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A cross-sectional study on metabolic similarities and differences between inpatients with schizophrenia and those with mood disorders

Yoriyasu Uju
National Center of Global Health and Medicine
Tetsuto Kanzaki (tkanzaki@cis.ac.jp)
Graduate School and Faculty of Pharmaceutical Sciences, Chiba University
Yuki Yamasaki
Graduate School and Faculty of Pharmaceutical Sciences, Chiba University
Tadayuki Kondo
National Center for Global Health and Medicine
Hideki Nanasawa
National Center for Global Health and Medicine
Yu Takeuchi
National Center for Global Health and Medicine
Yuta Yanagisawa
National Center of Global Health and Medicine
Shun Kusanishi
National Center for Global Health and Medicine
Chieko Nakano
National Center for Global Health and Medicine
Tetsuro Enomoto
National Center for Global Health and Medicine
Akahito Sako
National Center for Global Health and Medicine
Hidekazu Yanai
National Center for Global Health and Medicine
Shunichi Mishima
National Center for Global Health and Medicine
Seisuke Mimori
Chiba Institute of Science
Kazuei Igarashi
Amino Pharma Research Institute
Tsuyoshi Takizawa

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Chiba Institute of Science

Tatsuro Hayakawa

National Center for Global Health and Medicine

Primary research

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Abstract

Background

One of the main causes of death in psychiatric patients is cardiovascular diseases which are closely related with lifestyle-related diseases. Psychiatric disorders include schizophrenia and mood disorders, whose symptoms and treatment medicines are different, suggesting that they might have different metabolic disorders. Thus, we studied the differences of lifestyle-related diseases between schizophrenia and mood disorders in Japan.

Methods

This cross-sectional study was performed from 2015 to 2017. Study participants were 189 hospitalized patients (144 schizophrenia group, 45 mood disorders group) in the department of psychiatry at Kohnodai hospital. We examined physical disorders, metabolic status of glucose and lipid, estimated glomerular filtration rate (eGFR) and brain magnetic resonance imaging. We compared these data between inpatients with schizophrenia or mood disorders group and the standard. We quoted 'The National Health and Nutrition Survey in Japan 2015' by Ministry of Health, Labor and Welfare as the standard. In comparisons between schizophrenia and mood disorders groups, we used analysis of covariance or logistic regression analysis.

Results

The ratio of silent brain infarction (SBI) and cerebral infarction were significantly high in both groups compared with the standard. Schizophrenia group showed significantly higher prevalence of diabetes, low high-density lipoprotein (HDL) cholesterolemia, metabolic syndrome and smoking than the standard. Mood disorders group had significantly high prevalence of low HDL-cholesterolemia compared with the standard. Fasting blood glucose and HbA1c were significantly higher in schizophrenia group and female mood disorders group than the standard. Female mood disorders group had significantly decreased eGFR with increased ratio of eGFR < 60 ml/min than the standard. In comparison between both groups, eGFR and prevalence of smoking in mood disorders group were significantly lower than those in schizophrenia group by adjustment for age.

Conclusions

Participants of both groups had increased ratio of SBI and cerebral infarction, accompanied with glucose and lipid disorders. Distinct from schizophrenia group, mood disorders group showed significantly lower eGFR and prevalence of smoking.

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Background

It is well known that psychiatric patients have a short life expectancy. Henekens et al [1] reported that schizophrenic patients have approximately 15 years shorter life time than general population and more than 60% of deaths are due to coronary heart diseases in the United States. In the countries from Europe, Asia, Australia, Africa and Japan predicted life time is 11–22 years shorter than the general population [2, 3]. Crump et al [4] and Smith et al [5] also reported that cardiovascular diseases and malignancy are the main causes of death in psychiatric patients, and cardiovascular diseases are likely to be underrecognized and undertreated in schizophrenic patients. These facts indicate that cardiovascular diseases are one of the most important causes of short life expectancy in psychiatric patients.

Diabetes, smoking, hypertension, dyslipidemia, visceral type obesity and chronic kidney disease (CKD) are risk factors of cardiovascular diseases. Indeed, there are many reports that schizophrenic patients have a high rate of diabetes, smoking, low HDL-cholesterolemia, obesity and metabolic syndrome [6–8]. Psychiatric patients tend to have unhealthy eating habits, shortage of exercise and smoking [8]. It is probable that these unhealthy lifestyles are related with increased risk factors of cardiovascular diseases. Furthermore, schizophrenic patients usually are administered typical or atypical antipsychotics. Halfdanarson et al [9] reported that use of typical antipsychotics was decreased but that of atypical antipsychotics was elevated in the past 10 years globally. Some atypical antipsychotics cause adverse effects on glucose and lipid metabolism and induce diabetes and dyslipidemia [10, 11]. These side effects of antipsychotics also increase the risks of cardiovascular diseases.

Saku et al [12] and Kondo S et al [3] reported that the standardized mortality rate of schizophrenic patients with vascular diseases was higher than in the general population in Japan, but they did not show that the precise nature of vascular diseases. Recently, our study has shown that psychiatric inpatients have increased silent brain infarction (SBI) and cerebral infarctions compared with Japanese healthy controls, accompanied with high prevalence of diabetes and low HDL-cholesterolemia [13]. These results suggest that cerebral incidents are also important in quality of life in psychiatric patients of Japan.

Psychiatric patients of our previous study were hospitalized patients who were diagnosed as schizophrenic group 69.1%, mood disorders group 18.4% and others 12.5% [13]. Schizophrenia and mood disorders are primary psychiatric diseases, whose symptoms and treatment medicines are dissimilar. Atypical antipsychotics are the major medication used to treat schizophrenia [9], and anti-depressants and mood-stabilizers are used to treat mood disorders. Therefore, it is possible that there are different metabolic changes in patients with schizophrenia and mood disorders. This is an essential point to plan the lowering the incidence of lifestyle-related diseases and cardiovascular diseases in each psychiatric patient with schizophrenia or mood disorders.

In this present study, we investigated the similarities and differences of lifestyle-related diseases between schizophrenia and mood disorders in Japan. Decreased renal function is reported in hospitalized patients with female mood disorders.

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Methods

Study design and study subjects

This cross-sectional observational study was performed from January 2015 to December 2017 at Kohnodai Hospital, National Center for Global Health and Medicine. Study participants were 189 hospitalized patients (82 males and 107 females) in the Psychiatry Department at Kohnodai Hospital. 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 of mental and behavioral disorders. Then, several psychiatrists discussed the assessment of the diagnosis and treatments in every patient at the conference opening every week. We then classified participants by schizophrenia group (F2 group, schizophrenia (F20), acute and transient psychotic disorders (F23) and schizoaffective disorders (F25)), mood disorders group (F3 group, bipolar affective disorder (F31), depressive episode (F32) and recurrent depressive disorder (F33)) and other mental disorders (Alzheimer's disease, stimulant psychosis and somatoform disorders).

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

The definition of hypertension was above 140 mmHg of systolic blood pressure and/or above 90 mmHg of diastolic blood pressure [14]. Diabetes mellitus was defined as HbA1c over 6.5% and fasting plasma glucose (FPG) over 126 mg/dl [15]. High LDL-cholesterolemia (fasting serum LDL-cholesterol (LDL-C) ≥ 140 mg/dl) or low HDL-cholesterolemia (fasting serum HDL-cholesterol (HDL-C) < 40 mg/dl) or hypertriglyceridemia (fasting serum triglyceride (TG) ≥ 150 mg/dl) were described as dyslipidemia [16]. Patients were also counted as hypertension, diabetes or dyslipidemia if they used anti-hypertensive (Ca antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics and β-blockers) or hypoglycemic (insulins, glucagon-like peptide-1 receptor agonists, biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidines, dipeptidyl peptidase-4 inhibitors and sodium glucose transporter-2 inhibitors) or anti-dyslipidemic drugs (statins, fibrates and ezetimibe), respectively. The diagnosis of metabolic syndrome (Met-S) was followed according to the definition of the Japan Society for the Study of Obesity. Met-S was diagnosed when waist circumference (male≥85 cm, female≥90 cm) plus two of the following criteria are met: high blood pressure (≥ 130/85), reduced HDL-C (< 40 mg/dl) and/or raised TG (≥ 150 mg/dl), and raised fasting hyperglycemia (≥ 110 mg/dl) [17]. Cerebral infarction was diagnosed by the presence of neurological symptoms and signs corresponding to brain imaging. The definition of smokers was patients who smoked until one month before admission.

Data collections

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Information on patients' demographic data and medical history were obtained from their medical records. Body mass index (BMI) was calculated by their height and weight. Waist circumference was measured at a level midway between the lowest rib and the iliac crest. Hospital staff measured blood pressure on the right arm of a patient before breakfast. Blood samples were obtained from patients after 12 h starvation. Total cholesterol (TC) and TG were assayed by enzymatic method and 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 HPLC method, and fasting plasma glucose and creatinine were by enzymatic method. Estimated glomerular filtration rate (eGFR) was calculated by serum creatinine level, age and gender.

Brain imaging

The magnetic resonance imaging (MRI) examinations were performed in 5 mm thickness with 2 mm slice gap using a 1.5 T MRI system (Siemens Magnetom Symphony). Patients underwent T1- and T2-weighted MRI and fluid-attenuated inversion recovery (FLAIR) of the brain as described by Yoshida M et al [18]. FLAIR images were used to distinguish infarcts from dilated perivascular spaces. We diagnosed silent brain infarction (SBI) as follows: 1) spotty area ≥ 3 mm in diameter showing high density in T2 and FLAIR images and low density in T1 image, 2) lack of neurological signs explained by MRI lesions, 3) no medical history of clinical symptoms of stroke [19]. 790 elderly volunteers (330 females and 460 males, mean age 61.0 years old, range 40–88) were used as control of SBI [20]. All of 790 volunteers were living independently at home without apparent history of stroke or dementia.

Statistical analysis

We quoted 'The National Health and Nutrition Survey in Japan 2015' produced by the Japanese Ministry of Health, Labor and Welfare [21] as the healthy Japanese standard. This survey was performed in 6,655 persons (3,064 were male, 3,591 were female) chosen at random from all districts of Japan at November in 2015. Age of target persons was distributed from 1 to over 70 years old. For albuminuria, the data of the Takahata study was used [22].

Means or ratios in the standard group were calculated by adjusting sex and age configuration to patient group. Next, we estimated means or ratios with 95% of confidence intervals (CIs) of the patient group. Then we compared characteristics of F2 group or F3 group with those of each standard group.

In comparisons between F2 group and F3 group, first we used t-test in quantitative variables and Fisher's exact test in qualitative variables without any adjustments. Next, we estimated age-adjusted mean differences and Odds ratios between F2 and F3 groups, using analysis of covariance (ANCOVA) and logistic regression analysis, respectively. Quantitative variables were BMI, waist circumstance, systolic blood pressure, diastolic blood pressure, LDL-C, HDL-C, triglyceride, non-HDL-C, fasting blood glucose, HbA1c, serum creatinine and eGFR. Qualitative variables were prevalence of hypertension, diabetes mellitus, high LDL-cholesterolemia, low HDL-cholesterolemia, hypertriglyceridemia, metabolic syndrome, smoking, and ratios of cerebral infarction and SBI, eGFR < 60 ml/min and albuminuria. All analyses were

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Results

Profile of study participants

Table 1 shows the profile of study patients. Schizophrenia group (F2 group) were 144 persons, and mood disorders group (F3 group) were 45. The ratio of male to female was 1:1.32 (62 persons: 82 persons) in F2 group, and was 1:1.25 (20 persons: 25 persons) in F3 group, indicating a similar ratio of male to female in both groups. The average age was approximately 13 years older in F3 group than in F2 group.

Comparisons of physical characteristics and disorders between study participants of F2 group and F3 group

Female BMI was significantly higher in the F2 group compared with the age- adjusted Japanese standard population (the standard) but was lower in the male F3 group (Table 2). Waist circumference and blood pressure were not significantly different in either group except lower diastolic blood pressure of male F3 group. We calculated the prevalence of hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome and smoking in both study groups (Table 2). The ratio of low HDL-cholesterolemia was significantly higher in both groups than the standard. The ratio of diabetes was significantly high in the F2 group but was no significant different in the F3 group compared with the standard. These results are in accordance with the increased ratio of metabolic syndrome in the F2 group. However, the ratios of high LDL-cholesterolemia and hypertension showed no significant differences in both groups compared with the standard except lower ratio of hypertension in female F2 group, and the ratio of hypertriglyceridemia was significantly lower in both male groups. Interestingly, the prevalence of smoking was significantly higher in the F2 group than the standard (Table 2).

As far as brain MRI, 185 patients agreed to undergo brain imaging. 2 and 3 patients were diagnosed as cerebral infarction in F2 and F3 groups, respectively, by the presence of neurological symptoms and signs inferred from brain imaging. The ratio of SBI plus cerebral infarction were 0.234 and 0.477 in the F2 and F3 groups, respectively, and significantly higher than the age-adjusted ratio of each control (Table 2).

Next, we compared physical characteristics and disorders between F2 and F3 study participants directly (Table 2). The comparison of age-adjustment showed that prevalence of smoking in F2 group was only significantly higher than F3 group ($p = 0.0148$). Age-adjusted analysis shows no significant differences of BMI, blood pressure, the prevalence of hypertension and high LDL-cholesterolemia, and the ratio of cerebral infarction and SBI, in spite of their differences by simple analysis without age-adjustment.

Comparisons of metabolic characteristics between study participants of F2 group and F3 group

Table 3 shows serum blood levels of lipid and glucose, and renal function. Patients in the F2 group had significantly lower levels of HDL-C and TG than the standard except TG in the females. In F3 group, TG in males was significantly low but TG in females and HDL-C were not significantly different from the

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standard. LDL-C levels were not significantly different in either group compared with the standard. Non-HDL-C level was significantly low in male F2 and F3 groups. FPG and HbA1c were significantly higher in the F2 group and female F3 group than the standard.

Chronic kidney disease (CKD) is recognized as one of the important risk factors of cardiovascular diseases. The definition of CKD is continuous decreased GFR (GFR < 60 ml/min) and/or albuminuria [23]. The mean level of eGFR was 68.7 ml/min (95% CI was 61.4–76.1) in female F3 group and significantly lower than the age-adjusted mean of the standard (77.5 ml/min) (Table 3). We also calculated the ratio of eGFR lower than 60 ml/min. The ratio of eGFR lower than 60 ml/min was significantly higher in the female F3 group than the female standard, suggesting increased CKD. We also checked the urine albumin in subjects over 40 years old, another criterion of CKD definition [23]. The ratio of albuminuria tended to higher in the female F3 group than the female standard.

eGFR levels were not significantly different in the F2 group and male F3 group compared with each standard group (Table 3).

We compared metabolic characteristics between F2 and F3 study participants directly (Table 3). Female eGFR in F3 group was significantly lower than female F2 group in age-adjusted analysis ($p = 0.0225$). Age-adjusted analysis shows no significant differences of HbA1c and the ratio of eGFR < 60 ml/min, in spite of their differences by simple analysis without age-adjustment.

Psychiatric medications administered to study participants

In the F2 group, 76.6% of the psychiatric medications used is atypical antipsychotics, 21.4% is typical and 1.9% is other psychotropic medications. Among administered medicines in the F3 group, atypical antipsychotics accounted for 54.7%, antidepressants and mood stabilizers 34.0% and typical antipsychotics 9.4% (Table 4). Therefore, most of the schizophrenic patients were treated with antipsychotics, but mood disorders patients were treated with various psychotropic medications containing antidepressants and mood stabilizers.

Discussion

The present study shows that silent brain infarction and cerebral infarction were increased in patients with both schizophrenia and mood disorders, accompanied by glucose and lipid disorders. Differences between inpatients with schizophrenia and those with mood disorders were observed in renal function and prevalence of smoking.

Low HDL-cholesterolemia is defined by a serum level below 40 mg/dl [16]. We observed low HDL-cholesterolemia in this study. There are many reports that HDL-C level is low in medicated schizophrenia [24, 25], but is variable in depressive states. Sagud et al [26] reported that HDL-C was decreased in female bipolar affective disorders and depressions, but Shin et al [27] showed that elevated HDL-C level was associated with depressive symptoms. HDL-C levels are decided by not only lifestyle-related diseases, but

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own to lower serum HDL-C levels [24, 25]. It is

reported that antidepressants are associated with weight gain but have fewer effects on lipid and glucose metabolism [28, 29]. Usually, patients with schizophrenia use atypical or typical antipsychotics, but those with mood disorders are administered by not only antidepressants or mood stabilizers but atypical antipsychotics. Therefore, it is possible to think that drug variation is one of the reasons why HDL-C in depressive states is different in these reports.

Levels of serum TG and non-HDL-C were significantly low compared with the standard in both male F2 and F3 groups, and LDL-C was almost the same as the standard in both groups. Kingsbury et al [30] described lower levels of serum TG in ziprasidone-treated patients with schizophrenia. However, there were reports of high serum TG or LDL-C levels in schizophrenic patients [24, 31]. Furthermore, Sugai et al [32] showed that the levels of TG and LDL-C were higher in outpatients with schizophrenia than in inpatients. In patients with mood disorders, serum lipid levels are also variable. Hummel et al [33] reported that serum TG level was higher and LDL-C was lower than controls. Lehto et al [34] showed that serum TG and LDL-C were increased compared with controls. There was also a report that serum LDL-C was not changed in mood disorders patients [35]. These differences of TG and LDL-C levels might be dependent on the situation of the patients such as outpatients or inpatients, and drugs administered.

It is reported that the increased ratio of diabetes and high FPG are observed in patients with both schizophrenia and mood disorders, in accordance with high FPG and HbA1c in patients of the F2 group and female F3 group in our study. Stubbs et al [36] described that schizophrenic patients had at least double the risk of diabetes by meta-analysis. Newcomer JW [37] and Wysokinski A et al [38] showed that the prevalence of diabetes or the level of FPG was high in patients with schizophrenia and those with mood disorders. It is well known that poor lifestyle is one of the major causes of increased diabetes. There are also many reports that antipsychotics, especially atypical ones have side effects on glucose metabolism [10, 39]. Furthermore, Ji et al [40] also reported the genetic overlap between type 2 diabetes and major depressive disorders. Causes of increased diabetes or FPG in patients with schizophrenia and mood disorders remain to be elucidated.

There are several reports concerning psychiatric disorders and renal function. Tzeng et al [41] reported that schizophrenia is associated with a 25% increase in the risk of developing CKD for 3 years follow up period. There are other reports that the prevalence of CKD is not different between schizophrenic patients and control [4], and the incidence of end-stage renal disease is low in schizophrenic patients [42]. Rej S [43] and Kessing LV [44] showed that Li, mood stabilizing treatment for bipolar disorder, had an effect on renal function and induced CKD. This F3 group contained 8% Li users. eGFR in the female F3 group excluding Li users was 67.2 ml/min and the standard was 77.2 ml/min, which was significantly different, indicating that Li is not correlated with CKD in the F3 group in our study. We need to have an extended follow up renal function in these F2 and F3 patients.

As risk factors of developing CKD, there are lifestyle-related diseases, e.g., hypertension, diabetes, dyslipidemia, obesity and smoking [45]. Table 3 shows that eGFR was significantly lower in F3 group than F2 group by adjustment for age ($p = 0.0139$). By adjustments for age and prevalence of

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hypertension, there was significant difference between F2 group and F3 group (p = 0.0232). However, we have no significant differences by adjustment for smoking and diabetes (p = 0.2093 and p = 0.6309, respectively). These results mean that there is significant difference of eGFR between F2 and F3 groups which cannot be explained by age and hypertension. The causes of lowering eGFR in mood disorders remain to be clarified.

The ratios of SBI and cerebral infarction were higher in both F2 and F3 groups, compared with each control, indicating the increasing tendency to cerebrovascular changes. We did not detect significant differences between F2 and F3 groups by age-adjustment. There are reports about the relation of cerebrovascular changes to major depression. Yanai et al [46] reported that patients with depression and SBI were more likely to develop psychiatric and neurological disorders than those with depression without SBI. A 10 years follow-up study showed that the presence of SBI is associated with a relatively poor prognosis in patients with depression [47]. The term 'vascular depression' has been used to describe depression occurring later in life and characterized by cerebral changes related to depression onset. The mean age of the F3 group is 62.6 years old. Therefore, a part of SBI positive depressive patients might be vascular depression.

This study also has some limitations. First, it was a cross-sectional study. It is impossible to clarify the cause-effect relationship between diabetes, hypertension, lipid, eGFR and SBI. Second, patients in our study were inpatients. It is probable that lifestyle-related diseases and metabolic profiles are not same in inpatients and outpatients. Third, the number of mood disorders patients is small for classifying our results under each psychotic disorders, such as bipolar disorders and depressive disorders.

Conclusions

In conclusion, we found that patients with schizophrenia or mood disorders had increased ratio of SBI and cerebral infarction accompanied with glucose and lipid disorders in this study. Patients with mood disorders had decreased eGFR and prevalence of smoking.

Abbreviations

ANCOVA
analysis of covariance
BMI
Body mass index
CI
confidence interval
CKD
chronic kidney disease
eGFR
estimated glomerular filtration rate

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FLAIR
fluid-attenuated inversion recovery
FPG
fasting plasma glucose
HDL
high-density lipoprotein
LDL
low-density lipoprotein
MRI
the magnetic resonance imaging
N.A.
not apppicalble
N.S.
not significant
SBI
silent brain infarction
TG
triglyceride
TC
total cholesterol

Declarations

Ethics approval and consent to participate

This 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.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TKa and YU designed this study and major contributors in writing the manuscript. TKo, HN, YT, YYan, SK, CN, TE and SMis collected samples and obtained patients' informed consent. YYam, AS, HY, SMim, KI, TT and TH contributed to data collection, analysis and interpretation. All authors read and approved the final manuscript.

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Authors' information

[1]Depatment of Psychiatry, Kohnodai Hospital, National Center for Global Health and Medicine, 1-7-1, Kohnodai, Ichikawa City, Japan

[2]Depatment of Drug Informatics, Graduate School and Faculty of Pharmaceutical Sciences, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba City, Japan

[3]Department of Internal Medicine, Kohnodai Hospital, National Center for Global Health and Medicine, 1-7-1, Kohnodai, Ichikawa City, Japan

[4]Department of Diabetes, Endocrinology and Metabolism, Kohnodai Hospital, National Center for Global Health and Medicine, 1-7-1, Kohnodai, Ichikawa City, Japan

[5]Deptment of Clinical Medicine, Faculty of Pharmacy, Chiba Institute of Science, 15-8, Shiochi-cho, Choshi City, Japan

[6]Amine Pharma Research Institute, Innovation Plaza at Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba City, Japan

[7]Deptment of Biostatics, Faculty of Pharmacy, Chiba Institute of Science, 15-8, Shiochi-cho, Choshi City, Japan

Yoriyasu Uju and Tetsuto Kanzaki contributed equally to this work.

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Tables

Table 1 Profile of study participants

	F2	F3
Cases (n)	144	45
male	62	20
female	82	25
Age, years (mean±SD)	49.8±12.3	62.6±12.6
male	46.0±10.5	60.8±11.3
female	52.6±12.8	64.1±13.6
Diagnosis		
schizophrenia group (F2)	144	
schizophrenia (F20)	135	
acute and transient psychotic disorders (F23)	7	
schizoaffective disorders (F25)	2	
mood disorders group (F3)		45
bipolar affective disorder (F31)		30
depressive episode (F32)		2
recurrent depressive disorder (F33)		13

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Table 2 Comparisons of physical characteristics and disorders between F2 and F3 study participants

	F2				F3				F2 vs F3			
	Study group			Age-adjusted mean or ratio of standard group	Study group			Age-adjusted mean or ratio of standard group	T-test or Fisher's exact test p=	Age-adjusted		
	n	mean or ratio	95% CI		n	mean or ratio	95% CI			P=	mean differences (95%CI)	Odds ratios (95%CI)
Body mass index (BMI, kg/m2)	130	24.1*	23.2-24.9	23.1	43	22.9	21.3-24.4	23.2	N.S.	N.S.	0.53 (-1.3 - 2.4)	
male	56	24.7	23.4-26.1	23.9	19	21.7*	19.9-23.5	23.8	0.0018	N.S.	1.8 (-1.0 - 4.7)	
female	74	23.6*	22.5-24.7	22.5	24	23.8	21.3-26.2	22.8	N.S.	N.A.		
Waist circumference (cm)	119	85.2	82.7-87.6	82.9	39	83.6	79.2-88.1	84.3	N.S.	N.A.		
male	51	88.5	84.8-92.3	86.0	16	82.8	76.4-89.3	86.7	N.S.	N.A.		
female	68	82.6	79.4-85.9	80.5	23	84.2	77.7-90.6	82.6	N.S.	N.A.		
Systolic blood pressure (mmHg)	144	125.3	122.6-127.9	126	45	131.6	126.1-137.1	132.8	0.026	N.S.	-3.3 (-9.4 - 2.7)	
male	62	127.5	123.4-131.6	128.4	20	131.5	122.8-140.2	134.9	N.S.	N.A.		
female	82	123.5	120.1-127.0	124.2	25	131.7	124.1-139.3	131.2	0.031	N.S.	-3.2 (-10.8 - 4.3)	
Diastolic blood pressure (mmHg)	144	77.2	75.3-79.1	79.0	45	77.0	73.7-80.4	80.1	N.S.	N.A.		
male	62	80.4	77.6-83.1	82.0	20	77.1*	72.5-81.6	82.7	N.S.	N.S.	-0.3 (-6.4 - 5.9)	
female	82	74.8	72.3-77.2	76.7	25	77.0	71.9-82.1	78.1	N.S.	N.A.		
Hypertension	144	0.271	0.200-0.351	0.349	45	0.467	0.317-0.621	0.555	0.017	N.S.		0.6 (0.28 - 1.28)
male	62	0.355	0.237-0.487	0.367	20	0.450	0.231-0.685	0.590	N.S.	N.A.		
female	82	0.207*	0.126-0.311	0.336	25	0.480	0.278-0.687	0.527	0.011	N.S.		0.47 (0.17 - 1.32)
Diabetes mellitus	144	0.160*	0.104-0.230	0.089	45	0.156	0.065-0.295	0.145	N.S.	N.S.		2.00 (0.77 - 5.65)
male	62	0.194	0.104-0.314	0.105	20	0.100	0.012-0.317	0.193	N.S.	N.A.		
female	82	0.134	0.069-0.227	0.077	25	0.200	0.068-0.407	0.106	N.S.	N.S.		1.20 (0.33 - 4.44)
High LDL-cholestrolemia	140	0.264	0.193-0.345	0.241	44	0.364	0.224-0.522	0.252	N.S.	N.S.		0.85 (0.39 - 1.89)
male	60	0.283	0.175-0.414	0.237	19	0.211	0.061-0.456	0.215	N.S.	N.A.		
female	80	0.250	0.160-0.359	0.244	25	0.480	0.278-0.687	0.280	0.045	N.S.		0.46 (0.17 - 1.27)
Low HDL-cholesterolemia	139	0.209*	0.144-0.286	0.073	44	0.205*	0.098-0.353	0.092	N.S.	N.A		
male	59	0.322*	0.206-0.456	0.134	19	0.316	0.126-0.566	0.155	N.S.	N.A		
							026-	0.044	N.S.	N.A		

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			0.218				0.312				
Hypertriglyceridemia	143	0.210*	0.146-0.286	0.331	44	0.205*	0.098-0.353	0.354	N.S.	N.A	
male	62	0.258*	0.155-0.385	0.446	19	0.158*	0.034-0.396	0.436	N.S.	N.A	
female	81	0.173	0.098-0.273	0.243	25	0.240	0.094-0.451	0.292	N.S.	N.A	
Metabolic syndrome	115	0.209*	0.141-0.294	0.123	38	0.263	0.130-0.421	0.190	N.S.	N.A.	
male	49	0.306*	0.191-0.459	0.180	15	0.200	0.041-0.457	0.283	N.S.	N.A.	
female	66	0.136	0.062-0.236	0.068	23	0.304*	0.132-0.529	0.125	N.S.	N.S.	0.61 (0.17 - 2.13)
Prevalence of smoking	139	0.396*	0.314-0.482	0.237	40	0.125	0.042-0.268	0.176	0.0011	0.0148**	3.62 (1.29 - 10.4)
male	61	0.541*	0.409-0.669	0.395	16	0.188	0.041-0.457	0.326	0.013	N.A.	
female	78	0.282*	0.186-0.395	0.113	24	0.083	0.010-0.270	0.076	N.S.	N.A.	
Ratio of SBI and cerebral infarction	141	0.234*	0.155-0.297	0.141	44	0.477*	0.325-0.633	0.304	0.0039	N.S.	1.06 (0.426 - 2.64)

* means significantly different (P <0.05) between study group and standard group in F2 column and F3 column. Age-adjusted mean differences between F2 and F3 groups were estimated using ANCOVA and Odds ratios were calculated using logistic regression analysis. CI is an abbreviation of confidence interval. N.A. means not applicable. N.S. means not significant (P>0.05). ** is significantly different (P <0.05) between F2 group and F3 group by age-adjusted analysis in F2 vs F3 column.

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Table 3 Comparisons of metabolic characteristics between F2 and F3 study participants

	F2				F3				F2 vs F3			
	Study group			Age-adjusted mean or ratio of standard group	Study group			Age-adjusted mean or ratio of standard group	T-test or Fisher's exact test p=	Age-adjusted		
	n	mean or ratio	95% CI		n	mean or ratio	95% CI			P=	mean differences (95%CI)	Odds ratios (95%CI)
LDL-C (mg/dl)	139	113.6	107.2-120.0	118.7	44	113.5	103.2-123.8	121.3	N.S.	N.A.		
male	59	107.3	99.4-118.3	118	19	106.9	95.7-118.0	116.4	N.S.	N.A.		
female	80	118.3	110.6-126.0	119.2	25	118.6	102.2-135.1	125	N.S.	N.A.		
HDL-C (mg/dl)	139	53.9*	50.9-56.9	61.7	44	55.6	50.3-60.9	59.6	N.S.	N.A.		
male	59	48.7*	45.1-52.3	55.9	19	49	41.6-56.4	54.9	N.S.	N.A.		
female	80	57.7*	53.3-62.0	66	25	60.5	53.3-67.8	63	N.S.	N.A.		
Triglyceride (mg/dl)	143	115.5*	101.8-129.3	138.2	44	112*	92.7-131.3	141.9	N.S.	N.A.		
male	62	126.2*	102.2-150.1	160.2	19	111*	73.0-147.0	165	N.S.	N.A.		
female	81	107.4	91.3-123.5	121.1	25	113.6	91.7-135.4	124.3	N.S.	N.A.		
non-HDL-C (mg/dl)	139	137.0*	129.8-144.3	145.2	44	135.9*	124.4-147.5	148.7	N.S.	N.A.		
male	59	133.7*	121.1-146.3	148.1	19	128.9*	115.3-142.5	147.4	N.S.	N.A.		
female	80	139.5	130.8-148.2	143.1	25	141.3	123.2-159.4	149.6	N.S.	N.A.		
Fasting blood glucose (mg/dl)	144	117.7*	110.6-124.9	98.1	45	131.5*	108.6-154.4	101.6	N.S.	N.S.	-7.2 (-26.6 - 12.3)	
male	62	117.7*	105.6-129.8	95.5	20	126.8	84.2-169.4	101	N.S.	N.A.		
female	82	117.7*	108.9-126.5	98	25	135.2*	108.9-161.5	102.1	N.S.	N.S.	-11.1 (-33.5 - 11.4)	
HbA1c (%)	144	5.82*	5.69-5.95	5.57	45	6.02*	5.67-6.38	5.66	N.S.	N.S.	-0.01 (-0.34 - 0.32)	
male	62	5.91*	5.65-6.17	5.53	20	5.97	5.21-6.73	5.71	N.S.	N.A.		
female	82	5.75*	5.62-5.88	5.6	25	6.06*	5.78-6.35	5.63	0.029	N.S.	-0.12 (-0.40 - 0.16)	
serum creatinine (mg/dl)	144	0.696	0.657-0.734	0.733	45	0.778	0.703-0.853	0.736	0.045	N.A.		
male	62	0.788*	0.733-0.843	0.865	20	0.877	0.733-1.020	0.85	N.S.	N.A.		
female	82	0.626	0.578-	0.633	25	0.698	0.633-	0.644	N.S.	N.A.		
									0.0002			

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eGFR (ml/min)		87.1	83.3-90.8		45	72.4	66.0-78.8	77.3		0.0139**	10.3 (2.1 - 18.5)	
male	62	90.6	84.8-96.4	85.6	20	77.1	65.4-88.7	77	0.027	N.S.	9.9 (-4.0 - 23.8)	
female	82	84.4	79.5-89.4	84.8	25	68.7*	61.4-76.1	77.5	0.002	0.0225**	12 (1.7 - 22.3)	
Ratio of eGFG<60 ml/min	144	0.076	0.039-0.133	0.048	45	0.244	0.129-0.395	0.136	0.006	N.S.		0.45 (0.16 - 1.2)
male	62	0.048	0.010-0.135	0.035	20	0.150	0.032-0.379	0.135	N.S.	N.S.		0.48 (0.07 - 3.7)
female	82	0.098	0.043-0.183	0.058	25	0.320*	0.150-0.535	0.137	0.011	N.S.		0.36 (0.11 - 1.2)
Ratio of albuminuria (30mg/g Cr<) (40 years<)	93	0.043	0.012-0.107	0.100	33	0.152	0.051-0.319	0.122	N.S.	N.S.		0.34 (0.08 - 1.41)
male	37	0.027	0.001-0.142	0.101	14	0.071	0.002-0.339	0.115	N.S.	N.S.		0.53 (0.03 - 10.1)
female	56	0.054	0.011-0.149	0.099	19	0.211	0.061-0.456	0.127	N.S.	N.S.		0.27 (0.05 - 1.44)

* means significantly different (P $\leq$0.05) between study group and standard group in F2 column and F3 column. Age-adjusted mean differences between F2 and F3 groups were estimated using ANCOVA and Odds ratios were calculated using logistic regression analysis. CI is an abbreviation of confidence interval. N.A. means not applicable. N.S. means not significant (P>0.05). ** is significantly different (P $\leq$0.05) between F2 group and F3 group by age-adjusted analysis in F2 vs F3 column.

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Table 4 Psychiatric medications mainly administered to study participants

	F2	F3
no. of patients	144	45
Atypical antipsychotic	118 (76.6%)	29 (54.7%)
risperidone	52	
olanzapine	36	13
quetiapine	4	12
clozapine	8	
aripirazol	6	4
paliperidone	6	
blonanserine	4	
perospirone	2	
Typical antipsycotic	33 (21.4%)	5 (9.4%)
haloperidol	16	3
zotepine	6	1
pipamperone	5	
timiperone	3	
bromperidol	2	
perphenazine (PZC)	1	1
Others	3 (1.94%)	18 (34.0%)
antidepressant		
mirtazapine		7
sulpiride		1
mood stabilizer		
lithium carbonate	1	4
lamotrigine		2
valproate	2	2
carbamazepine		2
None	0	1 (1.9%)

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