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Epidemiological survey of first-episode psychosis in Nagasaki, Japan: Is the incidence rate of schizophrenia changing?

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The Determinants of Outcome of Severe Mental Disorders (DOSMeD) study, a global epidemiological study led by the World Health Organization, reported the annual incidence rate of schizophrenia from 1979 to 1980. In 2011, approximately 30 years later, we conducted a large-scale epidemiological study to investigate the incidence rate of first-episode schizophrenia in Nagasaki using the same method as the DOSMeD study. A telephone survey was conducted by researchers daily at 52 psychiatric hospitals, clinics, and institutes in Nagasaki. When a subject was confirmed, the researcher visited the medical facility in person to evaluate the patient's symptoms. Of 441,706 people in Nagasaki City, 131 people were surveyed in the way, resulting in the diagnosis of psychosis in 25 patients, 20 of whom were determined to have schizophrenia. These data were used to calculate the incidence rates of psychosis (1.00 per 10,000 population; 95% confidence interval [CI], 0.54-1.46) and schizophrenia (0.80 per 10,000 population; 95% CI, 0.38-1.21). The 95% CI for the incidence rate of psychosis did not include the incidence rate for psychosis (broad definition) reported in the DOSMeD study (2.02). However, the 95% CI for the incidence rate of schizophrenia did include the incidence rate for schizophrenia (restrictive definition) reported in the DOSMeD study (1.01). Although the incidence rate of psychosis appeared to be decreasing, no significant change was found in the incidence rate of schizophrenia, comparing the present findings with those of the survey conducted 30 years ago. The incidence rate of schizophrenia is said to vary with changes in gender differences, racial differences, urbanization, and immigration; we therefore considered this possibility. In the future, it is necessary to carry out longer-term surveys covering multiple cities using the same methods.

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Key words: first episode psychosis, incidence rate, schizophrenia, long-term survey, epidemiological study

Introduction

Schizophrenia often occurs when individuals are in their late teens to mid-30s [1]. In many cases, schizophrenia adversely affects social functioning, creating considerable burdens for families and leading to a national-level socioeconomic impact [2]. Therefore, the estimation of the incidence rate of schizophrenia is an important concern for national mental health

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planning.

A study on the Determinants of Outcome of Severe Mental Disorders (DOSMeD) was conducted from 1979 to 1980. This collaborative survey of the incidence rate of schizophrenia was carried out by the World Health Organization and several research institutions worldwide, including the Department of Neuropsychiatry of Nagasaki University (Nagasaki, Japan) [3,4]. This survey explored the annual incidence rates of schizophrenia per 10,000 population in eight cities worldwide, reporting values ranging from 1.5 (Aarhus) to 4.2 (Chandigarh/rural) using a broad diagnostic definition and from 0.7 (Aarhus) to 1.4 (Nottingham) using restrictive diagnostic criteria [3,4].

The Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study, a large-scale, multicenter epidemiological study of schizophrenia conducted in the United Kingdom, showed differences in terms of incidence rates by race and sex [5,6]. Regarding general incidence rates, the 2-year AESOP survey, conducted from 1997 to 1999, indicated the annual incidence rates per 10,000 population of psychosis and schizophrenia to be 3.5 and 1.3, respectively [5]. A comparison study of the AESOP data from three areas in 1997 and 2000 found that areas with higher numbers of residents of African Caribbean descent (e.g., southeast London, with an incidence rate of 5.5 per 10,000 person-years) had a significantly higher incidence rate of psychosis, compared with areas with lower numbers of these individuals (e.g., Nottingham, with an incidence rate of 2.5 per 10,000 person-years and Bristol, with an incidence rate of 2.2 per 10,000 person-years) [6].

According to a meta-analysis performed on the data from epidemiological studies conducted from 1950 to 2009 in the United Kingdom, the incidence rate of psychosis (mainly schizophrenia) was 3.2 per 10,000 population, and the incidence rate of schizophrenia alone was 1.5 per 10,000 population [7].

Urbanicity, sex, race, and immigration might affect the incidence rate of schizophrenia [8-14]. In particular, there have been reports of differences in schizophrenia incidence rates between urban and rural areas [8-11].

Since the DOSMeD study was conducted, there have been no large-scale surveys on the incidence rate of schizophrenia in Japan. Therefore, using an epidemiological survey, this study aimed to assess the incidence rate of new cases of psychosis, especially schizophrenia, in Nagasaki, which has a population of approximately 440,000 (a medium-sized city in Japan).

Materials and methods

This study was performed using methods submitted to and accepted by the Ethics Committee of Nagasaki University. The research plan was approved by the committee on March 11, 2011 (approval number: 11022320).

The study participants were patients with suspected new-onset psychosis who visited a psychiatric hospital or clinic in or around Nagasaki City (Nagasaki Prefecture, Japan) from August 1, 2011, to July 31, 2012. The participating institutions were 22 psychiatric hospitals in Nagasaki City and its surrounding areas, including Nagasaki University Hospital; 28 psychiatric clinics; and 2 public organizations—Nagasaki City Health Center and Nagasaki Prefectural Mental Health Welfare Center, together forming a case-finding network (CFN) of a total of 52 institutions. An outline of the case-finding system is shown in Figure 1.

The inclusion criteria for the survey were visiting one of these facilities for the first episode of psychosis and being aged 65 years or younger at the initial visit. At the initial visit, patients suspected of psychosis who resided in Nagasaki were included in the survey without restriction in terms of birthplace, nationality, age at onset, or family history.

In this study, the categories of "psychosis" and "schizophrenia" correspond, respectively, to the "broad diagnostic definition" and the "restrictive diagnostic definition" used in the DOSMeD study. We defined psychosis using the following *International Statistical Classification of Diseases, 10th revision* (ICD-10) criteria [15]. In F1 disorders (mental and behavioral disorders caused by psychoactive substance use), psychotic disorder and residual and late-onset psychotic disorder caused by psychoactive substance use were included. In F2 disorders (schizophrenia, schizotypal, and delusional disorders), all diagnostic categories were included. In F3 disorders (mood [affective] disorders), manic episode, bipolar affective disorder, depressive episode, and recurrent depressive disorder with psychotic symptoms were included. In F0 disorders (organic, including symptomatic, mental disorders) and F7 disorders (mental retardation), all categories were excluded. Finally, states below the psychosis threshold (e.g., post-schizophrenic depression, residual schizophrenia, simple schizophrenia, precursor state, or at-risk mental state) were excluded using the Comprehensive Assessment of At-risk Mental States (CAARMS) [16]. Thus, in cases where the severity, frequency, or duration of symptoms was below the threshold, some patients included in the above categories of psychosis in the ICD-10 might not have been diagnosed with "psychosis" in this study. For the same reason, some participants diagnosed with schizophrenia using ICD-10 criteria might not have

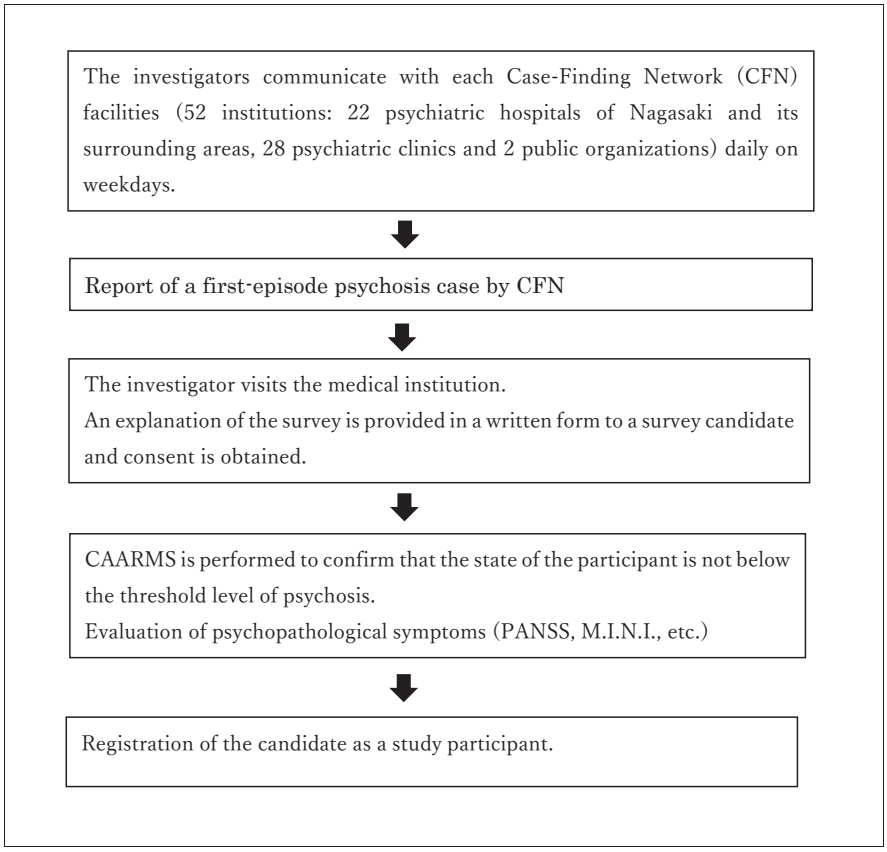

Figure 1. The case-finding system

been included in the category of "schizophrenia" in this study.

The investigators communicated with the 52 facilities by phone daily except on Saturdays, Sundays, and national holidays. New cases of first-episode psychosis presenting on Saturdays or Sundays were reported on Mondays, and those presenting on holidays were reported on the following day. At each facility, designated research collaborators confirmed the daily information regarding new patients by evening and reported the information to the investigator by phone. When there was a suspected case of first-episode psychosis, the investigator visited the facility with the approval of the outpatient clinician and with consent from the suspected patient and his/her family. First, it was confirmed that this patient resided in Nagasaki and was younger than 65 years and that it was the first episode of psychosis. Informed consent was obtained after requesting participation, explaining the aim of the survey, and providing the opportunity to refuse participation. A detailed evaluation interview was conducted only for cases who met the inclusion criteria.

For psychological assessment, the following tests were performed: the CAARMS to confirm that a patient was not below the psychosis threshold, the Positive and Negative Syndrome Scale (PANSS) [17] for overall symptom assessment including positive symptoms of schizophrenia, and the Mini-International Neuropsychiatric Interview [18] to assess the presence/absence of other psychiatric disorders. All evaluations were conducted by SK alone, and final diagnoses, based on the ICD-10, were made independently by two expert psychiatrists (SK and AI). All diagnoses were agreed upon by these two researchers.

In addition, family history, life history, pre-disease factors, and socioeconomic factors were evaluated using the Psychiatric and Personal History Schedule [3,4]. Finally, the duration of untreated psychosis (DUP) was investigated.

Results

Study participants

A total of 131 cases were identified through the CFN during the 12-month survey period from August 1, 2011, to July 31, 2012. Of these cases, 29 were interviewed, and 102 were excluded. Among the CFN facilities providing the cases, 78 (59.5%) were psychiatric hospitals and 53 (40.4%) were psychiatric clinics. In addition, regarding treatment-

based categorization, 99 cases (75.5%) were outpatients and 32 cases (24.4%) were inpatients.

A total of 102 cases were excluded for the following reasons: excluded at the stage of medical chart investigation because of the presence of disease conditions such as organic mental disorders or no obvious psychotic symptoms (n = 73), residence outside Nagasaki (n = 9), not meeting the age criteria (n = 8), treatment history prior to the study period (n = 10), having an initial visit prior to the study period (n = 1), and unknown disease condition with patient visiting only for examination (n = 1).

Among the 29 interviewed cases, psychosis was confirmed in 25. One case was below the psychosis threshold, two cases were excluded because the patients did not meet the geographic residence criteria (interviews were erroneously performed for non-Nagasaki residents based on misinformation), and one case had a treatment history at a medical institution prior to the study period. Figure 2 presents the course of case detection.

Interviewed participants

The characteristics of the interviewed participants are summarized in Table 1. The mean age was 38.8 (SD: 16.5) years for all individuals with psychosis (n = 25) and 38.7 (SD: 17.1) years for those with schizophrenia (n = 20). The first, second, and third quartiles of participant age were 22, 40, and 53 years, respectively, for psychosis and 22, 40.5, and 52 years, respectively, for schizophrenia. Figure 3. shows the box-and-whisker plot of age of the participants. In this study, the results showed the mean age of participants with psychosis or schizophrenia to be the late 30s.

The male-to-female ratio was 7:18 for participants with psychosis and 5:15 for those with schizophrenia. The proportion of women was much higher than that of men in this study.

The mean DUP for participants with psychosis was 1124 (SD: 2216) days, whereas the mean DUP for participants with schizophrenia was 1151 (SD: 2323) days. The first, second, and third quartiles of DUP were 20.5, 60, and 512.5 days,

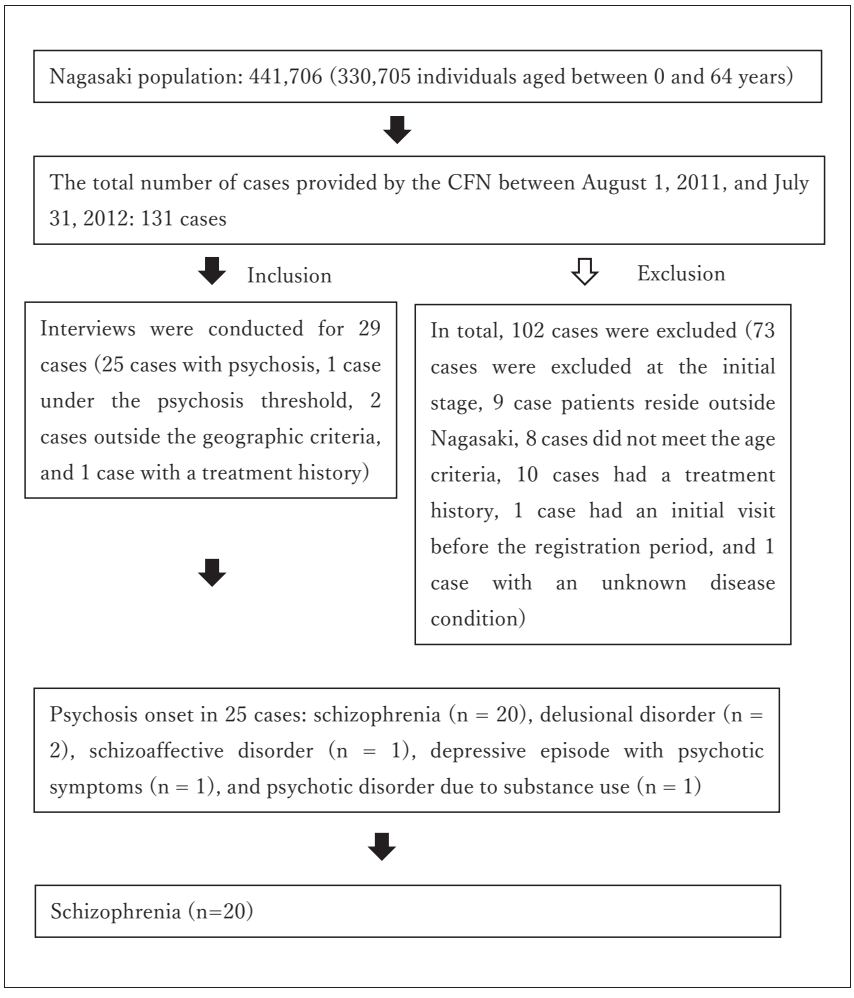

Figure 2. The course of case detection

Table 1. Participant characteristics

	Psychosis	Schizophrenia
Number of participants	25	20
Age		
Mean age	38.8 (SD: 16.5)	38.7 (SD: 17.1)
the first, second and third quartiles	22, 40, 53	22, 40.5, 52
Male-to-female ratio (male/female)	0.32(7:18)	0.33(5:15)
DUP (days)		
Mean	1124 (SD:2216)	1151 (SD:2323)
the first, second and third quartiles	20.5, 60, 512.5	20, 52.5, 665
CAARMS		
Unusual thought content	3.8 (SD:2.3)	3.7 (SD:2.4)
Non-bizarre ideas	5.4 (SD:1.5)	5.5 (SD:1.6)
Perceptual abnormalities	4.8 (SD:1.7)	5.0 (SD:1.5)
Disorganized speech	0.9 (SD:1.9)	0.9 (SD:1.8)
PANSS		
Positive scale	23.3 (SD:6.6)	22.9 (SD:7.1)
Negative scale	13.4 (SD:7.3)	14.1 (SD:7.8)
General Psychopathology scale	35.2 (SD:11.6)	36.6 (SD:9.7)
Total score	71.9 (SD:18.5)	73.5(SD:18.7)

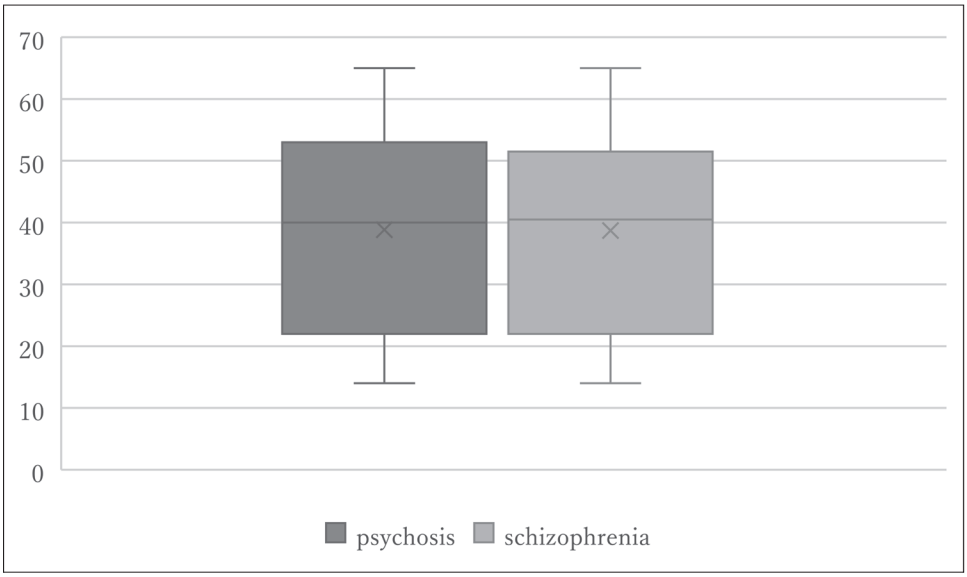

Figure 3. Box-and-whisker plot of age of participants

respectively, for participants with psychosis and 20, 52.5, and 665 days, respectively, for those with schizophrenia. Figure 4, a box-and-whisker plot displaying the DUP for participants with psychosis and those with schizophrenia, shows that there were some outliers in both groups.

The mean evaluation scores for the four subcategories ("unusual thought content," "non-bizarre ideas," "perceptual abnormalities," and "disorganized speech") of the CAARMS are shown for participants with psychosis and those with schizophrenia in Table 1. A simple comparison is not possible, but the subcategory "unusual thought content" had the highest score, and "disorganized speech" had the lowest score.

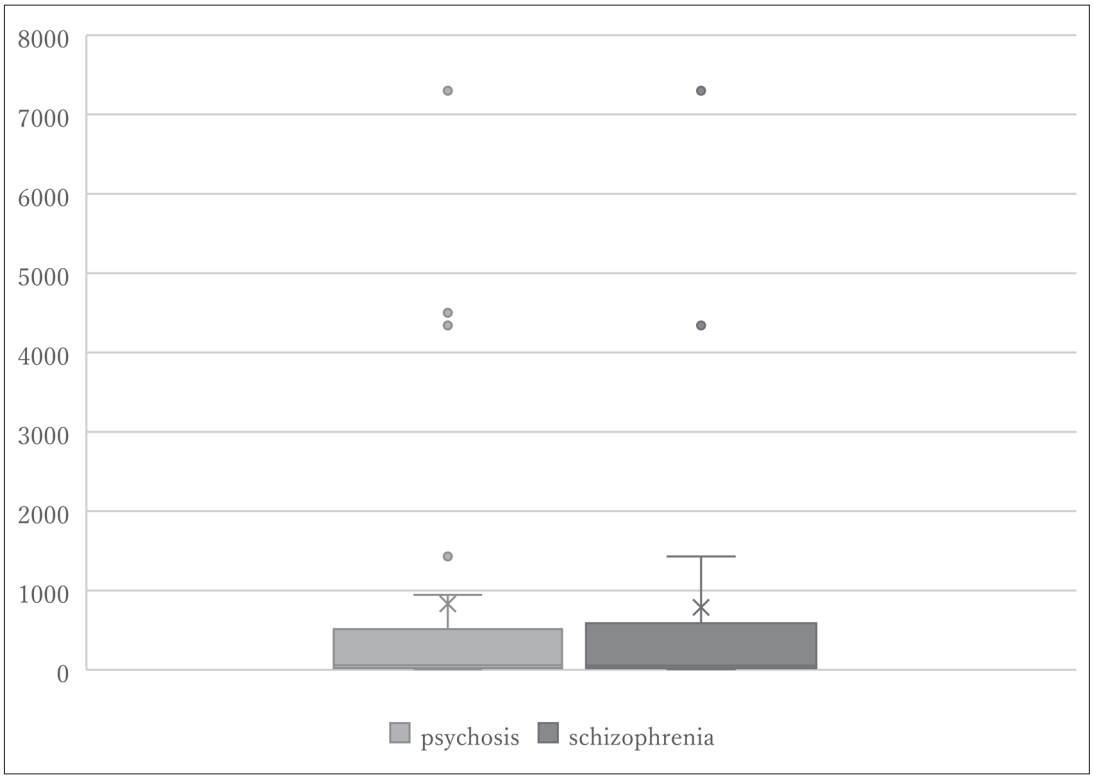

Figure 4. Box-and-whisker plot of duration of untreated psychosis (DUP)

The mean total PANSS score was 71.9 (SD: 18.5) for participants with psychosis and 73.5 (SD: 18.7) for those with schizophrenia. The mean scores for the three subcategories—"Positive scale," "Negative scale," and "General Psychopathology scale"—were 23.3 (SD: 6.6), 13.4 (SD: 7.3), and 35.2 (SD: 11.6), respectively, for participants with psychosis and 22.9 (SD: 7.1), 14.1 (SD: 7.8), and 36.6 (SD: 9.7), respectively, for those with schizophrenia. These results tended to be higher for the positive symptom scores than for the negative symptom scores among both patient groups.

Incidence rate of first-episode psychosis and first-episode schizophrenia

Table 2 presents the results of the survey of the incidence rate. As mentioned above, there were 25 first-episode psychosis cases, including 20 cases of schizophrenia.

Adjusting the population of Nagasaki (2011 population: 441,706; population aged 0-64 years: 330,705) for age, the incidence of first-episode psychosis was 0.76 per 10,000 persons per year, and the incidence of first-episode schizophrenia was estimated to be 0.60 per 10,000 persons per year.

When participant age was set within the same range as that used in the DOSMeD study (15-54 years: 200,472 in 2011), there were 20 cases of first-episode psychosis, including 16 cases of schizophrenia, indicating an annual incidence rate of first-episode psychosis of 1.00 per 10,000 persons and an annual incidence rate of first-episode schizophrenia of 0.80 per 10,000 persons.

Because the 95% confidence interval for the incidence rate of psychosis (0.54 – 1.46) did not include the incidence rate for the "broad diagnostic definition" reported in the DOSMeD

Table 2. Incidence rates of psychosis and schizophrenia

Target age (years)	Population	Psychosis			Schizophrenia		
		Number of participants	Incidence rate (/10,000 persons /year)	95% Cl	Number of participants	Incidence rate (/10,000 persons /year)	95% Cl
0-64	330,705	25	0.76	0.45-1.06	20	0.60	0.33-0.88
15-54	200,472	20	1.00	0.54-1.46	16	0.80	0.38-1.21

study (2.02) [4], the incidence rate of psychosis appeared to be decreasing, comparing the present findings with those of the study conducted 30 years ago. However, the 95% confidence interval for the incidence rate of schizophrenia (0.38–1.21) did include the incidence rate for the "restrictive diagnostic definition" reported in the DOSMeD study (1.01) [4], indicating no significant change in the incidence rate of schizophrenia.

Discussion

In this study, the recent annual incidence rates of new-onset psychosis and schizophrenia were obtained with the same methods used in the DOSMeD study [3.4], which was conducted from 1979 to 1980 in many areas around the world, including Nagasaki, to estimate the incidence rate of schizophrenia in different cultures. The present study is valuable because it compared the incidence rates in the same region after a 30-year interval.

The results of the current study show that the incidence rate for the category of "psychosis" declined, compared with the incidence rate for the "broad diagnostic definition" reported in the DOSMeD study. In addition, the incidence rate for the category of "schizophrenia" in our study did not show any significant changes, compared with the incidence rate for the "restrictive diagnostic definition" reported in the DOSMeD study.

The comparison of the present study and the DOSMeD study illustrated that differences in terms of diagnostic definition can affect the results for incidence rates. In the DOSMeD study, the "broad diagnostic definition" was established using the ICD-9 [19] diagnostic criteria for schizophrenic psychosis, paranoid states, part of other nonorganic psychosis, part of alcoholic psychoses, and part of drug psychoses, as well schizophrenic psychoses, paranoid psychoses, and other psychoses [3,4][20-23]. The DOSMeD study's "restrictive diagnostic definition" indicated patients with schizophrenia exhibiting Schneider's first-rank symptoms [3,4][20-23]. In the current study, we used the ICD-10 to determine the diagnostic criteria and excluded the conditions falling below the threshold level for psychosis using the CAARMS, which led to the elimination of cases categorized under the ICD-9 criteria as latent schizophrenia, simple-type schizophrenia, and potentially of other conditions. Thus, because we used the CAARMS in this way, the broad diagnostic definition used in the current study was more restrictive than that used in the DOSMeD study, whereas the restrictive diagnostic definition used in the current study was similar to that used in the DOSMeD study. These factors were among the main causes of differences between the DOSMeD study and the current study.

Further, changes in demographics could have affected the results of the present study. The total population of Nagasaki when the DOSMeD study was conducted was 447,444, and the target population of individuals aged 15–54 years was 267,149 [3,4]. In 2011, when the current study was conducted, the total population of Nagasaki was 443,766, the target population of individuals aged 0–65 years was 330,705, and the population of 15–54-year-olds was 200,472. Thus, the apparent decrease in the population size of individuals in the target age range may have affected the results of the present study.

In addition, several reports have found urbanization and immigration to be important factors in the incidence rate of psychosis [8-14], which may have affected the results of the current study. Nagasaki's population density was 1103/km^2 at the time of the DOSMeD study[3,4] and 1093/km^2 at the time of the present study, indicating no major difference, the size of the younger population was smaller in 2011 than in 1979–1980, and there is no evidence of progressive urbanization. In addition, although there is a large population outflow from Nagasaki, migration into the city is limited, suggesting that there is no change in social conditions caused by immigration. Thus, problems related to urbanization and immigration do not seem to be relevant in this case.

Age and sex may also affect incidence rates [12,13]. Previous reports have shown that the incidence rate of schizophrenia peaks when patients are in their 20s [12]; however, in the present study, the mean age was 38.8 years for participants with psychosis and 38.7 years for those with schizophrenia, indicating a much later tendency in first-episode psychosis and schizophrenia. The male-to-female ratio of the participants in our study was 7:18 for participants with psychosis and 5:15 for those with schizophrenia, indicating that there were more women than men. Previous studies have reported that the incidence rate of schizophrenia is similar in men and women or slightly higher in men than in women [1,24]. Thus, our findings are not consistent with previous work. This may be influenced by the fact that some young male patients were excluded during the recruitment phase of this study because they had insufficient information to support their diagnosis and were difficult to distinguish from patients with other psychiatric disorders such as neurodevelopmental disorders.

There is evidence that DUP affects the severity and prognosis of psychosis [25-27]. In the current study, the mean DUP was 1124 (SD: 2216) days, and the first, second, and third quartiles of DUP were 20.5, 60, and 512.5 days, respectively.

Of the 25 cases, four remained untreated for more than 10 years, and the high mean DUP value is attributable to these outliers. A 2005 study re-analyzed the participants of the DOSMeD study [27], reporting a mean DUP of 9.9 months, with first, second, and third quartiles of DUP of 1, 4, and 12 months, respectively. Comparing the first and second quartiles between this 2005 study and our study shows that our findings for DUP were shorter.

As mentioned above, various factors affect the incidence rates of schizophrenia. Several studies have shown that the number of individuals diagnosed with schizophrenia may have decreased compared with findings in previous decades. Söderlund et al [28]. examined 210,000 individuals living in Stockholm from 1955 to 1967 and showed a gradually decreasing number of cases with schizophrenia and other types of psychosis (incidence rate of schizophrenia: 4.0/10,000 in 1955 and 1.9/10,000 in 1967). Kühl et al [29]. examined the incidence rate of schizophrenia and schizophrenia spectrum disorders from 2000 to 2012 in Denmark, finding significant decreases among those aged 33 years and older. In Japan, Fuse-Nagase et al [30]. investigated the percentage of students who took a leave of absence or withdrew from school because of schizophrenia from 1986 to 1987, from 1994 to 1995, and from 2013 to 2014 at 11 universities with 30,000–50,000 students. They found that this percentage declined over time. However, another report suggested the possibility of an increase in the incidence rate of early-onset schizophrenia [31], and a systematic review and meta-analysis presented evidence showing that there may have been no long-term change in the incidence rate of psychosis [7]. Therefore, it cannot be clearly concluded that there have been changes in the worldwide incidence rate of schizophrenia.

The current study has several limitations. First, differences in the definition of "psychosis" (broad diagnostic definition) make a precise comparison between the present study and the DOSMeD study difficult. Second, some findings of our study, including the age at onset and the male-to-female ratio, are not consistent with previous studies, and it is possible that not all new-onset cases of psychosis occurring during the study period were identified.

The results of the DOSMeD study suggested that there were no regional differences worldwide in the incidence rate of schizophrenia; however, it is currently recognized that the incidence rates of psychosis and schizophrenia differ depending on the region and environment [32,33]. In Japan, there has been some discussion regarding whether the incidence rates of new-onset psychosis and schizophrenia have changed or remained stable over the years [30], but this is the first study to present evidence showing no obvious change in the incidence rate of schizophrenia (restrictive diagnostic definition) compared with the situation about 30 years ago.

In future research on changes in the incidence rates of psychosis and schizophrenia, we will examine this rate over a longer period than the present 1-year investigation. It would also be useful to compare the incidence rates of multiple cities with environments that differ from that of Nagasaki in future work.

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