently predicted cognitive deterioration [2].

3.1.21. Family attitude

Girón and Gómez-Beneyto [30] found a significant relationship between poor empathic attitude in the relatives of schizophrenia patients and relapse in schizophrenia patients followed for 2 years. Critical attitude and poor empathic attitude may be independent dimensions of attitude, and whereas both maintain an independent relationship with relapse [30], only poor empathic attitude has shown predictive power for social functioning. Girón and Gómez-Beneyto [78] found a relationship between the empathic ability of the patient's relative and the social relations and occupational functioning of a person with schizophrenia in the period following hospitalization.

A diagnosis of schizophrenia versus schizophrenia-related disorder predicted help from the family during follow-up [8], possibly because parents recognize the more severe course of the illness in their offspring with a diagnosis of schizophrenia and, therefore, provide help in activities of daily living and treatment. Family involvement in help-seeking was independently associated with a shorter DUP [20].

3.2. International differences in the course of schizophrenia

The term 'course' refers to the pattern of progression of an illness over a period of time. It is generally accepted that for most patients, the course of schizophrenia is chronic, punctuated by acute exacerbations of severe psychotic symptoms that are

followed by full or partial remission. Functioning tends to decline over the first years of the illness and then to plateau. Treatment with antipsychotics reduces the severity of acute episodes, hastens resolution of symptoms, reduces the duration of hospitalization, and prolongs the period between relapses.

Initial evidence for the finding that schizophrenia may have a better outcome in low- and middle-income countries came from the WHO International Pilot Study of Schizophrenia (IPSS) and was further strengthened by two subsequent studies, the Determinants of Outcome of Severe Mental Disorders (DoSMED) and the International Study on Schizophrenia (ISoS) [79–81]. These data tend to be viewed as a benchmark (Table 1).

Table 1. Schizophrenia: patients falling into selected categories of course and outcome variables from WHO data [79]

Course and outcome category	Developing countries (%)	Developed countries (%)
Remitting course with full remission	62.8	36.8
Continuous or episodic psychotic illness, without full remission	35.7	18.7
In psychotic episodes for 25% of the follow-up period	18.4	18.7
In psychotic episodes for ≥75% of the follow-up period	15.1	20.2
In complete remission for 0% of the follow-up period	24.1	57.2
In complete remission for ≥75% of the follow-up period	38.3	22.3
No antipsychotics throughout the follow-up period	5.9	2.5
On antipsychotics ≥75% of the follow-up period	15.9	60.8
Never hospitalized	55.5	8.1
Impaired social functioning throughout the follow-up period	15.7	41.6
Unimpaired social functioning for ≥75% of the follow-up period	42.9	31.6

The findings from the WHO studies have always been criticized for a variety of reasons and researchers have called for re-examination of these data [82, 83]. Patel et al. [82] suggested that the apparent finding of a better outcome in developing countries needed re-examining because of methodological limitations, a lack of evidence on the specific socio-cultural factors apparently contributing to the better outcomes, rapid social and economic changes that are undermining family care systems for people with

schizophrenia in developing countries, and new evidence from cohorts in developing countries depicting poorer outcomes.

This section reports data on the course of schizophrenia in different countries and regions, taken from representative references published in the last 10 years. The papers were found by searching for onset (acute/chronic), remission, relapse, rehospitalisation, recovery, functioning and disability related to schizophrenia in different countries, and by review of the reference lists of papers. Most studies were first-episode patients; some studies included patients from the age of 15 years.

This section has been divided into the following sections:

- Data from developing/low- and middle-income/non-industrialized countries
- Data from developed/high-income/industrialized countries
- Published comparisons

Appendix 1 includes a summary of data from the papers (presented alphabetically by first author).

3.2.1. Developing/low- and middle-income/non-industrialized countries

Bali

Kurihara et al. [84] conducted a retrospective review of 51 schizophrenia patients in Bali who did not maintain contact with the mental health services.

At 5 years:

- 33.3% were classified as self-supportive
- 19.6% as semi-self-supportive
- 27.5% as socially adjusted to family or community
- 19.6% as maladjusted
- 0% as hospitalized

A total of 22 patients received antipsychotics and 29 patients did not. Compared with those who were treated, untreated patients showed a greater tendency to have either high or low symptom scores, and to be classified as either having best or worst outcome in terms of social adjustment. The authors noted that their results did not support the hypothesis that the outcome of schizophrenia patients without maintenance treatment was favourable in a non-industrialized society. They highlighted the fact that patients with both good and poor outcomes exist without maintenance treatment in this setting, and that a lack of treatment may be good for the subgroup of patients who do not need treatment and bad for the subgroup of patients who do.

A group of 46 schizophrenia patients from Bali were followed up at 5 and 11 years and categorized into best, medium and worst outcome groups [85]. No difference was found in symptoms or social adjustment between the 5- and 11-year follow-up groups

for the best and worst outcomes, indicating that outcome did not change in the long term (particularly for remission or severe deterioration). At 11 years, 23.9% were in remission and 19.6% were in partial remission. No patients were hospitalized at 11 years, but 60.9% had been re-hospitalized during the study.

In terms of functioning:

- 39.1% were classified self-supportive
- 13.0% were semi-self-supportive
- 15.2% were socially adjusted to family or community
- 32.6% were classified as maladjusted

With regard to employment, 37.0% worked full-time, 21.7% worked part-time, 41.3% did not work. A total of 63.0% were married. A total of 17.4% were on medication at the 11-year follow-up. The authors commented that the outcome of schizophrenia in Bali was slightly worse than that of other Asian countries. It was also noted that schizophrenia outcome in Bali was similar to that in developed countries, demonstrating that the medium- to long-term course of schizophrenic patients was stable and revealed neither marked deterioration nor significant improvement.

China

Ran et al. [86] studied a prevalence sample of 510 schizophrenia patients from rural communities in China. The sample included:

- 5.9% who had received regular treatment for≥1 year
- 42.7% who had received brief or irregular treatment
- 20.8% who had received traditional Chinese treatment
- 30.6% who had never received treatment

Among the no-treatment group at baseline, 32.1% were in full-time work, 45.5% could do part-time farm- or housework, and 22.4% could do no work. A total of 82.7% had more than mild disability; among these patients, impairment of social functioning was the most serious in 53.5%, serious in 14.7%, moderate in 10.9%, and mild in 20.9%. The never-treated group were followed for 2 years; there was no significant difference in clinical status between baseline and follow-up (Table 2).

Table 2. Clinical status at baseline and 2 years in never-treated patients in China [86]

Clinical status (%)	Baseline (n=156)	2-year follow up (n=95)
Complete remission	9.6	10.5
Partial remission	8.3	11.6
Marked symptoms	75.7	71.6
Deteriorated	6.4	6.3

The authors expected the natural course of schizophrenia to be favourable in rural China, but their findings indicated that the course was heterogeneous and poor. They noted, however, that while the clinical status of the never-treated patients was poor, occupational functioning was good and 77.6% were still able to work.

Ran et al. [87] reported findings from a prevalence sample of 510 schizophrenia patients from rural communities in China. At the point of the survey, 510 schizophrenia patients were identified in the following illness phases:

- 24.5% were in complete remission
- 13.4% were in partial remission
- 53.7% had marked symptoms
- 8.4% had deteriorated

A total of 30.6% patients never accepted any treatment, 5.9% were receiving antipsychotic drug treatment, 1.6% were hospitalized, 23.1% had been hospitalized at one time, 18.0% maintained irregular treatment for less than 2 months, and 20.8% had only used Chinese herbal medicine. A total of 43.1% were in full-time farm- or housework, 38.1% were in part-time farm- or housework, and 18.8% were not working. Of the 510 patients, 21.2% were single, 64.1% were married, 7.8% were widowed and 6.9% were divorced.

Ethiopia

In a cross-sectional survey of the onset and course of schizophrenia in 321 patients in Butajira (rural Ethiopia) carried out by Kebede et al. [88], onset was acute in 48.6% of the cases. The course of illness was reported to be continuous in 67.2% of the cases and episodic in about 10%; in a further 10%, the pattern of the course was unknown. The authors proposed that the reason for the high percentage of patients with a continuous course of illness that differed from the course reported in many first-episode studies might be due to the longer duration of the illness without any modern treatment (fewer than 10% of cases had started modern treatment before being screened for the study). Assessment of functioning revealed that 53% of patients had never been married, 54.7% were employed despite a continuous illness course (although employment for many was a basic agricultural job or domestic work), about 38% had children, 54.7% had formal education, and 7% were homeless.

In their study of symptoms and functional outcomes of this patient population, Kebede et al. [89] reported that most were antipsychotic-naive (63 incident and 208 prevalent cases). After a follow-up of an average of 2.5 (range 1–4) years, functioning was significantly reduced in this patient population, compared with the general population of the area at baseline and at follow-up. The level of functioning observed in these cases was also lower than that reported for cases from developed countries. It was

noted that these findings differed from other outcome studies that have reported better functional outcome for cases of schizophrenia from developing countries.

Alem et al. [90] reported on the onset and course of this predominantly treatment-naive cohort in a rural community setting in Ethiopia followed for up to 6 years. Among the 321 cases with schizophrenia, illness onset was acute in 67.2% and insidious in 32.8% of patients. The course of illness during follow-up was compared with the WHO findings [79] (Table 3) (although it should be noted that there are differences in this table compared with the WHO data in Table 1).

Table 3. Comparison of findings from Butajira and WHO (DOSMeD) data from developing and developed countries [90]

Course categories	Patients in course categories (%)		
	Butajira	WHO data on developing countries	WHO data on developed countries
Continuous illness with psychotic episodes or residual symptoms	30.8	35.7	60.9
Psychotic (≤5% of follow-up)	36.8	18.4	18.7
Psychotic (>75% of follow-up)	1.3	15.9	20.2
Complete remission (>75% of follow-up)	5.7	38.3	22.3
Receiving antipsychotics (>75% of follow-up)	12.9	15.9	60.8
Never received antipsychotics	9.1	5.9	2.5

The authors noted that the course of illness was as follows:

- Continuous in 30.8%
- Episodic/intermittent in 64–70%
- Nearly continuous, complete remission in 5.7%.
- Relapse did not occur in 22%

They highlighted the fact that the low rate experiencing continuous psychotic episodes, and the pattern of medication use in their study were similar to what was reported previously in other developing country studies. They maintained that their findings differed in the proportion attaining full remission for ≥75% of the follow-up period (5.7%), which was smaller than that found in the WHO developing country samples (stated in the paper as 10%). Rates of mortality were also high; 10.4% of the patient population died during follow-up.

This study claims to be the only community-based study on the outcome of schizophrenia in Africa and one of the very few worldwide focusing on a predominantly

rural community sample and treatment-naive majority. The authors noted that although the overall pattern of outcome of schizophrenia in this setting was comparable to that reported in developing countries, there was a clear tendency toward a poorer outcome that is likely to reflect the outcome in many sub-Saharan African countries where most patients live in the community with limited access to care. Although outcome in this setting appears better than in developed countries, the very low proportion of participants in complete remission supports the observation that the outcome of schizophrenia in developing countries may be heterogeneous rather than uniformly favourable.

India

Mojtabai et al. [91] studied first-contact patients in urban and rural Chandigarh, India, who had originally been recruited for the WHO DoSMED study. Patients were assessed at 2 and 15 years, and those with a poor 2-year course (continuous psychotic illness with no remission and symptoms present most of the time) were compared with all other course types. A total of 92% of patients with a poor 2-year course went on to have a poor long-term course of illness. Mortality at 15 years was 47% in the poor 2-year outcome group, and 11% in other 2-year outcome groups The authors noted that even in this developing country setting there was a subset of patients with a poor 2-year course and poor long-term outcomes.

Among a cohort of 72 never-treated chronic schizophrenia patents in Chennai, India, 68% received treatment with antipsychotics and were followed up for 1 year [92]. Evaluation of social functioning and disability revealed that outcomes were good ('best remission') in 29%. There was no impairment in social functioning in 35% and 51% had no impairment in occupational functioning at the end of 1 year.

A study of the course of schizophrenia among 90 schizophrenia patients in urban India conducted by Thara [93] revealed four basic patterns in the 61 patients completing the 20-year follow up:

- Complete remission (8.2%)
- Relapses with complete remission in between (39.3%)
- Relapses with partial remission in between (44.3%)
- Continuous illness (8.2%)

The most common course of illness was relapse with or without complete remission; over 20 years, more than 80% of the original cohort (90 patients) experienced relapses. A significant finding was the high employment rate; >75% of men were employed at the end of 20 years of illness. It was proposed that this was due to several factors, including the fact that the sample was largely low- and middle-class, so it was not too difficult for them to find jobs in the unskilled sector, and that the absence of state social security benefits created pressure to find work. Mortality in this study was high; after 20 years, 17% of the cohort (16 patients) had died, and suicide accounted for nearly half of all deaths (7 of 16).

Srivastava et al. [94] studied 122 schizophrenia patients who had completed 10 years of consistent treatment after first hospitalization in India: 30.5% were improved (reported as recovery), and 20% had no improvement. A total of 72.9% were able to live independently, and 40% were able to find employment. It was noted that the recovery rate reported in this study (30.5%) was within the range (16%–75%) reported in other long-term studies reporting recovery rates from 1978 to 2008.

Jamaica

Short-term relapse among Jamaican schizophrenia patients was reported to be low [95]. Among 317 first-contact patients (62% outpatients, 38% inpatients) in Jamaica, 264 (83%) were still being seen after 1 year. The overall relapse rate was 13%, with 83% showing no signs of relapse; 4% were lost to follow-up. In terms of functioning, 43% were employed in the 12-month follow-up period. Self-reported use of medication was 67%, and 45% of patients received monthly intramuscular depot medication. A total of 3 patients died during the study; none of the deaths were related to schizophrenia.

Russia

Kaleda [96] conducted a 15-year follow-up study from first episode among 278 male patients with juvenile-onset (at age 16–25 years) endogenous episodic psychosis (schizophrenia or schizoaffective disorder). Nosological evaluation at follow-up showed that among the 76.2% of the population who had confirmed schizophrenia (as opposed to schizoaffective psychosis), disease course was episodic progressive in 61.1% and recurrent in 15.1%. The types of course were:

- Single episode in 17.9% of patients (which is lower than the 25–30% reported in other studies)
- Regressive in 23.2% of patients
- Progressive in 25.1% of patients
- Chronic in 4.6% of patients

Most repeated episodes occurred during the first 5 years; 45.6% of episodes occurred in years 1–5, 36.6% of episodes occurred during years 6–10, and 17.8% of repeat episodes occurred during years 11–15. These findings were taken to indicate that the disease course is characterized by a gradual reduction in episode activity both during and after adolescence. At the time of follow-up, 95.4% of patients were in remission. Outcome was reported to be:

- "good" in 18.7%
- “relatively good" in 33.8%
- "relatively poor" in 30.2%
- "poor" in 17.2%

At follow-up, 14.4% of patients were unable to work and 25.2% were married.

Tunisia

Douki et al. [97] studied the course of schizophrenia in Tunisia, which is an emerging country, ranking half-way between the most and the least developed countries. Results indicated that the outcome of schizophrenia was similar to that seen in developed countries; a chronic course without remission was not unusual and long-stay patients accounted for a quarter of the hospital population. In terms of functioning, only 16.5% were married and 10% had a regular job in spite of a high level of education.

3.2.2. Developed/high-income/industrialized countries

Canada

A retrospective analysis of long-term outcome (10–16 years) of 142 first-episode schizophrenia patients in a Canadian urban centre revealed that hospitalization days decreased considerably after the first year, with a small minority of patients still needing episodic hospitalization after 4 years [10]. By the end of the study, 26.8% had never been re-hospitalized. Marital and occupational status were generally stable over time; the percentage of patients in normal/sheltered occupation was 20.1% on admission and 25.6% at the end of the study, the percentage of patients who were single was 78.8% on admission and 79.5% at the end of the study. The authors noted that these marital and occupational outcomes were worse than those reported by other studies, possibly due to differences between studies in the inclusion of patients with substance dependency, long illness duration, diagnostic criteria, duration of illness on admission, percentage of males, and age on admission, and cultural and socioeconomic differences in employment between different countries. Autonomy in living arrangements worsened; the percentage of patients who were living with family was 71.6% on admission and 30.8% at the end of the study. A total of 12% of patients died during the study, of which 7% had committed suicide. The 33% of patients who left the specialized psychiatric service in the area had better social functioning while they were followed, were hospitalized less afterwards, and had fewer suicides, indicating a better outcome. At the end of the study, 15% of the patients alive were well enough to function without seeking medical help and 25% were not taking antipsychotics. The authors concluded that a significant proportion of first-episode schizophrenia patients achieve moderate long-term outcome, and the stability of global functioning is more common than deterioration, as shown in most industrialized countries.

Denmark

Bertelsen et al. [98] investigated rates of recovery (no psychotic or negative symptoms, living independently, improved GAF score, working or studying) and institutionalization (hospitalization or living in supported housing) in a subset of 265 first-episode psychotic patients from the Danish OPUS trial (a randomized clinical trial comparing 2 years of intensive early intervention with standard treatment). Rates of recovery and

institutionalization were similar at 2 years and 5 years (recovery was 18% and institutionalization was 13%); the lack of change in these rates from 2–5 years contradicts the assumption that course of schizophrenia is progressive deterioration and supports the idea of an early plateau in the illness. The authors noted that of the 18% of patients who had recovered after 5 years, only 29% received antipsychotic medication; this finding supports the proposal that schizophrenia is not necessarily chronic, as one-third recovered without medication. According to WHO criteria, the course of illness in the 2 years preceding the 5-year follow up was:

- Apsychotic in 37%
- Episodic in 17%
- Continuous in 46%

A lack of remission after 2 years was associated with a continuous course of illness at 5 years.

Denmark and Norway

Simonsen et al. [99] reported 1-year outcomes from 301 patients with first-episode psychosis from four healthcare sectors in Norway and Denmark. All patients received standardized treatment. Diagnosis of schizophrenia was confirmed in 27.9% and schizophreniform disorder in 21.6% of patients. At 1 year, 66% were in remission, 11% in relapse, and 23% were continuously psychotic.

Germany

The study by Röpcke and Eggers [100] assessed outcomes at 15 years for 39 German patients treated for schizophrenia in adolescence (mean age at onset 16.0 years). Of the original patient population, 71% could be re-examined. At 15 years, 85% had had at least one re-admission. Onset was insidious in 61%.

Outcome was reported to be:

- Good (remission) in 8%
- Moderate (partial remission) in 56%
- Poor (chronic illness, severe residual symptoms) in 36%

Global social functioning was reported to be slightly impaired in 21%, moderately impaired in 28%, and severely impaired in 51%. At the time of follow-up, 20% had a regular occupation, 36% were working in a sheltered institution or in a rehabilitation programme, and 31% were without any structured occupational or educational activity.

Israel

In a study of the course of schizophrenia in a national population-based cohort in Israel, Rabinowitz et al. [101] followed 6865 patients from first admission for schizophrenia

for 10 years. Of the 6865 patients, 354 died and 483 had initial hospitalization longer than a year, leaving 5990 for analysis of a 10-year follow-up. Classification of the patients into deteriorating, improving and stable (based on days hospitalized per year after the initial hospitalization) revealed three clusters of patients:

- 5.4% with a deteriorating course
- 12.8% improved
- 81.8% initial improvement followed by relative stability (including 6.4% who spent no time in hospital after initial admission)

It was concluded that the course of schizophrenia, reflected by the course of hospitalization, is predominantly characterized by systematic progressive deterioration for a minority of patients and systematic progressive amelioration for a majority of patients.

Italy

A total of 40 stable, antipsychotic-treated Italian schizophrenia patients were classified into three 'outcome' groups based on baseline symptoms and functioning (the 'good outcome' group had low symptom severity plus good social functioning, the 'poor outcome' group had higher symptom severity and social dysfunction, and the 'intermediate outcome' group were in-between) and followed up for 36 months [102]. The percentage of patients hospitalized (experiencing relapse) during follow-up was 25% in the good outcome group, 45% in the intermediate outcome group, and 87% in the poor outcome group. The percentage of patients in employment during follow-up was 58% in the good outcome group, 10% in the intermediate outcome group, and 0% in the poor outcome group. The authors concluded that the outcome of schizophrenia patients is multifaceted and generally poor, because at least 45% of the whole sample needed hospitalization. However, there also exists a group of patients characterized by low symptoms and good functioning, and at the opposite end of the scale, a group of patients who cannot achieve a satisfactory level of symptom control and daily functioning.

Netherlands

A 15-month inpatient intervention programme in 76 first-episode schizophrenia patients in the Netherlands resulted in a low relapse rate of 15% [103]. After completion of the 15-month study, 73 patients were referred to other agencies and followed for 5 years. After 5 years, 52% of patients had one or more psychotic relapses, 25% developed chronic positive symptoms and 23% did not have another psychotic episode. Social functioning was poor, with most patients dependent on their parents; 34% lived mainly with their parents, 40% lived alone, 12% lived with a partner, and 7% were chronically hospitalized. About 50% of patients were in paid employment (unskilled or semi-skilled) for at least some of the time.

Singapore

A long-term study from Singapore [104] described final outcome measures at 20 years for 402 first-episode schizophrenia patients.

At 20 years:

- 28.3% of patients had a good outcome (patient not receiving treatment, well and working)
- 37.0% had a fair outcome (patient not receiving treatment and not working, or receiving outpatient treatment and working)
- 34.7% had a poor outcome (patient receiving treatment and not working, or receiving inpatient treatment)

On the whole, the changes in the final outcome (based on the work and treatment status of the patients) over the 20-year period were reported to be minimal and not statistically significant; 32.4% were working full time, 53.2% were not working, and 14.4% were working part time. At 20 years, 44.9% of patients were being treated as outpatients, 6.9% were being treated as inpatients, and 48.2% of patients were not on treatment. Suicide was greatest during the first 10 years; the suicide rate was 8.46 per 1000 patients per year in the first 10 years, 6.47 per 1000 patients per year in years 10–15, and 4.85 per 1000 patients per year in years 15–20. The authors concluded that most patients with schizophrenia had a good/fair outcome at 20 years.

Spain

San et al. [105] conducted a multicentre, cross-sectional study in more than 100 mental health facilities within Spain. Data from 1010 patients were analysed; at the time of the study:

- 44.8% were in complete remission (but only 10.2% showed adequate social and/or vocational functioning)
- 34.4% were in partial remission
- 20.8% were not in remission

A total of 15.7% patients were in paid employment at the time of the assessment.

USA

Robinson et al. [43] assessed 118 patients in their first episode of schizophrenia (70% of patients) or schizoaffective disorder (30% of patients) and after 5 years of treatment in the USA. Full recovery required concurrent remission of positive and negative symptoms and adequate social/vocational functioning. After 5 years, 47.2% achieved symptom remission, but only 25.5% had adequate social functioning for 2 years or more, and even fewer (13.7%) met full recovery criteria for 2 years or longer. It was

concluded that although some patients with first-episode schizophrenia can achieve sustained symptomatic and functional recovery, the overall rate of recovery during the early years of the illness is low.

In the study by Harrow et al. [106], 64 schizophrenia patients from the Chicago Follow-up Study were assessed as inpatients and then reassessed five times over 15 years. Patients were evaluated for recovery (no major symptoms, working half-time or more, and the absence of a very poor social activity level) for 1 or more years. Over the 15-year period, the percentage of schizophrenia patients in recovery varied from 10% at the 2-year follow-up to 19% or more at each of the subsequent follow-ups. Cumulative recovery data indicated that by the 15-year follow up, 41% of the patients had experienced one or more periods of recovery at some point. It was also noted that most patients did not exhibit severe social isolation. They concluded that more than 50% of schizophrenia patients did not have a disorder that was chronic and continuous, but that their disorder was episodic, and among the more vulnerable and less resilient patients, episodes were more frequent and severe, with slower recovery. Further findings from this study were that a significantly larger percentage of schizophrenia patients not on antipsychotics showed periods of recovery and better global functioning compared with patients receiving medication [19]. These data were taken to indicate that there was a subgroup of schizophrenia patients who do not immediately relapse while off antipsychotics and experience intervals of recovery, and that not all schizophrenia patients need to use antipsychotic medications continuously throughout their lives.

3.2.3. Published comparisons

Bali and Tokyo

Kurihara et al. [107] compared the outcome of schizophrenia among 51 patients in Bali (a non-industrialized Asian society) and 40 patients in Tokyo (an industrialized Asian society). At 5 years, no significant differences were found in symptoms, social adjustment or re-admission rates between the two groups. The cumulative length of hospital stay was shorter in Bali (mean 76.4 days) compared with Tokyo (358.2 days), and the percentage of patients receiving antipsychotics was lower in Bali (25.5%) than in Tokyo (87.5%). The authors concluded that while clinical outcomes were not superior in Bali, patients in this country tended to be able to live in society without antipsychotics. It was suggested that this was due to the stable extended family structure and community system, which meant that the burden of care was shared, plus a more benign view of mental illness.

Europe: Bulgaria, Germany, Ireland, the Netherlands, the Czech Republic and the UK

Wiersma et al. [108] studied the long-term course of social disability after 1, 2 and 15 years among first-episode schizophrenia incidence cohorts from the WHO ISoS study in six European centres in Bulgaria, Germany, Ireland, The Netherlands, Czech Republic

and UK. At 15 years, 9% of the original cohort had died and 15% were lost to follow-up, leaving 349 patients (75%) for analysis. A total of 61% of the cohort had an acute illness onset. A deteriorating course was more frequent than late improvement, and the investigators considered that nearly half of the patients (48%) had an unfavourable course.

The stability of the course of schizophrenia was reported as follows:

- Prominent all the time (19%)
- Deteriorating course (29%)
- Late improvement (10%)
- Early improvement (36%)
- Never prominent (7%)

The course of social disability was as follows:

- No disability: 13% at baseline, 19% at 1 year, 21% at 2 years, and 14% at 15 years
- Severe disability: 41% at baseline, 31% at 1 year, 34% at 2 years, and 25% at 15 years

At 15 years, 62% of patients lived with their family or friends, 25% lived alone, 8% were living in sheltered accommodation, and 6% were in a psychiatric hospital.

Europe: France, Germany and the UK

In the European Schizophrenia Cohort (EuroSC) study [109], schizophrenia patients from France, Germany and the UK were followed for 2 years. At baseline, the overall sample was characterized by long-term illness; respondents had been ill for >14 years in all sites and almost all had been hospitalized at some point. Overall, an episodic course was the most common course (about 60% of patients); 25% of patients had a continuous course. There was some inter-country heterogeneity in course type (Table 4).

Table 4. The course of schizophrenia in European countries in the EuroSC study [109]

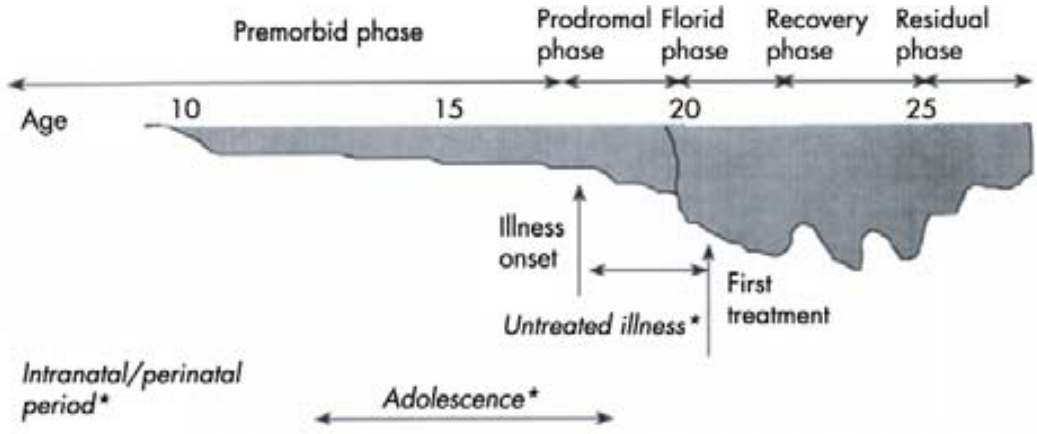
Classification of longitudinal course, n (%)	France (n=288)	Germany (n=618)	UK (n=302)	All (n=1208)
Time since first contact (years) mean (SD)	14.3 (9.9)	14.5 (9.9)	14.2 (10.6)	14.4 (10.1)
Episodic with residual symptoms	125 (43.4)	315 (51.0)	61 (20.2)	450 (41.5)
Episodic with no residual symptoms	31 (10.8)	154 (24.9)	50 (16.6)	235 (19.5)
Continuous	108 (37.5)	77 (12.5)	119 (39.4)	304 (25.2)
Single episode in partial remission	6 (2.1)	25 (4.0)	14 (4.6)	45 (3.7)
Single episode in full remission	2 (0.7)	14 (2.3)	30 (9.9)	46 (3.8)
Other or unspecified pattern	16 (5.6)	10 (1.6)	27 (8.9)	53 (4.4)
Admitted to a psychiatric ward	284 (98.6)	573 (92.7)	284 (94.0)	1141 (94.5)

3.2.4. Comparison of international differences in outcomes

The large number of studies conducted to date have, overall, contributed to relatively little advance compared to the two seminal WHO studies. Several methodological aspects impair comparisons between studies, which limits the ability to draw firm conclusions on international differences in the course of schizophrenia. First, studies do not share a common definition of schizophrenia. Not only has the concept of the disorder changed over time, with clinical descriptions and diagnostic criteria changing in several definitions, but also the main mental disorders classifications, namely DSM and ICD, still show very important differences in the definition of the disorder. Second, the studies assessed different types of outcomes and used different scales to measure outcomes. While some studies focus on clinical outcomes, others focus on social functioning, and the definition of good outcomes varies among studies (for a review see Cohen [83]). Third, mental health services availability and actual treatment received by the patients show considerable regional differences. While some studies in less developed nations report on high rates of untreated cases, the proportion is greatly lower in high-income countries. This confounding effect of medication impairs the comparison among countries. Fourth, country classification has changed over time and it is not clear if differences depend on economic, cultural, family or social structure aspects. While the early studies classified countries as economically developed or developing, later studies classified countries as high-, middle- or low-income, which does not convey the message that high-income countries are more developed. Fifth, the sampling methods used in each study show large differences. Sixth, studies do not usually account for mortality. Finally, the studies have different follow-up periods.

The course of schizophrenia does not seem to follow a monotonic course. As shown in Figure 1, after the premorbid and prodromal phases, patients usually experience an initial period of psychotic episodes in which increasing impairment may appear. After this phase, which may last around 5 years, patients may experience a stabilization phase, and after 10 to 15 years of the disorder, patients may experience a small improvement in outcomes [110].

Figure 1. An example of the course of schizophrenia showing the different phases of the illness. Taken from Minzberg et al [111]



It is also debatable why international differences, when present, appear. Several reasons have been proposed to explain why patients in low- and middle-income countries have better outcomes. The main explanations are:

- Family relationships: in low-income countries, family cohesion may be more conducive to recovery. Besides, family expressed emotion may differ between settings and may be higher in high-income countries [112].
- Informal economies may facilitate reintegration into work roles, which may be the rule rather than the exception in low-income countries.
- Segregation of the mentally ill in hospitals or other institutions has occurred more often in high-income countries.
- Community cohesion, since communities may differ on dimensions of social integration/isolation.

However, much qualitative and quantitative research needs to be conducted to clarify these hypotheses.

4 HYPOTHESES

The hypotheses of this dissertation are:

1) Patients with schizophrenia who start a new antipsychotic medication for the treatment of an episode of schizophrenia experience a higher response rate in developing than in economically developed countries
2) Response rate to antipsychotic treatment in patients with schizophrenia is higher in females than in males
3) Response rate to antipsychotic treatment in patients with schizophrenia with a younger age of onset is lower compared to patients with a later onset
4) Patients with a good social functioning at baseline experience higher response rates to antipsychotic treatment
5) Response rate to antipsychotic treatment decreases with longer duration of disease in schizophrenia
6) Patients with schizophrenia who start a new antipsychotic medication for the treatment of an episode of schizophrenia experience a higher clinical and functioning remission rate in developing than in economically developed countries
7) Clinical and functioning remission rate to antipsychotic treatment in patients with schizophrenia is higher in females than in males
8) Clinical and functioning remission rate in patients with schizophrenia with a younger age of onset is lower compared to patients with a later age of onset
9) Patients with a good social functioning at baseline experience higher clinical and functioning remission rates to antipsychotic treatment
10) Clinical and functioning remission rate to antipsychotic treatment decreases with longer duration of disease in schizophrenia

5 OBJECTIVES

The overall objectives of this dissertation are to describe the course of patients with schizophrenia during three years and to study the differences between regions with different levels of development.

The specific objectives of this dissertation are:

1) To describe the frequency of treatment response in outpatients with schizophrenia in different regions of the world
2) To analyse the demographic (age, gender, marital status) and clinical factors (age of onset, time since onset, severity of disease, functioning) associated with response
3) To describe the frequency of clinical and functional remission in outpatients with schizophrenia in different regions of the world
4) To analyse the demographic (age, gender, marital status) and clinical factors (age of onset, time since onset, severity of disease, functioning) associated with clinical and functional remission

6 METHODOLOGY

The Schizophrenia Outpatient Health Outcomes (SOHO) study was a 3-year, prospective, observational study primarily designed to assess the comparative costs and outcomes associated with antipsychotic use in outpatients initiating or changing antipsychotic medication for schizophrenia (with an emphasis on olanzapine compared with other antipsychotics). SOHO was conducted in 10 Western European countries [113, 114], and in 27 countries across 4 continents as the Intercontinental SOHO (IC-SOHO) [115]. Data from all 37 participating countries was pooled to produce the Worldwide-SOHO (W-SOHO) dataset [116]. The SOHO studies were non-interventional, with all treatment (including flexible dosing and use of concomitant therapies and medications) at the discretion of the treating psychiatrist. No medications were provided by the study sponsor; investigators were free to prescribe any antipsychotic medication indicated for schizophrenia. Patients were assessed at study entry and during scheduled study visits at 3, 6, 12, 18, 24, 30 and 36 months post-baseline. The study was approved and conducted in accordance with local (country) ethics and regulatory requirements; all patients consented to participate.

The complete list of publications from the SOHO study is given in Appendix 2.

6.1. Patient Population

To ensure the study population was representative of actual clinical practice, minimal selection criteria were applied. All patients aged 18 years or over who met *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) [117] or *International Classification of Diseases* 10th edition (ICD-10) [118] criteria for schizophrenia, and who were initiating or changing antipsychotic medication at study entry in an outpatient, ambulatory, or community setting (or in hospital during an admission scheduled for the initiation or change for up to two weeks) were considered eligible unless they were participating in another study that included a treatment intervention and/or an investigational drug. Study sites were established in 37 countries across 6 regions. The enrolment period was intentionally long to avoid interfering with standard medical practice. To ensure that a similar number of patients started on olanzapine and any other antipsychotic treatment, enrolment of patients in most countries followed a non-randomised process which asked the participating investigators to alternate recruitment between two groups: patients initiating or changing to olanzapine (group 1), and patients initiating or changing to non-olanzapine medication therapy (group 2). This deliberate over-sampling of olanzapine patients was done in order to facilitate comparisons between the

two groups, as per the primary objective. Importantly, the antipsychotic treatment prescribed to each patient was wholly based on the opinion of the treating psychiatrist; patients were asked to participate in the study after they had received their medication prescription.

6.2. Measures

All assessment tools were chosen for simplicity and ease of use, bearing in mind the observational nature of the study, cross-cultural relevance, and practical needs such as translation. The Clinical Global Impressions Severity Scale - Schizophrenia version (CGI-SCH) [119] was used to assess symptom severity across positive, negative, depressive and cognitive subdomains in addition to overall symptomatology from 0 (normal, not at all ill) to 7 (among the most severely ill). A detailed patient history was taken at baseline, capturing clinical information (including duration of illness, current and past medications, reasons for treatment initiation or change, CGI-SCH score, adverse events) in addition to key socio-demographic, functional and health service use data, such as age, alcohol and substance abuse/dependency, housing and employment status, occurrence of violent or aggressive behaviour, suicidality, previous hospital admissions, and outpatient clinic visits. The presence of violent or aggressive behaviour was captured as a positive response to the question: "Has the patient exhibited verbal or physical hostility/aggression in the past 6 months?". The location and type of the principal practice of participating investigators was also collected. Antipsychotic medication use in the 6 months prior to study entry was captured at baseline; antipsychotics taken upon presentation to each visit (drug name, formulation and dosage) and those prescribed at the visit were also recorded. Concomitant medications were recorded by medication class (anticholinergics, antidepressants, anxiolytics/hypnotics, mood stabilisers). Physicians were asked to select all applicable reasons for modification to antipsychotic therapy from the following options; lack of or incomplete effectiveness of the medication therapy, intolerability to the medication therapy, lack of or incomplete compliance/adherence with the medication therapy, patient's request. No guidance was provided, this was based on the clinical opinion of the investigator during patient assessment and, where appropriate, multiple reasons could be selected. Extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) judged to be associated with antipsychotic medication therapy were assessed by the physician at each study visit and are reported as the presence or absence of symptoms. Similarly, patient-reported sexual functioning in the 4 weeks prior to assessment is reported as a binary outcome. Patient-reported health-related quality of life and health status were assessed using the EuroQoL EQ-5D scale and Visual Analogue Scale (EQ-VAS); the EQ-VAS requires patients to indicate their current health status on a scale from 0 (worst imaginable health) to 100 (best imaginable health) [120, 121]. Self-reported health-related quality of life data are not available for patients in the Czech Republic, Egypt, Romania, Saudi Arabia, and Slovakia due to the absence of validated translations during study development.

6.3. Data collection intervals and study duration

The core study spans a period of 3 years from the baseline data collection for each patient.

As this study had a non-interventional and observational design, the protocol had no recommendations or requirements for baseline or post-baseline treatment visits scheduled specifically for the study. Data collection for the study occurred during visits within the normal course of therapy. The normal practice outpatient visit at which patients were enrolled served as the time for baseline data collection (T1).

Regardless of whether the medication was initiated or changed in the outpatient setting or in hospital, the enrolment and baseline data collection was conducted by the participating psychiatrist (or his/her designee) who also assumed primary responsibility for care in the outpatient setting.

For each subsequent data collection target, there was an allowable range of 1 month prior to and after the target month. Thus, data was collected during the following post-baseline target intervals:

- T2 (3 month post-baseline target; range 2–4 months post-baseline)
- T3 (6 month post-baseline target; range 5–7 months post-baseline)
- T4 (12 month post-baseline target; range 11–13 months post-baseline)
- T5 (18 month post-baseline target; range 17–19 months post-baseline)
- T6 (24 month post-baseline target; range 23–25 months post-baseline)
- T7 (30 month post-baseline target; range 29–31 months post-baseline)
- T8 (36 month post-baseline target; range 35–37 months post-baseline)

There were various reasons why patient participation in the study could be discontinued:

a. Patient consent is withdrawn
b. Participation in another study that includes a treatment intervention and/or an investigational drug
c. Decision of the respective participating psychiatrist (e.g. knows the patient has moved)
d. The patient changes to a different psychiatrist who is not participating in the study
e. For patients enrolled during a planned inpatient admission, the patient was not discharged from hospital within 2 weeks of the medication initiation, enrolment, and baseline data collection
f. Suicide
g. Death by causes other than suicide
h. Sponsor decision
i. Other

6.4. Dataset

Raw datasets from each of the two studies were merged using common rules for data management. Both studies used an identical case report form, so the SOHO and IC-SOHO databases had a very similar data structure. Both databases had similar quality checks and cleaning rules when they existed as separate studies. During the data merge, if any variables

did not share common cleaning rules it was agreed that the most stringent rule would be applied to the entire dataset. All merging, cleaning and validation was performed using Statistical Application Software (SAS) (SAS Institute, Cary, N.C). Cohorts based on geographic region were established for use in this analysis.

The merged W-SOHO database comprises a total of 17,384 patients recruited from 37 countries. Of these 37 countries, 57% (n=21)[1] are considered to be emerging or developing economies based on International Monetary Fund (IMF) guidelines (as Puerto Rico is not a member of the IMF, it is of indeterminate status) [122]. This represents 31% (n=5455) of the study population. Using the World Bank classifications (which are based on Gross National Income), lower-middle (n=8), upper-middle (n=10) and high income (n=18) countries[2] are all represented in this study population [123]. For analysis purposes, the countries were grouped into 6 regions: East Asia (Korea n=821, Malaysia n=105, Taiwan n=297); Central and Eastern Europe (Czech Republic n=477, Hungary n=189, Lithuania n=100, Poland n=599, Romania n=136, Russia n=159, Slovakia n=301, Slovenia n=214); Northern Europe (Denmark n=31, France n=915, Germany n=2869, Ireland n=53, Netherlands n=160, UK n=263); Southern Europe (Greece n=690, Italy n=2869, Israel n=76[3], Portugal n=166, Spain n=1987); Latin America (Argentina n=349, Chile n=152, Colombia n=197, patients from Costa Rica, El Salvador, Guatemala and Honduras were pooled n=267, Mexico n=1019, Peru n=96, Puerto Rico n=217, Venezuela n=269); North Africa & Middle East (Algeria n=300, Egypt n=183, Turkey n=662, Saudi Arabia n=196). Of the 1563 participating psychiatrists, the majority were working in either combined private/public or public practice in an urban setting when enrolment began.

Overall, the W-SOHO study population is a moderately ill group of outpatients aged 38 (± 13 years), with a median disease history of 7 years (interquartile range 1 to 16 years), 10% of whom were receiving an antipsychotic medication for schizophrenia for the first time (Table 5). As shown in Table 5, regional variations were evident in most demographic and clinical characteristics. In particular, East Asian patients were consistently less severe.

Only participants with at most one missing visit (except the final one) were included in the analysis. For participants with one missing visit, values from the previous visit were carried forward and used to impute the values of the missing visit. Results from the 3-month visit were not used in the analysis unless data from the 6-month visit were missing; in such cases, data from the 3-month visit were used in the imputation.

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[1] Algeria, Argentina, Chile, Colombia, Costa Rica, Czech Republic, Egypt, El Salvador, Guatemala, Honduras, Hungary, Lithuania, Malayasia, Mexico, Poland, Peru, Romania, Russia, Saudi Arabia, Turkey, Venezuela.

[2] Lower Middle Income = Algeria, Colombia, Egypt, El Salvador, Guatemala, Honduras, Peru, Turkey; Upper Middle Income = Argentina, Chile, Costa Rica, Malaysia, Lithuania, Mexico, Poland, Romania, Russia, Venezuela; High Income = Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Portugal, Puerto Rico, Netherlands, UK, Saudi Arabia, Slovakia, Slovenia, South Korea, Spain (no data available for Taiwan).

[3] Israel has been included in the 'Southern Europe' grouping based on ethnicity, economic and health care systems.

Approximately one-third of the participants (36.3%) were lost to follow-up before the end of the study at 3 years and were not included in the analysis. The percentage varied across regions.

The highest attrition rate was in East Asia (62.8%), followed by Africa and Middle East (47.7%), Latin America (41.7%), North Europe (37.5%), South Europe (28.2%) and Central and Eastern Europe (26.9%). There were small differences in participant characteristics between those included and not included in the analyses, both overall and by region.

Table 5. Demographic and clinical characteristics of patients in each region at study entry

Characteristic	All patients	East Asia	Europe			Latin America	North Africa & Middle East
			Central and Eastern Europe	Northern Europe	Southern Europe		
Number of patients	17384	1223	2175	4291	5788	2566	1341
Proportion of all patients, %	100	7.0	12.5	24.7	33.3	14.8	7.7
Number of countries	37	3	8	6	5	11	4
Number of investigators	1563	92	215	503	354	274	125
Gender, % women	43.3	50.0	52.4	46.6	38.9	41.6	34.7
Age, mean (SD), years	38.0 (12.8)	35.0 (11.0)	38.0 (12.4)	40.7 (13.6)	38.8 (12.6)	35.7 (12.5)	32.5 (10.1)
Duration of illness, median (interquartile range),[1] years	7.0 (1.0 to 16.0)	5.0 (1.0 to 11.0)	6.0 (1.0 to 15.0)	6.0 (1.0 to 16.0)	9.0 (2.0 to 19.0)	8.0 (2.0 to 17.0)	5.0 (1.0 to 11.0)
Never received an antipsychotic for schizophrenia, %	9.9	6.9	5.3	12.2	9.2	11.8	12.3
Schizophrenia-related admission to an inpatient facility (past 6 months), %	34.4	31.6	32.8	36.3	31.2	40.8	34.5
CGI-SCH overall score, mean (SD)	4.4 (1.0)	3.9 (1.0)	4.3 (1.0)	4.3 (1.0)	4.5 (1.0)	4.5 (1.1)	4.7 (1.0)

[1]Calculated from age of the patient at the first service contact for schizophrenia.

CGI-SCH = Clinical Global Impressions Severity Scale – Schizophrenia version.

7 RESULTS (PUBLICATIONS)

Article 1

Novick D, Haro JM, Hong J, Brugnoli R, Lepine JP, Bertsch J, Karagianis J, Dossenbach M, Alvarez E. Regional differences in treatment response and three year course of schizophrenia across the world. J Psychiatric Research 2012;46:856-864.

Article 2

Haro JM, Novick D, Bertsch J, Karagianis J, Dossenbach M, Jones PB. Cross-national clinical and functional remission rate: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) study. Br J Psychiatry 2011;199:194-201.

Article 1.

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Regional differences in treatment response and three year course of schizophrenia across the world

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ABSTRACT

Data from the Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO) study was used to determine the frequency of response and describe the course of disease in outpatients with schizophrenia in different regions of the world. The W-SOHO study was a 3-year, prospective, observational study that included over 17,000 outpatients with schizophrenia from 37 countries classified into six regions (Northern Europe, Southern Europe, Latin America, East Asia, Central & Eastern Europe, North Africa & Middle East). Cox proportional-hazards regression was employed to assess the factors associated with response. Multinomial logistic regression was used to assess the correlates of disease course. We found that approximately two-thirds of the patients (66.4%) achieved response during the 3-year follow up. Response rates varied across regions, and were highest in North Africa & Middle East (84.6%) and Latin America (78.6%) and lowest in Southern Europe (62.1%) and East Asia (60.9%). There were significant differences between the regions in the proportion of patients experiencing continuous remission, remission plus relapse and a persistent symptomatic course, and between the regions in the duration of remission. Overall, Latin America, East Asia, and North Africa & Middle East had more favorable outcomes because they had the largest proportion of people who achieved continuous remission, the longest time in remission and lowest percentage with a persistent symptomatic course. Having good social functioning at baseline was consistently associated with better clinical outcome. These results seem to indicate that patients from Latin America, East Asia, North Africa & Middle East may have a more favorable disease course than patients from European nations.

1. Introduction

Over the past 30 years, cross-cultural psychiatry has embraced the notion that schizophrenia has a better course and outcome in the countries of the developing world (Cohen et al., 2008). Murphy and Raman (1971) were among the first to make this observation with a 12-year follow up of mental hospital patients living in Mauritius, Africa. The Mauritian study reported that approximately 60% of the schizophrenic patients were functioning normally and had no relapse during follow up after hospital discharge, while the proportion was around 40% in a comparable British sample. Using similar methods, Leff et al. (1990) found the two-year relapse rate for first-episode patients to be 37% in Chandigarh, North India, compared with 52% in Hallow, the UK (Macmillan et al., 1986). The UK case note study also reported a lower relapse rate among the Asian migrants in the first 12 months after hospital discharge, compared with their white counterparts (Birchwood et al., 1992).

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The most compelling evidence for this finding comes from three cross-cultural schizophrenia research programs of the World Health Organization (WHO), which improved the comparability of sampling, measurement and outcomes across culture. The three WHO studies – The International Pilot Study of Schizophrenia (IPSS) (WHO, 1979), the Determinants of Outcome of Severe Mental Disorders (DOSMeD) (Jablensky et al., 1992) and their successor, the long-term (15- and 25-year) International Study of Schizophrenia (ISoS) (Harrison et al., 2001) – all confirmed that patients living in less economically developed regions have better outcomes than those living in more industrialized regions. While the exact nature of socio-cultural factors contributing to this observation has been the subject of much debate (Kulhara and Chakrabarti, 2001), close family support, greater opportunities for social reintegration, and more positive attitude towards mental illness in less developed countries have been offered as possible explanations (Birchwood et al., 1992).

Given that most of these studies were conducted 2–3 decades ago, the present study aimed to revisit this issue to investigate whether the geographical differences in the prognosis of schizophrenia are still present today, using the large naturalistic 3-year W-SOHO (Worldwide-Schizophrenia Outpatient Health Outcomes) study conducted in 37 countries across six regions (Northern Europe, Southern Europe, Central and Eastern Europe, East Asia, North Africa and Middle East, Latin America). The specific objectives of the present analysis were three-fold: (1) to determine the frequency of response in outpatients with schizophrenia in different regions of the world, (2) to describe the course of schizophrenia in different regions of the world and (3) to analyze the socio-demographic and clinical factors associated with these outcomes.

2. Subjects and methods

2.1. Study design

The Schizophrenia Outpatient Health Outcomes (SOHO) study was a 3-year, international, prospective, observational study primarily designed to assess the comparative costs and outcomes associated with antipsychotic use in outpatients initiating or changing antipsychotic medication for schizophrenia (with an emphasis on olanzapine compared with other antipsychotics). SOHO was conducted in 10 Western European countries (EU-SOHO) (Haro et al., 2003a, 2005), as well as in 27 countries across 4 continents as the Intercontinental SOHO (IC-SOHO) (Dossenbach et al., 2005). Data from all 37 participating countries have been pooled to produce the Worldwide-SOHO (W-SOHO) dataset. A total of 17,384 patients were included in the W-SOHO dataset; details of the study are available elsewhere (Karagianis et al., 2009). The study was approved and conducted in accordance with local (country) ethics and regulatory requirements; all patients consented to participate.

Participating psychiatrists offered enrolment to adult patients (at least 18 years of age) initiating or changing antipsychotic medication for the treatment of schizophrenia, who presented within the normal course of care in the outpatient setting. The diagnosis of schizophrenia was made by the participating psychiatrists using standard diagnostic criteria [Diagnostic and Statistical Manual of Mental Disorders Fourth edition (APA, 1994) or International Classification of Diseases 10th edition (WHO, 1992)].

As the initial objective of SOHO was to compare the outcomes of patients starting olanzapine with other antipsychotics, the study was designed to provide two patient cohorts of approximately equal size: (1) patients starting olanzapine, and (2) patients starting any other antipsychotic. This deliberate over-sampling of olanzapine patients was done to facilitate comparisons between the two groups, as per the primary objective. Importantly, the antipsychotic treatment prescribed to each patient was wholly based on the opinion of the treating psychiatrist; patients were asked to participate in the study after they had received their medication prescription. In addition, patients were not required to continue taking the medication initiated at baseline. Changes in medication, dosing and concomitant medication were possible at any time as determined by the treating psychiatrist.

Data collection for the study occurred at the baseline visit as well as follow-up visits (i.e., 3, 6, 12, 18, 24, 30 and 36 months post-baseline) within the normal course of care. Socio-demographic data were recorded at the baseline assessment. Clinical severity was assessed at each visit using a scale based on the Clinical Global Impressions Severity Scale – Schizophrenia version (CGI-SCH), which evaluates symptom severity across positive, negative, depressive and cognitive sub-domains in addition to overall symptoms from 1 (normal, not ill) to 7 (among the most severely ill). This scale has been validated against the PANSS (Haro et al., 2003b). Single-item closed questions were employed to assess alcohol/substance abuse/dependency (The patient never suffered from diagnosed alcohol dependency or abuse in the past/suffered in the past/currently suffers), suicide attempts (How many times has the patient attempted suicide since last visit?), occurrence of violent or aggressive behavior (Has the patient exhibited verbal or physical hostility/aggression since last visit?), and functional status (e.g., relationships, housing conditions, work and social contacts). Other information collected at follow-up visits included antipsychotic medication (drug name, formulation, dosage and reasons for medication change if applicable), concomitant medication (anticholinergics, antidepressant, anxiolytics/hypnotics and mood stabilizers), adverse events, quality of life, and health service use.

2.2. Statistical analysis

Patients with at most one missing visit (except the last one) were eligible for inclusion in the present analysis ($n = 11{,}078$, 64% of the baseline sample). For patients with one missing visit, values from the previous visit carried forward were used to impute the values of the missing visit.

Approximately two-thirds of the patients (36.3%) were lost-to-follow up or had several missing visits and were not included in the analysis. There was some variation across regions in the attrition rate; the highest attrition rate was in East Asia (62.8%), followed by Africa and the Middle East (47.7%), Latin America (41.7%), Northern Europe (37.5%), Southern Europe (28.2%) and Central and Eastern Europe. There were small differences in patient characteristics between the patients included and not included in the analyses, both overall and by region.

2.2.1. Regional classification

The 37 countries participating in the study were grouped into six regions as follows: *Northern Europe* (France, Germany, UK, Netherlands, Ireland, Denmark) ($n = 2682$); *Southern Europe* (Spain, Italy, Portugal, Greece, Israel [Israel was included in the Southern Europe group based on ethnicity, economic and health care systems]) ($n = 4154$); *Central and Eastern Europe* (Czech Republic, Hungary, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia) ($n = 1589$); *East Asia* (Korea, Malaysia, Taiwan) ($n = 455$); *North Africa and Middle East* (Algeria, Egypt, Saudi Arabia, Turkey) ($n = 701$); and *Latin America* (Argentina, Chile, Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Peru, Puerto Rico, Venezuela) ($n = 1497$).

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2.2.2. Definition of response

Response was defined as a decrease of at least 2 points in the CGI-SCH overall score from baseline during follow up. Patients who had a CGI-SCH score of 1 or 2 (i.e., not ill or minimally ill) at baseline were excluded, and thus a total of 10,630 patients were included in this analysis. Clinical remission was defined as achieving CGI-SCH overall, positive, negative and cognitive symptom scores lower than or equal to 3 on the scale from 1 to 7 for 6 months (i.e., for two consecutive visits) plus no inpatient admission during the same period. This definition of clinical remission was based on the Andreasen criteria as presented and validated in previous reports of the SOHO study (Haro et al., 2003b, 2007).

2.2.3. Definition of disease course

Remission was defined as a score of 3 (mild severity) or less on the CGI overall severity score, the CGI positive symptoms score, the CGI negative symptoms score and the CGI cognitive symptoms score that was maintained for a period of 6 months or more (Haro et al., 2007). In addition, the patient should not have been hospitalized during the period. This definition of clinical remission was based on the Andreasen criteria (Andreasen et al., 2005) and validated in a previous report from the SOHO study (Haro et al., 2007).

Relapse was defined, for those patients achieving remission, as an increase in the score of the above CGI scales to higher than 3 or being hospitalized (Haro et al., 2006).

Three course patterns were defined according to remission/relapse status over the 3 years:

1) continuous remission; patients who achieved remission and maintained remission until the end of the study
2) remission plus relapse; patients who achieved remission and had a relapse
3) persistent symptomatic course; patients who never achieved remission.

2.2.4. Descriptive analysis

Baseline characteristics of the 11,078 study individuals were described in each of the six regions. Differences in baseline characteristics between patients who responded and did not respond to treatment and patients who experienced different courses of disease were compared using chi-square or Fisher's exact tests for categorical variables and Wilcoxon Mann–Whitney tests or Kruskal Wallis tests for continuous variables. For all comparisons, the level of significance was 0.05.

2.2.5. Regression analysis

A Kaplan–Meier survival curve was used to estimate the time to response, in each of the six regions. The Cox proportional-hazards model was employed to examine the baseline factors associated with time to response.

The following covariates were considered and adjusted in the model: *socio-demographic variables* (region, gender); *clinical variables* (age at first treatment for schizophrenia, time since first treatment, first time ever receiving treatment for schizophrenia, alcohol abuse in the past, substance abuse in the past, suicide attempts ever, CGI-SCH positive/negative/depressive/cognitive scores, hostility); and *social functioning variables* (having a spouse/partner, living independently, having paid employment, being socially active). Southern Europe was chosen as the reference category in the models because it was the region with the largest number of patients. Stepwise model reduction was conducted by dropping from the model the non-significant variables at the 0.05 level. Data from the Cox regression models were presented as hazard ratios (HR), 95% confidence intervals (CIs) and *P* values.

A multinomial regression model was used to analyze the variables associated to each of the courses. The covariates that were taken into account were: *socio-demographic variables* (region, gender); *clinical variables* (age at first treatment for schizophrenia, time since first treatment, first time ever receiving treatment for schizophrenia, current alcohol abuse, current substance abuse, CGI-SCH total score, hostility); and *social functioning variables* (having a spouse/partner, living independently, having paid employment, being socially active). Stepwise model reduction was conducted by dropping from the model the non-significant variables at the 0.05 level. Data from the logistic regression models were presented as odds ratios (OR), 95% confidence intervals (CIs) and *P* values.

A linear regression model was used to analyze the factors associated with a longer time of remission, using the numerical outcome duration of remission (from 0 to 30 months). A backward reduction method was used to select the covariates included in the model, using the same list as described above.

All statistical analyses were conducted using SAS version 9.0.

3. Results

3.1. Differences between regions at baseline

Baseline characteristics of the study sample are shown in Table 1. There were significant differences between the regions for these characteristics, highlighting interesting differences between the regions. The percentage of patients receiving treatment for the first time, for example, was lower for Central and Eastern Europe (5.4%), and East Asia (3.3%) than for the other regions (range 8.8–10.7%). Age at first treatment was 6 years later in Northern Europe (at a mean age of 30.9 years) than in Latin America (mean age 24.1 years). Alcohol abuse ranged from a low of 3.8% in East Asia to a high of 13.1% in Southern Europe; alcohol abuse in the other regions ranged from 8.0 to 11.1%. Substance abuse was also lowest in East Asia (3.1%) and highest in Southern Europe (12.2%); substance abuse in the other regions ranged from 3.4 to 10.2%. Suicide attempts were lowest in Southern Europe (22.3%) and highest in Northern Europe (31%). The percentage of patients living independently was lowest in North Africa and the Middle East (24%) and highest in Northern Europe (62.7%).

3.2. Response rate by region

Approximately two-thirds of the patients (n = 7062, 66.4% = 7062/10630) achieved response during the 3-year follow up. Table 2 summarizes the frequency of response for each of the six regions of the world. Response rates varied across regions, with the highest rates in North Africa and Middle East (84.6%) and Latin America (78.6%).

The Kaplan–Meier survival curve showed that time to response was shorter in North Africa and Middle East and Latin America. Response mostly occurred in the first six months (see Fig. 1).

3.3. Response rate by baseline patient characteristics

Response rate by baseline patient characteristics are summarized in Table 3. Compared with patients who did not achieve response, those who achieved response were more frequently younger, previously untreated, had a shorter duration of illness, had less alcohol abuse in the past, exhibited more hostile behavior at study entry, had better social functioning and more likely to be in paid employment, but had more severe symptoms at study entry. Males had a lower frequency of response than females.

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Table 1
Baseline characteristics of the W-SOHO overall sample (n = 11,078) and of patients in each of the six regions.

	Northern Europe (n = 2682)	Southern Europe (n = 4154)	Central & Eastern Europe (n = 1589)	East Asia (n = 455)	North Africa & Middle East (n = 701)	Latin America (n = 1497)	Overall (n = 11,078)	P value
Male (%)	52.2	61	47.9	53.5	62.3	57.3	56.3	<0.0001
First time ever receiving treatment (%)	10.7	8.8	5.4	3.3	8.9	10.5	8.8	<0.0001
Age, mean (SD) years	41.5 (13.1)	39.5 (12.6)	38.5 (12.3)	35.2 (10.2)	33.7 (10.0)	36.0 (12.2)	38.9 (12.6)	
Age at first treatment, mean (SD) years	30.9 (11.1)	27.1 (9.3)	28.6 (9.7)	25.9 (7.9)	26.4 (8.6)	24.1 (7.8)	27.7 (9.8)	<0.0001
Duration of illness, mean (SD) years	10.7 (10.4)	12.4 (11.2)	10.1 (9.8)	9.5 (8.6)	8.4 (8.4)	12.0 (10.9)	11.3 (10.6)	<0.0001
CGI-SCH overall severity score, mean (SD)	4.3 (1.0)	4.5 (1.0)	4.2 (0.9)	3.8 (1.0)	4.7 (1.1)	4.5 (1.1)	4.4 (1.0)	<0.0001
CGI-SCH positive score, mean (SD)	3.7 (1.4)	3.9 (1.4)	3.5 (1.4)	3.7 (1.3)	4.5 (1.4)	4.1 (1.3)	3.8 (1.4)	<0.0001
CGI-SCH negative score, mean (SD)	4.0 (1.3)	4.1 (1.3)	4.1 (1.2)	3.2 (1.2)	4.1 (1.4)	4.0 (1.4)	4.0 (1.3)	<0.0001
CGI-SCH depressive score, mean (SD)	3.4 (1.4)	3.5 (1.3)	3.3 (1.3)	2.8 (1.1)	3.3 (1.5)	3.4 (1.5)	3.4 (1.3)	<0.0001
CGI-SCH cognitive score, mean (SD)	3.9 (1.3)	3.7 (1.3)	3.9 (1.2)	2.8 (1.2)	3.8 (1.4)	3.9 (1.4)	3.8 (1.3)	<0.0001
Alcohol abuse ever (%)	10.9	13.1	8	3.8	9.4	11.1	10.9	<0.0001
Substance abuse ever (%)	9.8	12.2	3.4	3.1	5.1	10.2	9.2	<0.0001
Any suicide attempt ever (%)	31	22.3	25.7	23.6	23	27.9	25.7	<0.0001
Hostility (%)	22.3	29.6	23	27.1	47.8	40.1	29.4	<0.0001
Having a spouse or partner (%)	36.6	24.7	38	39.2	29.1	29.1	30.9	<0.0001
Living independently (%)	62.7	37.2	48.7	31.2	24	24.1	42.2	<0.0001
Paid employment (%)	23.2	17.3	20	16.3	19.1	17.6	19.2	<0.0001
Socially active (%)	73.2	66.3	60.7	61.9	42.4	55.3	64	<0.0001

Total n varies for each variable due to missing data. For variables given as percentages, the percentages refer to the total n available for that variable.
CGI-SCH = Clinical Global Impression severity scale–Schizophrenia version (ranges from 1 = normal, not at all ill to 7 = among the most severely ill).

3.4. Factors associated with time to response

The Cox regression results in Table 4 show the factors associated with achieving an earlier response during the 3-year follow up. Region was one of the most important predictors of response. Compared with patients in Southern Europe, patients in North Africa and Middle East (HR 1.62, 95% CI: 1.45; 1.80, $P < 0.0001$) and Latin America (HR 1.56, 95% CI: 1.45; 1.70, $P < 0.0001$) achieved a quicker response.

Baseline characteristics that were significantly associated with achieving a quicker response were receiving treatment for schizophrenia for first time, higher CGI-SCH positive, negative, depressive and cognitive score, having hostile or aggressive behaviors at baseline, and having good social functioning (having a spouse/partner and being in paid employment). Being male, being older at first treatment for schizophrenia, and a longer duration of illness were associated with a longer time to response.

3.5. Course pattern by region

Course pattern by region is summarized in Table 5. There were significant differences between the regions in the proportion of patients experiencing continuous remission, remission plus relapse and a persistent symptomatic course ($P < 0.0001$). There were also significant differences between the regions in the duration of remission ($P < 0.0001$). The percentage of patients with continuous remission ranged from a low of 45.7% (in Northern and Southern Europe) to a high of 67.4% (in North Africa & the Middle East), the percentage of patients with remission plus relapse ranged from 13.6% (in North Africa & the Middle East) to 20.5% (Latin America), the percentage of patients with a persistent symptomatic course ranged from 15.1% (East Asia) to 39.3% (Southern Europe). The mean duration of remission ranged from 13.02 months (Southern Europe) to 19.13 months (East Asia). Overall, Latin America, East Asia, and North Africa and the Middle East had the best outcomes because they had the largest proportion of people who achieved continuous remission, the longest time in remission and lowest percentage with a persistent symptomatic course.

Table 2
Response rates for each of the six regions.

	Response	
	n/N	%
Northern Europe	1638/2553	64.2
Southern Europe	2518/4053	62.1
Central & Eastern Europe	968/1519	63.7
East Asia	248/407	60.9
North Africa & Middle East	571/675	84.6
Latin America	1119/1423	78.6
Overall	7062/10630	66.4

3.6. Course by baseline characteristics

Course by baseline patient characteristics is also summarized in Table 5. There were significant differences between several characteristics for the different courses. Compared with patients experiencing continuous remission, patients experiencing a persistent symptomatic course tended to be male, to be older, to have a longer duration of illness, to have a higher overall symptom score, to more frequently abuse alcohol and to have worse social

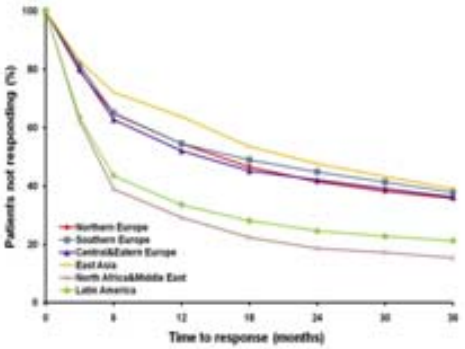

Fig. 1. Kaplan–Meier estimates of time to response by region.

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Table 3
Baseline characteristics of patients achieving and not achieving response during follow up.

	Response		*P* value
	No response (n = 3568)	Response (n = 7062)	
Male (%)	58.3	55.8	0.0152
First time ever receiving treatment (%)	5.0	11.0	<0.0001
Age, mean (SD) years	41.3 (12.8)	37.7 (12.4)	<0.0001
Age at first treatment, mean (SD) years	28.1 (9.9)	27.5 (9.8)	<0.0001
Duration of illness, mean (SD) years	13.2 (11.2)	10.4 (10.2)	<0.0001
CGI-SCH overall, mean (SD)	4.0 (0.8)	4.7 (0.9)	<0.0001
CGI-SCH positive, mean (SD)	3.5 (1.3)	4.1 (1.4)	<0.0001
CG-SCHI negative, mean (SD)	3.9 (1.1)	4.2 (1.3)	<0.0001
CG-SCHI depressive, mean (SD)	3.2 (1.2)	3.6 (1.4)	<0.0001
CGI-SCH cognitive, mean (SD)	3.6 (1.2)	4.0 (1.3)	<0.0001
Alcohol abuse ever (%)	12.0	10.4	0.0144
Substance abuse ever (%)	9.0	9.3	0.5772
Any suicide attempts ever (%)	25.6	26.2	0.4790
Hostility (%)	24.1	32.9	<0.0001
Having a spouse or partner (%)	28.0	32.0	<0.0001
Living independently (%)	42.9	41.0	0.0610
Paid employment (%)	15.9	20.0	<0.0001
Socially active (%)	65.5	62.1	0.0007

CGI-SCH = Clinical Global Impression-Schizophrenia scale.

functioning (i.e., not living independently, less socially active and not in a relationship with a spouse or partner) at baseline. In contrast, there were smaller differences between patients experiencing continuous remission and those who experienced a relapse after remission. Compared with patients experiencing continuous remission, patients who relapsed after remission tended to be male, were less likely to be in paid employment, were less socially active and abused alcohol more frequently.

3.7. Factors associated with course

Odds ratios from the regression model for factors associated with the three different courses of schizophrenia are shown in Table 6. Compared with patients in Southern Europe, patients in East Asia, North Africa and the Middle East, and Latin America were more likely to be in continuous remission than experiencing a persistent symptomatic course.

With regard to baseline characteristics, patients who were younger at first treatment, had a shorter duration of illness, receiving treatment for first time, or who were in paid employment, socially active, in a relationship with a spouse or partner, living independently or presenting hostility were more likely to be in continuous remission than experiencing a persistent symptomatic course. Being male, a higher CGI overall severity score or having had alcohol abuse were associated to a higher likelihood of experiencing a persistent symptomatic course.

Table 4
Baseline factors associated with achieving response during the 3-year follow up (Cox regression).

Region/characteristic	Response		
	HR	95% CI	*P* value
Region			
Northern Europe (vs. Southern Europe)	1.05	0.98; 1.12	0.2029
Central & Eastern Europe (vs. Southern Europe)	1.08	0.99; 1.17	0.0864
East Asia (vs. Southern Europe)	1.00	0.87; 1.17	0.9593
North Africa & Middle East (vs. Southern Europe)	1.62	1.45; 1.80	<0.0001
Latin America (vs. Southern Europe)	1.56	1.45; 1.70	<0.0001
Characteristic			
Male (vs. female)	0.86	0.82; 0.91	<0.0001
Being older at first treatment (by additional year)	0.99	0.99; 0.99	<0.0001
Longer duration of illness (by additional year)	0.99	0.98; 0.99	<0.0001
First time ever receiving treatment (yes vs. no)	1.23	1.12; 1.35	<0.0001
Any suicide attempts ever (yes vs. no)	0.96	0.90; 1.01	0.1345
Higher CGI-SCH positive score	1.18	1.16; 1.21	<0.0001
Higher CGI-SCH negative score	1.06	1.03; 1.09	<0.0001
Higher CGI-SCH depressive score	1.10	1.07; 1.12	<0.0001
Higher CGI-SCH cognitive score	1.05	1.03; 1.08	<0.0001
Hostile behaviors (yes vs. no)	1.12	1.06; 1.19	<0.0001
Spouse or partner (yes vs. no)	1.15	1.08; 1.22	<0.0001
Paid employment (vs. unemployed/unpaid)	1.24	1.16; 1.32	<0.0001
Socially active (vs. no social activities)	1.05	0.99; 1.11	0.1157

Values are Hazard ratios (HR) obtained from the Cox regression model. An HR < 1 indicates a lower likelihood of achieving response. CGI-SCH = Clinical Global Impression-Schizophrenia scale; CI = confidence interval.

3.8. Factors associated with the duration of remission

Estimates of the effect of baseline factors on the duration of remission from the least squares mean regression model are shown in Table 7. Compared with patients in Southern Europe, patients in Northern Europe were estimated to experience a mean of 1.3 months shorter in remission during the 3-year follow up, while remission was estimated to be a mean of 3.3 months longer in Asia, 4.8 months longer in Latin America, and 6.2 months longer in Africa and the Middle East.

With regard to baseline characteristics, remission was estimated to be shorter by a mean of 1.5 months in males than in females and 2.2 months in current alcohol abuse patients. Remission was estimated to be longer by a mean of 3.9 months in first treatment patients, 2.5 months among those in paid employment, 1.6 months in those who were socially active, and 1.6 months in those in a relationship with spouse or partner.

4. Discussion

4.1. Regional differences in the prognosis of schizophrenia

The results of the W-SOHO study revealed the existence of regional differences in the prognosis of schizophrenia in terms of response and disease course. Consistent with the prevailing notion, patients living in less economically developed regions had a higher frequency of response during follow up, compared with those in Europe. The frequency of response during the 3-year follow up was higher in the less developed regions of North Africa/Middle East (84.6%) and Latin America (78.6%) than in the three European regions (62.1–64.2%). Moreover, the variations in response rates between regions were not accounted for by differences in baseline clinical and socio-demographic characteristics.

The results of the W-SOHO study also revealed the existence of regional differences in the prognosis of schizophrenia in terms of course. Patients living in less developed regions had a more favorable disease course; continuous remission was lowest in Northern and Southern Europe (45.7%), and highest in North Africa and the Middle East (67.4%), remission plus relapse was lowest in North Africa and the Middle East (13.6%), and a persistent symptomatic course was lowest in East Asia (15.1%) and highest in Southern Europe (39.3%). The mean duration of remission was lowest in Southern Europe (13.02 months) and highest in East Asia (19.13 months). Overall, Latin America, East Asia, and North Africa and the Middle East had the best outcomes because they had the largest proportion of people who achieved remission, the longest time in remission and lowest percentage with a persistent symptomatic course. The results of regression modeling confirmed that compared with patients in Southern Europe, patients outside Europe were more likely to be in continuous remission, or remission plus relapse than experiencing a persistent symptomatic course, and that remission was more

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Table 7
Estimate of the effect of baseline factors associated with the duration of remission (months) (least squares mean regression model).

Region/characteristic	Estimate	95% CI	P value
Region			
Southern Europe	0	–	–
Northern Europe	−1.3471	−1.999; −0.695	<0.0001
Central & Eastern Europe	0.1307	−0.607; 0.869	0.7286
East Asia	3.3083	2.045; 4.571	<0.0001
North Africa & Middle East	6.2440	5.136; 7.352	<0.0001
Latin America	4.8428	4.084; 5.602	<0.0001
Characteristic			
Age at first treatment, mean (SD) years (for each additional year)	−0.04697	−0.075; −0.019	0.0009
Duration of illness, mean (SD) years (for each additional year)	−0.1290	−0.154; −0.104	<0.0001
Overall symptoms (CGI-SCH total score), mean (SD) (for each additional point)	−3.2865	−3.536; −3.037	<0.0001
Male (%)	−1.4887	−1.990; −0.987	<0.0001
First time ever receiving treatment (%)	3.9288	3.004; 4.854	<0.0001
In paid employment (%)	2.4566	1.804; 3.110	<0.0001
Socially active (%)	1.6107	1.093; 2.131	<0.0001
In a relationship with a spouse or partner (%)	1.5843	1.008; 2.160	<0.0001
Current alcohol abuse (%)	−2.1747	−3.792; −0.558	0.0084

4.2. Other socio-demographic predictors of response and course

Our results indicate there are several other baseline predictors of outcome. Better social functioning at baseline (having a spouse or partner, working for pay, living independently) was associated with a better clinical outcome (i.e., higher likelihood of response). This is in agreement with previous findings that social integration and participation are powerful predictors of a favorable clinical course (Perkins et al., 2004; Robinson et al., 2004). While this could be attributed to the protective role of social support, we cannot rule out the possibility that patients having a good prognosis may be more likely to be engaged in relationships or achieving paid employment. Additionally, the effect of current functioning could convey the effect of pre-morbid functioning. Pre-morbid function is one of the most important predictors of the course of schizophrenia (Ciudad et al., 2009). As we have not measured pre-morbid functioning, we cannot separate its effects from the effect of current social functioning (San et al., 2007). Consistent with the literature, being female and having no previous treatment for schizophrenia were also associated with a greater likelihood of response (Angermeyer et al., 1990; Grossman et al., 2006; Usall et al., 2003).

Patients with a shorter duration of illness had a greater likelihood of achieving response. This finding is fairly consistent with the view that schizophrenia, over the long term, tends to have a deteriorating course (Eaton et al., 1992; Huber, 1997). As with duration of illness, hostility was also associated with response. In this case, hostility may be related to higher response in part due to its frequent co-occurrence with positive symptoms, which tend to be associated with a better response to pharmacological treatment (Amore et al., 2008; Palao et al., 1994).

Our results indicate that there are several other baseline predictors of course. Patients experiencing continuous remission tended to be younger, with a short duration of illness, a low overall symptom score, experiencing their first treatment for schizophrenia, and with good social functioning (i.e., living independently, in paid employment, socially active and in a relationship with a spouse or partner). In contrast, those experiencing a persistent symptomatic course tended to be older, with a longer duration of illness, worse symptom scores, were more likely to be male, and to have poor social functioning. Remission was estimated to be shorter in males than in females, and longer in patients receiving treatment for schizophrenia for the first time, and with good social functioning (in paid employment, socially active, and in a relationship with spouse or partner). These findings of a better course in women and related to good social functioning are in line with previous findings (Doering et al., 1998; Simonsen et al., 2007; Emsley et al., 2007; Gaebel and Pietzcker, 1987).

4.3. Comparison with other studies

The findings from this analysis reinforce the findings from the WHO studies. This evidence is important as the findings from the WHO studies have been criticized for a variety of reasons (Patel et al., 2006; Cohen et al., 2008). Patel and co-workers (Patel et al., 2006), for example, suggested that the apparent finding of a better outcome in developing countries needed re-examining for a number of reasons, including methodological limitations, a lack of evidence about the specific socio-cultural factors contributing to the better outcomes, rapid social and economic changes that are undermining family care systems for people with schizophrenia in developing countries, and new evidence from cohorts in developing countries depicting poorer outcomes.

There are some differences between our study and previous studies in non-European countries. All patients included in the W-SOHO dataset had received antipsychotic treatment, whereas some studies conducted in less developed countries included patients who received no treatment. Ran and colleagues (Ran et al., 2001), for example, studied a prevalence sample of 510 schizophrenia patients from rural communities in China that included patients who had received regular treatment for a year or less, only brief, or irregular treatment, or traditional Chinese treatment, and 30% were patients who had never received treatment. In the retrospective review of 52 schizophrenia patients in Bali conducted by Kurihara et al. (Kurihara et al., 2002), 29 of the patients had not received treatment.

There are some similarities and some differences between the findings of the current analysis and other studies conducted in non-European countries. In the cross-sectional survey of the course of schizophrenia in 321 patients in Butajira (rural Ethiopia) carried out by Kebede et al., (Kebede et al., 2003), the course of illness was reported to be continuous in 67% of the cases and episodic in about 10%, and in a further 10%, the pattern of the course was unknown. In the current analysis, persistent symptomatic course was 19%, remission plus relapse was 14%, and continuous remission was 67% in the North Africa and Middle East region, so findings for remission plus relapse were roughly similar. Kebede and colleagues suggested that the reason for the high percentage of patients with a continuous course of illness in this region might be due to the longer duration of the illness without any modern treatment (fewer than 10% of cases had started modern treatment before being screened for the study). The study of the course of schizophrenia among 90 schizophrenia patients in urban India conducted by Thara (Thara, 2004) revealed that among the 61 patients completing the 20-year follow up, more than 80% of the original cohort (90 patients) experienced relapses. In the current analysis, persistent symptomatic course was 15%, remission plus relapse was 20%, and continuous remission was 65% in the East Asia region, so findings for remission plus relapse were different.

There are some similarities between the findings of the current analysis and other studies conducted in Europe. Röpcke and Eggers (2005) assessed outcomes for 39 German patients treated for schizophrenia; of the original patient population, 71% could be re-examined. At 15 years, the course pattern was reported to be good (remission) in 8%, moderate (partial remission) in 56%, and poor (chronic illness, severe residual symptoms) in 36%. In the current analysis, while continuous remission was reported to be 46% and

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Table 5
Course pattern by region and patient characteristics at baseline.

Region/characteristic	Total number	Continuous remission	Remission + relapse	Persistent symptomatic course	Duration of remission	*P* value
Region		Number (%)	Number (%)	Number (%)	Months, mean (SD)	
						<0.0001[a]
Northern Europe	2392	1093 (45.7)	362 (15.1)	937 (39.2)	13.05 (12.57)	
Southern Europe	3741	1708 (45.7)	562 (15.0)	1471 (39.3)	13.02 (12.60)	
Central & Eastern Europe	1568	766 (48.9)	255 (16.3)	547 (34.9)	14.79 (12.84)	
East Asia	450	294 (65.3)	88 (19.6)	68 (15.1)	19.13 (13.09)	
North Africa & Middle East	668	450 (67.4)	91 (13.6)	127 (19.0)	18.07 (11.75)	
Latin America	1475	871 (59.1)	302 (20.5)	302 (20.5)	18.14 (11.89)	
Characteristic		Continuous remission	Remission + relapse	Persistent symptomatic course		
Age, mean (SD) years		37.64 (12.34)	37.90 (12.47)	41.14 (12.84)	–	<0.0001
Age at first contact, mean (SD) years		27.72 (9.61)	27.53 (10.00)	27.65 (9.95)	–	0.2074
Duration of illness, mean (SD) years		10.16 (9.99)	10.36 (10.11)	13.59 (11.50)	–	<0.0001
Overall symptoms (CGI-SCH total score), mean (SD)		4.20 (1.04)	4.21 (1.03)	4.74 (0.87)	–	<0.0001
Male (%)		2753 (53.5)	923 (56.0)	2084 (60.8)	–	<0.0001
First time ever receiving treatment (%)		569 (11.0)	142 (8.6)	177 (5.1)	–	<0.0001
Living independently (%)		2250 (43.5)	714 (43.2)	1319 (38.3)	–	<0.0001
In paid employment (%)		1203 (23.3)	320 (19.4)	387 (11.3)	–	<0.0001
Socially active (%)		3432 (67.1)	1051 (64.2)	1944 (56.8)	–	<0.0001
In a relationship with a spouse or partner (%)		1728 (34.3)	523 (33.0)	831 (24.8)	–	<0.0001
Current alcohol abuse (%)		90 (1.7)	36 (2.2)	109 (3.2)	–	<0.0001

[a] Differences between regions for continuous remission vs. remission + relapse vs. persistent symptomatic course; differences between regions for duration of remission, and differences in course between characteristics.

likely to be longer outside Europe. Thus the message is highly consistent with that of response – that the course of schizophrenia is better outside Europe. These results are in line with the earlier WHO findings (WHO, 1979; Jablensky et al., 1992; Harrison et al., 2001).

Surprisingly, patients in East Asia had a similar rate of response to patients in South of Europe but a longer time in remission. Since response is also influenced by baseline severity, a possible explanation of the lower response rate is that patients were rated as less severe at baseline.

Table 6
Odds ratios (regression model) for factors associated with the three different courses of schizophrenia (continuous remission, remission plus relapse and persistent symptomatic course).

Region/characteristic	Course type	Odds ratio	95% CI[a]	*P* value
Region				
Northern Europe vs. Southern Europe	Continuous remission vs. persistent symptomatic course	0.781	0.685; 0.891	<0.0002
	Remission + relapse vs. persistent symptomatic course	0.802	0.673; 0.957	0.0144
Central & Eastern Europe vs. Southern Europe	Continuous remission vs. persistent symptomatic course	0.917	0.789; 1.064	0.2528
	Remission + relapse vs. persistent symptomatic course	0.965	0.792; 1.175	0.7224
East Asia vs. Southern Europe	Continuous remission vs. persistent symptomatic course	2.496	1.826; 3.413	<0.0001
	Remission + relapse vs. persistent symptomatic course	2.084	1.423; 3.052	0.0002
North Africa & Middle East vs. Southern Europe	Continuous remission vs. persistent symptomatic course	3.816	2.939; 4.956	<0.0001
	Remission + relapse vs. persistent symptomatic course	2.235	1.585; 3.152	<0.0001
Latin America vs. Southern Europe	Continuous remission vs. persistent symptomatic course	2.639	2.225; 3.130	<0.0001
	Remission + relapse vs. persistent symptomatic course	2.599	2.103; 3.213	<0.0001
Characteristic				
Age at first treatment (for each additional year)	Continuous remission vs. persistent symptomatic course	0.991	0.985; 0.996	0.0014
	Remission + relapse vs. persistent symptomatic course	0.991	0.983; 0.998	0.0146
Duration of illness (for each additional year)	Continuous remission vs. persistent symptomatic course	0.974	0.969; 0.979	<0.0001
	Remission + relapse vs. persistent symptomatic course	0.973	0.966; 0.979	<0.0001
Overall symptoms (CGI-SCH total score (for each additional point)	Continuous remission vs. persistent symptomatic course	0.549	0.518; 0.581	<0.0001
	Remission + relapse vs. persistent symptomatic course	0.563	0.524; 0.605	0.0016
Male vs. female	Continuous remission vs. persistent symptomatic course	0.7211	0.640; 0.790	<0.0001
	Remission + relapse vs. persistent symptomatic course	0.801	0.698; 0.919	0.0015
First time ever receiving treatment (yes vs. no)	Continuous remission vs. persistent symptomatic course	2.099	1.695; 2.598	<0.0001
	Remission + relapse vs. persistent symptomatic course	1.618	1.233; 2.124	0.0005
In paid employment (yes vs. no)	Continuous remission vs. persistent symptomatic course	1.724	1. 490; 1.994	<0.0001
	Remission + relapse vs. persistent symptomatic course	1.362	1.130; 1.642	0.0012
Socially active (yes vs. no)	Continuous remission vs. persistent symptomatic course	1.320	1.186; 1.469	<0.0001
	Remission + relapse vs. persistent symptomatic course	1.224	1.063; 1.409	0.0050
In a relationship with a spouse or partner (%)	Continuous remission vs. persistent symptomatic course	1.343	1.189; 1.517	<0.0001
	Remission + relapse vs. persistent symptomatic course	1.322	1.129; 1.548	0.0005
Living independently (%)	Continuous remission vs. persistent symptomatic course	1.160	1.031; 1.305	0.0138
	Remission + relapse vs. persistent symptomatic course	1.238	1.060; 1.445	0.0069
Alcohol abuse ever (%)	Continuous remission vs. persistent symptomatic course	0.656	0.471; 0.915	0.0129
	Remission + relapse vs. persistent symptomatic course	0.814	0.534; 1.240	0.3378
Hostility (%)	Continuous remission vs. persistent symptomatic course	1.129	1.009; 1.265	0.0351
	Remission + relapse vs. persistent symptomatic course	1.349	1.166; 1.560	<0.0001

[a] Wald.

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remission plus relapse was 15% (higher and lower, respectively, than in the Röpcke and Eggers study), a persistent symptomatic course was reported in 39% of patients in the Northern European region, which was similar to the 36% with chronic illness and severe residual symptoms in the Röpcke and Eggers study.

When comparing the results of our study with other international studies, we need to highlight the consistency of the methodology in all of the participating countries of W-SOHO, enabling direct comparison among the data and strengthening the findings.

4.4. Limitations

The present results need to be interpreted in the context of the following limitations of the study. Firstly, the W-SOHO studies were originally designed to assess the comparative costs and outcomes associated with treatment. The present results as such emerged only from secondary analyses formulated to test regional differences in response and course. Secondly, although the 37 countries participating in the W-SOHO study belong to six regions of the world with different economic and cultural characteristics, the countries may not be representative of these regions and they also had different sample sizes. In addition, the participating psychiatrists in W-SOHO in each country may not be representative of the whole country. Thirdly, although our findings were adjusted for clinical and sociodemographic characteristics of patients across different regions, there could be unobserved differences across the regional cohorts which may confound our results. Finally, we have not collected detailed information on the socio-cultural environment of the patients, which could have influenced outcomes. This limits the direct exploration of the reasons for the regional differences.

4.5. Conclusion

The W-SOHO study has added to prevailing evidence that there exist cross-national differences in outcomes among outpatients with schizophrenia, with higher rates of response and a more favorable disease course among patients from Africa, Asia and Latin America than patients from Europe. Social integration and participation consistently predicted a better clinical prognosis.

Role of funding source

The W-SOHO study was funded by Eli Lilly & Company. The study was designed in conjunction with an international panel of experts in the area of psychosis. The authors had unrestricted access to the data.

Contributors

Diego Novick participated in the design of the present study, coordinated the field work and drafted the manuscript. Enric Alvarez, Jihyung Hong, Roberto Brugnoli, Jean Pierre Lepine, Jamie Karagianis and Martin Dossenbach participated in the design of the present study and provided critical review of the manuscript. Josep Maria Haro participated in the design of the present study, in the development of the statistical analysis strategy and also provided critical review of the manuscript. Jordan Bertsch carried out the statistical analysis. All authors have read and approved the final manuscript.

Conflicts of interest

Diego Novick is a full-time Lily employee. Jamie Karagianis and Martin Dossenbach are full-time Lilly employees and shareholders. Josep Maria Haro has acted as a consultant, received grants, or acted as a speaker in activities sponsored by the following companies: Astra-Zeneca, Eli Lilly, Glaxo-Smith-Kline, and Lundbeck. Jihyung Hong is currently doing her PhD at LSE and also working as a consultant for Eli Lilly and Company. Roberto Brugnoli has acted as a consultant, received grants, or acted as a speaker in activities sponsored by the following companies: BMS, Eli Lilly, Innovapharma and Sigma-Tau. Jean Pierre Lepine received economic compensation for participation in the Schizophrenia Outpatient Health Outcomes Advisory Board. Jordan Bertsch was a statistical consultant for the SOHO study. Enric Álvarez has received consulting and educational honoraria from several pharmaceutical companies including Eli Lilly, Sanofi-Aventis, Lundbeck, Pfizer, he has participated as a main local investigator in clinical trials for Eli Lilly, Bristol-Myers and Sanofi-Aventis, and also as a national coordinator of clinical trials for Servier and Lundbeck. Enric Álvarez, has no other kind of commercial relationships with pharmaceutical companies.

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Cross-national clinical and functional remission rates: Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) study†

Josep Maria Haro, Diego Novick, Jordan Bertsch, Jamie Karagianis, Martin Dossenbach and Peter B. Jones

Background
Evidence suggests that schizophrenia may have a better outcome for individuals living in low- and middle-income countries compared with affluent settings.

Aims
To determine the frequency of symptom and functional remission in out-patients with schizophrenia in different regions of the world.

Method
Using data from the Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO) study we measured clinical and functional remission in out-patients with schizophrenia in different regions of the world, and examined sociodemographic and clinical factors associated with these outcomes. The 11 078 participants analysed from 37 participating countries were grouped into 6 regions: South Europe, North Europe, Central and Eastern Europe, Latin America, North Africa and Middle East, and East Asia.

Results
In total, 66.1% achieved clinical remission during the 3-year follow-up (range: 60.1% in North Europe to 84.4% in East Asia) and 25.4% achieved functional remission (range: 17.8% in North Africa and Middle East to 35.0% in North Europe). Regional differences were not explained by participants' clinical characteristics. Baseline social functioning, being female and previously untreated were consistent predictors of remission across regions.

Conclusions
Clinical outcomes of schizophrenia seem to be worse in Europe compared with other regions. However, functional remission follows a different pattern.

Declaration of interest
J.M.H is a consultant for Lilly and Lundbeck and has received honoraria from AstraZeneca, Lundbeck and Lilly. D.N., J.K. and M.D. are Lilly employees. J.B. was a statistical consultant for the SOHO study. P.B.J. received grant support from GlaxoSmithKline and honoraria from Bristol-Myers Squibb and Otsuka for lecturing.

The International Pilot Study of Schizophrenia (IPSS)[1] and the Determinants of Outcome of Severe Mental Disorders (DOS) study[2] were conducted over 25 years ago by the World Health Organization (WHO) to analyse regional differences in the incidence and outcomes of schizophrenia. Outcomes over 2–5 years varied among the different areas: participants living in low- and middle-income countries had better outcomes than those in high-income areas.[3,4] This unexpected finding was confirmed in the long-term (15 and 25 years) International Study of Schizophrenia (ISoS) coordinated by the WHO.[5,6] The reasons for better outcomes in low- and middle-income countries are not fully understood and much debated, but it has been suggested that sociocultural factors including close family support and interactions may play an important role.[7]

Some researchers have questioned whether schizophrenia really does have a better course and outcome in low- and middle-income countries.[8,9] These authors highlighted the methodological limitations of the WHO studies, the lack of evidence on specific sociocultural factors as contributing to the better outcomes, and cited new evidence of poor prognosis of schizophrenia from studies in low- and middle-income countries.

In addition to the WHO studies, other long-term follow-up studies have focused on the course of schizophrenia.[10–13] These studies have shown considerable heterogeneity in outcomes, but have tended to be single-country studies. There has not been any recent multinational study with a large enough sample size to analyse whether the geographic differences in outcome seen in the WHO studies are still present today.

Studies have shown that more individuals with schizophrenia achieve clinical remission than functional remission,[14] and some people may experience functional remission despite ongoing symptoms,[15] indicating that different factors may predict symptom versus functional remission. However, clinical remission is associated with better functional outcome than non-remission.[16]

The aims of this study are to determine the frequency of symptom and functional remission in out-patients with schizophrenia in different regions of the world. We will also analyse the sociodemographic and clinical factors associated with both outcomes. We hypothesise that there will be differences in symptom and functional remission between regions, and that each dimension will follow different patterns.

Method

Study design

The Schizophrenia Outpatient Health Outcomes (SOHO) study was a 3-year, prospective, observational study primarily designed to assess the comparative costs and outcomes associated with antipsychotic use in out-patients initiating or changing antipsychotic medication for schizophrenia (with an emphasis on olanzapine compared with other antipsychotics). The SOHO study was conducted in 10 Western European countries,[19,20] and in 27 countries across 4 continents as the Intercontinental SOHO (IC-SOHO).[21] Both studies shared the same methodology. Three-year data from both studies have been published elsewhere.[22,23]

See editorial, pp. 173–175, this issue.

Data from all 37 participating countries have been pooled to produce the Worldwide-SOHO (W-SOHO) data-set, which includes a total of 17 384 participants. The SOHO studies were non-interventional, with all treatment (including flexible dosing and use of concomitant therapies and medications) at the discretion of the treating psychiatrist. No medications were provided by the study sponsor; investigators were free to prescribe any antipsychotic medication indicated for schizophrenia. Individuals were assessed at study entry and during scheduled study visits at 3, 6, 12, 18, 24, 30 and 36 months post-baseline. The study was approved and conducted in accordance with local (country) ethics and regulatory requirements; all participants consented to participate.

Participant population

To ensure the study population was representative as much as possible of actual clinical practice, minimal selection criteria were applied. All individuals aged 18 years or over, who met DSM-IV[24] or ICD-10[25] criteria for schizophrenia, and who were initiating or changing antipsychotic medication at study entry in an out-patient, ambulatory or community setting (or in hospital during an admission scheduled for the initiation or change for up to 2 weeks) were considered eligible unless they were participating in another study that included a treatment intervention and/or an investigational drug. Study sites were established in 37 countries across 6 regions. Patient enrolment began in September 2000 for SOHO and in November 2000 for IC-SOHO; the last participant was enrolled in December 2001. The main objective of the study was to compare the outcomes of participants starting olanzapine with other antipsychotics. Participants were enrolled in two groups of similar size: one included those starting olanzapine, and the other included those starting any other antipsychotic. This deliberate oversampling of people taking olanzapine was done to facilitate comparisons between the two groups, as per the primary objective. Importantly, the antipsychotic treatment prescribed to each person was wholly based on the opinion of the treating psychiatrist; individuals were asked to participate in the study after they had received their medication prescription. The enrolment period was intentionally long to avoid interfering with standard medical practice and no minimum number of participants was required per participating psychiatrist.

Measures

All assessment tools were chosen for simplicity and ease of use, bearing in mind the observational nature of the study, cross-cultural relevance and practical needs such as translation into different languages. The Clinical Global Impressions – Schizophrenia (CGI-SCH) scale[26] was used to assess symptom severity across positive, negative, depressive and cognitive subdomains in addition to overall symptoms from 1 (normal, not at all ill) to 7 (among the most severely ill). A detailed patient history was taken at baseline, capturing clinical information (including duration of illness, current and past medications, reasons for treatment initiation or change, CGI-SCH score, adverse events) in addition to key sociodemographic, functional and health service use data such as age, alcohol and substance misuse/dependency, housing and employment status, suicidality, hostility (has the patient exhibited verbal or physical hostility/aggression in the past 6 months?) and previous hospital admissions and out-patient clinic visits. This information was obtained from all available sources (direct patient and family interview, clinical chart). The location and type of the principal practice of participating investigators was also collected.

Statistical analysis

Only participants with at most one missing visit (except the final one) were included in the analysis. For participants with one missing visit, values from the previous visit were carried forward and used to impute the values of the missing visit. Results from the 3-month visit were not used in the analysis unless data from the 6-month visit were missing; in such cases, data from the 3-month visit were used in the imputation.

The 37 countries participating in the study were grouped into 6 regions as follows: North Europe (France, Germany, UK, The Netherlands, Ireland, Denmark); South Europe (Spain, Italy, Portugal, Greece, Israel (Israel has been included in the South Europe group based on ethnicity, economic and healthcare systems)); Central and Eastern Europe (Czech Republic, Hungary, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia); Latin America (Argentina, Chile, Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Peru, Puerto Rico, Venezuela); North Africa and Middle East (Algeria, Egypt, Saudi Arabia, Turkey); and East Asia (Korea, Malaysia, Taiwan).

Approximately a third of the participants (36.3%) were lost to follow-up before the end of the study at 3 years and were not included in the analysis. The percentage varied across regions. The highest attrition rate was in East Asia (62.8%), followed by Africa and Middle East (47.7%), Latin America (41.7%), North Europe (37.5%), South Europe (28.2%) and Central and Eastern Europe (26.9%). There were small differences in participant characteristics between those included and not included in the analyses, both overall and by region. All statistical analyses were done using SAS version 9.1 for Windows.

Definition of remission

Clinical remission was defined as achieving CGI-SCH overall, positive, negative and cognitive symptom scores lower than or equal to 3 on the scale from 1 to 7 for 6 months (i.e. for two consecutive visits) plus no in-patient admission during the same period. As two consecutive visits were considered this meant clinical remission could not occur before the 12-month visit. This definition of clinical remission was based on the Andreasen criteria as presented and validated in previous reports of the SOHO study.[26,27]

Functional remission was defined as having good social functioning for a period of 6 months (two consecutive visits). Good social functioning included those participants who had: (a) a positive occupational/vocational status, i.e. paid or unpaid full- or part-time employment, being an active student in university or housewife; (b) independent living; and (c) active social interactions, i.e. having more than one social contact during the past 4 weeks or having a spouse or partner. Functional remission was also defined from the 12-month visit.

Descriptive analysis

Baseline characteristics were described overall and for each of the six regions for those participants with no more than one missing visit ($n = 11\,078$). In addition, the baseline characteristics of participants who did and did not achieve clinical remission and functional remission at some point during the 3-year follow-up were summarised using descriptive statistics. Differences between the groups who did and did not achieve remission were compared using chi-squared or Fisher's exact tests for categorical data and Wilcoxon or Mann–Whitney tests for numerical variables. For all comparisons, the level of significance was 0.05. The baseline sociodemographic and clinical variables compared included: number of participants, gender, age, previously untreated, age at first treatment for schizophrenia, duration of illness (years since

first treatment for schizophrenia), alcohol dependency, substance misuse, suicide attempts, overall CGI-SCH, positive CGI-SCH, negative CGI-SCH, depressive CGI-SCH, cognitive CGI-SCH, hostility, adherence, body mass index, marital status, living independently, having paid employment and being socially active.

Regression model

Logistic regression models were used to identify variables independently associated with clinical remission and those associated with functional remission for the overall W-SOHO sample. Stepwise model reduction was conducted by dropping from the model any non-significant variables. Data from the logistic regression models are presented as odds ratios (OR), 95% confidence intervals and *P*-values. The CGI was treated as a continuous variable in the models. The odds ratios in this case and other continuous variables estimate the change in the response variable by point of change in variable. The logistic regression models were repeated by region, including all significant covariates in any of the regions.

Results

The overall W-SOHO sample analysed included 11 078 participants with at most one missing visit. The number of participants in each of the six regions was: South Europe ($n = 4154$); North Europe ($n = 2682$); Central and Eastern Europe ($n = 1589$); Latin America ($n = 1497$); North Africa and Middle East ($n = 701$); and East Asia ($n = 455$). Table 1 summarises the baseline characteristics of the overall W-SOHO sample and of participants in each of the six regions.

Of the 11 078 participants analysed, 7322 (66.1%) achieved clinical remission during the 3-year follow-up, whereas only 2811 (25.4%) achieved functional remission during follow-up. Table 2 summarises the frequency of clinical and functional remission for each of the six regions. The frequency of clinical remission ranged from 60.1% in North Europe to 84.4% in East Asia, and the frequency of functional remission ranged from 17.8% in North Africa and Middle East to 35.0% in North Europe.

Compared with participants who did not achieve clinical remission, those who achieved clinical remission in the overall sample were more frequently women, younger, had a shorter duration of illness, previously untreated, had less alcohol and substance misuse in the past, fewer suicide attempts in the past, had a good level of social functioning at baseline (more frequently working for pay, having a spouse or partner, living independently and being socially active) and lower symptoms at baseline (Table 3). Similarly, comparisons between participants who did and did not achieve functional remission (Table 3) showed that those achieving functional remission also had an older age at first contact and displayed less hostility at baseline, but had no difference in depressive symptoms at baseline or a history of substance misuse and suicide attempts.

Logistic regression analysis of factors independently associated with achieving clinical remission at some point during the 3-year follow-up for the overall sample (Table 4) showed that region was one of the most important predictors of clinical remission: compared with South Europe, individuals in the regions of North Africa and Middle East, Latin America and East Asia were significantly more likely to achieve clinical remission. Other baseline factors significantly associated with an increased likelihood of clinical remission were: being female, first treatment for schizophrenia ever, having good social functioning at baseline (paid employment, spouse/partner, being socially active), displaying hostile behaviour and having higher depressive symptoms at baseline. In contrast, older age at first treatment, a longer duration of illness, history of substance misuse and higher clinical severity at baseline (overall severity, positive, negative and cognitive symptoms) were associated with a lower likelihood of achieving clinical remission.

Table 1 Baseline characteristics of the Worldwide Schizophrenia Outpatient Health Outcomes (W-SOHO) sample ($n = 11\,078$) and participants in each of the six regions[a]

	East Asia ($n = 455$)	North Africa and Middle East ($n = 701$)	Latin America ($n = 1497$)	Central and Eastern Europe ($n = 1589$)	North Europe ($n = 2682$)	South Europe ($n = 4154$)	Total ($n = 11\,078$)
Male, %	53.5	62.3	57.3	47.9	52.2	61.0	56.3
Never treated, %	3.3	8.9	10.5	5.4	10.7	8.8	8.8
Age, years: median (IQR)	33.3 (56.1)	31.8 (54.4)	34.4 (60.5)	37.4 (61.9)	39.9 (71.4)	29.8 (71.0)	37.1 (71.5)
Age at first treatment, years: median (IQR)	25.0 (53.0)	24.0 (61.0)	22.0 (50.0)	27.0 (61.0)	28.0 (79.0)	25.0 (70.0)	25.0 (79.0)
Duration of illness, years: median (IQR)	7.4 (55.1)	5.8 (38.9)	9.1 (56.5)	7.0 (51.0)	7.9 (65.3)	9.8 (63.9)	8.5 (65.3)
CGI-SCH score,[b] mean (s.d.)							
Overall severity	3.8 (1.0)	4.7 (1.1)	4.5 (1.1)	4.2 (0.9)	4.3 (1.0)	4.5 (1.0)	4.4 (1.0)
Positive	3.7 (1.3)	4.5 (1.4)	4.1 (1.3)	3.5 (1.4)	3.7 (1.4)	3.9 (1.4)	3.8 (1.4)
Negative	3.2 (1.2)	4.1 (1.4)	4.0 (1.4)	4.1 (1.2)	4.0 (1.3)	4.1 (1.3)	4.0 (1.3)
Depressive	2.8 (1.1)	3.3 (1.5)	3.4 (1.5)	3.3 (1.3)	3.4 (1.4)	3.5 (1.3)	3.4 (1.3)
Cognitive	2.8 (1.2)	3.8 (1.4)	3.9 (1.4)	3.9 (1.2)	3.9 (1.3)	3.7 (1.3)	3.8 (1.3)
Alcohol misuse ever, %	3.8	9.4	11.1	8.0	10.9	13.1	10.9
Substance misuse ever, %	3.1	5.1	10.2	3.4	9.8	12.2	9.2
Any suicide attempt ever, %	23.6	23.0	27.9	25.7	31.0	22.3	25.7
Hostility, %	27.1	47.8	40.1	23.0	22.3	29.6	29.4
Having a spouse or partner, %	39.2	29.1	29.1	38.0	36.6	24.7	30.9
Living independently, %	31.2	24.0	24.1	48.7	62.7	37.2	42.2
Paid employment, %	16.3	19.1	17.6	20.0	23.2	17.3	19.2
Socially active, %	61.9	42.4	55.3	60.7	73.2	66.3	64.0

a. Total *n* varies for each variable because of missing data. Total *n* and numbers by categories are available from the authors on request. For variables given as percentages, the percentages refer to the total *n* available for that variable.
b. CGI-SCH, Clinical Global Impression – Schizophrenia scale (ranges from 1, normal (not at all ill) to 7, among the most severely ill).

Table 2 Remission rates for the W-SOHO sample ($n = 11\,078$) and for each of the six regions

	Clinical remission n/N (%)[a]	Functional remission n/N (%)[a]
East Asia	384/455 (84.4)	112/455 (24.6)
North Africa and Middle East	558/701 (79.6)	125/701 (17.8)
Latin America	1189/1497 (79.4)	430/1497 (28.7)
Central and Eastern Europe	1034/1589 (65.1)	344/1589 (21.6)
North Europe	1611/2682 (60.1)	940/2682 (35.0)
South Europe	2546/4154 (61.3)	860/4154 (20.7)
Total	7322/11 078 (66.1)	2811/11 078 (25.4)

a. Differences among regions $P < 0.001$.

Logistic regression showed that region was also an important predictor of achieving functional remission (Table 4): compared with participants in South Europe, those in Latin America and North Europe were significantly more likely to achieve functional remission, whereas individuals in Central and Eastern Europe were significantly less likely to achieve functional remission. Baseline social functioning (independent housing, paid employment, spouse/partner and being socially active) was another important predictor of functional remission, together with being female, never treated for schizophrenia before study entry and a higher depressive symptom score at baseline. Older age at first treatment and a longer duration of illness were significantly associated with less likelihood of functional remission. The magnitude of the effect of independent housing and having paid employment at baseline on functional remission was particularly large (odds ratio around 6).

Table 5 summarises the baseline factors independently associated with achieving clinical remission and Table 6 those for achieving functional remission for each of the six regions. Being previously untreated was generally associated with a greater chance of clinical remission across all regions, whereas a higher negative symptoms score was associated with less chance of clinical remission. The strongest predictors of an increased odds of functional remission across all or nearly all regions were the social functioning variables (being in paid employment, living in independent housing or being socially active). Being female, previously treated, and having a spouse/partner was associated with a greater chance of functional remission in some regions, whereas an older age at first treatment and a longer duration of illness were associated with less chance of remission in all three European regions and Latin America.

Discussion

Study limitations

The W-SOHO study is the largest prospective observational study on the outcome of schizophrenia in an out-patient setting. However, there are several limitations that must be considered when discussing the results. First, although the 37 countries participating in the W-SOHO study belong to 6 regions of the world with different economic and cultural characteristics, the countries are not necessarily representative of these regions and some regions, such as East Asia, had a relatively small number of participants. In addition, the centres or investigators participating in the study in each country may not be representative of the whole country. Second, although sociodemographic and clinical characteristics were assessed in individuals participating and were taken into account in the analyses, we cannot rule out that different types of individuals with schizophrenia were enrolled in different countries, that there were other confounding variables not recorded in the study and that service contexts and residual confounding may be influencing the results. Third, we did not collect detailed information on the cultural environment of the participants, which could have influenced outcomes, and limits the exploration of the reasons for the regional differences. Fourth,

Table 3 Baseline characteristics of participants achieving and not achieving clinical or functional remission in the W-SOHO sample ($n = 11\,078$)

	Clinical remission			Functional remission		
	Remission ($n = 7322$)	No remission ($n = 3756$)	*P*	Remission ($n = 2811$)	No remission ($n = 8267$)	*P*
Male, %	54.3	60.2	<0.0001	47.5	59.3	<0.0001
Never treated, %	10.5	5.5	<0.0001	13.7	7.1	<0.0001
Age, years: median (IQR)	37.7 (12.3)	41.0 (12.8)	<0.0001	37.5 (10.5)	39.3 (13.2)	<0.0001
Age of first treated, mean (s.d.)	27.7 (9.7)	27.8 (10.1)	0.6540	28.7 (8.9)	27.4 (10.1)	<0.0001
Duration of illness, mean (s.d.)	10.2 (10.0)	13.3 (11.4)	<0.0001	9.1 (9.1)	12.0 (11.0)	<0.0001
CGI-SCH score, mean (s.d.)						
Overall severity	4.2 (1.0)	4.7 (0.9)	<0.0001	4.2 (1.1)	4.4 (1.0)	<0.0001
Positive	3.7 (1.4)	4.1 (1.4)	<0.0001	3.7 (1.5)	3.9 (1.4)	<0.0001
Negative	3.8 (1.3)	4.5 (1.2)	<0.0001	3.7 (1.3)	4.1 (1.3)	<0.0001
Depressive	3.3 (1.3)	3.6 (1.3)	<0.0001	3.4 (1.4)	3.4 (1.3)	0.3359
Cognitive	3.6 (1.3)	4.2 (1.2)	<0.0001	3.6 (1.3)	3.8 (1.3)	<0.0001
Alcohol misuse ever, %	10.0	12.8	<0.0001	9.0	11.6	0.0001
Substance misuse ever, %	8.6	10.5	0.0009	8.4	9.5	0.0841
Any suicide attempt ever, %	24.1	29.2	<0.0001	24.7	26.1	0.1536
Hostility, %	29.5	29.0	0.5607	25.0	30.8	<0.0001
Having a spouse or partner, %	33.9	25.2	<0.0001	52.5	23.6	<0.0001
Living independently, %	43.7	39.1	<0.0001	75.1	31.0	<0.0001
Paid employment, %	22.8	12.1	<0.0001	45.4	10.3	<0.0001
Socially active, %	67.0	58.2	<0.0001	74.8	60.3	<0.0001

CGI-SCH, Clinical Global Impression – Schizophrenia scale.

Table 4 Baseline factors associated with achieving clinical and functional remission during the 3-year follow-up for the W-SOHO sample (n = 11 078)[a]

	Clinical remission			Functional remission		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
North Africa and Middle East (v. South Europe)	2.82	2.19–3.64	<0.0001	0.89	0.66–1.20	0.4293
Central and Eastern Europe (v. South Europe)	0.91	0.78–1.05	0.1893	0.71	0.59–0.86	0.0004
East Asia (v. South Europe)	1.87	1.37–2.55	<0.0001	1.02	0.75–1.39	0.8843
Latin America (v. South Europe)	2.50	2.11–2.96	<0.0001	2.14	1.77–2.59	<0.0001
North Europe (v. South Europe)	0.79	0.69–0.89	0.0002	1.34	1.15–1.56	0.0002
Female (v. male)	1.28	1.15–1.42	<0.0001	1.60	1.42–1.81	<0.0001
Age at first treatment	0.99	0.98–0.99	<0.0001	0.97	0.96–0.97	<0.0001
Duration of illness	0.98	0.97–0.98	<0.0001	0.96	0.96–0.97	<0.0001
Never treated (yes v. no)	2.01	1.62–2.50	<0.0001	1.50	1.21–1.86	0.0002
Alcohol misuse (yes v. no)	0.98	0.83–1.16	0.8319	0.86	0.68–1.07	0.1664
Substance misuse (yes v. no)	0.78	0.65–0.94	0.0083	1.06	0.84–1.34	0.5973
CGI-SCH score						
Overall severity	0.75	0.69–0.82	<0.0001	0.99	0.90–1.09	0.8388
Positive	0.91	0.87–0.95	<0.0001	0.99	0.94–1.05	0.7742
Negative	0.79	0.74–0.83	<0.0001	0.95	0.89–1.01	0.0991
Depressive	1.08	1.03–1.12	0.0008	1.07	1.02–1.13	0.0087
Cognitive	0.85	0.81–0.90	<0.0001	0.96	0.91–1.02	0.1916
Hostile behaviours (yes v. no)	1.19	1.06–1.33	0.0028	0.91	0.79–1.05	0.1829
Spouse or partner (yes v. no)	1.35	1.20–1.51	<0.0001	2.16	1.90–2.45	<0.0001
Independent housing (v. dependent housing)	1.08	0.97–1.21	0.1786	6.00	5.22–6.89	<0.0001
Paid employment (v. unemployed/unpaid)	1.47	1.27–1.69	<0.0001	5.66	4.94–6.48	<0.0001
Socially active (v. no social activities)	1.22	1.10–1.35	0.0002	1.50	1.32–1.71	<0.0001

CGI-SCH, Clinical Global Impression – Schizophrenia scale.
Values are odds ratios (OR) obtained from the logistic regression model. An OR <1 indicates a lower likelihood of achieving remission.

Table 5 Baseline factors associated with achieving clinical remission during the 3-year follow-up for each of the six regions[a]

	Odds ratio (95% CI)					
	East Asia	North Africa and Middle East	Latin America	Central and Eastern Europe	North Europe	South Europe
Female (v. male)	1.26 (0.62–2.58)	1.78 (1.03–3.08)*	0.85 (0.61–1.17)	1.40 (1.09–1.78)*	1.09 (0.89–1.34)	1.46 (1.23–1.73)*
Age at first treatment	0.97 (0.93–1.01)	0.98 (0.95–1.02)	0.98 (0.96–1.00)	0.98 (0.97–1.00)*	0.99 (0.98–1.00)	0.99 (0.98–1.00)*
Duration of illness	1.00 (0.96–1.03)	0.98 (0.95–1.01)	0.96 (0.94–0.97)*	0.97 (0.96–0.99)*	0.98 (0.97–0.99)*	0.97 (0.97–0.98)*
Never treated (yes v. no)	2.67 (0.29–24.57)	1.51 (0.50–4.52)	2.12 (1.08–4.19)*	2.42 (1.23–4.75)*	2.77 (1.84–4.16)*	1.57 (1.12–2.12)*
Alcohol misuse (yes v. no)	0.14 (0.03–0.76)*	0.80 (0.33–1.91)	0.73 (0.42–1.26)	1.83 (1.11–3.00)*	0.97 (0.70–1.35)	0.91 (0.70–1.17)
Substance misuse (yes v. no)	2.28 (0.27–19.04)	0.96 (0.28–3.23)	1.13 (0.62–2.08)	0.61 (0.31–1.19)	0.64 (0.45–0.90)*	0.86 (0.66–1.12)
Suicide attempts in past (yes v. no)	0.71 (0.35–1.43)	0.72 (0.41–1.26)	0.92 (0.66–1.28)	1.16 (0.88–1.54)	1.05 (0.84–1.30)	0.85 (0.70–1.02)
CGI-SCH score						
Overall severity	0.92 (0.49–1.73)	0.69 (0.46–1.03)	0.95 (0.74–1.22)	0.59 (0.47–0.74)*	0.67 (0.56–0.80)*	0.79 (0.70–0.90)*
Positive	0.74 (0.49–1.11)	1.07 (0.84–1.36)	0.90 (0.77–1.04)	0.92 (0.82–1.02)	0.87 (0.80–0.95)*	0.92 (0.86–0.99)*
Negative	0.71 (0.48–1.04)	0.76 (0.59–0.99)*	0.83 (0.71–0.97)*	0.84 (0.73–0.97)*	0.82 (0.74–0.91)*	0.75 (0.68–0.81)*
Depressive	1.10 (0.80–1.52)	0.95 (0.78–1.17)	1.02 (0.91–1.15)	1.25 (1.12–1.39)*	1.06 (0.97–1.15)	1.09 (1.01–1.17)*
Cognitive	0.76 (0.55–1.05)	0.85 (0.65–1.09)	0.84 (0.72–0.97)*	0.92 (0.80–1.05)	0.87 (0.78–0.97)*	0.85 (0.79–0.92)*
Hostile behaviours (yes v. no)	0.87 (0.42–1.79)	1.06 (0.63–1.77)	1.14 (0.83–1.57)	1.03 (0.76–1.39)	1.67 (1.32–2.13)*	1.09 (0.91–1.29)
Spouse or partner (yes v. no)	1.33 (0.64–2.75)	1.89 (0.93–3.82)	1.81 (1.21–2.70)*	1.32 (1.01–1.72)*	1.20 (0.97–1.50)	1.34 (1.09–1.65)*
Independent housing (v. dependent housing)	0.71 (0.34–1.50)	0.90 (0.44–1.81)	2.19 (1.39–3.45)*	1.06 (0.81–1.39)	1.10 (0.89–1.37)	0.98 (0.82–1.18)
Paid employment (v. unemployed/unpaid)	2.96 (0.78–11.21)	0.87 (0.43–1.75)	0.64 (0.41–1.01)	1.28 (0.91–1.80)	1.74 (1.34–2.25)*	1.77 (1.40–2.25)*
Socially active (v. no social activities)	1.32 (0.66–2.63)	1.39 (0.81–2.39)	1.37 (1.00–1.86)*	1.03 (0.80–1.33)	1.16 (0.93–1.44)	1.28 (1.08–1.51)*

CGI-SCH, Clinical Global Impression – Schizophrenia scale.
a. Values are odds ratios (OR) obtained from the logistic regression model. An OR <1 indicates a lower likelihood of achieving remission.
*P < 0.05.

data were collected at 6-month intervals and limited information was gathered between assessment visits. Fifth, data were only collected over 3 years and, therefore, are unlikely to represent the full course of schizophrenia: some individuals may have experienced remission at a later time. Sixth, given the limitations of the ascertainment tools, our methods do not allow us to separate the effects of regional clinical practices (and therefore their ratings on the CGI-SCH) of the participating psychiatrists from the predictors of outcome analysed. Seventh, interrater reliability was not assessed given the large number of participating investigators. However, measures were chosen based on clarity and ease of use. Eighth, participants included in the analysis are those

Table 4 Baseline factors associated with achieving functional remission during the 3-year follow-up for each of the six regions

	Odds ratio (95% CI)					
	East Asia	North Africa and Middle East	Latin America	Central and Eastern Europe	North Europe	South Europe
Female (v. male)	0.59 (0.33–1.05)	1.50 (0.77–2.90)	1.68 (1.22–2.31)*	1.18 (0.83–1.66)	1.41 (1.12–1.78)*	2.28 (1.81–2.86)*
Age at first treatment	0.99 (0.95–1.03)	1.01 (0.98–1.06)	0.97 (0.95–0.99)*	0.95 (0.93–0.97)*	0.95 (0.94–0.96)*	0.98 (0.97–0.99)*
Duration of illness	1.01 (0.98–1.05)	0.99 (0.95–1.03)	0.97 (0.95–0.98)*	0.95 (0.92–0.97)*	0.95 (0.93–0.96)*	0.96 (0.95–0.98)*
Never treated (yes v. no)	0.94 (0.16–5.41)	2.02 (0.59–6.92)	1.85 (1.15–2.97)*	2.80 (1.41–5.56)*	1.37 (0.93–2.03)	1.23 (0.82–1.84)
Alcohol misuse (yes v. no)	0.42 (0.07–2.58)	1.75 (0.56–5.45)	0.88 (0.49–1.58)	0.66 (0.30–1.45)	1.00 (0.68–1.48)	0.70 (0.47–1.04)
Substance misuse (yes v. no)	0.81 (0.10–6.49)	0.67 (0.14–3.27)	1.46 (0.81–2.64)	0.49 (0.15–1.62)	1.18 (0.79–1.76)	1.08 (0.73–1.60)
Suicide attempts in past (yes v. no)	1.05 (0.57–1.94)	0.84 (0.39–1.79)	0.94 (0.66–1.34)	1.14 (0.78–1.67)	1.05 (0.82–1.35)	0.92 (0.71–1.20)
CGI-SCH score						
Overall severity	1.13 (0.69–1.87)	1.31 (0.81–2.11)	0.78 (0.61–0.99)*	1.00 (0.74–1.36)	0.87 (0.71–1.06)	1.07 (0.89–1.27)
Positive	0.88 (0.62–1.14)	0.99 (0.72–1.35)	1.09 (0.94–1.26)	0.88 (0.76–1.02)	0.98 (0.89–1.09)	1.02 (0.93–1.12)
Negative	0.82 (0.60–1.13)	0.84 (0.60–1.15)	1.13 (0.97–1.32)	0.81 (0.67–0.97)*	0.94 (0.83–1.06)	0.97 (0.86–1.09)
Depressive	0.97 (0.73–1.29)	1.18 (0.90–1.54)	1.06 (0.94–1.19)	1.10 (0.94–1.28)	1.05 (0.95–1.16)	1.14 (1.03–1.27)*
Cognitive	0.99 (0.73–1.35)	0.93 (0.66–1.32)	1.00 (0.87–1.16)	0.96 (0.80–1.16)	1.01 (0.89–1.14)	0.95 (0.86–1.05)
Hostile behaviours (yes v. no)	0.91 (0.49–1.71)	0.94 (0.48–1.81)	0.80 (0.58–1.10)	0.91 (0.60–1.37)	0.96 (0.73–1.27)	0.92 (0.72–1.18)
Spouse or partner (yes v. no)	0.88 (0.49–1.56)	3.61 (1.82–7.16)*	2.34 (1.67–3.28)*	2.29 (1.61–3.27)*	1.69 (1.33–2.15)*	2.69 (2.14–3.38)*
Independent housing (v. dependent housing)	2.70 (1.47–4.98)*	7.98 (4.07–15.66)*	5.52 (3.92–7.79)*	2.45 (1.70–3.54)*	6.47 (4.85–8.63)*	8.96 (6.96–11.52)*
Paid employment (v. unemployed/unpaid)	1.94 (0.99–3.78)	7.57 (3.73–15.36)*	3.54 (2.44–5.12)*	11.20 (7.86–15.96)*	6.29 (4.85–8.17)*	6.26 (4.85–8.07)*
Socially active (v. no social activities)	2.26 (1.17–4.38)*	1.06 (0.56–1.98)	1.41 (1.04–1.93)*	1.49 (1.03–2.15)*	1.96 (1.50–2.57)*	1.37 (1.08–1.73)*

CGI-SCH, Clinical Global Impression – Schizophrenia scale.
a. Values are odds ratios (OR) obtained from the logistic regression model. An OR <1 indicates a lower likelihood of achieving remission.
*P < 0.05.

requiring a treatment change in routine clinical practice, which allowed us to study treatment outcomes but are obviously not representative of the overall patient population. Ninth, attrition was highest in the regions with the highest remission rates, which could explain some of the findings if attrition was higher in individuals with severe schizophrenia. Finally, our definition of clinical remission required a low level of symptoms for at least 6 months, consistent with the definition proposed by Andreasen.[28] However, our definition of remission was based on the CGI-SCH, which is a valid but less specific measure of clinical severity than other scales such as the Positive and Negative Syndrome Scale (PANSS).[29] Previous analyses have shown a good agreement between this and Andreasen's definition.[27]

Regional differences in outcomes

With these limitations in mind, the results of the W-SOHO study show that the clinical outcomes of schizophrenia seem to be worse in Europe compared with other regions. Remarkably, the regional differences were different for functional remission. The frequency of clinical remission was lower in the three European regions (60–65%) than in East Asia, Latin America, and North Africa and Middle East (79–84%). Participants living in the latter three regions had a much greater likelihood of achieving clinical remission than those living in South Europe. Moreover, the variations in clinical remission rates between regions were not accounted for by differences in baseline clinical and socio-demographic characteristics evaluated in the study. Economic development, cultural factors such as family support or other country characteristics may explain the differences. Differences in economic development are not necessarily translated to differences in the course of schizophrenia. For example, South Europe and Central and Eastern Europe show similar clinical remission rates but have different levels of economic development. Our findings support the earlier WHO studies reporting differences in outcomes between regions.[1–6]

However, regional differences in functional remission followed a different pattern. Although it was more likely for individuals in Latin America to achieve functional remission compared with South Europe, there were no clear differences with East Asia or North Africa and Middle East. A new pattern emerged when compared with Central and Eastern Europe and North Europe; Central and Eastern Europe seemed to have a lower functional remission rate compared with South Europe, whereas North Europe tended to have a higher functional remission rate.

When comparing the descriptive and regression differences between the regions, we wanted to highlight that the logistic model showed that individuals with schizophrenia in Central and Eastern Europe were significantly less likely to achieve functional remission than those in South Europe. However, this was not detected in the descriptive analysis, probably due to the fact that some social functioning variables (independent housing and having a spouse/partner) are confounding variables.

Although this is somewhat speculative, differences in remission rates seem to be the result of economic, cultural and environmental factors more than differences in schizophrenic disorder. The same diagnostic criteria were applied in all regions and similarities in predictors of outcome were seen across the regions, which may indicate similar characteristics of the disorder. The reasons for the better clinical outcome in low- and middle-income countries are unknown but may be related to differences in the balance between treatment and vulnerability experienced by the individuals.[30] Differences in functional remission between regions were mostly driven by differences in independent living and paid employment. Thus, these differences in functional remission rates may be influenced by differences in access to accommodation, the presence of rehabilitation services and social benefits, the development of specific policies for individuals with severe mental disorders and the level of societal stigma about mental illness.

Our results indicate that there are several other baseline predictors of outcome. We found that women were more likely to achieve remission compared with men. This is consistent with

many reports that women with schizophrenia experience better outcomes than men.[31,32] Younger age, shorter duration of illness and no previous treatment for schizophrenia were also associated with a better chance of achieving remission, whereas substance misuse was associated with a lower chance of clinical remission, especially in North Europe. Our findings are consistent with systematic reviews and meta-analyses, which found that a shorter duration of untreated psychosis is associated with better symptomatic and functional outcomes in high-income and low- and middle-income countries.[33,34] Although it has been reported that comorbid substance misuse is highly prevalent in schizophrenia and associated with poorer clinical outcomes,[35] most of the evidence is based on studies in Western countries; the prevalence and impact of substance use disorders among people with schizophrenia in low- and middle-income countries has not been well studied. The frequency of alcohol or substance misuse was low in the overall W-SOHO population at baseline compared with other samples,[36] and its role as an independent predictor of remission varied across regions. Further work on substance misuse as a factor influencing outcome of schizophrenia across a wide range of countries is needed.

Higher symptom severity at baseline in terms of positive, negative, cognitive and overall symptoms was associated with less likelihood of clinical remission, but the severity of these symptoms was not significantly associated with functional remission. However, a higher level of depressive symptoms at baseline was associated with a higher likelihood of achieving both clinical and functional remission in the logistic regression analyses of the overall W-SOHO population. This supports previous findings that high levels of depressive symptoms at baseline predict favourable short-term outcomes in individuals with schizophrenia.[37] However, other researchers have found that people with depressive symptoms have poorer long-term functional outcomes.[38]

Social functioning variables were important prognostic factors for remission in all regions. Participants with a spouse/partner, in paid employment and who were socially active at baseline were more likely to achieve clinical and functional remission, supporting previous findings that better baseline social functioning is associated with recovery (when defined as achieving symptomatic plus functional remission).[17] The direction of the causality, however, may not be clear. For example, although working appears to help people recover from schizophrenia,[39] the converse may also be true, i.e. individuals who maintain work are those who have a good prognosis. In the W-SOHO population at baseline, the frequency of paid employment was low (19%), ranging from 16% in East Asia to 23% in North Europe. This is similar to the employment rates reported for people with schizophrenia in Western countries,[40] which vary both between and within countries. However, fully dissecting the role of social functioning on outcomes in schizophrenia is complicated because clinical changes can have an impact on social functioning.[39] There are also high rates of stigma and discrimination against people with schizophrenia across countries,[41] which can have an impact on their social functioning.[42]

The W-SOHO study has shown that there are cross-national differences in outcomes among out-patients with schizophrenia. Outcomes in terms of remission seem to be better for people living in low- and middle-income regions, especially Latin America. In general, the regional variation in outcome persisted even after adjusting for clinical and sociodemographic variables at baseline. Several predictive factors were identified suggesting that outcome differences are related to cultural and environmental factors rather than to differences in the disorder itself.

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8 SUMMARY OF RESULTS

The overall W-SOHO sample analysed included 11,078 patients with at most one missing visit. The number of patients in each of the 6 regions was: South Europe (n=4154); North Europe (n=2682); Central and Eastern Europe (n=1589); Latin America (n=1497); North Africa and Middle East (n=701) and East Asia (n=455). Table 6 summarizes the baseline characteristics of the overall W-SOHO sample and of patients in each of the 6 regions. As shown in Table 6, there were significant differences between regions for these characteristics, highlighting interesting differences between the regions. The percentage of patients receiving treatment for the first time, for example, was lower for Central and Eastern Europe (5.4%), and East Asia (3.3%) than for the other regions (range 8.8–10.7%). Age at first treatment was 6 years later in Northern Europe (at a mean age of 30.9 years) than in Latin America (mean age 24.1 years). Suicide attempts were lowest in Southern Europe (22.3%) and highest in Northern Europe (31%). The percentage of patients living independently was lowest in North Africa and the Middle East (24%) and highest in Northern Europe (62.7%).

Table 6. Baseline characteristics of the W-SOHO overall sample (n=11,078) and of patients in each of the six regions

	Northern Europe (n=2682)	Southern Europe n=4154)	Central & Eastern Europe (n=1589)	East Asia (n=455)	North Africa & Middle East (n=701)	Latin America (n=1497)	Overall (n=11,078)	P value
Male (%)	52.2	61	47.9	53.5	62.3	57.3	56.3	<0.0001
First time ever receiving treatment (%)	10.7	8.8	5.4	3.3	8.9	10.5	8.8	<0.0001
Age, mean (SD) years	41.5 (13.1)	39.5 (12.6)	38.5 (12.3)	35.2 (10.2)	33.7 (10.0)	36.0 (12.2)	38.9 (12.6)	
Age at first treatment, mean (SD) years	30.9 (11.1)	27.1 (9.3)	28.6 (9.7)	25.9 (7.9)	26.4 (8.6)	24.1 (7.8)	27.7 (9.8)	<0.0001
Duration of illness, mean (SD) years	10.7 (10.4)	12.4 (11.2)	10.1 (9.8)	9.5 (8.6)	8.4 (8.4)	12.0 (10.9)	11.3 (10.6)	<0.0001
CGI-SCH overall severity score, mean (SD)	4.3 (1.0)	4.5 (1.0)	4.2 (0.9)	3.8 (1.0)	4.7 (1.1)	4.5 (1.1)	4.4 (1.0)	<0.0001
Alcohol abuse ever (%)	10.9	13.1	8	3.8	9.4	11.1	10.9	<0.0001
Substance abuse ever (%)	9.8	12.2	3.4	3.1	5.1	10.2	9.2	<0.0001
Any suicide attempt ever (%)	31	22.3	25.7	23.6	23	27.9	25.7	<0.0001
Hostility (%)	22.3	29.6	23	27.1	47.8	40.1	29.4	<0.0001
Having a spouse or partner (%)	36.6	24.7	38	39.2	29.1	29.1	30.9	<0.0001
Living independently (%)	62.7	37.2	48.7	31.2	24	24.1	42.2	<0.0001
Paid employment (%)	23.2	17.3	20	16.3	19.1	17.6	19.2	<0.0001
Socially active (%)	73.2	66.3	60.7	61.9	42.4	55.3	64	<0.0001

Total n varies for each variable due to missing data. For variables given as percentages, the percentages refer to the total n available for that variable.

CGI-SCH = Clinical Global Impression severity scale–Schizophrenia version (ranges from 1 = normal, not at all ill to 7 = among the most severely ill)

8.1 Response rate

Approximately two-thirds of the patients (n=7062, 66.4% = 7062/10630) achieved response during the 3-year follow-up. Response rates varied across regions, with the highest rates in North Africa and Middle East (84.6%) and Latin America (78.6%).

The Kaplan-Meier survival curve showed that time to response was shorter in North Africa and Middle East and Latin America.

The comparison of the response rate by baseline patient characteristics showed that, compared with patients who did not achieve response, those who achieved response were more frequently younger, previously untreated, had a shorter duration of illness, had less alcohol abuse in the past, exhibited more hostile behaviour at study entry, had better social functioning and more likely to be in paid employment, but had more severe symptoms at study entry. Males had a lower frequency of response than females.

8.2 Factors associated with time to response

A Cox regression model was used to analyse the factors associated with achieving an earlier response during the 3-year follow up. Region was one of the most important predictors of response. Compared with patients in Southern Europe, patients in North Africa and Middle East (Hazard Ratio [HR] 1.62, 95% CI: 1.45; 1.80, P<0.0001) and Latin America (HR 1.56, 95% CI: 1.45; 1.70, P<0.0001) were achieved a quicker response.

Baseline characteristics that were significantly associated with achieving a quicker response were receiving treatment for schizophrenia for first time, higher CGI-SCH positive, negative, depressive and cognitive score, having hostile or aggressive behaviours at baseline, and having good social functioning (having a spouse/partner and being in paid employment). Being male, being older at first treatment for schizophrenia, and longer duration of illness were associated with a longer time to response.

8.3 Clinical remission and factors associated with it

Of the 11,078 patients analysed, 7322 (66.1%) achieved clinical remission during the 3-year follow-up. The frequency of clinical remission ranged from 60.1% in North Europe to 84.4% in East Asia, and the frequency of functional remission ranged from 17.8% in North Africa and Middle East to 35.0% in North Europe.

A logistic regression model was used to analyse the factors independently associated with achieving clinical remission at some point during the 3-year follow-up. The model showed that region was one of the most important predictors of clinical remission: compared with South Europe, patients in the regions of North Africa and Middle East, Latin America and East Asia were significantly more likely to achieve clinical remission. Other baseline factors significantly associated with an increased likelihood of clinical remission were: being female, first treatment

for schizophrenia ever, having good social functioning at baseline (paid employment, spouse/partner, being socially active), displaying hostile behaviour and having higher depressive symptoms at baseline. In contrast, older age at first treatment, a longer duration of illness, history of substance abuse and higher clinical severity at baseline (overall severity, positive, negative and cognitive symptoms) were associated with a lower likelihood of achieving clinical remission.

8.4 Course pattern and factors associated with course

Course of schizophrenia was evaluated by the proportion of time in which the patients experienced remission and also was divided into the distinct types: continuous remission, remission and relapse, and persistent symptomatic course. There were significant differences between the regions in the proportion of patients experiencing continuous remission, remission plus relapse and a persistent symptomatic course. There were also significant differences between the regions in the duration of remission. The percentage of patients with continuous remission ranged from a low of 45.7% (in Northern and Southern Europe) to a high of 67.4% (in North Africa & the Middle East), the percentage of patients with remission plus relapse ranged from 13.6% (in North Africa & the Middle East) to 20.5% (Latin America), the percentage of patients with a persistent symptomatic course ranged from 15.1% (East Asia) to 39.3% (Southern Europe). The mean duration of remission ranged from 13.02 months (Southern Europe) to 19.13 months (East Asia). Overall, Latin America, East Asia, and North Africa and the Middle East had the best outcomes because they had the largest proportion of people who achieved continuous remission, the longest time in remission and lowest percentage with a persistent symptomatic course.

With regard to baseline characteristics, patients who were younger at first treatment, had a shorter duration of illness, receiving treatment for first time, or who were in paid employment, socially active, in a relationship with a spouse or partner, living independently or presenting hostility were more likely to be in continuous remission than experiencing a persistent symptomatic course. Being male, a higher CGI overall severity score or having had alcohol abuse were associated to a higher likelihood of experiencing a persistent symptomatic course.

8.5 Factors associated with duration of remission

Compared with patients in Southern Europe, patients in Northern Europe were estimated to experience a mean of 1.3 months shorter in remission during the 3-year follow up, while remission was estimated to be a mean of 3.3 months longer in Asia, 4.8 months longer in Latin America, and 6.2 months longer in Africa and the Middle East.

With regard to baseline characteristics, remission was estimated to be shorter by a mean of 1.5 months in males than in females and 2.2 months in current alcohol abuse patients. Remission was estimated to be longer by a mean of 3.9 months in first treatment patients, 2.5 months among those in paid employment, 1.6 months in those who were socially active, and 1.6 months in those in a relationship with spouse or partner.

8.6 Functional remission and factors associated with it

Around one quarter of the patients (2811 patients, 25.4% of total) achieved functional remission during follow-up. A logistic regression model showed that region was also an important predictor of achieving functional remission: compared with patients in South Europe, patients in Latin America and North Europe were significantly more likely to achieve functional remission, whereas patients in Central and Eastern Europe were significantly less likely to achieve functional remission. Baseline social functioning (independent housing, paid employment, spouse/partner and being socially active) was another important predictor of functional remission, together with being female, never treated for schizophrenia before study entry and a higher depressive symptom score at baseline. Older age at first treatment and a longer duration of illness were significantly associated with less likelihood of functional remission. The magnitude of the effect of independent housing and having paid employment at baseline on functional remission was particularly large.

9 DISCUSSION

The results of the W-SOHO study revealed the existence of regional differences in the prognosis of schizophrenia in terms of response, remission and disease course. Consistent with the prevailing notion, patients living in less economically developed regions had a higher frequency of response during follow-up, compared with those in Europe. The frequency of response during the 3-year follow-up was higher in the less developed regions of North Africa/Middle East (84.6%) and Latin America (78.6%) than in the three European regions (62.1–64.2%). The frequency of clinical remission was lower in the three European regions (60–65%) than in the regions of East Asia, Latin America and North Africa/Middle East (79–84%). Patients living in the latter 3 regions had a much greater likelihood of achieving clinical remission than patients living in South Europe. Moreover, the variations in response and remission rates between regions were not accounted for by differences in baseline clinical and socio-demographic characteristics.

9.1. International differences in outcomes

Our findings support the earlier WHO studies reporting differences in outcomes between regions [80, 81, 124–127].

The results of the W-SOHO study also revealed the existence of regional differences in the prognosis of schizophrenia in terms of course. Patients living in less developed regions had a more favourable disease course: continuous remission was lowest in Northern and Southern Europe (45.7%), and highest in North Africa and the Middle East (67.4%); remission plus relapse was lowest in North Africa and the Middle East (13.6%); and a persistent symptomatic course was lowest in East Asia (15.1%) and highest in Southern Europe (39.3%). The mean duration of remission was lowest in Southern Europe (13.02 months) and highest in East Asia (19.13 months). Overall, Latin America, East Asia, and North Africa and the Middle East had the best outcomes because they had the largest proportion of people who achieved remission, the longest time in remission and the lowest percentage with a persistent symptomatic course. The results of regression modelling confirmed that, compared with patients in Southern Europe, patients outside Europe were more likely to be in continuous remission or remission plus relapse than experience a persistent symptomatic course, and that remission was more likely to be longer. Thus, the message is highly consistent with that of response – that is, the course of schizophrenia is better outside Europe. These results are in line with the earlier WHO findings [81, 124, 125].

Surprisingly, patients in East Asia had a similar rate of response to patients in Southern Europe but a longer time in remission. Since response is also influenced by baseline severity, a possible explanation of the lower response rate is that patients were rated as less severe at baseline.

The consistency with previous studies is important as the findings from the WHO studies have been criticized for a variety of reasons [82, 83]. Patel and co-workers [82], for example, suggested that the apparent finding of a better outcome in developing countries needed re-examining for a number of reasons, including methodological limitations, a lack of evidence about the specific socio-cultural factors contributing to the better outcomes, rapid social and economic changes that are undermining family care systems for people with schizophrenia in developing countries, and new evidence from cohorts in developing countries depicting poorer outcomes.

There are some differences between our study and previous studies in non-European countries. All patients included in the W-SOHO dataset had received antipsychotic treatment, whereas some studies conducted in less developed countries included patients who received no treatment. Ran and colleagues [86], for example, studied a prevalence sample of 510 schizophrenia patients from rural communities in China that included patients who had received regular treatment for a year or less, only brief or irregular treatment, or traditional Chinese treatment, and 30% were patients who had never received treatment. In the retrospective review of 52 schizophrenia patients in Bali conducted by Kurihara et al. [84], 29 of the patients had not received treatment.

There are some similarities and differences between the findings of the current analysis and other studies conducted in non-European countries. In the cross-sectional survey of the course of schizophrenia in 321 patients in Butajira (rural Ethiopia) carried out by Kebede et al., [88], the course of illness was reported to be continuous in 67% of cases, episodic in about 10%, and of an unknown pattern in a further 10%. In the current analysis, there was a persistent symptomatic course in 19%, remission plus relapse in 14%, and continuous remission in 67% of participants in the North Africa and Middle East region. Thus, the findings for remission plus relapse were roughly similar. Kebede and colleagues [88] suggested that the reason for the high percentage of patients with a continuous course of illness in this region might be due to the longer duration of the illness without any modern treatment (fewer than 10% of cases had started modern treatment before being screened for the study). The study of the course of schizophrenia among 90 schizophrenia patients in urban India conducted by Thara [93] revealed that among the 61 patients completing the 20-year follow-up, more than 80% of the original cohort (90 patients) experienced relapses. In the current analysis, a persistent symptomatic course was seen in 15% of patients, remission plus relapse in 20%, and continuous remission in 65% in the East Asia region, so the findings for remission plus relapse were different.

Other studies conducted in Europe have mostly included small sample sizes. Röpcke and Eggers [100] assessed outcomes in 39 German patients treated for schizophrenia; of the original patient population, 71% could be re-examined. At 15 years, the course pattern was reported to be good (remission) in 8%, moderate (partial remission) in 56%, and poor (chronic illness, severe residual symptoms) in 36%. In the current analysis, while continuous remission

was reported in 46% and remission plus relapse in 15% (higher and lower, respectively, than in the Röpcke and Eggers study), a persistent symptomatic course was reported in 39% of patients in the Northern European region, which was similar to the 36% with chronic illness and severe residual symptoms in the Röpcke and Eggers study [100].

When comparing the results of our study with other international studies, we need to highlight the consistency of the methodology in all of the participating countries of W-SOHO, enabling direct comparisons of the data and strengthening the findings.

Although this is somewhat speculative, differences in remission rates seem to be due to economic, cultural and environmental factors more than to differences in schizophrenic disorder. The same diagnostic criteria were applied in all regions and similarities in predictors of outcome were seen across the regions, which may indicate similar characteristics of the disorder. The reasons for the better clinical outcome in developing countries are unknown but may be related to differences in the balance between treatment and vulnerability experienced by the patients [128].

Differences in functional remission between regions were mostly driven by differences in independent living and paid employment. Thus, the differences in functional remission rates may be influenced by differences in access to accommodation, the presence of rehabilitation services and social benefits, the development of specific policies for individuals with severe mental disorders, and the level of societal stigma on mental illness.

Regional differences in functional remission followed a different pattern. While it was more likely for patients in Latin America to achieve functional remission compared with South Europe, there were no clear differences with East Asia or North Africa/Middle East. A new pattern emerged when compared to Central and Eastern Europe and North Europe; Central and Eastern Europe seemed to have a lower functional remission rate compared to South Europe, while North Europe tended to have a higher functional remission rate.

When comparing the descriptive and regression differences between the regions, we want to highlight that the logistic model showed that patients in Central and Eastern Europe were significantly less likely to achieve functional remission than patients in South Europe. However, this was not detected in the descriptive analysis, probably due to the fact that some social functioning variables (independent housing and having a spouse/partner) are confounding variables.

A large amount of research has been conducted over the past decade into social environmental risk factors for schizophrenia (e.g. the effect of urbanization, immigrant status, deprivation) [129–131], although little appears to be have emerged about these factors as prognostic indicators of outcome.

Some reasons that have been reported to explain the better course in developing rather than developed countries are largely based on the belief that community and family life in the developing world is widely intact and provides a nurturing environment that facilitates recovery. In the review of schizophrenia studies conducted by Bromet et al. [18], residing in a developed rather than a developing country, for example, was reported to be associated with

a poorer long-term outcome. In the 20-year follow-up study conducted by Thara [93], global functioning of schizophrenia patients in developing countries was reported to be much better than those from developed nations. These findings have always been questioned and, more recently, have been strongly criticized [82]. In a review of outcome studies in developing countries, Burns [132] reported that the political, social and economic conditions now present in many countries in Africa, Latin America and Asia has led to poverty, inequality, and poor mental health services, and are significant psychosocial stressors that are unlikely to support better outcome in schizophrenia. In their systematic review of studies of outcomes in low- and middle-income countries, Cohen et al. [83], proposed that the situation is more complex than has been previously reported and that more research is needed to understand outcomes in these countries.

9.2. Other socio-demographic predictors of response, remission and course

We found that women were more likely to achieve remission compared with men. This is consistent with many reports that women with schizophrenia experience better outcomes than men [134, 135].

Patients with a shorter duration of illness had a greater likelihood of achieving response. This finding is fairly consistent with the view that schizophrenia, over the long term, tends to have a deteriorating course [110, 135]. As with duration of illness, hostility was also associated with response. In this case, hostility may be related to higher response in part due to its frequent co-occurrence with positive symptoms, which tend to be associated with a better response to pharmacological treatment [136, 137).

Younger age and no previous treatment for schizophrenia were also associated with a better chance of achieving and maintaining remission, whereas substance abuse was associated with a lower chance of clinical remission, especially in North Europe. Our findings are consistent with systematic reviews and meta-analyses, which found that a shorter duration of untreated psychosis is associated with better symptomatic and functional outcomes in high-income and low/middle-income countries [138, 139]. Although it has been reported that comorbid substance misuse is highly prevalent in schizophrenia and associated with poorer clinical outcomes [140], most of the evidence is based on studies in Western countries; the prevalence and impact of substance use disorders among people with schizophrenia in less developed countries has not been well studied. The frequency of alcohol or substance abuse was low in the overall W-SOHO population at baseline compared with other samples [141], and its role as an independent predictor of remission varied across regions. Further work on substance abuse as a factor influencing outcome of schizophrenia across a wide range of countries is needed.

Social functioning variables were very important prognostic factors for response and remission in all regions. Patients with a spouse/partner, in paid employment, and who were socially active at baseline were more likely to achieve clinical and functional remission, supporting previous findings that better baseline social functioning is associated with recovery (when defined as achieving symptomatic plus functional remission) [142]. The direction of causality,

however, may not be clear. For example, although working appears to help people recover from schizophrenia [143], the converse may also be true; i.e. patients who maintain work are those who have a good prognosis. In the W-SOHO population at baseline, the frequency of paid employment was low (19%), ranging from 16% in East Asia to 23% in North Europe. This is similar to the employment rates reported for people with schizophrenia in Western countries [144], which vary both between and within countries. However, fully dissecting the role of social functioning on outcomes in schizophrenia is complicated because clinical changes can impact on social functioning [143]. There are also high rates of stigma and discrimination against people with schizophrenia across countries [145], which can impact on their social functioning [146]. The effect of current functioning could convey the effect of premorbid functioning. Premorbid functioning is one of the most important predictors of the course of schizophrenia [147]. As we did not measure premorbid functioning, we cannot separate its effects from the effect of current social functioning [105]. Consistent with the literature, being female and having no previous treatment for schizophrenia were also associated with a greater likelihood of response [133, 134, 148].

10 LIMITATIONS

The W-SOHO study is the largest prospective observational study on the outcome of schizophrenia in the outpatient setting. However, there are several limitations that must be considered when discussing the results. First, although the 37 countries participating in the W-SOHO study belong to 6 regions of the world with different economic and cultural characteristics, the countries are not necessarily representative of these regions and some regions, such as East Asia, had a relatively small number of patients. In addition, the centres or investigators participating in the study in each country may not be representative of the whole country. Second, although socio-demographic and clinical characteristics were assessed in participating patients and were taken into account in the analyses, we cannot rule out that different types of patients were enrolled in different countries, that there were other confounding variables not recorded in the study, and that service contexts and residual confounding may be influencing the results. Third, we did not collect detailed information on the cultural environment of the patients, which could have influenced outcomes, and limits exploration of the reasons for the regional differences. Fourth, data was collected at 6-month intervals and limited information was gathered between assessment visits. Fifth, data was only collected over 3 years and, therefore, is unlikely to represent the full course of schizophrenia: some patients may have experienced remission at a later time. Sixth, given the limitations of the ascertainment tools, our methods do not allow us to separate the effects of regional clinical practices (and therefore their ratings on the CGI-SCH) of the participating psychiatrists from the predictors of outcome analysed. Seventh, inter-rater reliability was not assessed given the large number of participating investigators. However, measures were chosen based on clarity and ease of use. Eighth, patients included in the analyses were those requiring a treatment change in routine clinical practice, which allowed us to study treatment outcomes but are obviously not representative of the overall patient population. Ninth, attrition was highest in the regions with highest remission rates, which could explain some of the findings if attrition were higher in more severe patients. Tenth, our definition of clinical remission required a low level of symptoms for at least 6 months, consistent with the definition proposed by Andreasen [149]. However, our definition of remission was based on the CGI-SCH, which is a valid but less specific measure of clinical severity than other scales such as PANSS. Previous analyses have shown a good agreement between this and Andreasen's definition [150].

Finally, the W-SOHO studies were originally designed to assess the comparative costs and outcomes associated with treatment. The present results emerged only from secondary analyses formulated to test regional differences in response and course.

11 CONCLUSIONS

The main conclusions of this dissertation are presented for each of the proposed hypothesis:

1) Patients with schizophrenia who start a new antipsychotic medication for the treatment of an episode of schizophrenia experience a higher response rate in developing than in economically developed countries.
2) Response rate to antipsychotic treatment in patients with schizophrenia is higher in females than in males.
3) Response rate to antipsychotic treatment in patients with schizophrenia with a younger age of onset is higher compared to patients with a later onset.
4) Patients with a good social functioning at baseline experience higher response rates to antipsychotic treatment.
5) Response rate to antipsychotic treatment decreases with longer duration of disease in schizophrenia.
6) Patients with schizophrenia who start a new antipsychotic medication for the treatment of an episode of schizophrenia experience a higher clinical and functioning remission rate in developing than in economically developed countries.
7) Clinical and functioning remission rate to antipsychotic treatment in patients with schizophrenia is higher in females than in males.
8) Clinical and functioning remission rate in patients with schizophrenia with a younger age of onset is higher compared to patients with a later age of onset.
9) Patients with a good social functioning at baseline experience higher clinical and functioning remission rates to antipsychotic treatment.
10) Clinical and functioning remission rate to antipsychotic treatment decreases with longer duration of disease in schizophrenia.

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13 APPENDICES

Appendix 1. Summary of data from studies on international differences in course of schizophrenia (presented alphabetically by first author)

Author	Country	Duration (years)	Methodology/ sample type	Functioning			Mortality/ Suicide (%)	Hospitalization/ outcome	Course
				Single/ married	Working	Housing status			
Abdel-Baki et al., 2011 [10]	Canada	10–16	Retrospective, 142 first-episode patients	78.8% single on admission; 79.5% at study end	20.1% on admission; 25.6% at study end	Living with family: 71.6% at admission; 30.8% at study end	12% mortality including 7% suicide	• 26.8% never been hospitalized at study end • 8.5% hospitalized at study end	• 26.8% never rehospitalized • 15% able to function without medical help • 25% not taking antipsychotics
Alem et al., 2009 [90]	Ethiopia	6	Prospective, 321 schizophrenia patients, mainly antipsychotic naive	–	–	2.5% homeless	–	–	Onset: • 67.2% acute • 32.8% insidious Course: • continuous 30.8% • episodic/intermittent in 64–70% • nearly continuous, complete remission 5.7%. • no relapse 22%
Bebbington et al., 2005 [109]	European countries: France Germany UK	–	1208 chronic schizophrenia patients, baseline data	Single: France 71.5%; Germany 54.2%; UK 67.2%	In employment: France 12.9%; Germany 30.3%; UK 11.5%	Living alone: France 35.8%; Germany 33.2%; UK 36.1%	Suicide or self-harm attempt: France 36.1%; Germany 34.8%; UK 48.6%	Overall functioning quite good	Course overall: • Episodic with residual symptoms 41.5% • Episodic with no residual symptoms 19.5% • Continuous 25.2% • Single episode in partial remission 3.7% • Single episode in full

			remission 3.8% • Other or unspecified pattern 4.4% • Admitted to a psychiatric ward 94.5% France: • Episodic with residual symptoms 43.3% • Episodic with no residual symptoms 10.8% • Continuous 37.5% • Single episode in partial remission 2.1% • Single episode in full remission 0.7% • Other or unspecified pattern 5.6% • Admitted to a psychiatric ward 98.6% Germany: • Episodic with residual symptoms 51% • Episodic with no residual symptoms 24.9% • Continuous 39.4% • Single episode in partial remission 4.6% • Single episode in full remission 9.9% • Other or unspecified pattern8.9% • Admitted to a psychiatric ward 94.0% UK: • Episodic with residual symptoms 20.2% • Episodic with no residual

									symptoms 16.6% • Continuous 39.4% • Single episode in partial remission 4.6% • Single episode in full remission 9.9% • Other or unspecified pattern 8.9% • Admitted to a psychiatric ward 94.0%
Bertelsen et al., 2009 [98]	Denmark	5	Prospective, comparison of 2 years of intensive intervention vs. standard treatment in 265 first-episode patients	–	–	–	–	–	Both groups at 5 years: • recovery 18% • institutionalization 13% Course in the 2 years before the 5-year follow up: • apsychotic in 37% • episodic in 17% • continuous in 46%
Di Michele & Bolino, 2004 [102]	Italy	3	Prospective, 40 stable, antipsychotic-treated outpatients		58% in good outcome group; 10% in intermediate outcome group; 0% in poor outcome group	–	–	25% in good outcome group; 45% in intermediate outcome group; 87% in poor outcome group	Relapse: • 25% in the good outcome group • 45% in the intermediate outcome group • 87% in the poor outcome group
Douki et al., 2007 [97]	Tunisia	–	Prevalence study of 266 patients admitted to hospital	16.5% married	10% in regular employment	–	–	-	A chronic course without remission was not unusual
Harrow et al., 2005 [106]	USA	15	Prospective, 64 first-episode schizophrenia patients	–	–	–	–	Most patients did not exhibit severe social isolation	• 41% experienced ≥1 periods of recovery • >50% did not have a chronic, continuous course of illness, instead had episodic disease; among the more vulnerable and less resilient patients,

									episodes were more frequent and severe, with slower recovery
Harrow & Jobe, 2007 [19]	USA	15	Prospective, 64 first-episode schizophrenia patients	–	–	–	–	A significantly larger % of schizophrenia patients not on antipsychotics showed periods of recovery and better global functioning compared with patients receiving medication	
Hickling et al., 2001 [95]	Jamaica	1	Prospective, 317 first-contact patients; (62% outpatients, 38% inpatients)	–	43% employed 57% unemployed	–	0% suicide	Self-reported use of medication 67%; of which 45% received monthly intramuscular depot medication	Relapse 13% Drop out 4%
Kaleda, 2009 [96]	Russia	15	Prospective, 278 male first-episode patients with endogenous episodic psychosis (76.2% confirmed schizophrenia)	25.2% married	14.4% unable to work	–	–	Outcome was: "good" in 18.7%; “relatively good" in 33.8%; "relatively poor" in 30.2%; "poor" in 17.2%	Course: • single episode in 17.9% • regressive in 23.2% • progressive in 25.1% • chronic in 4.6%
Kebede et al., 2003 [88]	Ethiopia	–	Cross-sectional survey, 321 schizophrenia cases in a rural community	53% never married	54.7% employed	7% homeless	–	–	48.6% acute onset Course: • 67.2% continuous • 10% episodic • 10% unknown
Kebede et al., 2005 [89]	Ethiopia	2.5	Cross-sectional survey of 63 incident and 208 prevalent cases of	–	–	–	–	Functioning reduced compared with general	

			schizophrenia, mostly antipsychotic naive					population and with schizophrenia patients from developed countries.	
Kua et al., 2003 [104]	Singapore	20	Prospective, 402 first-episode patients	–	32.4% working full time; 53.2% not working; 14.4% working part time		Suicide rate: 8.46 per 1000 patients per year in years 1–10; 6.47 per 1000 patients per year in years 10–15; 4.85 per 1000 patients per year in years 15–20	28.3% good outcome (patient not receiving treatment, well and working); 37.0% fair outcome (patient not receiving treatment and not working, or receiving outpatient treatment and working); 34.7% poor outcome (patient receiving treatment and not working, or receiving inpatient treatment)	• 44.9% being treated as outpatients • 6.9% being treated as inpatients • 48.2% not on treatment
Kurihara et al., 2000 [107]	Comparison of Bali and Tokyo	5	Prospective, 51 first-episode patients in Bali; 40 first-episode patients in Tokyo	–	–	–	–	Cumulative length of hospital stay shorter in Bali ($p<0.01$): Bali mean 76.4 days; Tokyo 358.2 days % receiving antipsychotics lower in Bali ($p<0.01$): Bali	No significant difference in symptoms, social adjustment or re-admission rates

								25.5%; Tokyo 87.5%	
Kurihara et al., 2002 [84]	Bali	5	Retrospective review of 51 schizophrenia patients who did not maintain contact with the mental health services; 22 received antipsychotics, 29 did not	–	–	–	–	33.3% self-supportive; 19.6% semi-self-supportive; 27.5% socially adjusted to family or community; 19.6% maladjusted; 0% hospitalized	-
Kurihara et al., 2005 [85]	Bali	11	Prospective, 46 first-episode patients	63% (minus 1 divorced, 1 widowed)	37.0% full-time; 21.7% part-time; 41.3% did not work	100% lived with family		No patients hospitalized at 11 years, but 60.9% re-hospitalized during study Functioning: 39.1% self-supportive; 13.0% semi-self-supportive; 15.2% socially adjusted to family or community; 32.6% maladjusted. 17.4% on medication at 11 years	23.9% remission 19.6% partial remission
Liszen et al., 2001 [103]	Netherlands	5	Prospective, 76 first-episode patients	–	About 50% were in paid employment (unskilled or semi-skilled) for at least	34% lived mainly with their parents; 40% lived alone; 12% lived with a partner;	–	-	• 52% had one or more psychotic relapses • 25% developed chronic positive symptoms • 23% did not have another psychotic episode

					some time	7% were chronically hospitalized			
Mojtabai et al., 2001 [91]	India	2, 15	Prospective, 209 first-episode patients; comparison of 2-year outcome and 15-year outcome	–	–	–	Mortality at 15 years: 47% in poor 2-year outcome group; 11% in other 2-year outcome groups		92% of patients with a poor 2-year outcome (continuous psychotic illness with no remission and symptoms present most of the time) had a poor long-term course at 15 years
Rabinowitz et al., 2007 [101]	Israel	10	Cohort study, 5990 first-admission patients	–	–	–	–	–	• 5.41% deteriorated • 12.75% improved • 81.8% initial improvement followed by relative stability (including 6.42% who spent no time in hospital after the initial admission)
Ran et al., 2001 [86]	China	2	Prevalence sample, 510 schizophrenia patients; 30.6% never-treated patients		At baseline, never-treated patients: 32.1% full-time work; 45.5% part-time farm- or housework; 22.4% no work. At 2 years: 77.6% of never-treated patients were able to work	–	–	At baseline, never-treated patients, impairment of social functioning was: most serious in 53.5%; serious in 14.7%; moderate in 10.9%; mild in 20.9%	Clinical status in never-treated patients: • 10.5% complete remission • 11.6% partial remission • 71.6% marked symptoms • 6.3% deteriorated
Ran et al., 2003 [87]	China	–	Prevalence sample, 510 schizophrenia patients	21.2% single; 64.1% married; 7.8% widowed; 6.9% divorced	43.1% full-time farm- or housework; 38.1% part-time farm- or housework;		–		• 24.5% complete remission • 13.4% partial remission • 53.7% marked symptoms • 8.4% deteriorated

					18.8% not working				
Robinson et al., 2004 [43]	USA	5	118 first-episode patients (70% schizophrenia, 30% schizoaffective disorder)	–	–	–	–	25.5% of those with symptom remission had adequate social functioning for ≥2 years	• 47.2% achieved symptom remission • 13.7% full recovery criteria for ≥2 years
Röpcke and Eggers, 2005 [100]	Germany	15	Retrospective, 39 first-episode adolescent-onset patients		20% regular occupation; 36% working in a sheltered institution or a rehabilitation programme; 31% without any structured occupational or educational activity		–	Global social functioning: slightly impaired in 21%; moderately impaired in 28%; severely impaired in 51%.	Course: • good (remission) in 8% • moderate (partial remission) in 56% • poor (chronic illness, severe residual symptoms) in 36%.
San et al., 2007 [105]	Spain	–	Cross-sectional study of 1010 schizophrenia patients	–	15.7% in paid employment	–	–	–	• 44.8% complete remission (but only 10.2% showed adequate social and/or vocational functioning) • 34.4% partial remission • 20.8% not in remission
Simonsen et al., 2007 [99]	Denmark and Norway	1	Prospective, 301 first-episode psychosis (27.9% schizophrenia, 21.6% schizophreniform disorder)	–	–	–	–	–	• 66% in remission • 11% in relapse • 23% continuously psychotic
Srinivasan et al., 2001 [92]	India	1	Prospective, 72 never-treated patients receiving treatment for the first time	–	51% had no impairment in occupational functioning at 1 year	–	–	35% had no impairment in social functioning at 1 year	'Best remission' in 29%

Srivastava et al., 2009 [94]	India	10	Retrospective review of 122 schizophrenia patients who completed 10 years of treatment after first hospitalization	–	40% employed	72.9% living independently	–	–	• 30.5% improved (reported as recovery) • 20% no improvement
Thara, 2004 [93]	India	20	Prospective and retrospective study of 90 first-onset patients	–	>75% of men	–	17% mortality (50% of which was due to suicide)	–	Course: • Complete remission 8.2% • Relapses with complete remission in between 39.3% • Relapses with partial remission in between 44.3% • Continuous illness 8.2%
Wiersma et al., 2000 [108]	European countries: Bulgaria Germany Ireland Netherlands Czech Republic UK	15	Cohort study of 349 first-episode schizophrenia patients	–	–	62% lived with family or friends; 25% lived alone; 8% lived in sheltered accommodation; 6% in a psychiatric hospital.	–	Course of social disability: No disability was 13% at baseline, 19% at 1 year, 21% at 2 years, and 14% at 15 years. Severe disability was 41% at baseline, 31% at 1 year, 34% at 2 years, and 25% at 15 years	61% acute onset Course: • prominent all the time 19% • deteriorating 29% • late improvement 10% • early improvement 36% • never prominent 7%

Appendix 2. Summary of published papers from the SOHO study

Authors	Journal and Year	Title	Brief Description	Main results
Haro JM, Edgell ET, Jones PB, Alonso J, Gavart S, Gregor KJ, Wright P, Knapp M.	Acta Psychiatr Scand. 2003;107(3):222-32.	The European Schizophrenia Outpatient Health Outcomes (SOHO) study: rationale, methods and recruitment.	Detailed explanation of the study design.	More than 10,000 schizophrenic patients initiating a new treatment were recruited from ten European countries.
Haro JM, Edgell ET, Novick D, Alonso J, Kennedy L, Jones PB, Ratcliffe M, Breier A.	Acta Psychiatr Scand. 2005;111(3):220-31.	Effectiveness of antipsychotic treatment for schizophrenia.	Analysis of the 6-month antipsychotic treatment response.	At 6 months more than 50% of the patients responded. Olanzapine and clozapine showed the best response rates.
Lambert M, Haro JM, Novick D, Edgell ET, Kennedy L, Ratcliffe M, Naber D.	Acta Psychiatr Scand. 2005;111(3):232-43.	Olanzapine vs. other antipsychotics in actual out-patient settings: six months tolerability results.	Analysis of the 6-month antipsychotic tolerability results.	Risperidone and typical antipsychotics showed a higher frequency of EPS. Patients treated with olanzapine and clozapine had higher weight increases.
Gasquet I, Haro JM, Novick D, Edgell ET, Kennedy L, Lepine JP.	Int Clin Psychopharmacol. 2005;20(4):199-205.	Pharmacological treatment and other predictors of treatment outcomes in previously untreated patients with schizophrenia.	Analysis of the 6-month outcomes of the previously untreated patients.	More than 900 previously untreated patients were analysed. Olanzapine showed a better response than risperidone. However, patients taking olanzapine gained more weight than patients taking risperidone.
Novick D, Bousono M, Suarez D, Olivares JM, Montejo AL, Haro JM, Edgell ET, Ratcliffe M.	Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(6):972-82.	Use of concomitant medication with antipsychotic treatment in outpatients with schizophrenia.	Analysis of the 6-month use of concomitant medication.	Olanzapine, clozapine and quetiapine were associated with less use of anticholinergics and olanzapine, depot typicals and amisulpride were associated with less use of anxiolytics.
Usall J, Suarez D, Haro JM.	Psychiatry Res. 2007 3;153(3):225-231.	Gender differences in response to antipsychotic treatment in outpatients with schizophrenia.	Analysis of the 6-month gender differences regarding treatment effectiveness.	Women had better outcomes, but the differences were not homogenous for all the antipsychotics. The highest gender differences were found in typical antipsychotics and clozapine. No differences were found for risperidone.

Haro JM, Kontodimas S, Negrin MA, Ratcliffe M, Suarez D, Windmeijer F.	Appl Health Econ Health Policy. 2006;5(1):11-25.	Methodological aspects in the assessment of treatment effects in observational health outcomes studies.	Review of methodological approaches to address selection and observer bias in effectiveness observational studies by using SOHO data.	Comparing the CGI scores rated by psychiatrists and the EQ-5D utilities scores rated by the patients there was no evidence of observer bias in favour of olanzapine
Novick D, Haro JM, Suarez D, Lambert M, Lépine JP, Naber D.	Psychopharmacology (Berl). 2007;191(4):1015-22.	Symptomatic remission in previously untreated patients with schizophrenia.	Analysis of the 2-year remission outcomes of the previously untreated patients.	70% of patients achieved remission. Type of medication, symptom severity and previous functioning were predictors of remission.
Haro JM, Novick D, Suarez D, Alonso J, Lépine JP, Ratcliffe M.	J Clin Psychopharmacol. 2006;26(6):571-8.	Remission and relapse in the outpatient care of schizophrenia.	Analysis of the 3-year remission and relapse outcomes.	During the 3 years 65% of the patients remitted and 25% relapsed. Olanzapine showed better results than risperidone, quetiapine and typicals for both outcomes.
Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D.	Eur Neuropsychopharmacol. 2007;17(4):235-44.	Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results.	Analysis of the 3-year antipsychotic treatment discontinuation in the SOHO study and comparison to the CATIE study.	Rates of antipsychotic treatment maintenance were higher than the CATIE rates. However, in both studies olanzapine and clozapine (*) showed the highest rates of medication maintenance.
Suarez D, Haro JM, Novick D, Ochoa S.	J Clin Epidemiol. 2008:61:525-30.	Marginal structural models might overcome confounding when analysing multiple treatment effects in observational studies.	Re-analysis of the 3-year remission results by using a novel methodological approach.	Olanzapine and clozapine showed similar results in terms of remission.

SOHO: Schizophrenia Outpatient Health Outcomes; CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness; EPS: ExtraPyramidal Symptoms; CGI: Clinical Global Impression; EQ-5D: Euro Quality of life 5 Dimensions.(*) Clozapine was not included in Phase I of CATIE study. However, it was included in Phase II.