Global Health & Medicine. 2020; 2(3):178-183.
BRIEF REPORT
DOI: 10.35772/ghm.2020.01008

Metabolic changes of Japanese schizophrenic patients transferred from hospitalization to outpatients

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Abstract: It is well known that schizophrenic patients have high incidence of metabolic syndrome and life-style related diseases. There are reports that the rates of these diseases are increased more in outpatients than inpatients, but are also reports that the rates are not different between both patient groups. These differences might be related to the length of hospitalization. Hospitalization of Japanese psychiatric patients is about 300 days, much longer than western countries (below 50 days). Therefore, we investigated lipid and glucose metabolism of schizophrenic patients transferred from hospitalization to outpatients at Kohnodai hospital with a mean of 80 days hospitalization period to clarify metabolic characteristics in Japanese patients. Study participants were 144 schizophrenia inpatients and 109 outpatients at Kohnodai Hospital. These 109 outpatients were followed for approximately 2 years, without changes of administrated drugs, and from 144 inpatients. Data from outpatients were obtained at 6 months, 1 year and 2 years after their discharge. Outpatients 2 years after discharge had significantly higher levels of total cholesterol, triglyceride and non-high density lipoprotein (non-HDL) cholesterol than inpatients, accompanied with an increase of body weight. Serum HDL-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels had no significant difference between both groups. These lipids and glucose levels also showed the same tendency in outpatients 0.5 year and 1 year after discharge as those after 2 years. We found that schizophrenic patients in our study appeared to have changes of lipid metabolism 2 years after their discharge, but no significant changes of glucose metabolism, such as FPG and HbA1c.

***Keywords*:** schizophrenia, inpatients, glucose metabolism, lipid metabolism, outpatients

Introduction

There are many reports of increased death rate and short life expectancy in psychiatric patients (*1,2*). It is reported that atherosclerotic diseases play an important role in their cause of death (*3,4*). Schizophrenic patients are shown to have an increased ratio of life-style related diseases such as, hypertension, diabetes, dyslipidemia and so on (*5,6*). They also have a tendency towards unhealthy lifestyles, which are shortness of exercise, inappropriate diet customs, and increased smoking rates (*7*). These lifestyles are thought to be one of the causes of developing atherosclerosis.

Meta-analysis of prevalence of metabolic syndrome and metabolic abnormalities of schizophrenia by Mitchell *et al.* (*8*) showed that the rates of metabolic syndrome had minor differences in countries (the United States (32.5%), Finland (34.5%), Spain (30.2%) and Turkey (30.1%)), but had almost no differences between outpatients (31.8%) and inpatients (30.4%), and males (34.8%) and females (34.8%). It was also reported that the rates of the diagnosis of diabetes among schizophrenia patients were similar in either outpatients or inpatients, and were approximately 2 times compared with the rates of diabetes among controls (*9*).

Sugawara *et al.* and Sugai *et al.* (*10,11*) investigated in Japan the incidence of metabolic syndrome, obesity, hypertension, diabetes and dyslipidemia in schizophrenic patients. There have been few previous studies that compare the lipid and glucose levels in outpatients with those of inpatients except reports from Mitchell *et al.*

and Osborn *et al.* (*8,9*). They reported that the incidence of these life-style related diseases and serum levels of triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and fasting plasma glucose (FPG) in Japanese outpatients were higher than those in inpatients (*10-12*). For example, the rate of metabolic syndrome was 34.2% and 13.0% in outpatients and inpatients, respectively. The mean length of hospitalization of Japanese psychiatric patients was about 300 days in 2011 much longer than such patients in Australia, Europe and North America (mean lengths are below 50 days) (*13*). The long duration of hospitalization may affect the metabolic condition of the patients because of controlled meals, exercise and so on in hospitals. The mean hospitalization time of schizophrenia is approximately 80 days in the psychiatric department of Kohnodai hospital. This is an intermediate hospitalization time between traditional Japan, and Europe and North America.

In this present study, we investigated the similarities and differences of lipid and glucose metabolism in the same patients transferred from hospitalization to outpatients at the psychiatric department of Kohnodai hospital to clarify the metabolic changes of outpatients and inpatients in Japan.

Patients and Methods

Study subjects

The diagnosis of psychiatric disorder was established as follows. Trained psychiatrists carried out a diagnostic interview of the patients and reviewed information from the patients' relatives. A diagnosis was made using the ICD-10 classification. Then, several psychiatrists discussed the assessment of the diagnosis and treatments in every patient at the conference opening every week. We picked up schizophrenia (F20), acute and transient psychotic disorders (F23) and schizoaffective disorders (F25) as schizophrenia group (F2 group).

This study was performed from January 2016 to December 2018 at Kohnodai Hospital, National Center for Global Health and Medicine. Study participants were 144 of F2 group inpatients (62 males and 82 females) and 109 outpatients (45 males and 64 females) in the Psychiatry Department at Kohnodai Hospital. 109 outpatients were followed for approximately 2 years from 144 discharged patients. We selected these 109 persons without changes of administered drugs, which were psychotropic, anti-dyslipidemic and hypoglycemic drugs during these 2 years. Then, these outpatients were the same inpatients except for 35 non-selected persons.

The study protocol was approved by the Ethics Committees of Chiba University (No.182) and the National Center for Global Health and Medicine (No.1837). All participants were provided with a written informed consent form, and explanation and participation agreement were performed in accordance with the Declaration of Helsinki principles.

Diagnosis of somatic diseases in study participants

Diabetes mellitus was defined as hemoglobin A1c (HbA1c) over 6.5% and FPG over 126 mg/dL (*14*). High LDL-cholesterolemia (fasting serum LDL-cholesterol (LDL-C) ≥ 140 mg/dL) or low high density lipoprotein (low HDL)-cholesterolemia (fasting serum HDL-cholesterol (HDL-C) < 40 mg/dL) or hypertriglyceridemia (fasting TG ≥150 mg/dL) were described as dyslipidemia (*15*). Patients were also counted as diabetic if they used hypoglycemic drugs (insulins, glucagon-like peptide-1 receptor agonists, biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidines, dipeptidyl peptidase-4 inhibitors and sodium glucose transporter-2 inhibitors). Patients using statin and/or ezetimibe were counted as hyper LDL-cholesterolemia and those using fibrates were hypertriglyceridemia.

Data collections

Information on patients' demographic data was obtained from their medical records. Body mass index (BMI) was calculated by their height and weight. Blood samples were obtained from patients after 12 h starvation.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), total bilirubin (T-Bil), blood urea nitrogen (BUN) and creatinine (Cr) levels were measured using the consensus method of the Japan Society of Clinical Chemistry (JSCC) (*16*). Total cholesterol (TC), TG and FPG were assayed by enzymatic method and high density lipoprotein-cholesterol (HDL-C) was by direct method. LDL-C was calculated by Friedewald formula from TC, TG and HDL-C (TC-TG/5-HDL-C) and non-HDL cholesterol (non-HDL-C) was TC minus HDL-C. HbA1c was measured by the high performance liquid chromatography (HPLC) method. Estimated glomerular filtration rate (eGFR) was calculated by serum creatinine level, age and gender (*17*).

Data from outpatients were obtained at approximately 6 months, 1 year and 2 years after their discharge.

Statistics

Data from inpatients and outpatients were compared by paired *t* test.

Results and Discussion

Profile of study participants

Table 1 shows the profile of study patients. 109 outpatients were followed during 2 years without changes of administered drugs from 144 inpatients. The ratio of

male to female was 1:1.42 (45 persons: 64 persons) and the average age was 51.3 years old in outpatients. The ratio of hypertriglyceridemia was significantly higher in the outpatient group compared to the inpatient group.

Blood parameters of study participants in hospitalization and outpatients 2 years after their discharge

Table 2 shows serum blood levels of lipids and glucose, and liver and renal functions in patients with hospitalization (inpatients) and outpatients approximately 2 years after their discharge. We chose patients, which had blood parameters both during hospitalization and as outpatients 2 years after their discharge. Outpatients showed significantly higher levels of TC, TG and non-HDL-C than inpatients, accompanied with an increase of body weight and BMI. Serum HDL-C and LDL-C levels had no significant difference between inpatients and outpatients. Indicators of glucose metabolism, FPG and HbA1c were not significantly different in both groups.

Table 1. Profile of study participants

Variables	Inpatients	Outpatients
Cases (*n*)	144	109
Male	62	45
Female	82	64
Age, years (means ± SD)	49.3 ± 11.7	51.3 ± 11.7
Male	47.0 ± 11.2	49.0 ± 11.6
Female	50.9 ± 11.9	52.9 ± 11.7
Diagnosis of physical disorders (ratio)		
Diabetes mellitus	0.160	0.138
Dyslipidemia		
High LDL-cholestrolemia	0.264	0.284
Low HDL-cholesterolemia	0.209	0.202
Hypertriglyceridemia	0.210	0.358*

*indicates significant difference ($p < 0.05$) between inpatient and outpatient groups.

There were no significant differences in parameters of liver function, AST, ALT, γ-GTP and T-Bil between inpatients and outpatients. Concerning renal function, BUN, Cr and eGFR had no significant differences between both groups.

Changes of blood parameters of patients transferred from hospitalization to outpatient care 6 months, 1 year and 2 years after their discharge

Table 3 shows serum blood levels of lipid and glucose, and liver and renal functions in patients with hospitalization and outpatients approximately 6 months, 1 year and 2 years after their discharge. We chose patients, which had blood parameters at hospitalization and all these 3 points after their discharge. Outpatients from either point of 6 months, 1 year or 2 years after their discharge showed significantly higher levels of TC and TG compared with inpatients (Table 3-A). Serum non-HDL-C was significantly higher in outpatients from either point of 6 months or 1 year after their discharge than inpatients. However, serum LDL-C and HDL-C in outpatients were not significantly changed at either point compared with those in inpatients. There were also no significant differences of FPG and HbA1c between either point of outpatients and inpatients (Table 3-B).

As for liver function parameters, serum levels of AST, γ-GTP and T-Bil were not significantly different between inpatients and outpatients at 6 months, 1 year and 2 years after their discharge (Table 3-C). Serum ALT was only significantly increased in outpatients 1 year and 2 years after their discharge compared with inpatients. Concerning renal function, serum levels of BUN had no significant difference between inpatients and outpatients (Table 3-D). Serum Cr and eGFR also showed no significant differences between inpatients and outpatients except for 1 year after their discharge. Significant

Table 2. Blood parameters of study participants in hospitalization and outpatients

Variables	*n*	Inpatients	Outpatients	*p* value
TC (mg/dL)	89	190.1 ± 43.4	200.0 ± 44.3	0.0221
TG (mg/dL)	88	124.5 ± 93.6	168.3 ± 139.0	0.0026
HDL-C (mg/dL)	77	52.5 ± 16.8	52.2 ± 15.6	NS
LDL-C (mg/dL)	80	113.8 ± 37.8	115.5 ± 37.1	NS
Non-HDL-C (mg/dL)	77	138.8 ± 44.3	148.7 ± 45.7	0.0336
FPG (mg/dL)	91	113.4 ± 26.9	118.8 ± 31.8	NS
HbA1c (%)	91	5.83 ± 0.72	5.88 ± 0.78	NS
AST (IU/L)	96	33.9 ± 65.0	22.4 ± 12.6	NS
ALT (IU/L)	95	28.0 ± 27.9	26.4 ± 23.3	NS
γ-GTP (IU/L)	64	48.4 ± 67.6	57.4 ± 152.6	NS
T-Bil (mg/ dL)	73	0.610 ± 0.697	0.488 ± 0.230	NS
BUN (mg/ dL)	96	11.6 ± 5.55	11.4 ± 4.77	NS
Cr (mg/ dL)	96	0.691 ± 0.217	0.706 ± 0.237	NS
eGFR (mL/min)	96	87.6 ± 22.7	83.5 ± 19.7	NS
Body weight (kg)	28	68.1 ± 17.7	72.6 ± 16.4	0.0318
BMI (kg/m^2)	28	24.6 ± 5.48	26.3 ± 5.54	0.0292

Values are indicated as means ± SD. NS means no significant difference between inpatients and outpatients. It was approximately 2 years between blood examinations of inpatients and outpatients.

Table 3-A. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ lipids ~

Variables	*n*	Means ± SD (mg/dL)	*p* value
TC-0	42	183.1 ± 35.6	
TC-0.5	42	202.5 ± 39.6	0.0032
TC-1	42	200.6 ± 39.1	0.0028
TC-2	42	199.3 ± 40.9	0.0155
TG-0	39	107.9 ± 89.1	
TG-0.5	39	151.6 ± 95.5	0.0081
TG-1	39	151.6 ± 98.9	0.0200
TG-2	39	155.3 ± 121.2	0.0331
HDL-C-0	33	53.9 ± 17.9	
HDL-C-0.5	33	56.3 ± 14.5	NS
HDL-C-1	33	56.0 ± 16.4	NS
HDL-C-2	33	54.8 ± 16.4	NS
LDL-C-0	32	107.6 ± 35.1	
LDL-C-0.5	32	114.1 ± 32.0	NS
LDL-C-1	32	113.5 ± 32.6	NS
LDL-C-2	32	114.3 ± 31.4	NS
Non-HDL-C-0	32	133.0 ± 40.0	
Non-HDL-C-0.5	32	149.0 ± 41.6	0.0153
Non-HDL-C-1	32	144.9 ± 37.7	0.0483
Non-HDL-C-2	32	143.2 ± 34.2	NS

TC (TG, HDL-C, LDL-C or non-HDL-C)-0, -0.5, -1 and -2 mean serum TC (TG, HDL-C, LDL-C or non-HDL-C) levels at inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

Table 3-B. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ glucose ~

Variables	*n*	Means ± SD	*p* value
FPG-0	43	109.6 ± 20.3 (mg/dL)	
FPG-0.5	43	115.8 ± 23.8	NS
FPG-1	43	113.9 ± 20.1	NS
FPG-2	43	118.5 ± 26.8	NS
HbA1c-0	40	5.84 ± 0.56 (%)	
HbA1c-0.5	40	5.80 ± 0.44	NS
HbA1c-1	40	5.83 ± 0.48	NS
HbA1c-2	40	5.87 ± 0.61	NS

FPG (or HbA1c)-0, -0.5, -1 and -2 mean serum FPG (or HbA1c) levels as inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

Table 3-C. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ liver function ~

Variables	*n*	Means ± SD	*p* value
AST-0	38	21.3 ± 20.3 (IU/L)	
AST-0.5	38	19.2 ± 11.2	NS
AST-1	38	21.7 ± 9.12	NS
AST-2	38	20.8 ± 9.17	NS
ALT-0	38	20.4 ± 16.0(IU/L)	
ALT-0.5	38	22.4 ± 21.0	NS
ALT-1	38	25.9 ± 17.1	0.0096
ALT-2	38	25.3 ± 17.2	0.0329
γ-GTP-0	29	32.4 ± 39.6 (IU/L)	
γ-GTP-0.5	29	28.4 ± 26.3	NS
γ-GTP-1	29	28.9 ± 31.4	NS
γ-GTP-2	29	30.4 ± 25.3	NS
T-Bil-0	26	0.428 ± 0.277 (mg/dL)	
T-Bil-0.5	26	0.406 ± 0.199	NS
T-Bil-1	26	0.472 ± 0.176	NS
T-Bil-2	26	0.427 ± 0.254	NS

AST (ALT, γ-GTP or T-Bil)-0, -0.5, -1 and -2 mean serum AST (ALT, γ-GTP or T-Bil) levels as inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

Table 3-D. Changes of blood parameters of patients transferred from hospitalization to outpatient care ~ renal function ~

Variables	*n*	Means ± SD (mg/dL)	*p* value
BUN-0	48	11.3 ± 4.75	
BUN-0.5	48	11.4 ± 4.25	NS
BUN-1	48	11.3 ± 3.23	NS
BUN-2	48	11.3 ± 3.75	NS
Cr-0	48	0.647 ± 0.172	
Cr-0.5	48	0.667 ± 0.152	NS
Cr-1	48	0.681 ± 0.157	0.0307
Cr-2	48	0.660 ± 0.141	NS
eGFR-0	48	89.3 ± 23.3	
eGFR-0.5	48	84.4 ± 19.9	NS
eGFR-1	48	82.3 ± 19.2	0.0092
eGFR-2	48	84.7 ± 20.0	NS

BUN (Cr or eGFR)-0, -0.5, -1 and -2 mean serum BUN (Cr or eGFR) levels as inpatients, 0.5 year, 1 year and 2 years after their discharge, respectively. NS indicates no significant difference compared with the level of inpatients.

increasing Cr and decreased eGFR were observed in outpatients 1 year after their discharge compared with inpatients.

The present study shows that Japanese schizophrenic patients transferred from hospitalization to outpatient care have increased serum TC, TG and non-HDL cholesterol levels during 2 years after their discharge, but no changes of FPG and HbA1c levels for these 2 years.

In our study, serum TG level was significantly increased in outpatients than in inpatients accompanied with an increase of body weight and BMI in outpatients, similar to other Japanese reports (*10,11,18*). Recent reviews indicated that serum TG levels of schizophrenic inpatients were almost the same as controls, but those of outpatients were increased by 30-40% compared with controls (*19,20*). The differences of TG levels between outpatients and inpatients might be related to the circumstances of hospitalization, because serum TG levels are easily influenced by exogenous factors such as exercise and/or diets.

Cholesterol in the body is mainly derived from internal cholesterol synthesis (*21*). External diet uptake contributes to body cholesterol by only 10-30% (*22*). Furthermore, serum LDL-C level is regulated by VLDL synthesis in the liver and LDL-receptor uptake in various tissues (*23*). It is probable that serum LDL-C is hard to change by exogenous factors compared to serum TG. Serum LDL-C level of outpatients in our study was almost the same as in Sugai's paper (LDL-C: 115.5 mg/dL *vs.* 117.6 mg/dL, respectively) (*11*). But, those levels in inpatients were higher in our study than Sugai's paper (LDL-C: 113.8 mg/dL *vs.* 106.9 mg/dL,

respectively) (*11*). The mean hospitalization time is 80 days in Kohnodai hospital, which is much shorter than their report (mean hospitalization time is over 300 days). This long hospitalization might be related to changes of life-style and severity of psychotic symptoms, which induce weight loss and decreased synthesis of cholesterol (*18*). Therefore, these results suggest that there are some differences of lipid metabolism between inpatients and outpatients in Japan.

Serum TC contains mainly LDL-C, HDL-C and cholesterol of VLDL or remnant lipoproteins. Even though, LDL-C and HDL-C were almost the same levels between inpatients and outpatients, suggesting that VLDL and/or remnant lipoproteins are increasing in outpatients. This is one of the reasons why non-HDL-C level was increased in outpatients because cholesterol of VLDL and remnant lipoproteins are counted as non-HDL-C.

Serum HDL-C levels have complex mechanisms. Usually, serum high TG levels were accompanied with serum low HDL-C levels because TG and cholesterol are exchanged in HDL by cholesterol ester transfer protein (*24*). But, this is not the case. Outpatients showed high serum TG levels but no significant changes of serum HDL-C compared with inpatients. HDL-C metabolism in psychiatric patients still remains to be elucidated.

Concerning glucose metabolism, FPG and HbA1c levels were not significantly changed during the 2 years after their discharge (FPG: from 113.4 mg/dL to 118.8 mg/dL; HbA1c: 5.83% to 5.88%, inpatients to outpatients, respectively), this is different from Sugawara's report (*10*). FPG level of inpatients was 90.6 mg/dL in their report, which is lower than our study, in accordance with the long hospitalization time. That of outpatients in their report was 115.7 mg/dL, similar to our study. As described by Kanzaki *et al.* (*25*), FPG and HbA1c levels were already significantly higher in Kohnodai hospitalized psychiatric patients compared with the Japanese standard. Therefore, we need to follow glucose metabolism in outpatients.

Concerning liver functions, AST, γ-GTP and T-Bil were not significantly changed until 2 years after discharge. ALT was significantly increased at 1 year and 2 years after discharge. These increases are within standard levels (< 30 IU/L). eGFR was significantly decreased and serum creatinine level significantly increased after 1 year from their discharge. This tendency was also observed at 6 months and 2 years after their discharge. High blood pressure is one of the causes of renal dysfunction (*26*). We did not check blood pressure in all outpatients, but systolic and diastolic blood pressure had a tendency to be higher in outpatients than inpatients (data not shown). We need to check and follow liver functions, renal functions and blood pressure as well as lipid and glucose metabolism in outpatients with schizophrenia.

This study also has some limitations. First, it was an observation study. It is impossible to clarify the cause-effect relationship between life-style related conditions and increased serum TC and TG. Second, follow up period in outpatients was 2 years. We need to catch changes of glucose metabolism, renal and liver functions for a long time follow up in outpatients.

In conclusion, we found that serum triglycerides, total cholesterol and non-HDL cholesterol levels of schizophrenic patients were increased, but blood glucose and HbA1c levels were not changed during 2 years after their discharge.

Acknowledgements

This study was supported by Grants from Chiba Foundation for Health Promotion & Disease Prevention (Chiba, Japan) to Tetsuto Kanzaki (No. II-2, 2016).

References

1. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry. 2017; 4:295-301.
2. Kondo S, Kumakura Y, Kanehara A, Nagato D, Ueda T, Matsuoka T, Tao Y, Kasai, K. Premature deaths among individuals with severe mental illness after discharge from long-term hospitalisation in Japan: a naturalistic observation during a 24-year period. BJPsych Open. 2017; 3:193-195.
3. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. Am Heart J. 2005; 150:1115-1121.
4. Crump C, Winkleby MA, Sundquist K, Sundquist J. Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry. 2013; 170:324-333.
5. Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ Open. 2013; 3:e002808.
6. Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. J Clin Psychiat. 2006; 67:25-30.
7. Jakobsen AS, Speyer H, Norgaard HCB, Karlsen M, Hjorthoj C, Krogh J, Mors O, Nordentoft M, Toft U. Dietary patterns and physical activity in people with schizophrenia and increased waist circumference. Schizophr Res. 2018; 199:109-115.
8. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. Schizophr Bull. 2013; 39:306-318.
9. Osborn DPJ, Wright CA, Levy G, King MB, Deo R, Nazareth I. Relative risk of diabetes, dyslipidaemia, hypertension and the metabolic syndrome in people with severe mental illnesses: systematic review and metaanalysis. BMC Psychiatry. 2008; 8:84.
10. Sugawara N, Yasui-Furukori N, Sato Y, Kishida I, Yamashita H, Saito M, Furukori H, Nakagami T,

Hatakeyama M, Kaneko S. Comparison of prevalence of metabolic syndrome in hospital and community-based Japanese patients with schizophrenia. Ann Gen Psychiatry. 2011; 10:21.
11. Sugai T, Suzuki Y, Yamazaki M, Shimoda K, Mori T, Ozeki Y, Matsuda, H, Sugawara N, Yasui-Furukori N, Minami Y, Okamoto K, Sagae, T, Someya T. High Prevalence of Obesity, Hypertension, Hyperlipidemia, and Diabetes Mellitus in Japanese Outpatients with Schizophrenia: A Nationwide Survey. PLoS One. 2016; 11:e0166429.
12. Sugai T, Suzuki Y, Yamazaki M, Shimoda K, Mori T, Ozeki Y, Matsuda H, Sugawara N, Yasui-Furukori N, Minami Y, Okamoto K, Sagae T, Someya T. Difference in prevalence of metabolic syndrome between Japanese outpatients and inpatients with schizophrenia: A nationwide survey. Schizophr Res. 2016; 171:68-73.
13. OECD Health Statics 2019. *http://www.oecd.org/els/health-systems/health-data.htm* (accessed February 18, 2020).
14. Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, Ito C, Inagaki N, Iwamoto Y, Kasuga M, Hanafusa T, Haneda M, Ueki K. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetol Int. 2010; 1:2-20.
15. Teramoto T, Sasaki J, Ishibashi S, *et al.* Diagnostic criteria for dyslipidemia. J Atheroscler Thromb. 2013; 20:655-660.
16. Ogawa Z, Ito H. The standardization of enzyme assay in Japan. Jpn J Electroph. 1998; 42:295-298.
17. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert. J, de Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2005; 67:2089-2100.
18. Sugai T, Suzuki Y, Yamazaki M, Shimoda K, Mori T, Ozeki Y, Matsuda H, Sugawara N, Yasui-Furukori N, Minami Y, Okamoto. K, Sagae T, Someya T. High prevalence of underweight and undernutrition in Japanese inpatients with schizophrenia: a nationwide survey. BMJ Open. 2015; 5:e008720.
19. Osborn DPJ. Nazareth I, King MB. Risk for coronary heart disease in people with severe mental illness cross-sectional comparative study in primary care. Br J Psychiatry. 2006; 188:271-277.
20. Saari K, Jokelainen J, Veijola J, Koponen H, Jones PJ, Savolainen M, Järvelin M-R, Lauren L, Isohanni M, Lindeman S. Serum lipids in schizophrenia and other functional psychoses: a general population northern Finland 1966 birth cohort survey. Acta Psychiatr Scand. 2004; 110:279-285.
21. Grundy SM, Ahrens EHJr, Davignon J. The interaction of cholesterol absorption and cholesterol synthesis in man. J lipid Res. 1969; 10:304-315.
22. Nissinen MJ, Gylling H, Miettinen TA. Resonses of surrogate markers of cholesterol absorption and synthesis to changes in cholesterol metabolism during various amounts of fat and cholesterol feeding among healthy men. Br J Nutr. 2008; 99:370-378.
23. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009; 29:431-438.
24. Christen T, Trompet S, Noordam R, Blauw LL, Gast KB, Rensen PCN, Willems K van Dijk, Rosendaal FR, de Mutsert R, Jukema JW. Mendelian randomization analysis of cholesteryl ester transfer protein and subclinical atherosclerosis: A population-based study. J Clin Lipidol. 2018; 12:137-144.
25. Kanzaki T, Uju Y, Sekine K, *et al*. Increased Silent Brain Infarction Accompanied With High Prevalence of Diabetes and Dyslipidemia in Psychiatric Inpatients: A Cross-Sectional Study. Prim Care Companion CNS Disord. 2015; 17:115-121.
26. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M, Koyama A. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007; 71:159-166.

Received February 19, 2020; Revised May 26, 2020; Accepted June 4, 2020.

Released online in J-STAGE as advance publication June 10, 2020.

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