



## Original article

# Estimate dynamic changes of dysfunction and lifelong spent for psychiatric care needs in patients with schizophrenia

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## ABSTRACT

**Background:** Disturbance of functionality is one of the core features of schizophrenia, and has deleterious effects on a patient's employment, increased healthcare costs, and a large societal burden. Thus, if a patient's disability status could be predicted, and interventions needed identified in advance, poor outcomes could be prevented. To achieve this aim, we developed a method by which to assess dynamic changes of dysfunction and estimate the lifetime duration of disability in patients with schizophrenia, as a proxy for assessing their specialized healthcare needs.

**Methods:** The proposed method was developed based on a nationwide database and a cross-sectional survey. The primary analysis investigated the dynamic change in the proportion of patients with manifested disability over time, while the secondary analysis estimated the lifetime duration of disability, obtained as the proportion of patients with manifested disability multiplied by the survival probability throughout the life of patients.

**Results:** The average lifetime duration of manifested disability of global functioning was estimated to be 20.9 years, which represents approximately 73% of the whole lifetime of patients. The duration of disability in socially-useful activities was estimated to be 15.6 years, while that in personal and social relationships was 17.5 years. The female patients had a longer duration of manifested disability (22.9 years) than the male patients (19.5 years).

**Conclusions:** The developed method of analysis indicated that the longest lifetime durations of manifest disability were observed in the areas of socially-useful activities and personal and social relationships, and the proportions of patients with these disabilities rapidly increased at 200 months after diagnosis.

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## 1. Introduction

Schizophrenia is a disabling and severe mental disorder with a chronic clinical course, often resulting in progressive loss of self-care and psychosocial functions in affected individuals. The lifetime prevalence of schizophrenia is approximately 0.8–1% [1]. In the care of such patients, clinicians must continually assess their functionality to monitor progress and long-term prognosis in order to modify the treatment if necessary. Previous studies have indicated that a poor functional outcome was significantly

associated with higher subsequent direct/indirect costs [2–4] and increased healthcare utilization [2]. In other words, if a patient's functional disability status could be predicted, and interventions that might be required to improve functionality are identified in advance, poor outcomes could be prevented and healthcare resources could be saved. Furthermore, if the lifelong years for which a patient with schizophrenia suffers manifested disability could be measured beforehand, the healthcare resources for patients with schizophrenia could be appropriately allocated at different stages of prognosis by policy-makers, and the cost-effectiveness of care could be improved [5–7].

In order to achieve this aim, a method that relies on a nationwide database and a cross-sectional survey was developed to explore dynamic changes of functional disability in patients with schizophrenia over time and estimate the lifetime duration of

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disability in personal and social functioning in patients with schizophrenia, as a proxy for assessing their specialized healthcare needs.

## 2. Material and methods

### 2.1. Schizophrenia cohort

The research protocol was approved by the Ethical Committee for Human Research at the National Cheng Kung University. The Taiwanese National Health Insurance (NHI) program is a universal health program that was introduced in March 1995. By the end of 1999, approximately 99% of the Taiwanese population had enrolled in the NHI program. Therefore, the NHI database is representative of the entire Taiwan population. The NHI databases include a registry of beneficiaries, ambulatory care claims, inpatient claims, prescriptions dispensed at pharmacies, a registry of medical facilities, a registry of board-certified specialists and a registry of catastrophic illnesses. After careful review and approval by the Institutional Review Board, these databases were linked to individual personal identification numbers (PINs) to provide patient-level information on demographic characteristics, and PINs were then encrypted prior to data release for research purposes. The registry of catastrophic illnesses features up-to-date information regarding severe illnesses, including schizophrenia, dementia, end-stage renal disease, cancer, etc. In general, a patient must be evaluated and diagnosed by a board-certified physician in the specific field in order to write a certificate for an application, which then must be validated by another specialist before approval for registration as a victim of such illnesses. For patients with a catastrophic illness, co-payments for outpatient or inpatient care can be waived. We identified 52,299 patients who were diagnosed with schizophrenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], code 295) from the catastrophic illness register of the NHI during the period of 2000–2008. The index date of follow-up was defined as the date of the first application for a catastrophic illness certificate. In order to match the cross-sectional survey data in terms of age (the patient age of diagnosis ranged from 15 to 50 years in the survey data), we restricted the cohort to within the age range of 15–50 years, resulting in a final cohort of 42,339 patients. The all-cause mortality was extracted from the catastrophic illness records, which noted the occurrence of death. The NHI administration regularly checks patient status (death or invalidity) and notes these checks in the catastrophic illness records every month.

### 2.2. Collection of data regarding functionality and functional levels

Functionality was measured by conducting a cross-sectional survey of patients with schizophrenia analyzed after the date of first diagnosis. The sample size was 230 patients from 2 medical centers and one mental hospital in Taiwan (day-care wards, community rehabilitation centers, outpatient clinics). The inclusion criteria were: patients meeting the DSM-IV criteria for schizophrenia, and currently aged 20–60 years (age of diagnosis from 15 to 50 years). The exclusion criteria were: a) a severe and unstable major medical disease or a history of neurological disease; b) a history of alcohol or substance dependence or abuse, except for nicotine dependence; c) a history of head injury; d) receipt of electroconvulsive therapy within the previous 6 months; e) an intelligence quotient <70; f) severe vision deficiency, e.g., color blindness or any corrected visual acuity <0.5; and g) illiteracy or disability, and inability to read traditional Chinese characters.

The tool applied for assessment of the patients was the Personal and Social Performance scale (PSP), administered by psychiatrists in each hospital during the one-year study period. The PSP was

developed based on the social functioning component of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the social occupational functioning assessment scale (SOFAS). The reliability and validity of the PSP have been investigated in previous studies, and high test-retest reliability, a good inter-rater reliability [8], and high levels of correlation with the Global Assessment of Functioning (GAF) scale, the Activities of Daily Living (ADL) scale, the SOFAS scale and the Positive and Negative Syndrome Scale (PANSS) were observed [9,10]. The PSP consists of four domains: socially-useful activities; personal and social relationships; self-care; and disturbing and aggressive behaviors. Each domain is rated on a six-point Likert scale from 1 to 6, representing absent, mild, manifest but not marked, marked, severe and very severe. Higher domain scores indicated poorer functioning in that particular domain. A global score, which reflected global functioning, was derived from the levels of impairment in each of the four domains, ranging from 1 to 100. Higher global scores indicated better functioning on the global level. In this study, functional disability was measured according to the scores for each domain (a higher score indicating poorer functioning) and the global score (a lower score indicating poorer functioning).

### 2.3. Survival analysis and extrapolation to estimate life expectancy and expected years of life lost

We applied the Kaplan-Meier method to estimate the time-to-death of the schizophrenia cohort (obtained from the NHI catastrophic illness database). Lifetime survival was estimated using the semi-parametric extrapolation method [11,12]. The lifetime survival of the schizophrenia cohort was estimated for up to 900 months using a simple linear regression extrapolation of a logit transformation curve to assess the survival ratio between the schizophrenia cohort and a year-, age- and gender-matched reference population, which was generated by the Monto Carlo simulation method from life tables for the general population of Taiwan. The survival ratio between the schizophrenia cohort and the reference population assumed a constant excess hazard, the detailed method and mathematical proof of which have been described in a previous study [13]. The standard error of survival estimate was obtained through a bootstrap method of repeated sampling with replacement from a real dataset 100 times. The life expectancy (LE) of the schizophrenia cohort was estimated by summing the area under the estimated lifetime survival curve. The expected years of life lost (EYLL) was calculated as the difference in LE between the schizophrenia cohort and the age- and gender-matched reference population.

To validate the extrapolation method, the relative bias between the predictions and real values was estimated: the LE estimate (using extrapolation based on the first 5 years of follow-up) was compared with the Kaplan Meier estimate based on the actual 9-year follow-up period. The relative bias was less than 1% for the whole study population and for gender-stratified groups. The details are presented in Supplementary Table 1.

### 2.4. Estimations of proportions of patients with functional disabilities at different functional levels

Functional disability does not remain constant over time in patients with schizophrenia, and changes according to the duration of illness; therefore, a kernel-smoothing method was used to estimate the dynamic changes in functional disability [11]. To synchronize with clinical significance, we converted a patient's PSP score into two functional levels: less (mild) difficulty (global score: 71–100; domain score: 1–2) and manifested disability (global score  $\leq$ 70; domain score: 3–6). We classified the indicator

of manifested disability as 1; else, it would be 0. The proportion of patients of certain levels of functional disability at time  $t$  can be obtained by the function  $\frac{\sum_{x \in N(t)} \text{Indicator}}{\sum_{x \in N(t)} G(t)}$ , where  $N(t)$  is the number of patients and  $G(t)$  is the size of the population at time  $t$ . The proportions of patients at certain levels of functional disability across different time periods can be obtained by a kernel-smoothing method. Curves of dynamic changes of the proportions of patients with functional disability at different functional levels were obtained by calculating the moving average of the nearby or neighboring 10% to estimate the proportions of patients at different times. Hung et al. published a more detailed method of calculation [14]. In this study, the kernel-smoothed curves were obtained from the four domains of the PSP to illustrate dynamic changes in the proportions of patients with functional disability in particular domains over time.

2.5. Expected years of living with disability

To integrate the proportion of patients with functional disability and lifetime survival, we then multiplied the lifetime probability of survival at each time point by the proportions of patients with varying levels of different types of functional disability (four domains and global score) to obtain a lifetime functional disability-adjusted survival [14]. The area under the curve was the functional disability-adjusted life expectancy of the patients with schizophrenia, as shown in Supplementary Fig. 2. The unit of the area under the curve was years; thus, the area under the curve was the expected years of living with disability (EYLD), one EYLD representing 1 year of mild or manifested functional disability depending on the functional level; hence, 20 EYLDs represented 20 years of living with manifested disability for each patient. The equation used to estimate the lifetime durations at different functional levels can be illustrated as follows [14]:

$$EYLD_i = \int_0^{\infty} \hat{S}(t) \times \hat{P}_i(t) dt;$$

Where  $\hat{S}(t)$  represents the estimated lifetime survival function,  $\hat{P}_i(t)$  is the proportion of patients of a specific functional level, and  $i$  is the functional level.

2.6. Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study subjects. Apart from gender ( $n$  [%]), all variables were described using the mean (standard deviation [SD]). For inferential statistics, Chi-square tests and Student  $t$ -tests were used for comparison of gender and age between the schizophrenia

cohort obtained from the catastrophic illness data and the subjects enrolled in the cross-sectional survey. The proportions of patients with functional disability were obtained by a kernel-smoothing method with a moving average of the neighboring 10% of data points from the survey data. The Kaplan-Meier method was used to estimate the time-to-death of the schizophrenia cohort (obtained from the registry of catastrophic illnesses in the NHI database). The LE was calculated for the schizophrenia cohort by summing the area under the estimated lifetime survival curve, which was estimated by the Monto Carlo simulation method from life tables for the general population of Taiwan. The EYLL was calculated for the schizophrenia cohort as the difference in LE between the schizophrenia cohort and the age- and gender-matched general population (obtained from life tables). EYLD was the years of disability-adjusted survival expectancy, which was obtained according to the proportion of patients with functional disability (from the survey data) multiplied by the lifetime survival probability (from the schizophrenia cohort) over time throughout the patients' life. Detailed calculations for LE, EYLL and EYLD are presented in parts 2.4 and 2.5 of the Methods section. Regarding gender differences in the changes of functional disability (global and each domain) over time, we stratified the study groups by gender and compared the differences in LE, EYLL and EYLD in the female and male patients. In order to ensure internal consistency of estimations of LE, EYLL and EYLD, sensitivity analysis was performed on a random sample of 100 patients who had completed the cross-sectional survey. All significance levels were two-sided;  $P < 0.05$ . We performed statistical analyses using SAS software (version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA). Estimates of LE, EYLL and EYLD were easily obtained using iSQoL software, developed by Hwang's team and free to be downloaded from the following website: <http://www.stat.sinica.edu.tw/isqol/>.

3. Results

In the registry of catastrophic illnesses, a total of 42,339 patients with schizophrenia who had catastrophic illness certification were identified during the study period; 56% of the patients were male, and the mean age was 33.3 (9.1) years. The median follow-up duration for the schizophrenia cohort was 60.7 months (interquartile range, 49.8). The all-cause mortality rate was 70.7 per 100,000 person-years. In the cross-sectional survey of functional disability, 48% of the subjects were male. The means of the age at first diagnosis and current age were 24.5 (7.0) and 45.5 (10.7) years, respectively. The mean duration of illness was 20.8 (11.0) years. The gender distribution differed statistically between the cross-sectional survey data and the schizophrenia cohort ( $\chi^2 = 5.14, P = 0.02$ ). The age distribution (age of diagnosis) obtained

**Table 1**  
Characteristics of patients with schizophrenia from a cross-sectional sample.

	All patients (n = 230)		Male (n = 111)		Female (n = 119)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Diagnosis age (years)	24.5	(7.0)	24.4	(6.6)	24.5	(7.4)
Current age (years)	45.5	(10.7)	45.4	(10.9)	45.6	(10.6)
Duration of illness (years)	20.8	(11.0)	20.8	(11.0)	20.7	(11.0)
Personal and social performance						
Socially-useful activities	2.9	(1.0)	3.0	(1.1)	2.8	(1.0)
Personal and social relationships	3.0	(1.0)	3.2	(1.0)	2.9	(0.9)
Self-care	2.1	(1.2)	2.3	(1.3)	1.9	(1.2)
Disturbing and aggressive behavior	1.4	(0.7)	1.4	(0.6)	1.4	(0.7)
Global score	58.6	(14.7)	56.7	(16.2)	60.3	(13.0)

from the cross-sectional survey was significantly younger than that of the schizophrenia cohort ( $t = -19.0, P < 0.001$ ) (Table 1).

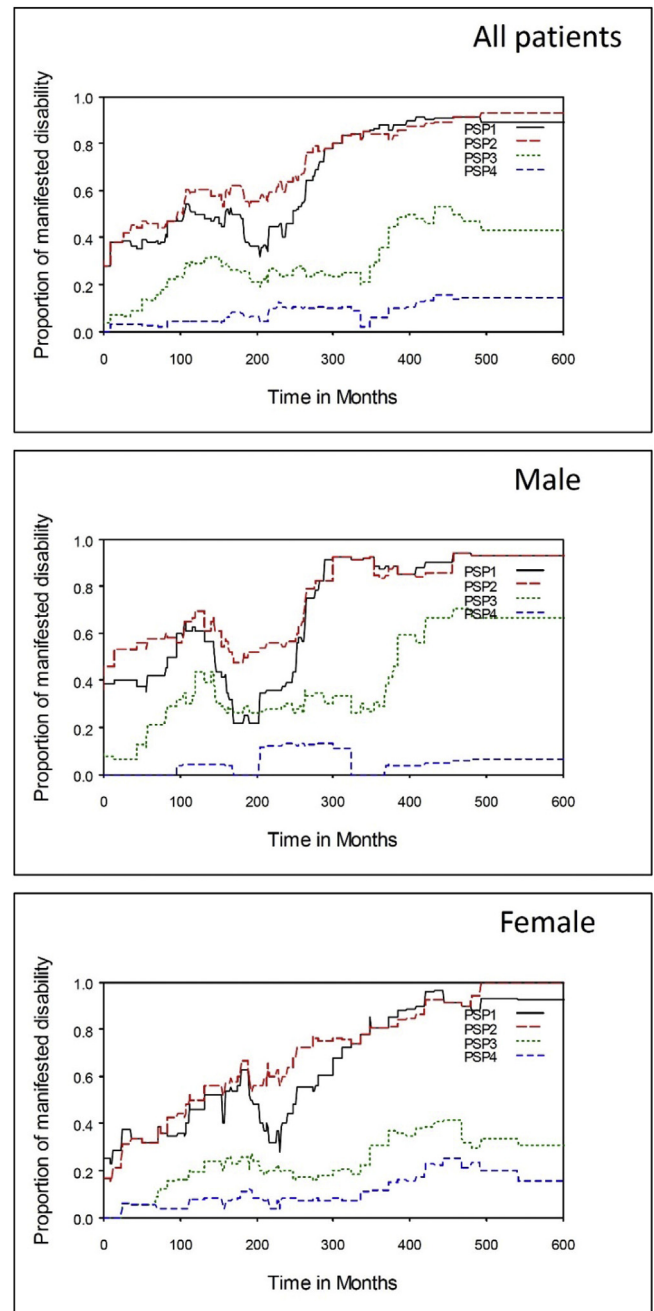
In terms of the dynamic changes of proportions of patients with different types of functional disability among the patients with schizophrenia, the proportions of patients with manifested disability in socially-useful activities and personal and social relationships were higher than the proportions of those with disability in self-care and disturbing and aggressive behavior, and increased as the duration of illness progressed. Stratified by gender, the proportions of patients with manifested disability in socially-useful activities and personal and social relationships were also higher than those with manifested disability in other domains in both the male and female patients. Among the female patients with schizophrenia, the proportions of patients with manifested disability in socially-useful activities and personal and social relationships were lower than the proportions of male patients at the initial diagnosis point, and gradually increased over time. The proportion of male patients with manifested disability in self-care was higher than that of female patients across the different time periods (Fig. 1).

As summarized in Table 2, the estimated LE and EYLL of the schizophrenia cohort were 28.5 (0.02) and 16.6 (0.03), respectively. Stratified by gender, the estimated LE and EYLL of the male patients with schizophrenia were 26.9 (0.02) and 16.6 (0.03), respectively, and those of the female patients with schizophrenia were 30.3 (0.02) and 17.0 (0.03), respectively. In terms of EYLD, the longest expected years of living with manifested disability for the different domains were observed for socially-useful activities (15.6 years) and personal and social relationships (17.5 years) among the patients with schizophrenia. The expected years of living with manifested disability in global functioning was 20.9 years, and approximately 73% of the lifetime of patients with schizophrenia was spent under a manifested disability status.

Stratified by gender, the female patients had higher expected years of living with manifest disability than the male patients (Table 2). As shown in Supplementary Table 2, the estimations of LE, EYLL and EYLD from a random sample of 100 patients who completed the cross-sectional survey were similar to the estimations obtained in the main analysis, and the expected years of living with manifest disability in socially-useful activities and personal and social relationships were longer than for other types of functional disability.

#### 4. Discussion

In this study, we proposed and demonstrated a method by which to estimate years spent under the status of manifested disability, which implies the lifetime psychiatric healthcare needs for patients with schizophrenia. The estimations were obtained by integrating the proportion of patients at a certain functional level with the probability of survival throughout the patient's life. Previous studies have published similar methods for the estimation of long-term physical disabilities [14], quality of life, medical expenditure [13], etc., for different chronic illnesses. However, this study was the first to use a specific clinical psychometric functionality scale for schizophrenia that could reflect changes in disease severity, indicate treatment benefits, and ascribe clinical meaning to healthcare needs. Previous studies applied measurements of EuroQol (EQ-5D) to estimate quality-adjusted life years (QALYs) for different treatments, but the EQ-5D cannot adequately reflect changes in negative symptoms, disorganized behaviors, depression, and social function in patients with schizophrenia [15–17], and is less sensitive in terms of correlation with changes of disease severity in patients with schizophrenia [16]. In addition, the onset of schizophrenia usually occurs in late adolescence or young adulthood, and the course of the disease is generally very



**Fig. 1.** Dynamic changes in the proportions of patients with functional disabilities in patients with schizophrenia.

PSP1 = socially-useful activities; PSP2 = personal and social relationships; PSP3 = self-care; PSP4 = disturbing and aggressive behaviors.

long, more than 4–5 decades. A patient's poor functional outcome was found to be significantly associated with higher subsequent costs [2–4] and increased healthcare utilization [2]. The method developed in this study provided information regarding both the dynamic changes of functional disability and the expected years of living with disability, which are directly useful for the evaluation of healthcare technology requirements in patients with schizophrenia or other chronic mental disorders. In addition, the quantification of EYLL was adjusted for age, which is crucial for control of confounding by lead time bias and useful for evaluation of the health benefits of early diagnosis of illnesses [18], including schizophrenia.

**Table 2**

Estimation of life expectancy (LE), expected years of life lost (EYLL), and expected years of living with disability (EYLD) stratified by functional disability (mean and SE).

	All patients (n = 230)	Male (n = 111)	Female (n = 119)
LE, mean (SE) years	28.53 (0.02)	26.87 (0.02)	30.26 (0.02)
EYLL, mean (SE) years	16.62 (0.03)	16.55 (0.03)	17.04 (0.03)
EYLD, mean (SE) years			
Four domains of functioning			
Socially-useful activities			
Years with mild difficulty (PSP: 1–2)	12.44 (0.97)	11.95 (1.28)	13.92 (1.35)
Years with manifested disability (PSP: 3–6)	15.61 (1.03)	14.94 (1.51)	16.61 (1.47)
Personal and social relationships			
Years with mild difficulty (PSP: 1–2)	10.54 (0.98)	9.32 (1.52)	12.34 (1.56)
Years with manifested disability (PSP: 3–6)	17.52 (0.9)	17.56 (1.3)	18.21 (1.56)
Self-care			
Years with mild difficulty (PSP: 1–2)	20.86 (0.82)	18.98 (1.17)	24.37 (1.18)
Years with manifested disability (PSP: 3–6)	7.00 (0.79)	8.01 (1.26)	6.01 (1.1)
Disturbing and aggressive behavior			
Years with mild difficulty (PSP: 1–2)	25.86 (0.49)	25.92 (0.47)	27.74 (0.93)
Years with manifested disability (PSP: 3–6)	1.88 (0.43)	1.2 (0.49)	2.6 (0.85)
Global score			
Years with mild difficulty (PSP: 71–100)	7.21 (0.94)	7.35 (1.36)	7.57 (1.3)
Years with manifested disability (PSP: ≤ 70)	20.88 (1.03)	19.52 (1.29)	22.98 (1.37)

The dynamic changes of functional disability in this study showed that the proportion of patients with manifested disability in disturbing and aggressive behaviors was substantially lower than the proportions of subjects with dysfunction in other domains of functionality. All the participants in this study had been regularly receiving antipsychotic medications and the results seemed to reflect the effectiveness of current medications and related interventions in terms of controlling aggressive behaviors. However, the proportions of patients with manifested disability in socially-useful activities and personal and social relationships rapidly increased at 200 months after diagnosis. This may indicate that current treatment modalities, mainly the prescription of psychotropic medications alone, are inadequate in terms of helping patients to improve their emotional and social skills and work in the community. Instead, integrated treatment, including pharmacological and psychosocial treatments, quality of life and psychosocial functionality improvement, is required in order to assist these people to move back into society under a stressful environment [19]. Previous studies have indicated that integrated treatment reduces the burden of illness and improves clinical outcomes significantly better than standard treatments for patients with schizophrenia, and this evidence supports our speculation [20–22]. The advantages of analysis of the dynamic changes in proportions of patients with functional disability we proposed are that prognosis of disability status can be assessed and physicians informed of which additional interventions are needed for patients with schizophrenia at different stages of the disease, which can prevent poor outcomes in patients with schizophrenia.

The idea of quantification of both EYLL and EYLD is similar to the currently popular method of DALY (disability-adjusted life years), developed in the global burden of disease (GBD) study, which considers both mortality and functional disability together. GBD represents a comprehensive regional and global research program of disease burden that assesses mortality and disability arising from major diseases, injuries, and risk factors [23]. The study introduced a metric – DALY – as a single measure to quantify the burdens of diseases, injuries and risk factors. GBD represents a collaboration of over 3000 researchers in more than 130 countries. The worldwide collaborators use the same approach to assess their population's health ([http://www.](http://www.healthdata.org/)

[healthdata.org/](http://www.healthdata.org/)). An updated GDB study was published by GBD 2016 Mortality Collaborators [24].

DALY is calculated as the sum of years of life lost (YLL) due to premature mortality and years lived with disability (YLD) associated with nonfatal injuries and disease [25]. While YLL depends on whether the cause of interest is coded as the underlying cause of death, it has been documented to underestimate the real figures in patients with cancer [26]. Similarly, it does not account for shortened life expectancies of schizophrenia patients who are coded as having suffered a stroke, probably because chronic treatment resulted in metabolic cardiovascular diseases. The EYLL we have proposed directly estimates the difference in life expectancy (LE) between patients with schizophrenia and an age- and sex-matched general population obtained from national life tables, which may reduce bias in the coding of a single cause of death. Moreover, the disability weights in YLD were measured according to the person trade-off method from selected general participants aged 18 to 65 years [27], which is not an actual reflection of disabling conditions in patients with specific diseases [28]. In this study, we proposed the use of proportions of patients with disability instead of disability weights, which are based on actual measurements (PSP scale) from patients to obtain data rather than assumed for people with certain diseases. In addition, EYLD can be stratified according to different domains (Table 2) to estimate the lifetime years spent with different types of functional disability, but the YLD cannot be used for such sophisticated estimation. Thus, the EYLL and EYLD proposed herein result in more detailed and accurate estimations for patients with schizophrenia and make up for disadvantages in the DALY method.

Nevertheless, some weaknesses related mainly to two main axes were identified in this study. First, patients were recruited from day-care wards, community rehabilitation centers and outpatient clinics from two medical centers and one mental hospital; therefore, generalization must be performed cautiously. Our results may only be inferred in patients with schizophrenia whose functional disabilities are mild and/or stable. Second, the sample size for the cross-sectional survey was relatively small, and the results may not necessarily represent the actual longitudinal dynamic changes of these patients. Further studies with more patients and repeated measurements throughout follow-up are

required in order to corroborate the results. However, our results are probably more accurate than simply multiplying the survival function by a mean value of the proportion of patients with disability. Third, the age of patients registered as having a catastrophic illness is usually older than the actual age at which subjects were first found to manifest disordered behavior. Therefore, using the registered age as the age of first diagnosis for all patients would result in underestimation of the EYLL owing to delays in registration. Finally, we only applied the PSP to assess functionality in this study, and did not apply any measurement related to mental health, for example, activities of daily living, cognitive ability, quality of life, etc. Further studies that include these more detailed evaluations are needed in the future.

In conclusion, we found that approximately 73% of the lifetime of a patient with schizophrenia is spent under a manifested disability status. The longest lifetime durations of manifested disability were observed for socially-useful activities and personal and social relationships. Stratification by gender showed that the female patients with schizophrenia had greater lifetime duration of manifested disability than the male patients. The results of dynamic changes of functional disability in different domains implied that integrated treatment is more effective than pharmacological treatment alone.

### Conflict of interest

The funding institutions of this study had no further role in the study design, the collection, analysis, and interpretation of data, the writing of this paper, or the decision to submit it for publication. The authors report no financial relationships with commercial interests.

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### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eurpsy.2018.07.009>.

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