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# Reduced prevalence of cardiovascular disease and metabolic syndrome-related disorders among Japanese long-term inpatients with schizophrenia

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## ABSTRACT

**Purpose:** Individuals with schizophrenia have a vastly reduced lifespan compared with the general population; comorbid cardiovascular disease (CVD) is the leading cause of death for them. Furthermore, these individuals are more likely to have metabolic syndrome-related disorders (MSDs), which increase CVD risk. We examined the medical records of long-term inpatients with schizophrenia to identify methods for preventing CVD and MSDs.
**Method:** A retrospective survey was conducted on 56 inpatients with schizophrenia. The prevalence rates of CVD and MSDs among inpatients with schizophrenia were compared with Japanese general population data from the 2010 National Health and Nutrition Examination Survey. Then, we compared the variables influencing CVD and MSDs between first- and second-generation antipsychotic drug groups.
**Results:** The prevalences of hyperlipidemia, diabetes mellitus, hypertension, myocardial infarction, and cerebral hemorrhage among individuals with schizophrenia were lower than those among the Japanese general population. This effect is likely attributable to the nursing care offered to individuals with schizophrenia, which includes dietary advice, moderate exercise support, and body weight and blood pressure measurement. Medication did not correlate with CVD or MSD prevalence.
**Discussion:** Long-term hospitalization appeared to be particularly useful in preventing CVD and MSDs; thus, nursing care equivalent to that provided in hospitals can reduce the prevalence of CVD and MSDs among patients with schizophrenia. Antipsychotic drugs might have only a minor influence on CVD and MSD prevalence with reliable nursing care. Japanese psychiatric personnel should attend to outpatients with schizophrenia, as this population is increasing and receives less care than do inpatients.

***Keywords: schizophrenia, cardiovascular disease, metabolic syndrome-related disorders, antipsychotic drugs, nursing care***

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## INTRODUCTION

The average lifespan of individuals with schizophrenia is 20–25 years shorter than that of individuals without schizophrenia [1-6]. Previous studies have revealed that comorbid cardiovascular disease (CVD) is the leading cause of death among patients with schizophrenia [7, 8]. The most notable contributor to the high CVD prevalence among individuals with schizophrenia is the higher likelihood of metabolic syndrome-related disorders (MSDs), such as hyperlipidemia (HL), diabetes mellitus (DM), and hypertension (HT), all of which increase CVD risk [9-11]. Antipsychotic drugs also substantially increase the likelihood of MSDs and CVD.

Previous studies have identified several risk factors for HL and DM among individuals with schizophrenia, in particular factors related to their intemperate lifestyle

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such as an unbalanced diet and excessive drinking and smoking [12, 13]. Brown et al. [14] reported that individuals with schizophrenia exercise extremely infrequently, which can cause HL, DM, and obesity. Gurpegui et al. [15] reported that outpatients with schizophrenia had an obesity rate of 90.4% and an extremely high smoking rate. Several other previous studies have reported similarly improper dietary habits among outpatients with schizophrenia [16-19].

Antipsychotic drugs also affect the onset of CVD. Jerrell et al. [20] reported that prescribing several antipsychotic drugs simultaneously leads to a significantly higher rate of CVD as opposed to prescribing a single drug. Joukamma et al. [21] reported that relative death risk increased significantly with each one-dose increase in antipsychotics. In particular, these drugs—specifically, multi-acting receptor-targeted antipsychotics (MARTAs) such as olanzapine and quetiapine—can cause weight gain, HL, and DM, because they have a strong affinity for histamine H1-receptors and a severe sedative effect.

There are two issues unique to Japanese individuals with schizophrenia that may increase their risk of developing CVD. First, the schizophrenia population is aging along with the general population in Japan; indeed, societal aging is occurring more rapidly in Japan compared to many other countries. In 2007, the proportion of elderly individuals in the Japanese general population was over 21%, thereby making Japan a super-aging society according to UN criteria. Several studies have reported the relation between CVD risk and aging [22, 23]. The second issue pertains to the recent mental health policy enacted by the Japanese government, which has changed routine care for schizophrenia from hospitalization to out-patient care. In the former mental health policy, individuals with schizophrenia were hospitalized in psychiatric wards for long periods, which was similar to the system in place in Europe and the US. The change in this policy, which reduces the daily life care for individuals with schizophrenia, will likely lead to an increase in the prevalence of CVD and the number of deaths due to CVD in these patients.

We conducted a retrospective survey of medical records of individuals with chronic schizophrenia in long-term hospitalization to clarify the causes of CVD in this population. We predicted that aging, unhealthy lifestyles, and antipsychotic drugs would have strong positive influences on the prevalence of CVD and MSDs. The primary objective was to compare the prevalence of CVD and MSDs between individuals with schizophrenia and the general population. The secondary objective was to analyze the influence of pharmacotherapy (i.e., antipsychotics) on CVD and MSD risk.

## SUBJECTS AND METHODS

### *Subjects*

Fifty-six inpatients with schizophrenia (23 males, 33 females) who had been hospitalized for over 5 years in the chronic ward at Showa University Karasuyama Hospital as of April 1, 2012 were selected for this study.

### *Outcome measures*

Age at survey date and hospital admission date, duration of disease and hospitalization time for schizophrenia, smoking behavior and alcohol consumption at time of hospital admission, and weight (kg) and body mass index (BMI, $kg/m^2$) at hospital admission and every 5 years thereafter were included as demographic variables. Weight was checked in the same month (or within 2 months) of the date of hospital admission.

To compare the prevalence of CVD and MSDs between individuals with schizophrenia and the Japanese public, we utilized data from the Japan National Health and Nutrition Examination Survey 2010, which was conducted by the Ministry of Health, Labour and Welfare. We investigated the following items at hospital admission and every 5 years thereafter: prevalence of HL, DM, HT, angina pectoris (AP), myocardial infarction (MI), arteriosclerosis obliterans (ASO), cerebral infraction (CI), cerebral hemorrhage (CH), subarachnoidal hemorrhage (SAH), and deep-vein thrombosis (DVT).

To investigate the relationship between CVD and MSDs and differences in antipsychotic medication, we extracted the type, number, and dosage (chlorpromazine equivalents, mg) of antipsychotic drugs from patient medical records. The 2008 equivalence chart of Inagaki and Inada was used to calculate antipsychotic drug dosage.

For the data analysis, we designated participants who had taken second-generation antipsychotic drugs (SGAs) for more than 5 years as the SGA group, and we designated participants who had taken first-generation antipsychotics (FGAs) for less than 5 years as the FGA group. Participants could only take FGAs before 1996, which is when risperidone was introduced into Japan. The SGA group consisted of those who eventually made the switch to either exclusively SGA or both SGA and FGA at the

discretion of the doctor. In contrast, the FGA group had never taken SGAs or had only used them temporarily. Accordingly, we assumed that the SGA group was strongly influenced by the SGAs, while this influence was minimal in the FGA group. We compared the following variables at hospital admission and every 5 years thereafter between the FGA and SGA groups: weight (kg), BMI (kg/m$^2$), the prevalence of CVD and MSDs, and number and dosage of antipsychotic drugs.

***Statistical methods and ethical considerations***

SPSS 19 was used to compare the FGA and SGA groups via chi-square tests, t-tests, and univariate Cox regression analysis.

This study was approved by the Medical Ethics Committee of Showa University School of Medicine, and all patient data were made anonymous. We paid particular attention to personal information protection.

## RESULTS

Almost all participants had been hospitalized in young adulthood, and most had a hospitalization duration of over 30 years. At the time of hospitalization, about 25% of participants were smokers, whereas only 3.6% consumed alcohol. Although approximately 40% of participants had a BMI exceeding 25 kg/m$^2$ at one point during the study period, it ultimately returned to a normal range. Five (20%) participants in the SGA group had taken only SGAs. The average age at date of survey in the FGA group was significantly higher than it was in the SGA group. The anamnestic rate of BMI over 25 kg/m$^2$ was significantly higher in the FGA group than it was in the SGA group, contrary to expectations (Table 1).

**Table 1.** Participant demographics.

| Measure | Total (n = 56) | FGA group (n = 31) | SGA group (n = 25) | P-value |
|---|---|---|---|---|
| Sex, n | | | | NS |
| Male | 23 | 13 | 10 | |
| Female | 33 | 18 | 15 | |
| Age, y | | | | |
| at date of survey | 63.9 ± 11.2 | 67.3 ± 8.8 | 59.8 ± 12.7 | < 0.05 |
| at date of hospital admission | 33.8 ± 13.5 | 29.4 ± 13.2 | 39.2 ± 12.1 | < 0.01 |
| Duration of illness, y | 40.1 ± 12.0 | 45.5 ± 10.2 | 35.2 ± 11.8 | < 0.001 |
| Duration of hospitalization, y | 30.2 ± 15.0 | 37.9 ± 13.2 | 20.6 ± 11.2 | < 0.0001 |
| Rate of tobacco use (%)* | 25 | 25.8 | 24 | NS |
| Rate of alcohol use (%)* | 3.6 | 3.2 | 4 | NS |
| Weight (kg)* | 57.5 ± 10.9 | 59.7 ± 10.9 | 54.8 ± 10.6 | NS |
| BMI (kg/m$^2$)* | 22.7 ± 3.2 | 23.6 ± 3.4 | 21.6 ± 2.7 | < 0.05 |
| Anamnestic rate of BMI over 25 (%)** | 46.4 | 64.5 | 24 | < 0.005 |
| Prescribing pattern of SGAs | | | | |
| 1 | | | 3 | |
| ≥ 2 | | | 2 | |
| FGA and SGA combination | | | 20 | |
| Antipsychotic dose to chlorpromazine equivalents per day (mg/day)** | 665.9 ± 495.1 | 668.4 ± 507.5 | 662.3 ± 489.6 | NS |
| Number of antipsychotic drug prescriptions per day (n/day)** | 1.65 ± 0.56 | 1.56 ± 0.41 | 1.76 ± 0.69 | NS |

Notes. Demographic information for the subject. Values are mean ± SD unless otherwise specified. NS = not significant at an alpha of 0.05. * at hospitalization; **during whole time period.
BMI = body mass index; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic.

The prevalence rates of HL, DM, HT, MI, and CH were lower for participants (mean age = 63.9 years) than for the general Japanese population in their 60s (Table 2). The data for the general Japanese population in their 50s and 70s are shown for reference.

There were no remarkable changes in participants' BMI from the date of hospital admission to 30 years after admission (Figure 1). Further, we noted that many medical records included dietetic therapy, exercise therapy, and daily life guidance against weight gain. Unexpectedly, at the final survey, the average BMIs of both the FGA and SGA groups had clearly decreased. According to the medical records, weight loss caused by aging or somatasthenia contributed to this outcome.

**Table 2**. Prevalence of cardiovascular disease and metabolic syndrome-related disorders among subjects and Japanese public.

| Group | HL | DM | HT | AP | MI | ASO | CI | CH | SAH | DVT |
|---|---|---|---|---|---|---|---|---|---|---|
| All patients, % **(n)** | 19.6 (11) | 14.3 (8) | 16.1 (9) | 3.6 (2) | 0 | 1.8 (1) | 0 | 1.8 (1) | 0 | 1.8 (1) |
| FGA group, % (n) | 19.3 (6) | 19.3 (6) | 19.3 (6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SGA group, % (n) | 20.0 (5) | 8.0 (2) | 12.0 (3) | 8.0 (2) | 0 | 4.0 (1) | 0 | 4.0 (1) | 0 | 4.0 (1) |
| **Japanese public** | | | | | | | | | | |
| 60s, % (n) | 24.3 (250) | 17.4 (178) | 62.0 (667) | 3.6 (62) | 1.9 (32) | * | * | 5.9 (100) | * | * |
| 50s, % (n) | 14.6 (95) | 9.6 (62) | 44.9 (312) | 1.8 (23) | 0.7 (8) | * | * | 2.2 (29) | * | * |
| 70s, % (n) | 31.3 (326) | 19.1 (198) | 76.5 (860) | 7.9 (142) | 4.4 (78) | * | * | 9.6 (173) | * | * |

Notes. Data of healthy individuals were obtained from the National Health and Nutrition Examination Survey in Japan, 2010.

*Arteriosclerosis obliterans, cerebral infraction, subarachnoidal hemorrhage, and deep-vein thrombosis were not investigated in the National Health and Nutrition Examination Survey, 2010.

HL = hyperlipidemia; DM = diabetes mellitus; HT = hypertension; AP = angina pectoris; MI = myocardial infarction; ASO = arteriosclerosis obliterans; CI = cerebral infraction; CH = cerebral hemorrhage; SAH = subarachnoidal hemorrhage; DVT = deep-vein thrombosis.

Most participants took one or two antipsychotic drugs. There was no difference in the number of drugs between the two groups across most of the survey period (Figure 2). However, because there were only three subjects in the SGA group at the final survey, there was an apparent increase in the number of antipsychotic drugs in the SGA group. In other words, the lack of data from the SGA group at the final survey influenced the analysis, which showed a nonsignificantly higher average number of drugs in the SGA group than in the FGA group.

On the other hand, there were significant differences in dosage (chlorpromazine-equivalents) at 10, 15, and 30 years after admission (Figure 3). The dosage in the FGA group increased by 3 times and that in the SGA group by 1.8 times from hospital admission to the final survey. The SGA group showed a particularly violent fluctuation in dosage. The reason for the increased dosage in the FGA group was to stabilize patients' mental states. In contrast, the change in the SGA group was due to a reduction in the sample size over time.

At hospital admission, the top five antipsychotic drugs used were levomepromazine (28.4%), chlorpromazine (27.6%), haloperidol (25.9%), perphenazine (3.4%), and propericiazine (3.4%). At the final survey date (April 1, 2012), the top five antipsychotic drugs used were olanzapine (22.9%), risperidone (14.3%), haloperidol (13.1%), levomepromazine (12.4%), and chlorpromazine (9.2%).

***Survival analysis of CVD and MSD***

Cox regression analysis indicated that the adjusted survival rate of CVD showed no significant differences between the groups, but there was an apparently meaningful trend (Exp(B) = 0.07 [confidence interval (CI): 0.01–1.44], P = 0.08) (Figure 4). The SGA group did not exhibit CVD onset before taking SGAs.

The adjusted survival rate of MSDs showed no significant difference between the FGA and SGA groups (Exp(B) = 0.46 [CI: 0.17–1.26], P = 0.13) (Figure 5).

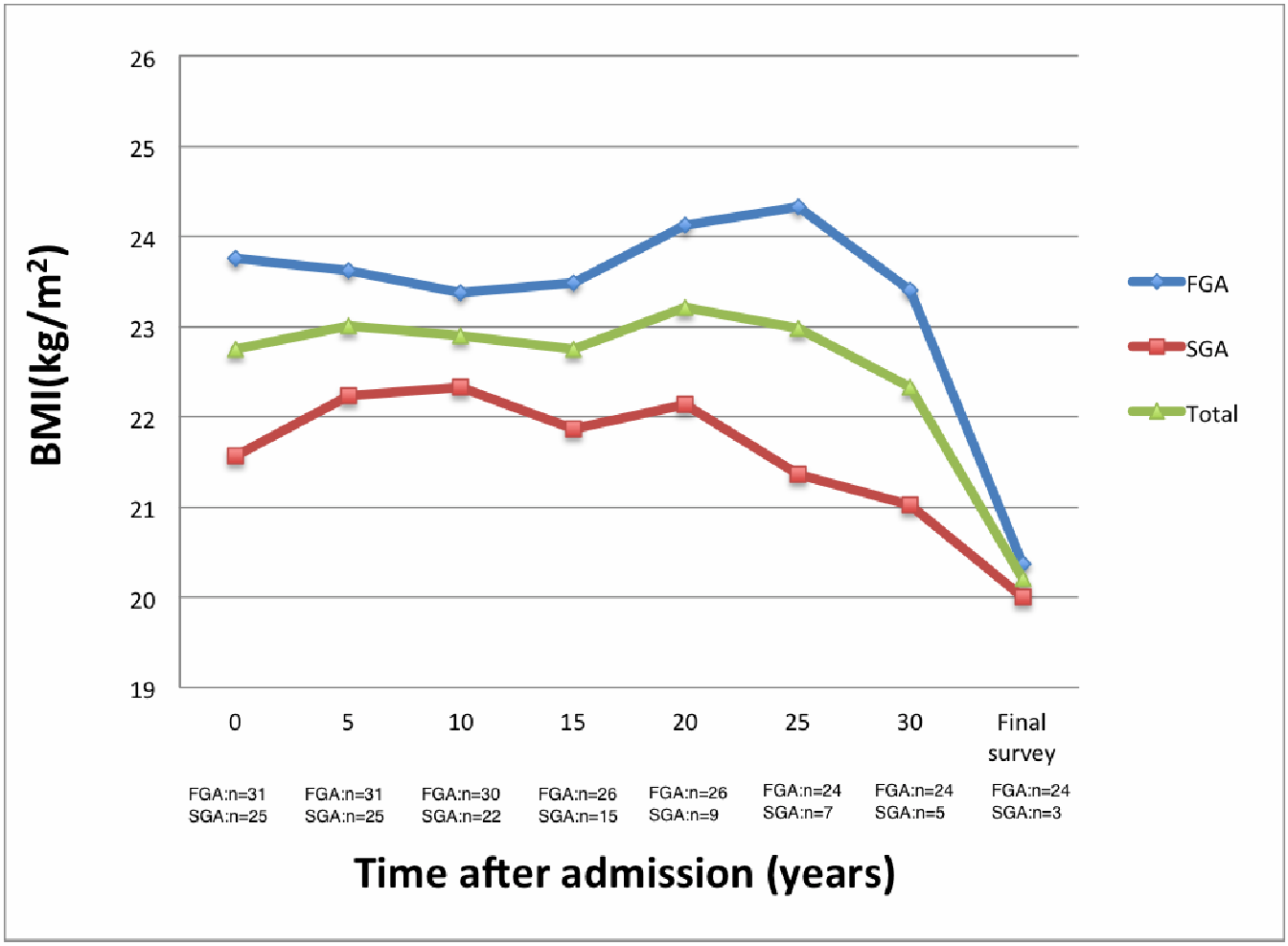


**Figure 1.** Change in BMI during hospitalization for the FGA group, the SGA group, and all participants from date of hospital admission to final survey date.

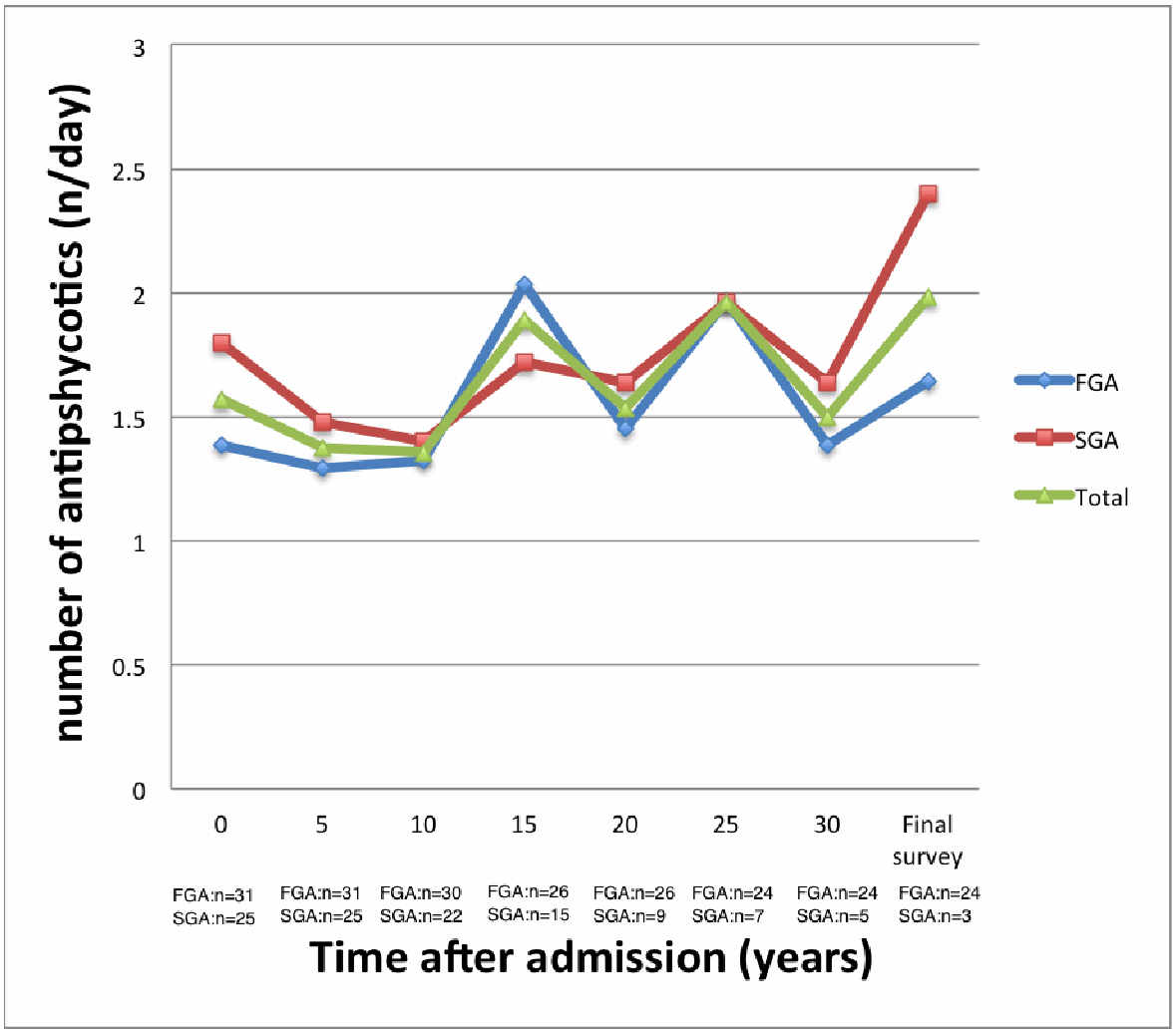


**Figure 2.** Change in number of antipsychotic drugs for the FGA group, the SGA group, and all participants from date of hospital admission to final survey date.

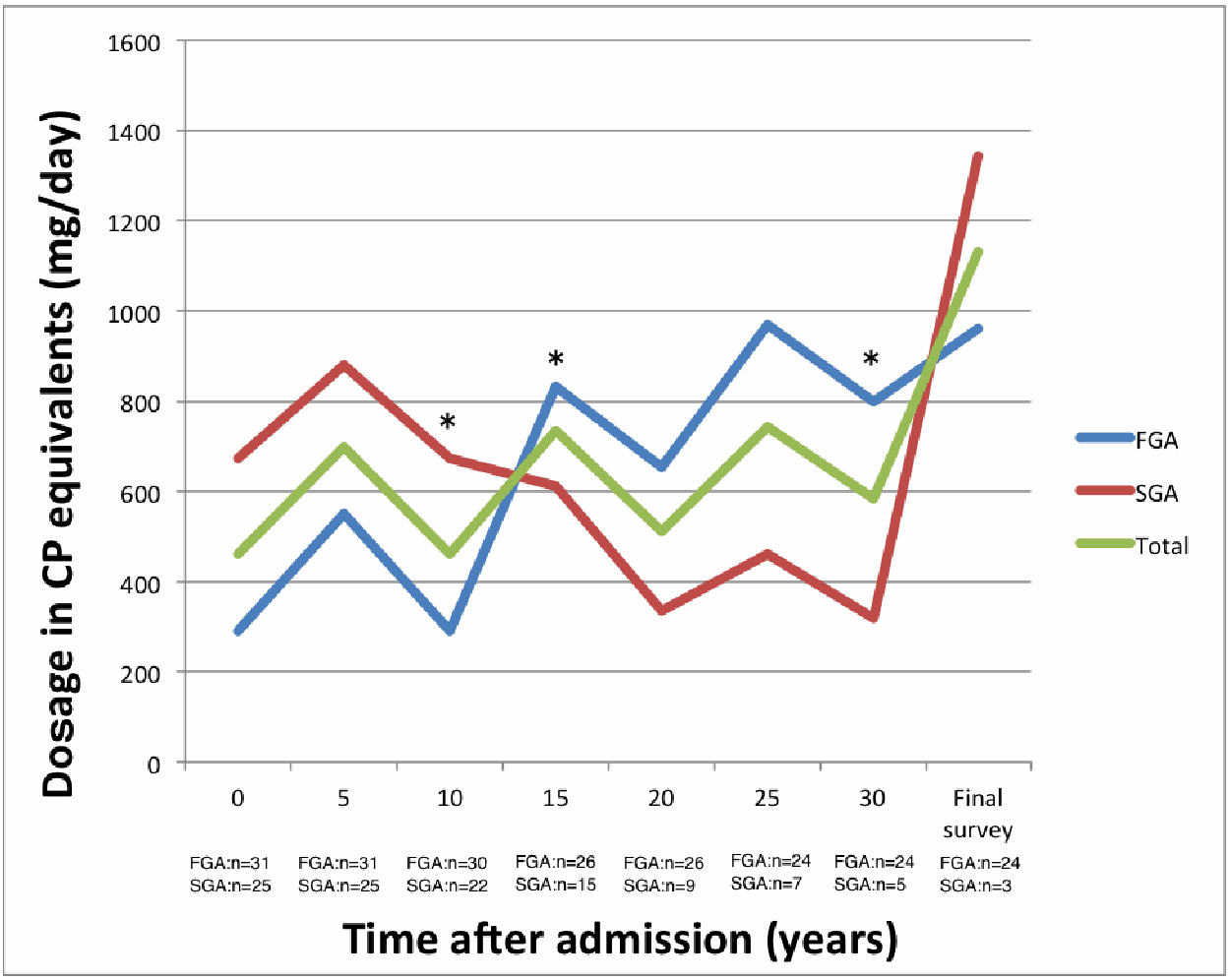


**Figure 3.** Change in antipsychotic dose to chlorpromazine equivalents for the FGA group, the SGA group, and all participants from date of hospital admission to final survey date.

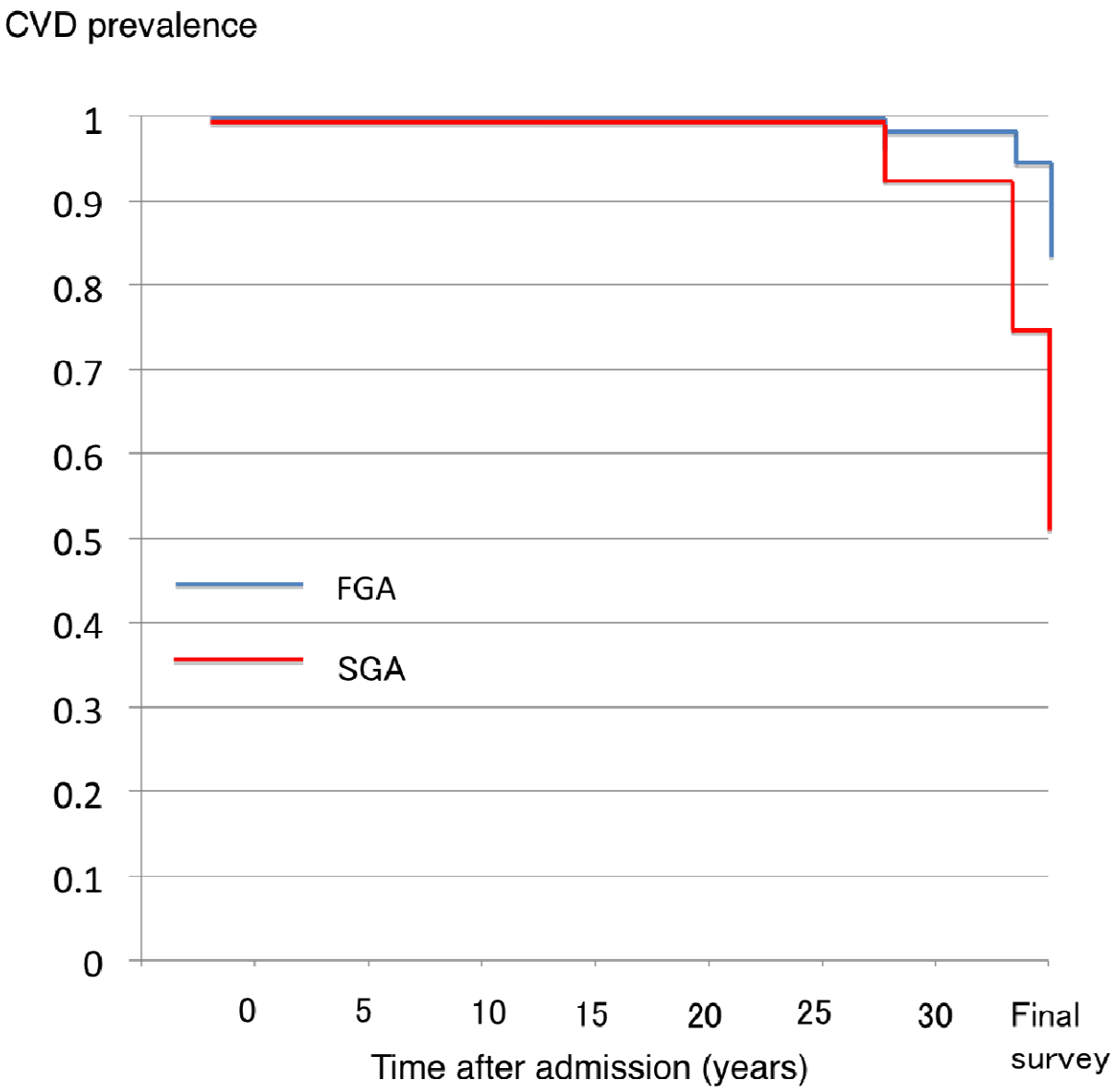


**Figure 4.** Survival function for cardiovascular disease between the FGA and SGA groups after adjusting for significant demographic variables.

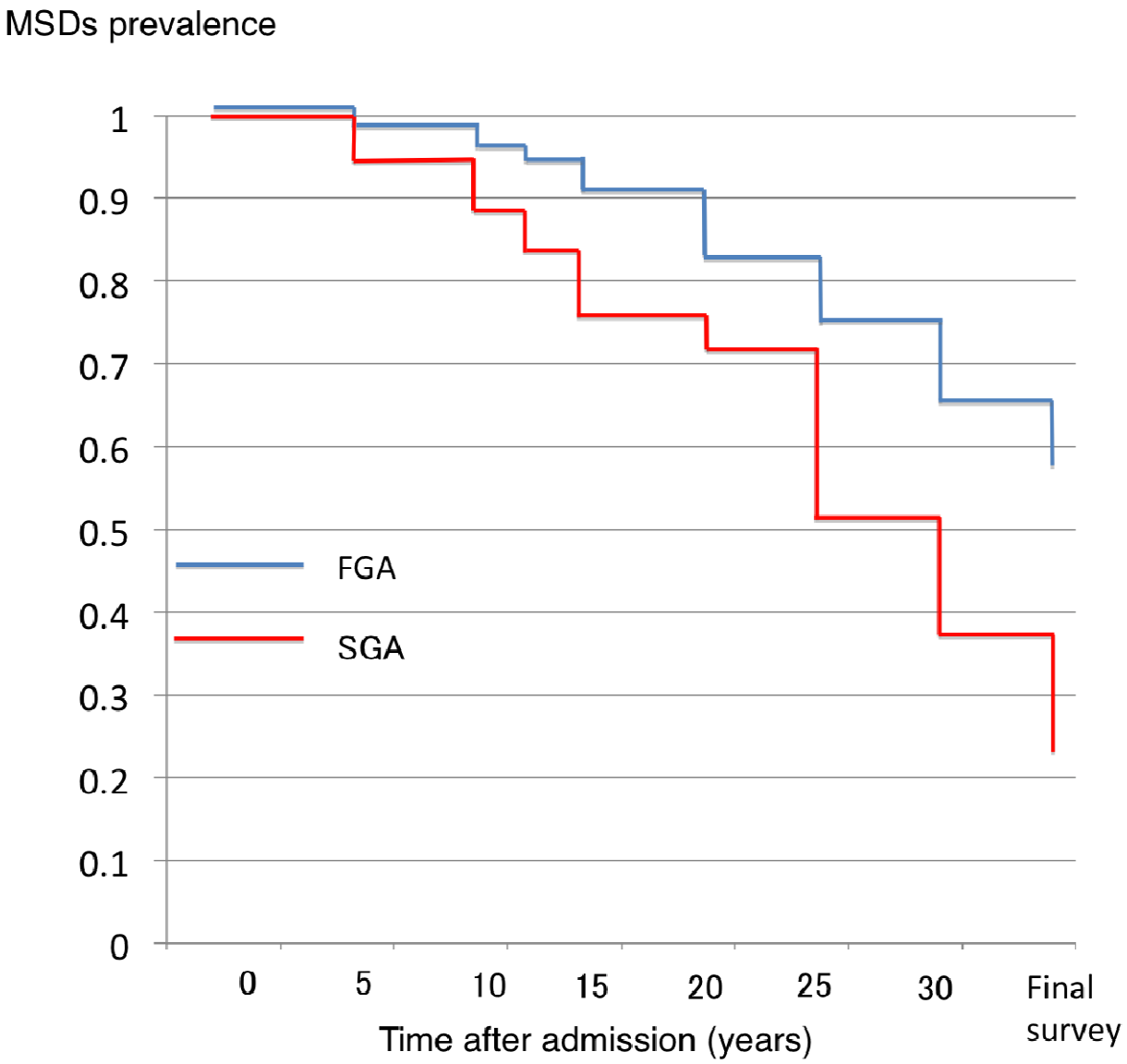


**Figure 5.** Survival function for metabolic syndrome-related disorders between the FGA and SGA groups after adjusting for significant demographic variables.

## DISCUSSION

We conducted a retrospective survey of the medical records in a chronic ward to identify means of preventing CVD and MSDs among individuals with schizophrenia.

We predicted that the prevalence of CVD and MSDs among inpatients with schizophrenia would be higher than in the general population, but our findings revealed the opposite. These contrary findings can be explained by the fact that long-term inpatients with schizophrenia undergo constant nursing care during hospitalization. Thus, it appears that long-term hospital care is particularly useful for the prevention of CVD and MSDs among individuals with schizophrenia. Furthermore, antipsychotic drug type appears to have only a minor influence on CVD and MSDs under reliable care.

The best way to prevent the onset of CVD and MSDs is to maintain a healthy lifestyle—particularly a lifestyle akin to that in long-term hospitalization, wherein food, smoking, and alcohol consumption are all tightly regulated. Mikami et al. [24] and Kurosawa et al. [25] have reported that fasting blood glucose level improves when obese patients with schizophrenia are hospitalized.

The prevalence rates of HL and DM among inpatients with schizophrenia were 19.6% and 14.3%, respectively, which are significantly lower than those among the same-age general population. This is again likely

attributable to nursing care, which helps hospitalized individuals maintain a healthy body weight and blood pressure. Medical records indicated that nurses in the chronic ward planned appropriate care for body weight and blood pressure control. In the case of diet and exercise therapy, nurses helped individuals with schizophrenia contact doctors, nutritionists, and occupational therapists and provided dietary advice and moderate exercise support, all of which seemed to be effective for preventing the onset of CVD and MSDs. Thus, regular check-ups for body weight and blood pressure for both inpatients and outpatients with schizophrenia appear to be the best, cheapest, and simplest way of reducing the prevalence of CVD and MSDs.

The impaired cognitive function and negative symptoms inherent to schizophrenia are both risk factors for increased rates of CVD and MSDs. Stanley et al. [26] reported that poor health control and unhealthy habits among individuals with schizophrenia contribute to the onset of chronic diseases and increased mortality rates. Many individuals with schizophrenia cannot consistently care for themselves due to impaired cognitive function. Hospitalization may mitigate the effects of impaired cognitive function and negative symptoms as a function of appropriate nursing care.

It is important to consider how antipsychotic drugs affect the metabolic system and onset of CVD. Our study found that 20 (80%) participants in the SGA group had taken both SGAs and FGAs, and the rest had only taken SGAs. We should have accounted for the likelihood that the SGA group's results were affected by not only the SGAs but also by the FGAs, which they had taken for decades before switching.

We hypothesized that patients taking SGAs would show greater body weight gain and higher prevalence rates of HL and DM compared to those taking FGAs. However, we found that medication differences were not correlated with the prevalence of CVD or MSDs. According to the Cox regression analysis, the adjusted survival rate of CVD and MSDs did not differ significantly between the FGA and SGA groups. Again, our results could be accounted for by the long-term hospitalization, which allowed participants to maintain a good physical condition. The medical records indicated that the interventions managed weight and blood pressure well for both medication groups. Using antipsychotic drugs while following a healthy lifestyle may minimize the adverse effects of schizophrenia.

Our study found that the diet and exercise therapy of Karasuyama Hospital, as well as nursing care, might be very useful and effective for the prevention of CVD and MSDs. To the best of our knowledge, there are no existing special diets or exercise plans to prevent CVD and MSDs among people with schizophrenia. A Cochrane review found that modest weight reduction can be achieved in people with schizophrenia via selective pharmacological and psychological interventions [27]. Exercise programs are feasible and may improve mental well-being and overall outcomes among patients with schizophrenia [28]. In the diet therapy employed by Karasuyama Hospital, the doctor determines a nutrition plan in collaboration with the nutritionist, patient, and nurse based on appropriate calorie intake. Additionally, nutritionists conduct nutrition assessments for each patient once every 3 months. Participants are also provided with a therapeutic diet to manage their DM, HT, and HL, and receive both individual and group-based nutrition lectures. Finally, nutritionists check patients' satisfaction with the flavor and taste of their food four times a year and reevaluate patients' diets according to the results of these checks. In the exercise therapy employed by Karasuyama Hospital, participants meet with an occupational therapist for about 30 minutes at a time in both individual and group exercise sessions. An appropriate exercise regimen for each individual is determined by the doctor in collaboration with the occupational therapist, patient, and nurse. For example, light exercises such as table tennis and dumbbell gymnastics can be prescribed for youths, yoga and mat stretching for women, and stretching in a sitting position for seniors. Due to their impaired cognitive function, individuals with schizophrenia must be provided with suitable and understandable diet and exercise plans.

In Japan, the prevalence of CVD and MSDs among individuals with schizophrenia may be increasing at a much faster rate compared to other countries because of the following reasons. First, as a super-aging society, the rate of population aging in Japan is extremely rapid. Second, recent changes to Japanese mental health policy has led to a transition from hospitalization to outpatient care for individuals with schizophrenia. As such, our study is very valuable because rates of long-term hospitalization in Japan are diminishing. Finally, Japan has a high rate of co-prescribing several antipsychotic drugs [29, 30]. These factors are unique to Japan, which means it is necessary to tailor strategies to resolve these Japan-specific problems. For instance, we recommend teaching healthy food habits, conducting regular blood examinations, and promoting physical management

(e.g., measurements of body weight and blood pressure). These care measures would be effective for both inpatients and outpatients.

There are, however, several limitations to be considered for the interpretation of our study findings. First, the sample was relatively small. Thus, our findings on the number and amount of antipsychotics, especially at the final survey, may have been influenced by the small sample. Second, data might be characteristically different depending on the number of years of hospitalization due to divergent social backgrounds and differences in the characteristics of hospitalization. That is, individuals hospitalized 30 years ago may have vastly different experiences from those hospitalized more recently. Third, we only used inpatient data, due to a lack of sufficient medical records for outpatients with chronic schizophrenia. Finally, we did not include data on long-term hospitalized inpatients who required intense physical treatment, those who had died, or those who had switched hospitals.

## CONCLUSIONS

The continuous nursing care, diet education and exercise therapy characteristic of long-term hospitalization are useful for reducing the prevalence of CVD and MSDs in schizophrenia. With a healthy lifestyle, any type of antipsychotic drug may effectively minimize the adverse effects associated with schizophrenia, such as CVD and MSDs. In the future, Japanese psychiatric personnel should pay attention to preventative health measures among outpatients with schizophrenia, a population that will continue to grow due to recent changes in Japanese mental health policy.

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