Association between serum folate levels and schizophrenia based on gender

Short running title: Folate and gender in schizophrenia

This manuscript is submitted to molecular psychiatry and psychobiology fields of the journal.

Yukiko Tomioka, MD[1], Makoto Kinoshita, MD, PhD[1], Hidehiro Umehara, MD, PhD[1], Tomohiko Nakayama, MD[1], Shin-ya Watanabe, MD, PhD[1], Masahito Nakataki, MD, PhD[1], Shusuke Numata, MD, PhD[1], and Tetsuro Ohmori, MD, PhD[1]

[1] *Department of Psychiatry, Institute of Biomedical Science, Tokushima University Graduate School, Tokushima, Japan*

Corresponding author: Shusuke Numata, MD, PhD

Department of psychiatry, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-8-15 Kuramoto-cho Tokushima 770-8503, Japan

TEL: 81-886-33-7130

FAX: 81-886-33-7131

E-mail address: shu-numata@umin.ac.jp

The number of words in the manuscript is 2124, and abstract is 243.

3 figures and 2 tables.

Abstract

Aim: Gender differences in serum folate concentrations are well known, but no studies have investigated the association between serum folate levels and schizophrenia based on gender. In this study in a Japanese population, we examined the difference in serum folate levels between patients with schizophrenia and non-psychiatric controls stratified by gender. The relationships between serum folate levels, plasma total homocysteine (tHcy) and serum vitamin B6 (pyridoxal) levels were also examined using data from our previous studies.

Methods: The serum folate concentrations of 482 patients diagnosed with schizophrenia and 1,350 non-psychiatric control subjects were measured. We conducted an analysis of covariance to examine the differences in serum folate levels between the two groups based on gender. Spearman's rank correlation was used to evaluate the relationships between folate, tHcy and vitamin B6 levels.

Results: In the control group, serum folate concentrations were higher in women than in men. Lower levels of serum folate were observed in both male and female patients with schizophrenia. An inverse correlation between serum folate and plasma tHcy and a weak positive correlation between serum folate and vitamin B6 were observed in the combined cohort.

Conclusion: Our findings suggest that (1) a low serum folate level may be associated with schizophrenia regardless of gender, and (2) folate administration may be beneficial for the treatment of schizophrenia. In schizophrenic patients with low serum folate levels, folate administration might result in improvements in high tHcy and an increase in low vitamin B6 levels.

Keywords

Introduction

Growing evidence relating to the pathophysiology of schizophrenia indicates a potential effect of altered one-carbon metabolism, including epigenetic dysregulation.[1-10] Folate and related B-vitamins are involved in one-carbon metabolism and in the production of S-adenosylmethionine, a universal methyl donor required for various reactions including the production of neurotransmitters.[11]

To date, several studies have investigated the relationship between blood folate levels and schizophrenia. Some studies have shown lower folate levels in patients with schizophrenia compared with controls,[12-20] whereas others did not observe such differences.[21-26] Recent meta-analyses have demonstrated decreased blood folate levels in schizophrenic patients in the group where all samples were pooled, as well as in the Asian population subgroup.[27,28] A recent large-scale cohort study described low serum concentrations of folate in men compared with women.[29] However, no association studies to examine the relationship between serum folate levels and schizophrenia by gender have been conducted.

The objective of the current study was to determine whether there was a significant difference in serum folate levels between patients with schizophrenia and non-psychiatric controls, stratified by gender, in a Japanese population. We also examined the relationships between serum folate levels, plasma total homocysteine (tHcy) and serum vitamin B6 (pyridoxal) levels using data of common participants from our previous studies.[4,9]

Methods

Participants

A total of 482 patients with schizophrenia (282 men, mean age 58.5 ± 9.9 years; 200 women, mean age 59.6 ± 10.5 years) were recruited from Tokushima University Hospital, Japan and its related psychiatric hospitals. Schizophrenia was diagnosed by at least two expert psychiatrists based on the DSM-IV criteria, extensive clinical interviews with the patients and a review of their medical records. Most of the patients were hospitalized and treated with various antipsychotic drugs. The median chlorpromazine equivalent dose was 550 mg/day (0 - 3,450 mg/day). For the control group, a total of 1,350 healthy individuals (443 men, mean age 38.3 ± 11.8 years; 907 women, mean age 43.0 ± 11.8 years) were recruited from hospital staff, students, and company employees, without structured interviews. A portion of the participants in the present study overlapped with those from our previous studies.[4,9] The current study was approved by the Ethics Committee of Tokushima University Hospital, and all enrolled participants provided their written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Measurement of serum folate concentrations

Non-fasting serum folate levels were measured by a chemiluminescent enzyme immunoassay (CLEIA) at SRL Laboratory (Tokyo, Japan) using an Access folate assay kit (Beckman Coulter, CA, USA). Serum folate concentration was measurable from 4.0 ng/ml to 20.0 ng/ml.

Statistical analysis

The demographic differences in age between schizophrenic patients and controls were compared using Welch's t-tests. The gender differences between patients and controls were compared using chi-squared tests. Folate concentration data were natural log-

transformed before the analysis because the raw serum folate concentration values did not follow a Gaussian distribution. When we compared the patient and control groups, a separate analysis of covariance was conducted by gender after adjusting for age. We used Spearman's rank correlation to examine the relationships between folate, tHcy and vitamin B6 levels. Statistical analyses were performed with R software (ver. 3.5.1), with the threshold for statistical significance at p=0.05.

Results

Demographic characteristics of participants

In the total population of 1,832 participants, the serum folate levels of 7 patients and 15 controls exceeded the upper limit of detection (>20.0 ng/ml). These samples were excluded from further analyses. The demographic characteristics of the 475 patients and 1,335 controls are presented in Table 1. Mean folate levels of the patient and control groups were 3.95 ± 2.17 (mean ± standard deviation) and 5.87 ± 2.69 ng/mL, respectively. There were significant differences in age and gender between the two groups (p < 0.05). The mean age of the patient and control groups were 58.9 ± 10.2 and 41.5 ± 12.0 years, respectively. The male:female ratios of the patient and control groups were 1.44 and 0.49, respectively.

Differences in serum folate levels between the patient and control groups by gender

Firstly, we examined the differences in the natural log-transformed serum folate levels and identified gender differences in these levels in the control group (p=1.6 × 10^{-8}). However, in the patient group, no significant gender differences were observed (p=0.087) (Fig. 1).

We then conducted a stratified analysis to separately examine the differences in natural log-transformed serum folate levels between the patient and control groups by gender. An analysis of covariance showed significantly lower serum folate levels in the patient group compared with the controls in both male and female cohorts (F(1, 716)=140.6, p=9.6 × 10^{-30}; F(1, 1088)=191.6, p=2.9 × 10^{-40}, respectively) (Fig. 2). Based on previous study,[30] the prevalence of low serum folate concentrations in male and female patients according to the 10th percentile was 36.8% and 49.2%, respectively.

Relationship between folate, tHcy and vitamin B6 in blood

We examined the relationship between serum folate levels and plasma tHcy, and the relationship between serum folate and vitamin B6 levels using data of the 1,155 common

participants from our previous studies.[4,9] The demographic characteristics of the 339 patients and 816 controls are presented in Table 2. In the 339 patients, the prevalence of low serum folate concentrations in male and female patients according to the control 10th percentile was 41.2% and 51.9%, respectively. The prevalence of high plasma tHcy concentrations in male and female patients according to the control 90th percentile was 34.8% and 34.1%, respectively. The prevalence of low serum vitamin B6 concentrations in male and female patients according to the control 10th percentile was 71.1% and 42.2%, respectively.

Examination of the correlation between the natural log-transformed serum folate and the natural log-transformed plasma tHcy levels revealed a significant inverse correlation between these levels in both the schizophrenic patients and the control group as well as in the combined cohort (r=−0.47, p=4.1×10^{-20}; r=−0.36, p=6.2×10^{-27}; r=-0.51, p=5.7×10^{-79}, respectively) (Fig. 3A). When we examined the correlation between the natural log-transformed serum folate and the natural log-transformed serum vitamin B6 levels, there was a significant weak positive correlation between these levels in the control group and in the combined cohort (r = 0.096, p = 6.0×10^{-3}; r = 0.28, p = 8.8×10^{-23}, respectively). In schizophrenic patients, no significant correlation was demonstrated (r = 0.027, p = 0.62) (Fig. 3B).

Discussion

Our study demonstrated that serum folate concentrations are higher in women than in men in this Japanese cohort of non-psychiatric subjects. These results were consistent with the results of a large population-based cross-sectional study conducted in Israe.[29] The findings suggest that different gender cut-off values may be required when defining low serum folate levels in patients.

Because we observed a gender difference in the serum folate concentrations of the control group, we also conducted an analysis of covariance by gender. The results demonstrated significantly lower levels of serum folate in the schizophrenia group compared with the control group in both male and female cohorts. These findings suggest that decreased serum folate levels may be a risk factor for schizophrenia in the Japanese population, regardless of gender. We previously demonstrated increased plasma tHcy and decreased serum vitamin B6 levels in schizophrenia. [4,9] Folate deficiency might be associated with schizophrenia by acting either through hyperhomocysteinemia and/or homocysteine-independent effects on neuronal progenitor division and/or altered one-carbon metabolism.[2] Two recent meta-analyses described lower peripheral blood levels of folate in schizophrenia.[27,28] Wang and colleagues conducted a meta-analysis of 26 serum studies (1,773 cases and 1,930 controls) and observed decreased serum folate levels in patients with schizophrenia.[28] In their subgroup analyses, they also observed decreased serum folate levels in patients with schizophrenia, before as well as after drugs.[28] Examination of the effect of antipsychotic drugs on serum folate levels in our present study revealed a weak inverse relationship between the equivalent dose of antipsychotics and the natural log-transformed serum folate levels (r=−0.12, p=5.7×10^{-3}). Moreover, folate levels in serum were negatively correlated in the schizophrenia group treated with high therapeutic doses of chlorpromazine equivalents (>400 mg/day).[23]

We examined the relationship between serum folate levels, plasma tHcy, and serum vitamin B6 levels. Two studies showed a negative correlation between serum folate and

tHcy concentrations in the control group as well as in the schizophrenia group.[17,30] Two other studies also showed a negative correlation between serum folate and tHcy concentrations in their schizophrenic patient cohorts.[14,31] However, two additional studies reported no correlations between serum folate and tHcy concentrations in a small series of schizophrenic patients.[15,16] Research on the relationship between serum folate and vitamin B6 concentrations includes one study reporting a positive correlation between serum folate and pyridoxal -5`-phosphate (PLP) values in both the schizophrenia group and in the control group.[30] However, in our study we observed a positive correlation only in the control group. This discrepancy may be due to the different forms of vitamin B6 (PLP vs. pyridoxal) and/or the small sample size of our patient cohort in examinations of the correlation between serum folate and vitamin B6 (10,765 samples will be needed to prove with r=0.027 and Power=0.8) and/or dietary patterns of patients.[32,33]

Our findings of decreased folate levels in patients with schizophrenia and the correlations between folate and tHcy, and folate and vitamin B6 in the combined cohort suggest that folate administration may be beneficial in the treatment of patients with schizophrenia. Folate administration increased low folate levels, resulting in improvements in high tHcy and low vitamin B6 levels. A meta-analysis of double-blind, placebo-controlled, randomized clinical trials suggested that antipsychotics supplemented with folate, folic acid, methylfolate, or folinic acid (pooled data) improved negative symptoms in schizophrenia.[34] Furthermore, Roffman and colleagues demonstrated that patients with schizophrenia receiving L-methylfolate exhibited convergent changes in ventromedical prefrontal physiology, altered limbic connectivity and increased cortical thickness as well as clinical improvements, including negative symptoms, in the randomized clinical trial.[35] Wang and colleagues recently reported that the degree of serum tHcy associated with long-term folic acid supplementation can be influenced by gender, methylenetetrahydrofolate reductase (MTHFR) C677T genotypes, baseline folate, tHcy, estimated glomerular filtration rate (eGFR), and smoking.[36] Further

studies should consider these factors when evaluating the therapeutic effect of folate supplementation in patients with schizophrenia.

The study has several limitations. We did not conduct general laboratory tests to exclude the participants with physical complications. We did not consider nutritional intake and food effects of participants because of a lack of data. We did not examine the relationship between serum folate levels and clinical symptoms as psychological symptoms were not evaluated at the time of blood collection. In addition, most of our patients were chronic hospitalized patients who were treated with antipsychotic drugs. Furthermore, this was a cross-sectional study, and the causal relationship between serum folate levels and schizophrenia was therefore not clarified. Finally, low serum folate levels have been observed in patients with depression and bipolar as well as schizophrenia.[37,38]

Conclusion

We observed decreased serum folate levels in patients with schizophrenia based on gender in a Japanese population. Significant correlations between blood folate, tHcy and vitamin B6 concentrations were observed in the combined samples. These findings provide further insights into the pathology and treatment of schizophrenia related to one-carbon metabolism.

Acknowledgements

Disclosure statement

Author contributions

Numata S designed the study and wrote the study protocol. Ohmori T and Numata S managed the research. Kinoshita M, Nakayama T, Numata S, Tomioka Y, Umehara H, and Watanabe SY collected the samples and conducted the experiments. Kinoshita M, Nakataki M, and Tomioka Y conducted the statistical analyses. Tomioka Y and Numata S wrote the publication draft. All authors have contributed to and have approved the final article.

Figure legends

Table 1.

Demographic characteristics of participants with measurable folate levels

SD = standard deviation; CP = chlorpromazine equivalents.

Table 2.

Demographic characteristics of participants with folate, tHcy, and pyridoxal data

SD = standard deviation; tHcy = total homocysteine.

Figure 1.

Gender differences in serum folate levels in the control and schizophrenic groups

Y-axis is the natural log-transformed serum folate value.

Left side is the control group, and right side is the schizophrenic group.

*** p ≤ .001.

Figure 2.

Differences in serum folate levels between the schizophrenic and control groups

Y-axis is the natural log-transformed serum folate value.

Left side is the male cohort, and right side is the female cohort.

*** p ≤ .001.

Figure 3.

(A) Correlation between serum folate levels and total plasma tHcy levels

Y-axis is the natural log-transformed serum folate value, and X-axis is the natural log-transformed total plasma tHcy value. The value of r represents Spearman's rank correlation coefficient.

(B) Correlation between serum folate levels and serum vitamin B6 levels

Y-axis is the natural log-transformed serum folate value, and X-axis is the natural log-

transformed serum pyridoxal value. The value of r represents Spearman's rank correlation coefficient.

Reference

1.   Frankenburg FR. The role of one-carbon metabolism in schizophrenia and depression. *Harv Rev Psychiatry.* 2007 Jul-Aug;**15**(4):146-60.

2.   Krebs MO, Bellon A, Mainguy G, Jay TM, Frieling H. One-carbon metabolism and schizophrenia: current challenges and future directions. *Trends Mol Med.* 2009 Dec;**15**(12):562-70.

3.   Kinoshita M, Numata S, Tajima A *et al.* DNA methylation signatures of peripheral leukocytes in schizophrenia. *Neuromolecular Med.* 2013 Mar;**15**(1):95-101.

4.   Nishi A, Numata S, Tajima A *et al.* Meta-analyses of Blood Homocysteine Levels for Gender and Genetic Association Studies of the MTHFR C677T Polymorphism in Schizophrenia. *Schizophr Bull.* 2014 Sep;**40**(5):1154-63.

5.   Arai M, Miyashita M, Kobori A, Toriumi K, Horiuchi Y, Itokawa M. Carbonyl stress and schizophrenia. *Psychiatry Clin Neurosci.* 2014 Sep;**68**(9):655-65.

6.   Kinoshita M, Numata S, Tajima A *et al.* Cumulative effect of the plasma total homocysteine-related genetic variants on schizophrenia risk. *Psychiatry Res.* 2016 Dec 30;**246**:833-837.

7.   Kinoshita M, Numata S, Tajima A *et al.* Effect of Clozapine on DNA Methylation in Peripheral Leukocytes from Patients with Treatment-Resistant Schizophrenia. *Int J Mol Sci.* 2017 Mar 14;**18**(3).

8.   Itokawa M, Miyashita M, Arai M *et al.* Pyridoxamine: A novel treatment for schizophrenia with enhanced carbonyl stress. *Psychiatry Clin Neurosci.* 2018 Jan;**72**(1):35-44.

9.   Tomioka Y, Numata S, Kinoshita M *et al.* Decreased serum pyridoxal levels in schizophrenia: meta-analysis and Mendelian randomization analysis. *J Psychiatry Neurosci.* 2018 May;**43**(3):194-200.

10.   Kuehner JN, Bruggeman EC, Wen Z, Yao B. Epigenetic Regulations in Neuropsychiatric Disorders. *Front Genet.* 2019 Apr 4;**10**:268.

11.   McGarel C, Pentieva K, Strain JJ, McNulty H. Emerging roles for folate and

related B-vitamins in brain health across the lifecycle. *Proc Nutr Soc.* 2015 Feb;**74**(1):46-55.

12.   Herrán A, García-Unzueta MT, Amado JA, López-Cordovilla JJ, Díez-Manrique JF, Vázquez-Barquero JL. Folate levels in psychiatric outpatients. Psychiatry Clin Neurosci. 1999 Aug;53(4):531-3.

13.   Goff DC, Bottiglieri T, Arning E *et al.* Folate, homocysteine, and negative symptoms in schizophrenia. *Am J Psychiatry.* 2004 Sep;**161**(9):1705-8.

14.   Lee YS, Han DH, Jeon CM *et al.* Serum homocysteine, folate level and methylenetetrahydrofolate reductase 677, 1298 gene polymorphism in Korean schizophrenic patients. *Neuroreport.* 2006 May 15;**17**(7):743-6.

15.   Petronijević ND, Radonjić NV, Ivković MD *et al.* Plasma homocysteine levels in young male patients in the exacerbation and remission phase of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008 Dec 12;**32**(8):1921-6.

16.   Kale A, Naphade N, Sapkale S *et al.* Reduced folic acid, vitamin B12 and docosahexaenoic acid and increased homocysteine and cortisol in never-medicated schizophrenia patients: Implications for altered one-carbon metabolism. *Psychiatry Res.* 2010 Jan 30;**175**(1-2):47-53.

17.   Kim TH, Moon SW. Serum homocysteine and folate levels in korean schizophrenic patients. *Psychiatry Investig.* 2011 Jun;**8**(2):134-40.

18.   Song X, Fan X, Li X *et al.* Serum levels of BDNF, folate and homocysteine: in relation to hippocampal volume and psychopathology in drug naïve, first episode schizophrenia. *Schizophr Res.* 2014 Oct;**159**(1):51-5.

19.   Misiak B, Frydecka D, Slezak R, Piotrowski P, Kiejna A. Elevated homocysteine level in first-episode schizophrenia patients— the relevance of family history of schizophrenia and lifetime diagnosis of cannabis abuse. *Metab Brain Dis.* 2014 Sep;**29**(3):661-70.

20.   Takano Y, Ozeki Y, Sekine M *et al.* Multi-regression analysis revealed a relationship between l-serine and methionine, a component of one-carbon metabolism,

in the normal control but not in the schizophrenia. *Ann Gen Psychiatry.* 2016 Aug 31;**15**(1):23.

21.   Susser E, Brown AS, Klonowski E, Allen RH, Lindenbaum J. Schizophrenia and Impaired Homocysteine Metabolism: A Possible Association. *Biol Psychiatry.* 1998 Jul 15;**44**(2):141-3.

22.   Ozcan O, Ipçioğlu OM, Gültepe M, Başoğglu C. Altered red cell membrane compositions related to functional vitamin B(12) deficiency manifested by elevated urine methylmalonic acid concentrations in patients with schizophrenia. *Ann Clin Biochem.* 2008 Jan;**45**(Pt 1):44-9.

23.   Eren E, Yeğin A, Yilmaz N, Herken H. Serum total homocystein, folate and vitamin B12 levels and their correlation with antipsychotic drug doses in adult male patients with chronic schizophrenia. *Clin Lab.* 2010;**56**(11-12):513-8.

24.   García-Miss Mdel R, Pérez-Mutul J, López-Canul B *et al.* Folate, homocysteine, interleukin-6, and tumor necrosis factor alfa levels, but not the methylenetetrahydrofolate reductase C677T polymorphism, are risk factors for schizophrenia. *J Psychiatr Res.* 2010 May;**44**(7):441-6.

25.   Bouaziz N, Ayedi I, Sidhom O *et al.* Plasma homocysteine in schizophrenia: determinants and clinical correlations in Tunisian patients free from antipsychotics. *Psychiatry Res.* 2010 Aug 30;**179**(1):24-9.

26.   Ayesa-Arriola R, Pérez-Iglesias R, Rodríguez-Sánchez JM *et al.* Homocysteine and cognition in first-episode psychosis patients. *Eur Arch Psychiatry Clin Neurosci.* 2012 Oct;**262**(7):557-64.

27.   Cao B, Wang DF, Xu MY *et al.* Lower folate levels in schizophrenia: A meta-analysis. *Psychiatry Res.* 2016 Nov 30;**245**:1-7.

28.   Wang D, Zhai JX, Liu DW. Serum folate levels in schizophrenia: A meta-analysis. *Psychiatry Res.* 2016 Jan 30;**235**:83-9.

29.   Cohen E, Margalit I, Shochat T, Goldberg E, Krause I. Gender differences in homocysteine concentrations, a population-based cross-sectional study. *Nutr Metab*

Cardiovasc Dis. 2019 Jan;**29**(1):9-14.

30.   Muntjewerff JW, van der Put N, Eskes T *et al.* Homocysteine metabolism and B-vitamins in schizophrenic patients: low plasma folate as a possible independent risk factor for schizophrenia. *Psychiatry Res.* 2003 Nov 1;**121**(1):1-9.

31.   Haidemenos A, Kontis D, Gazi A, Kallai E, Allin M, Lucia B. Plasma homocysteine, folate and B12 in chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2007 Aug 15;**31**(6):1289-96.

32.   Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. *J Psychiatr Res.* 2013 Feb;**47**(2):197-207.

33.   Kim EJ, Lim SY, Lee HJ *et al.* Low dietary intake of n-3 fatty acids, niacin, folate, and vitamin C in Korean patients with schizophrenia and the development of dietary guidelines for schizophrenia. *Nutr Res.* 2017 Sep;**45**:10-18.

34.   Sakuma K, Matsunaga S, Nomura I, Okuya M, Kishi T, Iwata N. Folic acid/methylfolate for the treatment of psychopathology in schizophrenia: a systematic review and meta-analysis. *Psychopharmacology (Berl).* 2018 Aug;**235**(8):2303-2314.

35.   Roffman JL, Petruzzi LJ, Tanner AS et al. Biochemical, physiological and clinical effects of l-methylfolate in schizophrenia: a randomized controlled trial. *Mol Psychiatry.* 2018 Feb;**23**(2):316-322.

36.   Wang B, Wu H, Li Y *et al.* Effect of long-term low-dose folic acid supplementation on degree of total homocysteine-lowering: major effect modifiers. *Br J Nutr.* 2018 Nov;**120**(10):1122-1130.

37.   Bender A, Hagan KE, Kingston N. The association of folate and depression: A meta-analysis. *J Psychiatr Res.* 2017 Dec;**95**:9-18

38.   Hsieh YC, Chou LS, Lin CH, Wu HC, Li DJ, Tseng PT. Serum folate levels in bipolar disorder: a systematic review and meta-analysis. *BMC Psychiatry.* 2019 Oct;**19**(1):305.
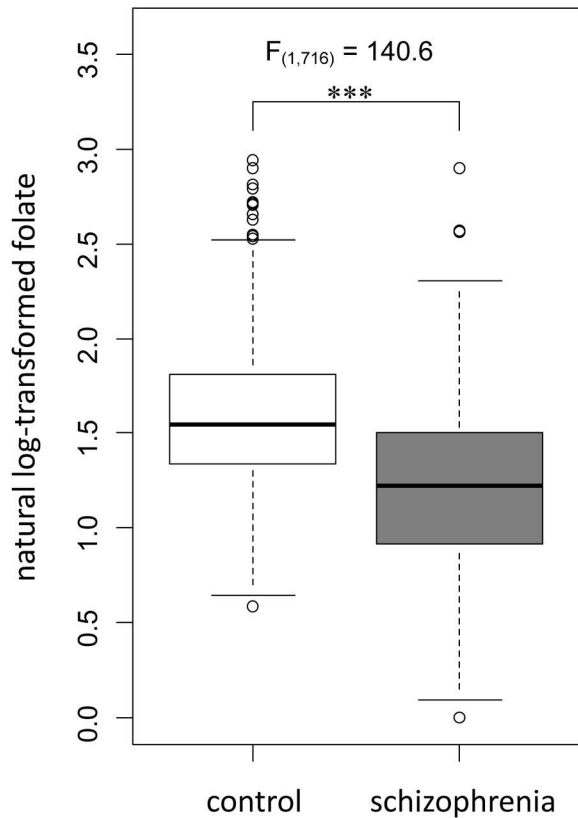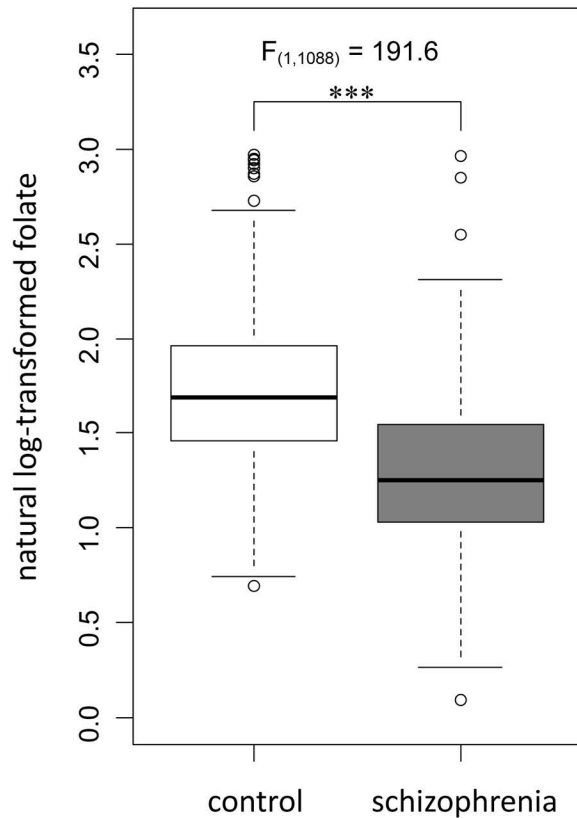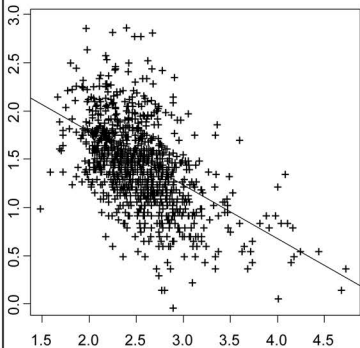
Control group
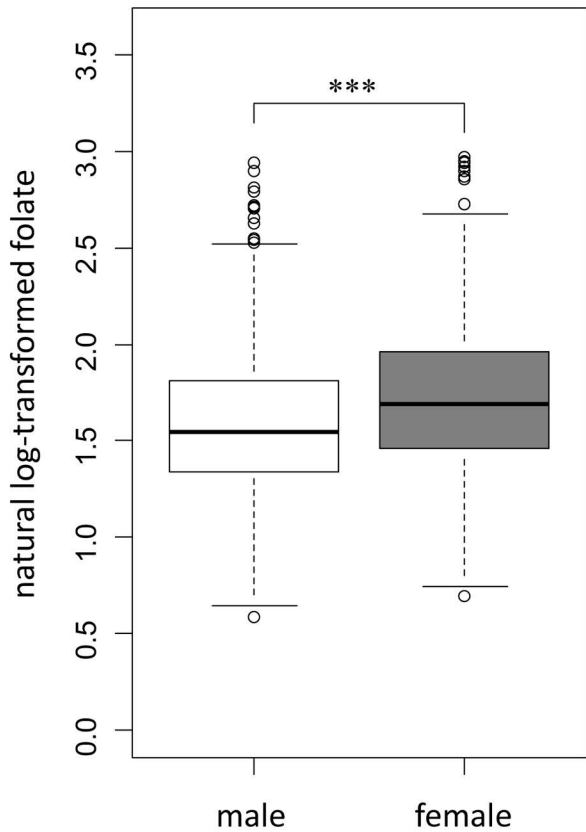
Schizophrenia group
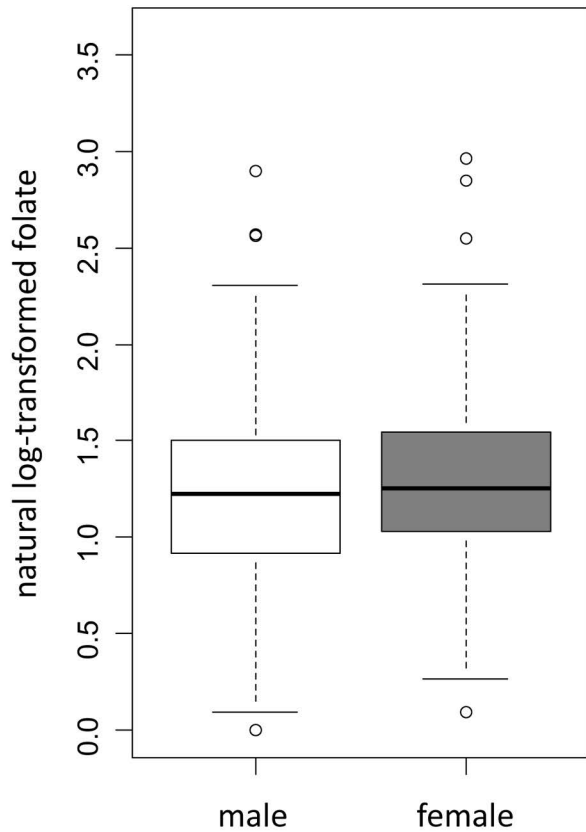
Male group

Female group

natural log-transformed folate

$F_{(1,716)} = 140.6$

***

$F_{(1,1088)} = 191.6$

***

control   schizophrenia

control   schizophrenia
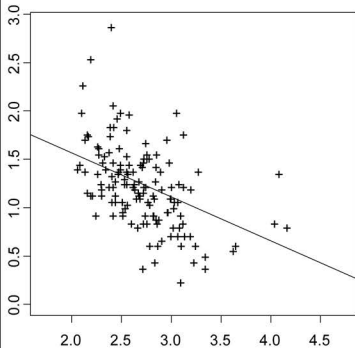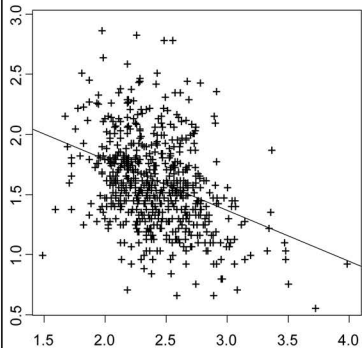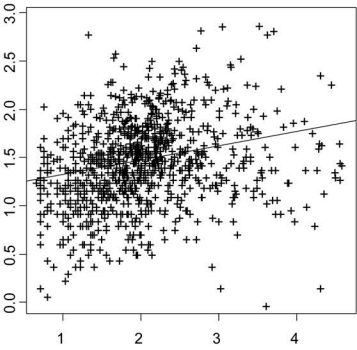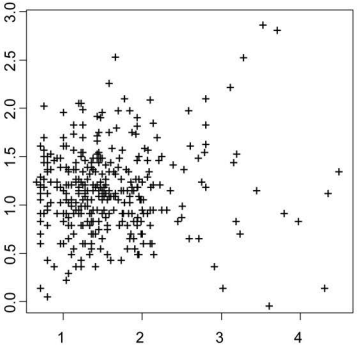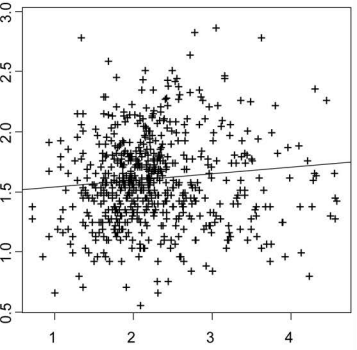
	Control + schizophrenia	**Schizophrenia**	**Control**
LN folate vs. LN tHcy			
r	-0.51	-0.47	-0.36
p	5.7×10^{-79}	4.1×10^{-20}	6.2×10^{-27}

	Control + schizophrenia	**Schizophrenia**	**Control**
LN folate vs. LN pyridoxal			
r	0.28	0.027	0.096
p	8.8×10^{-23}	0.62	6.0×10^{-3}

	N	mean age (SD)	mean folate(SD) ng/mL	median CP (min-max)
schizophrenia	475	58.9 (10.2)	3.95 (2.17)	550 (0-3450)
- male	280	58.5 (9.9)	3.83 (2.05)	600 (0-3450)
- female	195	59.4 (10.6)	4.12 (2.33)	550 (0-3365)
healthy control	1335	41.5 (12.0)	5.87 (2.69)	-
- male	439	38.4 (11.8)	5.41 (2.71)	-
- female	896	43.0 (11.8)	6.09 (2.66)	-
total	1810			

Table 1.

Demographic characteristics of participants with measurable folate levels

SD = standard deviation; CP = chlorpromazine equivalents.

	N	mean age (SD)	mean folate(SD) ng/mL
schizophrenia	339	58.5 (9.5)	3.67 (2.01)
healthy control	816	41.4 (12.3)	5.38 (2.29)
total	1155		

Table 2.

Demographic characteristics of participants with folate, tHcy, and pyri

SD = standard deviation; tHcy = total homocysteine.

mean tHcy(SD) nmol/mL	mean pyridoxal(SD) ng/mL
18.86 (12.92)	6.88 (9.52)
11.99 (4.81)	13.16 (13.87)

doxal data