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Association between oxidative stress-related genes polymorphisms and metabolic abnormalities among schizophrenia patients

Kentaro Oniki[1], Masamichi Ishioka[2], Natsumi Osaki[1], Yuki Sakamoto[1], Yuki Yoshimori[1], Tetsu Tomita[2], Ryoko Kamihashi[1], Shoko Tsuchimine[2], Norio Sugawara[3], Koji Otake[4], Yasuhiro Ogata[4], Junji Saruwatari[1,5], Norio Yasui-Furukori[2]

[1]*Division of Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Kumamoto University*
[2]*Department of Neuropsychiatry, Graduate School of Medicine, Hirosaki University*
[3]*Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry*
[4]*Japanese Red Cross Kumamoto Health Care Center*
[5]*Center for Clinical Pharmaceutical Sciences, Kumamoto University*

ABSTRACT

Purpose: Oxidative stress contributes to the development of schizophrenia and metabolic abnormalities among schizophrenia patients. This study investigated whether the oxidative stress-related genes polymorphisms affected the risk for metabolic abnormalities among schizophrenia patients or not.

Methods: A cross-sectional analysis was conducted among 256 schizophrenia patients and 194 age- and gender-matched controls. The effects of the polymorphisms of methylenetetrahydrofolate reductase (*MTHFR*) (rs1801133, C677T; rs1801131, A1298C) and glutathione S-transferase (*GST)T1* null, *GSTM1* null, *GSTK1* (rs1917760, G-1308T) on the risk for metabolic abnormalities were investigated by structural equation modeling.

Results: Among the female schizophrenia patients, the *MTHFR* rs1801133 T/T genotype increased the risk of overweight, and this genotype effect was associated with a risk of metabolic abnormalities. Among the schizophrenia patients with current-smoking status, the *MTHFR* rs1801133 T/T genotype also increased the risk of overweight, thus affecting the risk of metabolic abnormalities. The effects of *GSTK1* T allele carriers and *GSTM1* null genotypes on the increased risk of overweight were confirmed in the male schizophrenia patients and/or the patients with current-smoking status. In contrast, no association between the polymorphisms and risk of metabolic abnormalities was observed in control subjects.

Discussion: These findings suggest that the polymorphisms of oxidative stress-related genes, including *MTHFR*, may be a significant risk factor for overweight-related metabolic abnormalities among schizophrenia patients in relation to gender differences and/or smoking status. This information regarding the effect of high-risk genotypes may be used to prevent overweight and metabolic abnormalities.

Keywords: oxidative stress, polymorphism, overweight, metabolic syndrome, schizophrenia, structural equation modeling

Corresponding Author: Junji Saruwatari, Ph.D., Division of Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto 862-0973, Japan; Tel/Fax: +81-96-371-4512, E-mail: junsaru@gpo.kumamoto-u.ac.jp

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INTRODUCTION

A number of human studies have reported that schizophrenia patients are at an increased risk of obesity and metabolic abnormalities, such as elevations of blood pressure, triglyceride (TG) level, low-density lipoprotein cholesterol (LDL-C) and fasting glucose level [1, 2]. These metabolic abnormalities in schizophrenia patients are strongly associated with the development of metabolic diseases including type 2 diabetes and cardiovascular diseases in comparison with general populations [3, 4]. Schizophrenia patients with metabolic diseases are at an increased risk of poor adherence to treatments, an impaired cognitive function, a short life expectancy and a decline in the quality of life [4, 5]. The most common cause of premature death among schizophrenia patients is cardiovascular diseases [3]. Therefore, clarification of the risk factors for obesity and/or metabolic syndrome among schizophrenia patients can contribute to the early prevention of cardiovascular diseases and of the improvement of life expectancy and quality of life.

The use of atypical antipsychotic drugs (AAPs), poor dietary habits, a high rate of smoking and sedentary behavior contribute to metabolic abnormalities among schizophrenia patients [4, 5]. However, innate factors (e.g. genetic polymorphisms) also play an important role [6]. Substantial evidence implicates increased oxidative stress as a potential pathogenetic mechanism in schizophrenia, and schizophrenia patients are considered to be in a state of oxidative stress [7, 8]. Oxidative stress is also an established risk factor for aging and the development and/or progression of metabolic diseases, including type 2 diabetes and cardiovascular diseases [9]. Therefore, the genetic polymorphisms associated with oxidative stress may play a key role in not only the development of schizophrenia but also metabolic abnormalities in schizophrenia patients [7, 8].

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the folate/homocysteine metabolic pathway, and its reduced enzyme activity is associated with an elevated homocysteine level [10]. Elevated homocysteine is considered toxic to cells due to the increase in reactive oxygen species [10]. The *MTHFR* rs1801133 polymorphism (C677T), which leads to reduced enzyme activity, was reported as a risk factor for hyperhomocysteinemia [11]. Similarly, the *MTHFR* rs1801131 polymorphism (A 1298C) also leads to reduced enzyme activity and may be associated with the elevation of the homocysteine level [12]. The *MTHFR* polymorphism was reported to be associated with the risk of obesity and/or metabolic syndrome in schizophrenia patients, but there is little consensus regarding such associations [6, 13].

Glutathione *S*-transferase (GST) is a multifunctional enzyme involved in the cellular detoxification of xenobiotics, endogenous and/or exogenous toxic metabolites and free radicals [14]. The GST supergene family consists of soluble cytosolic GST: alpha (A), mu (M), pi (P), omega (O), theta (T), delta (D), sigma (S) and zeta (Z); mitochondrial GST kappa (K); and membrane-bound microsomal GST (MGST) [14]. The null (homozygous deletion) genotypes of *GSTM1* and *GSTT1* result in a complete lack of enzymatic activity [14]. Epidemiological studies have shown that *GSTM1* and *GSTT1* null genotypes are associated with the predisposition to metabolic diseases such as type 2 diabetes and cardiovascular disease, especially in smokers [15, 16]. We previously reported that the null genotype of *GSTM1* may be a risk factor for overweight and having decreased high-density lipoprotein cholesterol (HDL-C) in schizophrenia patients [17]. GSTK1 is considered to be not only an antioxidant enzyme but also a key regulator of adiponectin multimerization (activation) [18]. Adiponectin, an adipose tissue-specific hormone, has been reported to be associated with adipose tissue inflammation, insulin resistance, and mitochondrial dysfunction and to have an important role in the development of obesity and its related diseases [19, 20]. The mRNA level of *GSTK1* in adipose tissue was found to correlate negatively with obesity in both mice and humans [18, 21]. The function of *GSTK1* -1308G > T (rs1917760) is not fully clarified, but the variant alters the gene expression [22]. We recently showed that the *GSTK1* rs1917760 polymorphism leads to a decreased expression of *GSTK1* mRNA in human peripheral blood mononuclear cells (PBMCs) of schizophrenia patients, and the polymorphism was associated with a high body mass index (BMI) value in male schizophrenia patients [23].

Clarifying gender differences in metabolic diseases, including type 2 diabetes and cardiovascular diseases, is a necessary step toward personalized medicine and improved public health [24]. Since the development and progression of psychiatry diseases are potentially affected by sex hormones, care that takes into account gender differences will also contribute to the treatment and/or prevention of metabolic abnormalities in schizophrenia patients [25]. Although the precise mechanisms are unclear, female schizophrenia patients have a higher incidence of antipsychotic medicine-related side effect of metabolic abnormality than males [26]. Furthermore, since there are gender differences in blood levels of homocysteine and adiponectin among schizophrenia patients [27, 28], there may also be gender differences in the effects of the polymorphisms of *MTHFR* on the development and/or progression of obesity and metabolic syndrome among schizophrenia patients.

In the present study, we analyzed the association of the polymorphisms of *MTHFR* with the risk for overweight and metabolic status among schizophrenia patients, while also paying careful attention to gender differences and patient smoking status (a major source of oxidative stress). In addition, the effects of *GSTs* polymorphisms on the risk for overweight and metabolic status also analyzed for confirmation of our previous findings.

SUBJECTS AND METHODS

Subjects and study protocol

A retrospective cross-sectional case-control analysis was performed consisting of 256 schizophrenia patients (147 males and 109 females, age: 51.6 ± 14.7 years) recruited from Hirosaki University Hospital in Japan, and 194 age- and sex-matched control subjects (110 males and 84 females, age: 52.2 ± 9.0 years). The age-matched and sex-matched controls were recruited from participants in a 1-day or 2-day health screening program conducted at the Japanese Red Cross Kumamoto Hospital Health Care Center.

This study protocol was approved by the ethics committees of the Faculty of Life Sciences at Kumamoto University, the Hirosaki University School of Medicine and the Japanese Red Cross Kumamoto Health Care Center. All subjects provided their written informed consent before entry into the study.

Measurements

Prior to enrollment in the present study, all of the schizophrenia patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) criteria and had been received antipsychotic therapy for at least three months at Hirosaki University Hospital, Japan. All of the control subjects had not been diagnosed with schizophrenia prior to enrollment in the study. When schizophrenia patients and control subject were recruited, the subjects with psychosis due to general medical conditions, substance-related psychosis, or mood disorders with psychotic features were excluded. Overweight was defined as a body mass index (BMI) ≥ 25 kg/m^2. The presence of metabolic syndrome was assessed based on the definitions proposed by the NCEP ATP III for Asians [29]. The waist circumference was measured at the umbilical level in a standing position, to the nearest 0.1 cm, by a technician. Fasting blood glucose, HDL-C, LDL-C and TG levels were determined from fasting blood samples using the standard methods of the Japan Society of Clinical Chemistry. The blood pressure (BP) was measured several times after a 5-min rest with the subject in the sitting position, and the average of the measurements was used. The subjects' demographics and medical history were obtained from their medical records and by face-to-face interviews with medical staff members using a structured questionnaire.

Genotyping

Genomic DNA was extracted from whole blood using a DNA purification kit (Qiagen, Flexi Gene DNA kit; Hilden, Germany). The genotypes of *MTHFR* rs1801133 (C677T), *MTHFR* rs1801131 (A1298C) and *GSTK1* rs1917760 (-1308G>T) were determined using a real-time TaqMan allelic discrimination assay (Applied Biosystems, Foster City, CA, USA) according to the protocols provided by the manufacturer (assay nos. C_1202883_20, C_850486_20 and C_11980950_10, respectively). The null genotypes of *GSTM1* and *GSTT1* were determined using polymerase chain reaction (PCR) amplification based on the presence or absence of a PCR amplification product, using beta-globin as an internal control, as described previously [15]. To ensure genotyping quality, we included DNA samples as internal controls (i.e. hidden samples of a known genotype) and negative controls (water).

Table 1. The demographic characteristics of the schizophrenia patients and the control subjects.

		Schizophrenia patients (n=256)	Controls (n=194)	*P* value
Age (year)		51.6 ± 14.7	52.2 ± 9.0	0.560
Female (%)		109 (42.6%)	84 (43.3%)	0.923
BMI (kg/m^2)		25.4 ± 4.3	23.2 ± 3.2	<0.001
Overweight (%)		131 (51.2%)	49 (25.3%)	<0.001
Metabolic syndrome (%)		64 (25.0%)	24 (12.4%)	0.001
Waist circumstance (cm)		87.7 ± 12.2	82.8 ± 8.2	<0.001
Systolic BP (mmHg)		125.6 ± 18.9	117.1 ± 16.4	<0.001
Diastolic BP (mmHg)		77.2 ± 12.2	72.8 ± 11.0	<0.001
Fasting blood glucose (mg/dL)		106.7 ± 38.7	96.5 ± 20.5	<0.001
Triglyceride (mg/dL)		141.9 ± 118.9	120.6 ± 88.7	0.030
HDL-C (mg/dL)		52.1 ± 15.2	65.4 ± 17.4	<0.001
Treatment with AAP (s)		182 (71.1)	-	
Outpatient (%)		143 (55.9)	-	
Current-smoker (%)		77 (51.0%)[a]	81 (41.8%)	0.102
MTHFR C677T	C/C	89 (34.8)	64 (33.0)	0.207
	C/T	135 (52.7)	93 (47.9)	
	T/T	32 (12.5)	37 (19.1)	
MTHFR A1298C	A/A	173 (67.6)	124 (63.9)	0.597
	A/C	75 (29.3)	65 (33.5)	
	C/C	8 (3.1)	5 (2.6)	
GSTT1	present	135 (52.7)	99 (51.0)	0.775
	null	121 (47.3)	95 (49.0)	
GSTM1	present	136 (53.1)	100 (51.5)	0.775
	null	120 (46.9)	94 (48.5)	
GSTK1	G/G	128 (50.0)	91 (46.9)	0.510
	G/T	106 (41.4)	84 (43.3)	
	T/T	22 (8.6)	19 (9.8)	

[a]Calculated among 151 schizophrenia patients for whom smoking information could be collected.

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol

Statistical analyses

The data are presented as the mean ± standard deviation or frequency (%) of the subjects. Student's *t*-test and Fisher's exact test were used for comparisons of the continuous and categorical variables, respectively. The effects of the genotypes of *MTHFR*, *GSTM1*, *GSTT1* and *GSTK1* and other cofactors (i.e. age, inpatient/outpatient status, and/or with or without AAP except for aripiprazole) on the prevalence of overweight and components of metabolic syndrome (i.e. waist circumstance ≥ 90 cm [in males] or ≥ 80 cm [in females], systolic blood pressure ≥ 135 or diastolic blood pressure ≥ 85, fasting blood glucose ≥ 100, TG ≥ 150 and HDL-C < 40 [in males] or < 50 [in females)] were analyzed by a logistic regression analysis separately in the schizophrenia patients and the control subjects stratified by sex. These associations were measured as the odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of overweight and components of metabolic syndrome. In addition, to assess both the direct and indirect effects of the genotypes and other cofactors on the risk of developing overweight and components of metabolic syndrome, the associations were analyzed by structural equation modeling. The goodness-of-fit on the structural equation modeling was evaluated based on the following criteria: chi-square minimum discrepancy/degree of freedom ratio (CMIN/DF) ≤ 2.0, goodness of fit index (GFI) > 0.90, adjusted goodness of fit index (AGFI) > 0.90, normed fit index (NFI) ≥ 0.90, comparative fit index (CFI) ≥ 0.90 and root mean square error of approximation (RMSEA) < 0.05. A value of $P < 0.05$ was considered to be statistically significant. Structural equation modeling and other statistical analyses were performed using

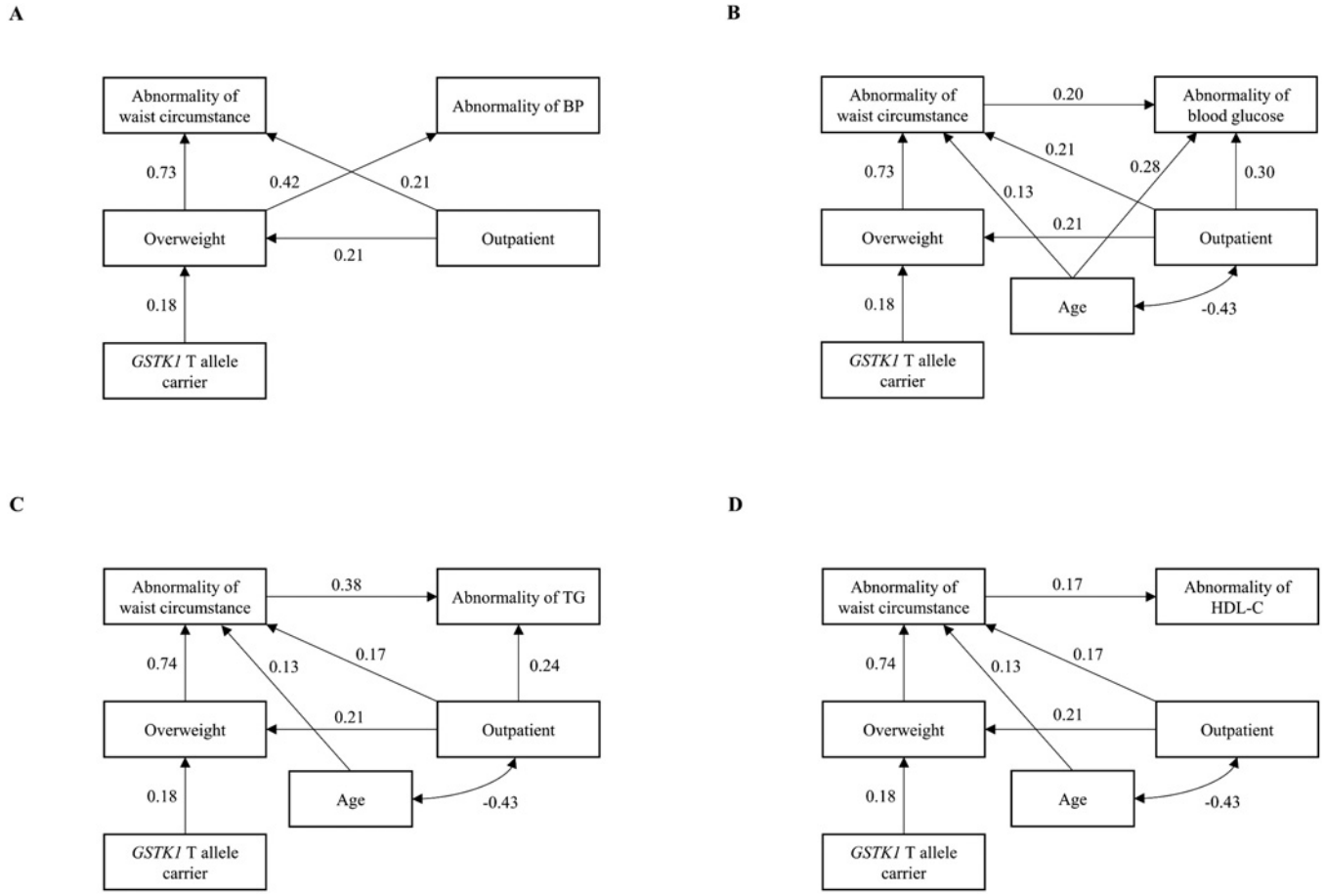

Figure 1. Structural equation modeling diagrams among the male schizophrenia patients.
These models show the associations of factors with abnormalities of the BP (A), fasting blood glucose (B), TG (C) and HDL-C (D). Lines with numbers represent significant paths with standardized β coefficients ($P < 0.05$). BP, blood pressure; GST, glutathione *S*-transferase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

the SPSS Amos software program (version 23.0; IBM Japan Inc., Tokyo, Japan) and the SPSS software package (version 23.0, IBM Japan Inc.), respectively.

RESULTS

Clinical characteristics of the subjects at baseline

Among the schizophrenia patients, the frequencies of *MTHFR* rs1801133 T allele, *MTHFR* rs 1801131 C allele and *GSTK1* rs1917760 T allele were 18.0%, 38.7% and 29.3%, respectively, and the genotype frequencies of the *GSTM1* null and *GSTT1* null were 46.9% and 47.3%, respectively. Among the control subjects, the frequencies of *MTHFR* rs1801133 T allele, *MTHFR* rs1801131 C allele and *GSTK1* rs1917760 T allele were 19.3%, 43.0% and 31.4%, respectively, and the genotype frequencies of the *GSTM1* null and *GSTT1* null were 51.5% and 51.0%, respectively. These observed genotype frequency distributions were consistent with the Hardy-Weinberg equilibrium ($P > 0.05$). The demographic characteristics of the schizophrenia patients and the control subjects are shown in Table 1. The values of BMI, waist circumstance, systolic and diastolic blood pressure, fasting blood glucose and TG, and the frequencies of overweight and metabolic syndrome were higher while the value of HDL-C was lower in schizophrenia patients than in control subjects (Table 1).

Effect of factors on the risk for overweight and components of metabolic syndrome

Supplemental Tables 1 and 2 show the associations of the risk for overweight and components of metabolic syndrome (i.e. abnormalities in waist circumstance, blood pressure, fasting blood glucose, TG and HDL-C) with the genotype, age, inpatient/outpatient status, and use of AAPs except for aripiprazole after stratifying according to gender in the schizophrenia patients as well as in the control subjects. In the female schizophrenia patients, the

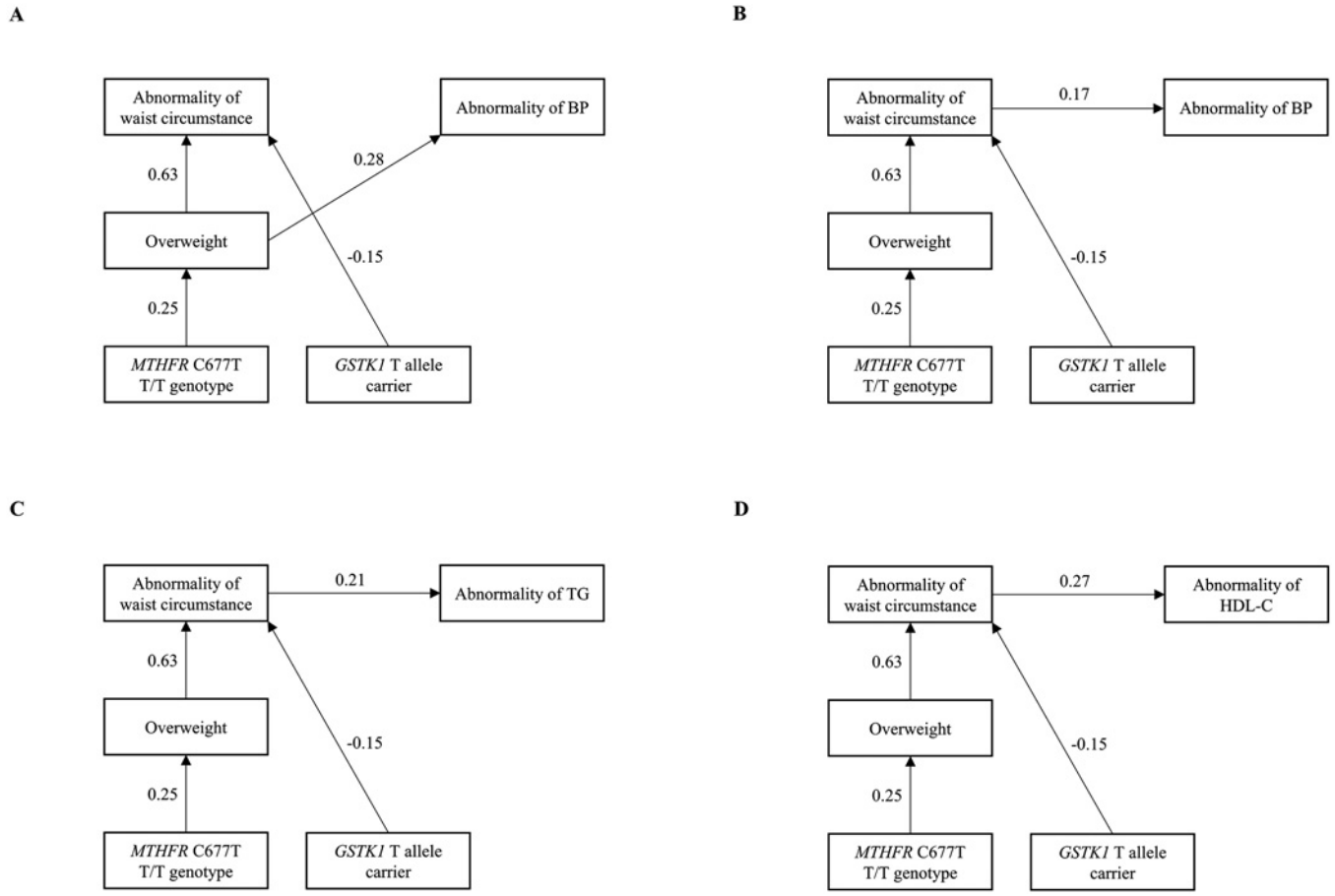

Figure 2. Structural equation modeling diagrams among the female schizophrenia patients.
These models show the associations of factors with abnormalities of the BP (A), fasting blood glucose (B), TG (C) and HDL-C (D). Lines with numbers represent significant paths with standardized β coefficients ($P < 0.05$). BP, blood pressure; GST, glutathione *S*-transferase; MTHFR, methylenetetrahydrofolate reductase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

MTHFR rs1801133 T/T genotype was significantly associated with the prevalence of overweight (Supplemental Table 1). In the male and female schizophrenia patients, *MTHFR* rs1801133 T/T, *GSTK1* T/T or G/T, and *GSTT1* null genotypes tended to be associated with the risk for overweight and/or abnormalities of waist circumstance, blood pressure, fasting blood glucose, TG and/or HDL-C (Supplemental Table 1). In contrast, no associations of the genotypes of *MTHFR* and *GSTs* with the risk for overweight and abnormalities of waist circumstance, blood pressure, fasting blood glucose, TG and HDL-C were observed in the control subjects (Supplemental Table 2)

Structural equation modeling

The structural equation models regarding the relationships of the genotypes and other factors with the risk for metabolic abnormalities among the male and female schizophrenia patients are shown in Figures 1 and 2, respectively. Among the male schizophrenia patients, structural equation models indicated that the *GSTK1* G/T and T/T genotypes increased the risk of overweight, and this genotype effect influenced the risk of developing metabolic abnormalities (Figure 1). In addition, outpatient status and increasing age were associated with an increase in the risk of overweight and metabolic abnormalities among male schizophrenia patients (Figure 1). Among the female schizophrenia patients, structural equation models indicated that the *MTHFR* rs1801133 T/T genotype increased the risk of overweight, and this genotype effect influenced the risk of developing metabolic abnormalities (Figure 2). In contrast, the *GSTK1* T allele was associated with a decrease in the risk of abnormality of waist circumstance among female schizophrenia patients (Figure 2).

To assess the effects of the smoking status on the relationship between genotypes and metabolic abnormalities, the structural equation models, strati-

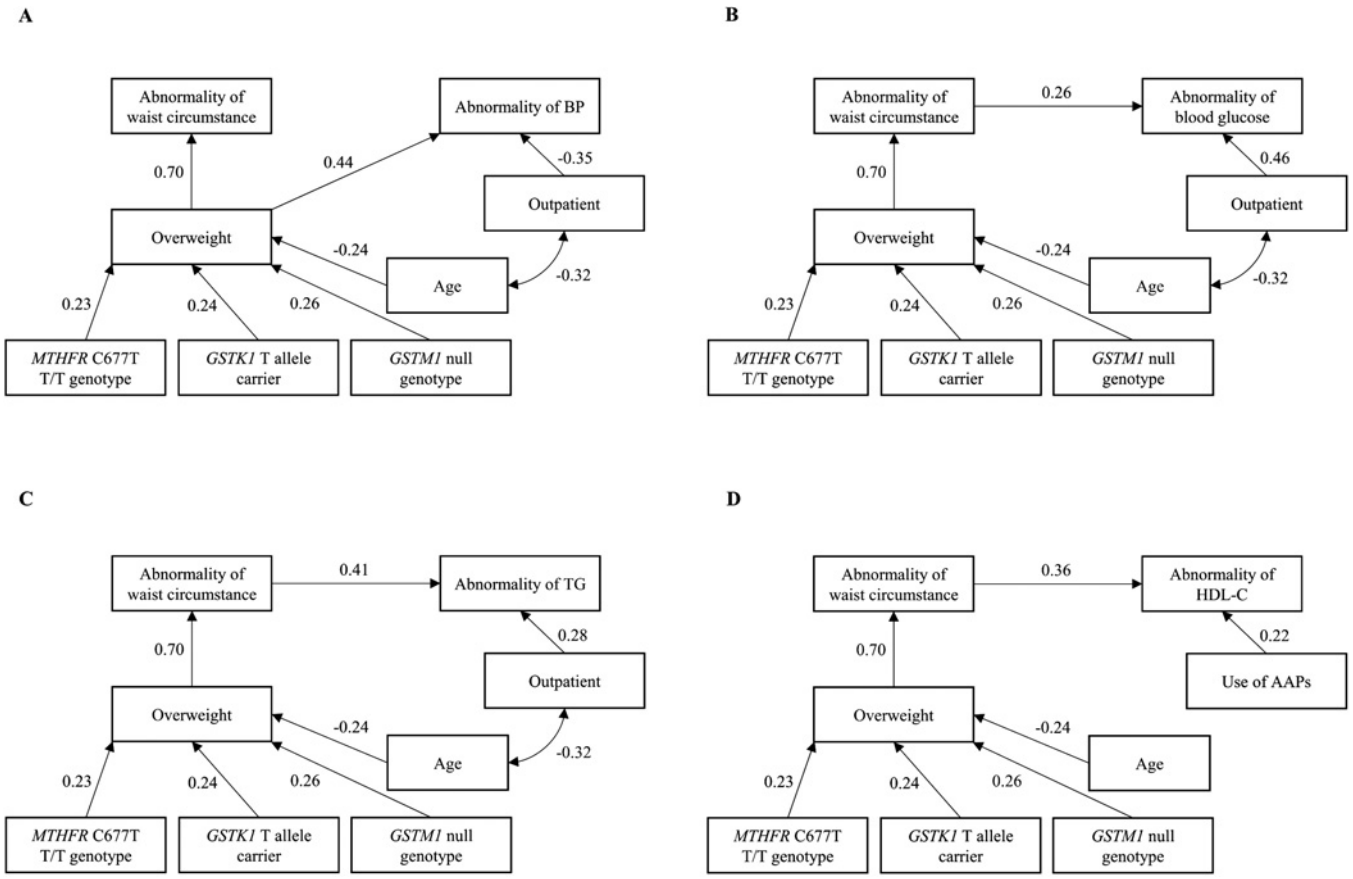

Figure 3. Structural equation modeling diagrams among the schizophrenia patients with current-smoking status.
These models show the associations of factors with abnormalities of the BP (A), fasting blood glucose (B), TG (C) and HDL-C (D). Lines with numbers represent significant paths with standardized β coefficients ($P < 0.05$). BP, blood pressure; GST, glutathione *S*-transferase; MTHFR, methylenetetrahydrofolate reductase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

fied by smoking status, are also shown in Figures 3 and 4. Among the schizophrenia patients with current-smoking status, the structural equation models indicated that the *MTHFR* rs1801133 T/T genotype, *GSTK1* G/T or T/T and *GSTM1* null genotype increased the risk of overweight, and this genotype effect influenced the risk of developing metabolic abnormalities (Figure 3). In addition, outpatient status, increasing age and the use of AAP were associated with an increase in the risk of overweight or metabolic abnormalities among the schizophrenia patients with current-smoking status (Figure 3). Furthermore, the effect of *MTHFR* rs 1801133 T/T genotype on the risk for overweight was observed in female schizophrenia patients with current-smoking status (standardized β coefficients: 0.77, $P < 0.001$), but not in male schizophrenia patients with current-smoking status ($P > 0.05$). Among the schizophrenia patients with non-smoking status, no associations of the genotypes with the risk of overweight or metabolic abnormalities were observed (Figure 4). In all structural equation models described above, the values of fitness statistics indicated a good fit for the structural equation models (CMIN/DF ≤ 2.0, GFI > 0.90, AGFI > 0.90, NFI ≥ 0.90, CFI ≥ 0.90 and RMSEA < 0.05).

DISCUSSION

This is the first study to clarify the effects of *MTHFR* rs1801133 T/T genotype on the risk for overweight and metabolic abnormalities in relation to gender differences and smoking status using a structural equation modeling in schizophrenia patients. We found that the *MTHFR* rs1801133 T/T genotype was associated with an increased risk of overweight and related metabolic abnormalities in female schizophrenia patients and in those with current-smoking status (Figures 2 and 3). However, no such genotype effect was observed in male schizophrenia patients, female schizophrenia pa-

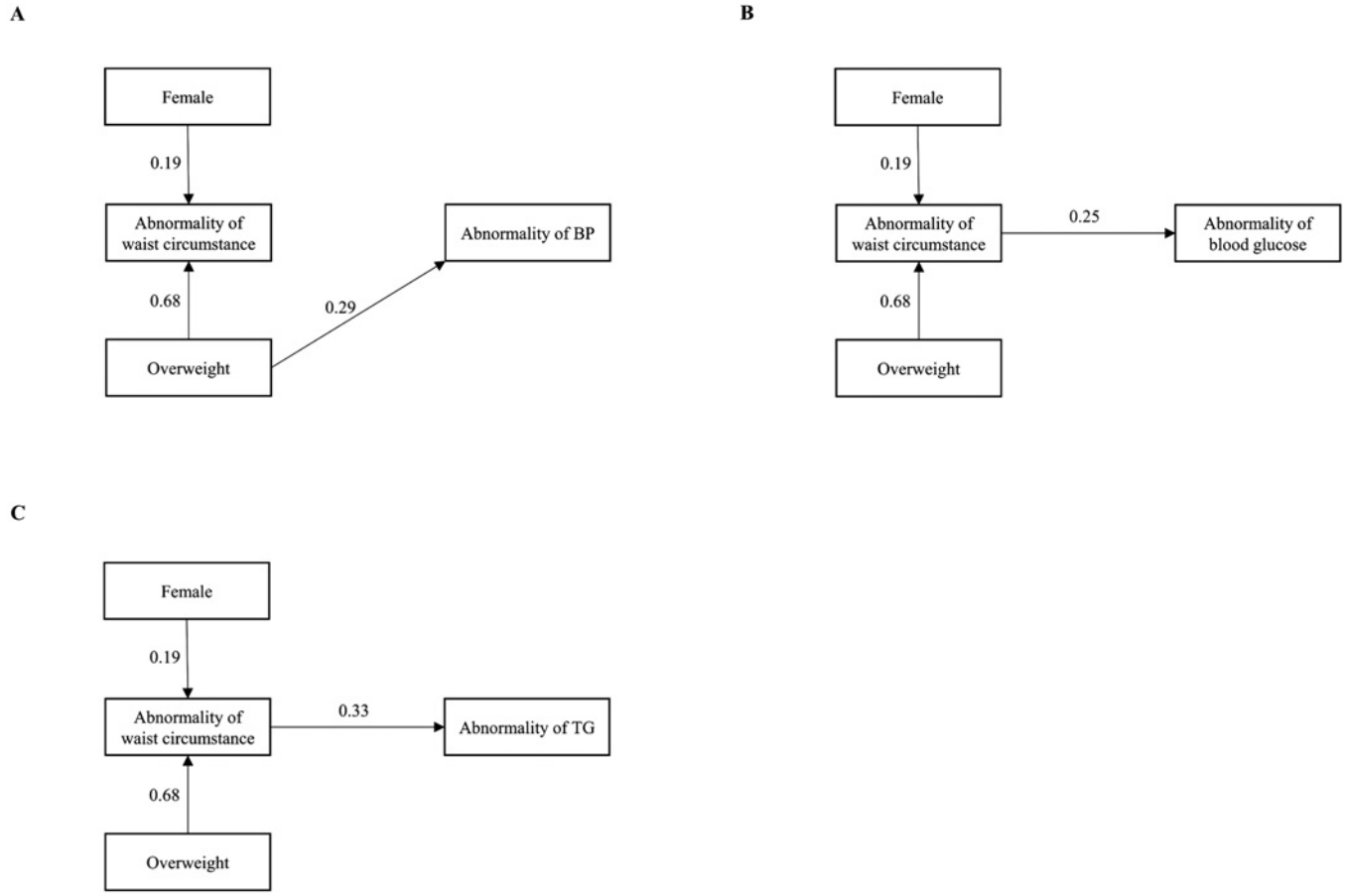

Figure 4. Structural equation modeling diagrams among the schizophrenia patients with non-smoking status. These models show the associations of factors with abnormalities of the BP (A), fasting blood glucose (B), TG (C). The model regarding the HDL-C could not be constructed. Lines with numbers represent significant paths with standardized β coefficients ($P < 0.05$). BP, blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

tients with non-smoking status or the control subjects (Figures 1 and 4). In the general population, the *MTHFR* rs1801133 polymorphism has been found to be an independent risk factor for developing metabolic syndrome in various ethnic groups (African Americans, American Caucasians, Asians and Europeans) [30, 31]. However, another cohort study has shown that the polymorphism was not associated with the risk for metabolic syndrome in a mixed population of Caucasians and African Americans [32]. A recent meta-analysis conducted in schizophrenia patients indicated that the *MTHFR* rs 1801133 polymorphism was associated with a risk of metabolic syndrome, although most studies were conducted in Caucasians being treated with AAPs [6]. MTHFR plays a key role in the folate metabolism pathway and induces the metabolism of homocysteine, a generator of reactive oxygen species [10]. Methionine synthase, vitamin B_{12} and MTHFR-synthesized N^5-methyltetrahydrofolate (methyl donor) synthesize methionine from homocysteine [10]. The *MTHFR* rs1801133T/T genotype decreases the enzyme activity by 60% [33], which results in the elevation of homocysteine and reduction of methionine. Since methionine is a systemic methyl group donator, the DNA of *MTHFR* rs 1801133 T/T genotype carriers is considered to be in a hypomethylated state [10]. In a previous report in schizophrenia patients, a hypomethylated state of DNA due to the *MTHFR* rs1801133 polymorphism was observed only in female patients [34]. Since variations in the degree of methylation were reported to be associated with the expression of various genes and the development of obesity, the *MTHFR* rs1801133 T/T genotype might be associated with the development of overweight due to changes in the expression of obesity-related genes [35]. Therefore, in female schizophrenia patients, the *MTHFR* rs1801133 T/T genotype and the combination of the genotype and current-smoking status may increase the levels of homocysteine and/or reactive oxygen species, which may result in over-

weight and metabolic abnormalities.

In this study, we confirmed that the *GSTK1* rs 1917760 T/T genotype and *GSTM1* null genotypes were associated with the increased risk of overweight and related metabolic abnormalities using a structural equation modeling approach, and these findings are in line with our previous results [17, 23]. Among them, we recently reported that the level of *GSTK1* mRNA was lower in carriers of the *GSTK1* rs1917760 T/T genotype than in those of the G/G genotype among schizophrenia patients [23]. Therefore, the decreased *GSTK1* mRNA level caused by the rs1917760 polymorphisms may be associated with a reduction in antioxidant activity and/or adiponectin multimerization, which may have resulted in the increased risk of overweight and related metabolic abnormalities among male schizophrenia patients.

There are some limitations in the present study. First, the present study was the cross-sectional study design and small sample size. Although the overall fits of the structural equation models were observed to be good, further longitudinal and large studies are needed to verify present findings. Second, we could not calculate the adjusted ORs of overweight by use of each AAP in the present study. Previous studies reported that there were differences in the effects of weight gain between each AAP [36, 37]. Finally, the effects of several potential factors related with the risk of overweight could not be analyzed (e.g. habits of diet and physical activity, duration of illness and schizophrenic symptoms).

In the present study, we clarified the associations of genotypes of oxidative stress-related genes, including *MTHFR* rs1801133 T/T genotype, with the risk of overweight and metabolic abnormalities in relation to gender differences and smoking status among schizophrenia patients using a structural equation modeling approach. The high prevalence of overweight and metabolic abnormalities has become a major concern in schizophrenia patients [3-5]. This information regarding the effect of high-risk genotypes in relation to gender differences and/or smoking status may be used to prevent overweight and metabolic abnormalities, although further investigations in larger and more diverse populations are needed to verify these findings.

CONFLICTS OF INTEREST

Dr. Yasui-Furukori has received grant/research support or honoraria from and spoken for Asteras, Dainippon, Eli Lilly, GlaxoSmithKline, Janssen-Pharma, Meiji, Mochida, Merck Sharp & Dohme, Otsuka, Pfizer, Takada, and Yoshitomi. The remaining authors declare that they have no conflict of interest.

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Supplemental Table 1. The effects of the factors on the risk of overweight and metabolic abnormalities among the male and female SCZ patients.

	Male SCZ patients		Female SCZ patients	
	Adjusted ORs [95% CIs]	*P*	Adjusted ORs [95% CIs]	*P*
Overweight				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	1.98 [0.98-3.98]	0.057	1.08 [0.48-2.45]	0.855
GSTT1 null (vs. present)	1.83 [0.90-3.70]	0.095	1.22 [0.56-2.66]	0.620
GSTM1 null (vs. present)	0.93 [0.46-1.86]	0.830	0.92 [0.41-2.06]	0.832
MTHFR rs1801133 T/T (vs. C/C or C/T)	0.52 [0.16-1.72]	0.283	5.58 [1.42-21.93]	0.014
MTHFR rs1801131 C/A, C/C (vs. A/A)	1.22 [0.57-2.61]	0.609	1.25 [0.52-3.02]	0.615
Age	0.98 [0.96-1.01]	0.187	1.00 [0.97-1.03]	0.926
Outpatient (vs. inpatient)	1.89 [0.87-4.12]	0.107	0.92 [0.36-2.35]	0.858
Use of AAPs (vs. non-use of AAPs)	0.83 [0.35-1.99]	0.679	0.91 [0.40-2.10]	0.829
Waist circumstance abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	1.27 [0.63-2.58]	0.505	0.55 [0.22-1.34]	0.185
GSTT1 null (vs. present)	1.74 [0.86-3.54]	0.125	1.78 [0.76-4.18]	0.184
GSTM1 null (vs. present)	0.81 [0.41-1.64]	0.564	0.71 [0.30-1.70]	0.438
MTHFR rs1801133 T/T (vs. C/C or C/T)	0.34 [0.10-1.19]	0.090	4.65 [0.93-23.23]	0.061
MTHFR rs1801131 C/A, C/C (vs. A/A)	1.03 [0.49-2.19]	0.934	1.85 [0.70-4.89]	0.218
Age	1.01 [0.98-1.03]	0.631	1.01 [0.97-1.04]	0.699
Outpatient (vs. inpatient)	3.02 [1.36-6.70]	0.007	1.03 [0.37-2.89]	0.958
Use of AAPs (vs. non-use of AAPs)	0.53 [0.22-1.28]	0.160	0.81 [0.32-2.04]	0.656
Blood pressure abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	0.81 [0.40-1.64]	0.561	0.76 [0.31-1.83]	0.537
GSTT1 null (vs. present)	1.98 [0.98-3.99]	0.056	1.35 [0.58-3.14]	0.487
GSTM1 null (vs. present)	0.82 [0.41-1.64]	0.576	1.74 [0.72-4.21]	0.223
MTHFR rs1801133 T/T (vs. C/C or C/T)	1.06 [0.34-3.35]	0.918	1.96 [0.61-6.26]	0.258
MTHFR rs1801131 C/A, C/C (vs. A/A)	1.60 [0.76-3.41]	0.220	0.77 [0.28-2.13]	0.609
Age	0.97 [0.95-1.00]	0.034	1.03 [0.99-1.06]	0.159
Outpatient (vs. inpatient)	0.82 [0.37-1.82]	0.630	2.41 [0.85-6.86]	0.099
Use of AAPs (vs. non-use of AAPs)	0.36 [0.15-0.87]	0.023	0.84 [0.34-2.06]	0.699
Fasting blood glucose abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	0.85 [0.41-1.79]	0.675	1.71 [0.72-4.07]	0.223
GSTT1 null (vs. present)	1.84 [0.88-3.83]	0.104	0.70 [0.31-1.57]	0.695
GSTM1 null (vs. present)	1.31 [0.64-2.70]	0.467	0.88 [0.38-2.04]	0.763
MTHFR rs1801133 T/T (vs. C/C or C/T)	1.53 [0.46-5.10]	0.492	1.33 [0.42-4.22]	0.631
MTHFR rs1801131 C/A, C/C (vs. A/A)	0.80 [0.37-1.76]	0.582	0.49 [0.18-1.32]	0.157
Age	1.05 [1.02-1.08]	0.002	1.04 [1.00-1.07]	0.057
Outpatient (vs. inpatient)	3.02 [1.36-6.70]	0.007	2.04 [0.75-5.55]	0.163
Use of AAPs (vs. non-use of AAPs)	1.61 [0.62-4.13]	0.327	1.90 [0.77-4.66]	0.162
TG abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	1.37 [0.64-2.91]	0.416	0.67 [0.26-1.73]	0.404
GSTT1 null (vs. present)	2.07 [0.98-4.38]	0.056	0.77 [0.31-1.89]	0.560
GSTM1 null (vs. present)	0.96 [0.46-2.01]	0.915	1.05 [0.41-2.67]	0.924
MTHFR rs1801133 T/T (vs. C/C or C/T)	1.42 [0.42-4.83]	0.576	0.34 [0.07-1.69]	0.186
MTHFR rs1801131 C/A, C/C (vs. A/A)	0.74 [0.32-1.69]	0.470	1.23 [0.45-3.34]	0.690
Age	0.99 [0.96-1.01]	0.334	1.01 [0.97-1.04]	0.732
Outpatient (vs. inpatient)	4.17 [1.79-9.72]	0.001	2.89 [0.91-9.24]	0.073
Use of AAPs (vs. non-use of AAPs)	1.04 [0.42-2.56]	0.930	0.93 [0.35-2.42]	0.874
HDL-C abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	1.01 [0.48-2.11]	0.982	0.80 [0.35-1.81]	0.589
GSTT1 null (vs. present)	0.90 [0.43-1.88]	0.781	1.26 [0.57-2.77]	0.563
GSTM1 null (vs. present)	1.42 [0.69-2.94]	0.343	1.27 [0.56-2.88]	0.561
MTHFR rs1801133 T/T (vs. C/C or C/T)	0.88 [0.25-3.09]	0.847	1.13 [0.36-3.55]	0.837
MTHFR rs1801131 C/A, C/C (vs. A/A)	1.29 [0.59-2.81]	0.530	0.60 [0.23-1.52]	0.280
Age	0.98 [0.96-1.01]	0.234	1.00 [0.97-1.04]	0.883
Outpatient (vs. inpatient)	0.69 [0.30-1.60]	0.387	0.63 [0.25-1.63]	0.341
Use of AAPs (vs. non-use of AAPs)	1.09 [0.44-2.72]	0.853	1.21 [0.52-2.82]	0.659

SCZ, schizophrenia; OR, odds ratio; CI, confidence interval; GST, glutathione *S*-transferase; MTHFR, methylenetetrahydrofolate reductase; AAP, atypical antipsychotic drug; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

Supplemental Table 2. The effects of the factors on the risk of overweight and metabolic abnormalities among the male and female control subjects.

	Male controls		Female controls	
	Adjusted ORs [95% CIs]	*P*	Adjusted ORs [95% CIs]	*P*
Overweight				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	1.98 [0.98-3.98]	0.057	1.08 [0.48-2.45]	0.855
GSTT1 null (vs. present)	1.83 [0.90-3.70]	0.095	1.22 [0.56-2.66]	0.620
GSTM1 null (vs. present)	0.93 [0.46-1.86]	0.830	0.92 [0.41-2.06]	0.832
MTHFR rs1801133 T/T (vs. C/C or C/T)	0.52 [0.16-1.72]	0.283	5.58 [1.42-21.93]	0.014
MTHFR rs1801131 C/A, C/C (vs. A/A)	1.22 [0.57-2.61]	0.609	1.25 [0.52-3.02]	0.615
Age	0.98 [0.96-1.01]	0.187	1.00 [0.97-1.03]	0.926
Waist circumstance abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	1.27 [0.63-2.58]	0.505	0.55 [0.22-1.34]	0.185
GSTT1 null (vs. present)	1.74 [0.86-3.54]	0.125	1.78 [0.76-4.18]	0.184
GSTM1 null (vs. present)	0.81 [0.41-1.64]	0.564	0.71 [0.30-1.70]	0.438
MTHFR rs1801133 T/T (vs. C/C or C/T)	0.34 [0.10-1.19]	0.090	4.65 [0.93-23.23]	0.061
MTHFR rs1801131 C/A, C/C (vs. A/A)	1.03 [0.49-2.19]	0.934	1.85 [0.70-4.89]	0.218
Age	1.01 [0.98-1.03]	0.631	1.01 [0.97-1.04]	0.699
Blood pressure abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	0.81 [0.40-1.64]	0.561	0.76 [0.31-1.83]	0.537
GSTT1 null (vs. present)	1.98 [0.98-3.99]	0.056	1.35 [0.58-3.14]	0.487
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MTHFR rs1801131 C/A, C/C (vs. A/A)	1.60 [0.76-3.41]	0.220	0.77 [0.28-2.13]	0.609
Age	0.97 [0.95-1.00]	0.034	1.03 [0.99-1.06]	0.159
Fasting blood glucose abnormality				
GSTK1 rs1917760 G/T or T/T (vs. G/G)	0.85 [0.41-1.79]	0.675	1.71 [0.72-4.07]	0.223
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Age	1.05 [1.02-1.08]	0.002	1.04 [1.00-1.07]	0.057
TG abnormality				
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GSTT1 null (vs. present)	0.90 [0.43-1.88]	0.781	1.26 [0.57-2.77]	0.563
GSTM1 null (vs. present)	1.42 [0.69-2.94]	0.343	1.27 [0.56-2.88]	0.561
MTHFR rs1801133 T/T (vs. C/C or C/T)	0.88 [0.25-3.09]	0.847	1.13 [0.36-3.55]	0.837
MTHFR rs1801131 C/A, C/C (vs. A/A)	1.29 [0.59-2.81]	0.530	0.60 [0.23-1.52]	0.280
Age	0.98 [0.96-1.01]	0.234	1.00 [0.97-1.04]	0.883

OR, odds ratio; CI, confidence interval; GST, glutathione *S*-transferase; MTHFR, methylenetetrahydrofolate reductase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.