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Gender differences in cognitive deficits in schizophrenia with and without diabetes

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Gender differences in cognitive deficits in schizophrenia with and without diabetes

Abstract

This study investigated gender differences in cognition in schizophrenia with and without diabetes. Cognition was assessed in 263 individuals with schizophrenia with age range (40-68): 67 males and 34 females with schizophrenia with diabetes; and 125 males and 37 females with schizophrenia without diabetes according to the repeatable battery for the assessment of neuropsychological status (RBANS). Fasting glucose, hemoglobin A1c (HbA1c) and lipid levels were measured. Results showed that male individuals performed worse on most cognitive tasks, especially attention, in schizophrenia with than without diabetes. This result was not observed in female individuals. Also, individuals of both genders showed higher fasting glucose and HbA1c in schizophrenia with than without diabetes. In schizophrenia with diabetes, males had significantly worse cognition than females in all cognitive domains. Higher HbA1c, lower high-density lipoprotein, and an earlier age of onset of schizophrenia were found in males compared with female individuals. HbA1c was negatively associated with attention and the RBANS total score for males but not for females. In schizophrenia without diabetes, males showed worse performance in immediate and delayed memory than females. This study support cognition was worse for males with schizophrenia irrespective of whether they have diabetes or not. However, diabetes exemplified the gender differences, especially in attention.

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Gender differences in cognitive deficits in schizophrenia with and without diabetes

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Running title: Gender differences in cognition in schizophrenia

ABSTRACT

This study investigated gender differences in cognition in schizophrenia with and without diabetes. Cognition was assessed in 263 individuals with schizophrenia with age range (40-68): 67 males and 34 females with schizophrenia with diabetes; and 125 males and 37 females with schizophrenia without diabetes according to the repeatable battery for the assessment of neuropsychological status (RBANS). Fasting glucose, hemoglobin A1c (HbA1c) and lipid levels were measured. Results showed that male individuals performed worse on most cognitive tasks, especially attention, in schizophrenia with than without diabetes. This result was not observed in female individuals. Also, individuals of both genders showed higher fasting glucose and HbA1c in schizophrenia with than without diabetes. In schizophrenia with diabetes, males had significantly worse cognition than females in all cognitive domains. Higher HbA1c, lower high-density lipoprotein, and an earlier age of onset of schizophrenia were found in males compared with female individuals. HbA1c was negatively associated with attention and the RBANS total score for males but not for females. In schizophrenia without diabetes, males showed worse performance in immediate and delayed memory than females. This study support cognition was worse for males with schizophrenia irrespective of whether they have diabetes or not. However, diabetes exemplified the gender differences, especially in attention.

Keyword: Schizophrenia; Diabetes; Gender; Cognition

1. Introduction

Schizophrenia is a severe psychiatric disorder characterized by multi-faceted deficits in neurocognitive function, including immediate memory, delayed memory, attention, language, and visuospatial/constructional domains [1-4]. Cognitive deficits are major impediments to social rehabilitation and predict poor clinical outcomes in individuals with schizophrenia [2]. Currently, the pathophysiological mechanism of cognitive deficits in schizophrenia is not clear.

Gender differences in cognition in schizophrenia may be due to differences in gender-related symptomatic expressions of the illness [5]. Therefore, the cognitive deficits characteristics of schizophrenia that differ based on gender can indicate areas of altered neurobiology and may provide new treatment approaches.

Gender differences in neuropsychological performance have been found in individuals with schizophrenia. Male individuals have an early age of onset, worse negative symptoms, and a worse response to antipsychotics than female individuals with schizophrenia [6-9]. A recent study found a lower prevalence of diabetes in male than female individuals with schizophrenia [10]. Our study and another two studies have indicated that male individuals with schizophrenia have more cognitive deficits than females [11-13]. However, other studies have reported the opposite or no gender differences in the cognitive deficits of schizophrenia [5, 14-16]. These conflicting results support that gender differences in the cognitive deficits in individuals with schizophrenia warrant further investigation.

The prevalence of diabetes has been reported to be two to four times higher in individuals with schizophrenia than the general population [17, 18]. Diabetes is also associated with cognitive deficits [19, 20]. Studies have found that individuals with schizophrenia with diabetes have worse cognitive deficits than schizophrenia without diabetes [21-23]. However,

whether diabetes affects the gender differences in the cognitive deficits of individuals with schizophrenia has not yet been investigated.

Several aspects of gender differences in diabetes have been found. Studies have shown that female individuals with diabetes have higher insulin levels, higher hemoglobin A1c (HbA1c) and poorer glycemic control than males [24]. It is known that insulin resistance, hyperglycemia, and lipid metabolic disorders can affect cognitive function [25-28]. Gender differences in cognitive deficits in diabetes have also been investigated. Many studies support that female individuals with diabetes have more cognitive deficits than males [29-31], whereas another study found that male individuals with diabetes had worse cognitive deficits than females [32]. Another study has also found no gender differences in the cognitive deficits of diabetes [33]. Therefore, whether the gender differences in the cognitive deficits are presented in schizophrenia with and without diabetes deserves further investigation.

The purpose of this study was to determine: (1) whether there are gender differences in the cognitive deficits in schizophrenia with and without diabetes; and (2) whether the gender differences in cognitive deficits are associated with specific clinical characteristics and symptom assessments.

2. Methods

2.1. Subjects

Two hundred and sixty-three individuals with schizophrenia (male/female=192/71) were recruited using a cross-sectional naturalistic design at Beijing HuiLongGuan Hospital, a Beijing City-owned psychiatric hospital. The data were collected from January 2008 to December 2012. The diagnoses for each patient were made by two independent and experienced psychiatrists and confirmed by the Structured Clinical Interview for DSM-IV (SCID). All individuals were aged between 40 and 68 years, had schizophrenia for at least 5

years, and were on stable doses of oral antipsychotic drugs for at least 12 months prior to entry into the study. Antipsychotic treatment consisted mainly of monotherapy with atypical antipsychotics (n=200), including clozapine (n=116), risperidone (n=66), quetiapine (n=8), olanzapine (n=4), aripiprazole (n=6), and typical antipsychotics (n=63), including haloperidol (n=16), chlorpromazine (n=13), perphenazine (n=13), sulpiride (n=18), and others (n=3). The mean antipsychotic dose (as chlorpromazine equivalents) was 415.3 ± 370.8 mg/day. The subjects were all inpatients. They were provided similar living situation and dietary patterns. Since admission, all individuals received dietetically balanced hospital meals, which were occasionally supplemented by gifts (usually fruit), and individuals had the opportunity of about an hour of physical exercise every day.

All participants underwent fasting blood glucose testing using standard procedures. Blood samples are collected in the morning as the same day as the cognitive function assessed. Diabetes was diagnosed as persistent fasting hyperglycemia (>126 mg/dL) or plasma glucose levels greater than 200 mg/dL at 2 hours after a 75 g oral glucose load. This is consistent with the 1999 World Health Organization diagnostic criteria for diabetes mellitus [34]. All of individuals with diabetes were receiving conventional medical treatment. The most commonly prescribed drugs were oral hypoglycemics such as metformin and repaglinide. None of the subjects used insulin.

Total 358 individuals were screened for the study. 95 individuals were excluded. More details, in the schizophrenia with diabetes patients, 26 cases were excluded due to diagnosed cerebral vascular disease, coronary heart disease, known neuropsychiatric or central nervous system diseases and 37 cases were excluded due to retinopathy, nephropathy, and retinopathy accompanied by nephropathy. In the schizophrenia without diabetes, 32 cases were excluded due to diagnosed cerebral vascular disease, coronary heart disease, known neuropsychiatric or central nervous system diseases. The exclusion criteria for renal disease are that serum

creatinine exceeds the upper limit of normal standard. Since these cardio-cerebrovascular and central nervous system diseases are known to be associated with cognitive impairments. Also, diabetic retinopathy and nephropathy are strongly linked to impairment in the cognitive domains [35, 36]. In addition, none of the individuals showed any audiovisual or motor coordination impairments that could affect the cognitive function tests. All participants provided signed, informed consent to participate in this study, which was approved by the Institutional Review Board of Beijing HuiLongGuan Hospital.

2.2. *Clinical assessment*

Two psychiatrists with more than five years of clinical practical experience, and who were blind to the clinical status and treatment conditions, assessed the patient's psychopathology using the positive and negative syndrome scale (PANSS) [37]. To ensure consistent and reliable ratings, the two psychiatrists simultaneously attended a training session to standardize their use of the PANSS prior to the study. Thereafter, they maintained an intra-class correlation coefficient of greater than 0.8 on the PANSS at repeated assessments throughout the study.

2.3. *Cognitive measures*

The repeatable battery for the assessment of neuropsychological status (RBANS) used to measure cognitive function was individually administered by trained investigators and supervised by a research psychiatrist [38]. RBANS is composed of 12 subtests used to calculate five age-adjusted index scores and a total score [39]. Test indices are: immediate memory (composed of list learning and story memory tasks); visuospatial/constructional (composed of figure copy and line orientation tasks); language (composed of picture naming and semantic fluency tasks); attention (composed of digit span and coding tasks); and delayed memory (composed of list recall, story recall, figure recall, and list recognition tasks). Our

group has previously translated RBANS into Chinese and its clinical validity and test-retest reliability have already been established among controls and individuals with schizophrenia [40]. To ensure consistent and reliable ratings, the two clinical psychiatrists simultaneously attended a training session to standardize their use of the RBANS prior to the study. Thereafter, they maintained an intra-class correlation coefficient of 0.92 on the RBANS at repeated assessments throughout the study. Also, the cognitive raters were blind to participants' diabetes status

2.4. Blood sampling

Venous blood from a forearm vein was collected from inpatients between 7 and 9 am following an overnight fast. All fasting blood glucose, hemoglobin A1c (HbA1c), cholesterol, triglyceride, high density lipoprotein, and low density lipoprotein products in the plasma were measured by a technician, who was blind to the diagnostic status of the subjects. The identity of the subjects was indicated by a code number maintained by the investigator until the biochemical analyses were completed.

2.5. Statistical analysis

The group comparisons for the demographic and clinical variables used chi-squared or fisher exact tests for the categorical variables and student t-tests or analysis of variance (ANOVA) for the continuous variables. The RBANS were analysed using a 2×2 ANOVA representing the between factors of diagnosis (schizophrenia with diabetes vs schizophrenia without diabetes) and gender (male vs female). For the RBANS comparisons, age and education were also included as covariates in the multivariate analysis of covariance (MANCOVA). They were included to examine significant diagnosis differences across dependent measures from the RBANS total score and its five cognitive domains. The independent predictors were diagnosis, gender, and diagnosis \times gender interaction. Effect

sizes (<0.1=trivial effect, 0.1–0.3=small effect, 0.3–0.5=medium effect, >0.5=large effect) were also calculated for the two-way comparisons and represented the mean difference (in standard deviation units) between the groups of interest. In the post hoc comparisons, a multiple testing correction was also performed. We assessed relationships between variables with Pearson's product moment correlation coefficients. Multiple regression models were used to quantify the amount of variance in cognitive functioning explained by the psychopathological variables after controlling for several potential confounders, such as age, education, and clinical variables.

In addition, a mediation analysis was performed to understand the relationship across gender, HbA1c and cognitive functions, and to examine whether HbA1c could mediate the association between gender and cognitive functions. In the mediation analysis, gender was an independent factor, cognitive functions were dependent factors, and HbA1c was the moderator, with age and education as the covariates.

SPSS version 19.0 was used to perform the statistical analysis. Data were presented as Mean±SD. All p-values were two-tailed at the significant level of $p<0.05$.

3. Results

3.1. Sample characteristics

Demographic and clinical characteristics are summarized in Table 1. Overall, there were no significant diagnosis differences (schizophrenia with diabetes vs schizophrenia without diabetes) in the demographic and clinical characteristics except for higher fasting glucose and HbA1c expression (both $p<0.001$). There were significant gender differences in the age of onset, PANSS positive symptoms, PANSS negative symptoms, PANSS general psychopathology, HbA1c, and high-density lipoprotein ($p<0.01-0.05$). However, there were no significant gender differences in age, education, duration of illness, total PANSS score,

antipsychotic dose (equivalent to chlorpromazine), fasting glucose, cholesterol, triglyceride, and low-density lipoprotein between schizophrenia with and without diabetes (all $p>0.05$). There was a significant interaction between diagnosis and gender in HbA1c expression ($p<0.05$).

Furthermore, data for schizophrenia with and without diabetes were analysed separately to assess gender differences in the demographic and clinical characteristics. Male individuals showed significantly lower PANSS scores in the general psychopathology subscales, higher PANSS scores in the negative symptom subscales, an earlier onset of schizophrenia, and lower high-density lipoprotein than females with schizophrenia with diabetes ($p<0.01-0.05$). Male individuals had significantly lower PANSS scores in the positive symptom and general psychopathology subscales, and higher PANSS scores in the negative symptom subscales than females with schizophrenia without diabetes ($p<0.001-0.01$). Moreover, both male and female individuals had significantly higher fasting glucose and HbA1c expressions in schizophrenia with than without diabetes ($p<0.001$).

3.2. Gender difference in cognitive performance in schizophrenia with and without diabetes

Table 2 shows the cognitive test scores for the total RBANS scores and all five indices in schizophrenia with and without diabetes. After controlling for age and education, the MANCOVA revealed statistically significant differences on the cognitive test scores between schizophrenia with and without diabetes ($F_{1,263}=5.8$, $p<0.001$). Furthermore, diagnosis differences (schizophrenia with diabetes vs schizophrenia without diabetes) were significantly for immediate memory, attention, and total RBANS scores ($p<0.001-0.05$). Gender differences were significant for all cognitive test scores ($p<0.001-0.05$). The diagnosis \times gender interaction effect only occurred in attention ($p<0.05$).

In order to decompose the two-way interaction, pair-wise post hoc comparisons showed that male individuals had significantly lower levels of RBANS total scores and RBANS subscores than females, with effect sizes ranging from 0.53 to 0.82 in schizophrenia with diabetes ($p < 0.01-0.05$). Male individuals showed significantly lower levels in immediate memory, delayed memory, and total BBANS scores, with effect sizes ranging from 0.40 to 0.54 in schizophrenia without diabetes ($p < 0.01-0.05$). Male individuals also had significantly lower cognitive test scores in almost all cognitive scores except for delayed memory ($p < 0.001-0.05$), with effect sizes ranging from 0.35 to 0.83 in schizophrenia with diabetes. There were no significant differences in the cognitive index scores in female individuals between schizophrenia with and without diabetes.

3.3. Gender difference in the relationship between cognitive performance and clinical variables in schizophrenia with and without diabetes

Schizophrenia with diabetes: multivariate regression analysis showed that the following variables were independently associated with the RBANS total score: HbA1c ($\beta = -4.665$, $t = -4.948$, $p < 0.001$), PANSS negative symptom score ($\beta = -4.665$, $t = -4.948$, $p < 0.001$, $p < 0.01$), PANSS general psychopathology subscale ($\beta = 0.518$, $t = 2.522$, $p < 0.05$), and gender ($\beta = 5.553$, $t = 2.108$, $p < 0.05$). Together, these factors predicted 42% of the variance of the total RBANS score. Almost all cognitive indices were negatively correlated with the negative PANSS symptom scale in schizophrenia with diabetes except for the visuospatial/constructional index. Further analyses were performed separately for the male and female individuals with schizophrenia with diabetes to assess gender differences in HbA1c associated with cognitive impairment. We hypothesized that the association of HbA1c with cognitive function was different in the male and female individuals. Table 3 shows the correlations between HbA1c and the cognitive performance measures in male and female individuals. For male individuals, HbA1c was significantly negatively associated with

the following parameters: attention ($r=-0.31$, $df=64$, $p<0.05$) and the RBANS total score ($r=-0.31$, $df=64$, $p<0.05$). However, no significant association was found between HbA1c and the cognitive scores in female individuals.

Schizophrenia without diabetes: multivariate regression analysis showed that the following variables were independently associated with the RBANS total score: education ($\beta=1.526$, $t=2.362$, $p<0.05$), and PANSS negative symptom score ($\beta=-0.668$, $t=-4.450$, $p<0.001$). Together, these factors predicted 30% of the variance of the total RBANS score. All cognitive indices were negatively correlated with the negative PANSS symptom scale in schizophrenia without diabetes. HbA1c was not found to be a contributor to any of the RBANS indices or its total score when the males and females were analyzed separately (all $p>0.05$).

3.4. Mediation analysis for the relationship across gender, HbA1c, and cognitive functions

As described above, male individuals had significantly lower cognitive function (almost all cognitive domains except for delayed memory) and a higher HbA1c concentration than female individuals in schizophrenia with diabetes. In the meantime, we found that HbA1c was negatively associated with attention for male individuals in schizophrenia with diabetes. We thus speculated that the relationship between gender and cognitive function might be mediated by HbA1c, and tested this hypothesis by carrying out the mediation analysis as below.

We used gender as an independent factor, attention score as a dependent factor, and HbA1c as a moderator, with age and education as the covariates. A statically significant mediation was observed. The model showed a reasonably good fit [$R^2=0.20$, $F_{(2,96)}=13.36$, $p<0.0001$].

As Fig. 1 illustrates, “a” value, a standardized regression coefficients for the relationship between gender and HbA1c was -0.25^* ($p < 0.05$), and “b” value, a standardized regression coefficients for the relationship between HbA1c and attention, was -0.41^{***} ($p < 0.001$). Both standardized regression coefficients were statistically significant.

The standardized indirect effect was $a * b = 0.10$. Then we tested the significance of this indirect effect using bootstrapping procedures. Unstandardized indirect effects were computed for each of the 10,000 bootstrapped samples, and the 95% CI was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. The bootstrapped unstandardized indirect effect was also 2.48. Most importantly, the 95% CI ranged from 0.74 to 4.72. Thus, the indirect effect was statistically significant, suggesting that the relationship between gender and attention was mediated by HbA1c in schizophrenia with diabetes.

In addition, we also explored the mediation possibility of HbA1c on the relationship between gender and RBANS total score (or other index) in schizophrenia without diabetes. However, for all of these analyses, no significant mediation effects were detected.

4. Discussion

The main findings of our current study were that: (1) males with schizophrenia had worse performance in cognitive function than females irrespective of diabetes, and this was worse in schizophrenia with diabetes, especially in attention; (2) HbA1c concentration was significantly higher in schizophrenia with than without diabetes in both genders. In addition, males had a higher HbA1c than females in schizophrenia with diabetes; and (3) interestingly, the significant association between gender and cognition may be mediated by HbA1c in schizophrenia with diabetes.

This study found that diabetes exemplified worse cognition for males than females. To the best of our knowledge, this is the first study to report that male individuals showed worse

cognitive deficits than females in all cognitive domains for schizophrenia with diabetes. However, gender differences were only indicated in immediate and delayed memory in schizophrenia without diabetes. Several studies have indicated that poorer glycemic control and higher HbA1c are significantly associated with cognitive deficits [21, 23, 41-45]. Studies have also shown that female individuals with diabetes have poorer glycemic control and a higher HbA1c concentration than males [24]. Many studies support that female individuals have more cognitive impairments than males with diabetes only [29-31]. However, it is different for individuals with diabetes only. Our study indicated that male individuals had a significantly higher HbA1c concentration than females in schizophrenia with diabetes. The HbA1c concentration reflects the mean glucose concentration over a period of 8 to 12 weeks from both fasting and postprandial glucose concentrations [45]. In this study, there was no significant difference in fasting glucose between males and females in schizophrenia with diabetes. However, the fact which male individuals had a higher HbA1c than females may reflect chronic long-term poorer glycemic control in males than females in schizophrenia with diabetes. Also, we found significant negative correlations for HbA1c with attention and the RBANS total score in males with schizophrenia with diabetes, but not for females. Moreover, we found that a significant association between gender and cognition was mediated by HbA1c in male individuals in schizophrenia with diabetes. Therefore, our results support that there is a worse cognitive performance in males than females in schizophrenia with diabetes. Furthermore, the males performed cognitive tasks worse in most of the cognitive domains, especially in attention in schizophrenia with than without diabetes. Also, individuals showed a higher fasting glucose and HbA1c in schizophrenia with than without diabetes. All of these results support that cognition is worse in males than females with schizophrenia irrespective of diabetes, but worse in schizophrenia with diabetes. The poorest

glycemic control might be the major reason leading to the worsened cognitive performance in males with schizophrenia with diabetes.

Currently, we are not sure exactly why males have a poorer glycemic control than females in schizophrenia with diabetes. However, both the current and other previous studies have found that males have worse negative symptoms, response to antipsychotics, and cognitive deficits than females with schizophrenia [6-9, 11-13]. This may affect more daily life and self-medical protection awareness for male individuals and lead to their poorer glycemic control. However, the exact mechanisms underlying the male disadvantage in cognitive performance and glycemic control in individuals with schizophrenia with diabetes warrants further investigation.

As discussed above, this study prompted a significantly greater gender difference in cognitive deficits for schizophrenia with than without diabetes. Previous studies supported that the early onset of schizophrenia might predict more serious nervous damage including cognitive deficits in individuals with schizophrenia [13, 46]. In the present study, we separated the schizophrenia patients into with and without diabetes subgroups. The early onset of schizophrenia was present in males rather than females with schizophrenia with diabetes, but the gender difference was not present in schizophrenia without diabetes. This may be one of the reasons leading to a significantly greater gender difference in cognitive deficits in schizophrenia with than without diabetes. Moreover, a previous study showed that lower high-density lipoprotein was related to cognitive deficits in individuals with diabetes [47]. Compared with females, males showed a significantly low level of high-density lipoprotein in schizophrenia with diabetes, but the gender difference was not indicated in schizophrenia without diabetes. This may be another reason leading to a significantly greater gender difference in cognition in schizophrenia with than without diabetes. In addition, both schizophrenia and diabetes are caused by multiple genetic variants [48]. The comorbidity link

between the two diseases may be influenced by shared genetic variants that exert pleiotropic effects (i.e. the same DNA sequence causes the psychopathology inherent to schizophrenia, cognitive deficits, and altered glucose metabolism) [48]. Whether these shared genetic variants have higher rates of gender differences in schizophrenia with than without diabetes warrants further investigation.

This study showed that attention was severely affected in male individuals with schizophrenia with diabetes. Our study found that male individuals showed a 19.7% decrease in attention in schizophrenia with than without diabetes. The poorer glycemic control may be one reason for the worsened cognition including attention in male individuals with schizophrenia with diabetes. Attention is significantly associated with the function of the bilateral prefrontal cortex and superior temporal gyrus brain regions [49]. Thus the differences in brain damage in these brain regions such as structure and neurotransmitter expression for schizophrenia with and without diabetes also warrants further investigation.

Males showed worse cognitive deficits than females both in schizophrenia with and without diabetes. The results support that the neuronal protective effects of estrogen may also play an important role in the female individuals who showed fewer cognitive deficits than males. This finding is also supported by a series of other studies [41-43, 50-52]. However, some studies have failed to find that estrogen has significant protective effects for cognitive function in females rather than males with diabetes only [29, 33]. To confirm whether estrogen has neuronal protective effects for females in schizophrenia with and without diabetes would require a longitudinal study which cannot be addressed within our current cross-sectional design. Moreover, female individuals with schizophrenia showed a greater improvement in cognitive deficits with antipsychotic treatment than males [6, 7]. This may be another reason why females have better cognitive function than males in schizophrenia with and without diabetes. Furthermore, cognition is significantly related to brain activity in the

bilateral prefrontal cortex and superior temporal gyrus [49]. Studies have reported that individuals with schizophrenia had brain structural abnormalities in the prefrontal, hippocampal, and temporal regions [49, 53]. It would be interesting to examine if gender differences in cognition in individuals with schizophrenia is related to differences in their brain structure. Lastly, post-mortem studies have shown altered abnormal neurotransmitter receptor expressions in the prefrontal cortex, temporal lobe, and superior temporal gyrus brain regions (such as the muscarinic M1 receptor and gamma-aminobutyric acid (GABA) receptor), which may contribute to the pathophysiology of cognitive impairment in schizophrenia [54-57]. Therefore, it would be interesting to investigate whether there are gender differences among these neurotransmitters in these brain regions in schizophrenia with and without diabetes.

This study also found that cognitive deficits were positively associated with the seriousness of negative symptoms both in schizophrenia with and without diabetes. Moreover, negative symptoms were worse in males than females in both schizophrenia with and schizophrenia without diabetes, which are consistent with our previous and other studies [58-60]. These results support that gender differences of cognitive deficits are significantly associated with severity of negative symptoms in schizophrenia with and without diabetes. It needs point out that there were no significant differences of PANSS total and subscores for males or female patients in schizophrenia with and without diabetes. Therefore, male patients performed worse cognition in schizophrenia with than without diabetes, which support gender differences rather than illness severity in the study. In addition, it is also possible that the clozapine may affect the results by influencing the diabetes control and complications. Our previous study has found that individuals taking clozapine performed worse in immediate and delayed memory than those taking typical antipsychotic, but exemplified better language performance than those taking risperidone [61]. However, multivariate

regression analysis did not find that cognition were associated with the duration of the disease, antipsychotic types and body mass index (BMI) in the study. It is worthy of noting that this is a cross-sectional design. We could not rule out those potential impacts of severity of schizophrenia and antipsychotic drug treatments for this study. Therefore, the currently results should be regarded as preliminary results. This limitation should be remedied in the future longitudinal study.

This study found that it is different for individuals with diabetes only, male individuals performed a significantly worse cognition than females in schizophrenia with diabetes. We also found male individuals had worse cognition than females irrespective of diabetes, but this was worse in schizophrenia with diabetes. These results note that health care workers need to give more attention to cognitive deficits in male individuals with schizophrenia with diabetes, especially in the attention domain.

There are some limitations in our study. First, although there were no significant differences in the gender distribution in schizophrenia with and without diabetes, fewer female subjects of chronic individuals were used. This was because female individuals ceased their treatment later in the course of the disease, received care via alternate means (family or residential facility), or had an improved treatment response and recovery compared to male individuals. Second, all of the individuals with schizophrenia in this study were chronic. We could not distinguish whether the diabetes in schizophrenia was caused by the antipsychotic treatments or whether it existed before the antipsychotic treatments. Third, we did not measure postprandial glucose concentration. Therefore, we could not completely confirm that male individuals had significantly poorer glycemic control than females even though we have found significant higher HbA1c concentration for schizophrenia males compared to females in schizophrenia with diabetes. Fourth, diabetes complication and other neurological diseases add extra level of complexity in analysis. For example, patient can not read well due to

visual problem which can affect cognitive performance. Patients with severe renal or cardiovascular diseases have to be sent to other specialised hospital (difficult to access these patients). At this stage, we do not have the data of the duration of diabetes, but we will collect these data for future study. Therefore, our results may not represent all schizophrenia with diabetes's situation. Fifth, studies showed that aerobic fitness could improve neurocognition in multiple domains in individuals with schizophrenia [62]. In our currently study, although individuals with schizophrenia have an opportunity of about physical exercise every day, however, we did not record about the details of aerobic exercise for individuals with schizophrenia. Therefore, we can not analyse the impact of aerobic exercise in cognitive function. This limitation should be remedied in the future investigation. Sixth, although individuals with schizophrenia were 40-68 years old, we could not completely exclude the potential impact of phase of menstrual on neurocognition and diabetes.

In conclusion, males with schizophrenia showed worse cognition than females irrespective of diabetes, but this was worse in schizophrenia with diabetes. Attention was severely affected in males in schizophrenia with diabetes. Poor glycemic control, metabolic lipoprotein disorders, and an early age of the onset of schizophrenia might have contributed to the worsened cognition for male individuals with schizophrenia with diabetes. It is worth noting that health care workers need to give more attention to cognitive deficits in male individuals with schizophrenia with diabetes, especially in the attention domain.

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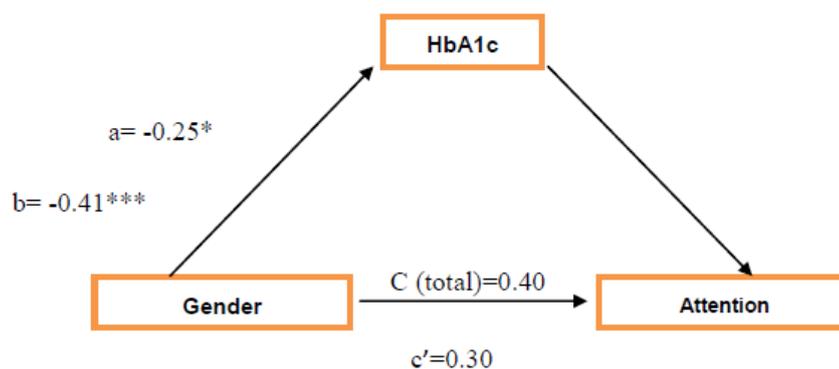


Fig. 1. Standardized regression coefficients for the relationship between gender and attention as mediated by HbA1c. The letters a, b and c' refer to estimated path coefficients. $*p < 0.05$, $***p < 0.001$. Among them, "a" value is a standardized regression coefficient for the relationship between gender and HbA1c, and "b" value is a standardized regression coefficient for the relationship between HbA1c and attention. C is the whole effect of gender on attention, and "c' " is the direct effect of gender on attention. $C = c' + a * b$.

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Table 1

Demographic and clinical data (Mean±SD) in schizophrenia with and without diabetes.

	Schizophrenia with diabetes		Schizophrenia without diabetes		Diagnosis F (p value)	Gender F (p value)	Diagnosis x Gender F (p value)
	Male (n=67)	Female (n=34)	Male (n=125)	Female (n=37)			
Age (years)	52.1±8.8	53.8±6.8	50.9±8.1	51.2±6.4	2.8 (0.093)	0.7 (0.401)	0.4 (0.553)
Education (years)	9.1±2.1	9.7±1.8	9.7±2.4	9.9±2.4	1.5 (0.228)	1.4 (0.235)	0.4 (0.529)
Age at onset (years)	24.1±5.1**	28.5±9.4	24.3±6.2	25.6±6.4	2.0 (0.154)	9.3 (0.002)	2.8 (0.093)
Duration of illness (years)	27.0±9.8	25.2±9.6	26.6±8.9	25.6±8.2	0.0 (0.962)	1.2 (0.281)	0.1 (0.760)
PANSS score							
Positive symptom subscale	13.0±9.7	15.4±11.9	11.6±4.0**	14.7±7.4	1.0 (0.323)	6.4 (0.012)	0.1 (0.739)
Negative symptom subscale	22.1±6.8*	19.8±7.5	22.1±7.2*	19.8±7.6	0.0 (0.957)	5.0 (0.027)	0.0 (0.941)
General psychopathology subscale	26.6±5.9*	28.9±7.6	25.9±4.9**	28.8±6.8	0.2 (0.629)	10.0 (0.002)	0.1 (0.717)
Total score	60.6±13.9	62.7±18.6	59.5±12.6	63.3±16.3	0.0 (0.901)	2.0 (0.158)	0.2 (0.670)
Antipsychotic types ^a							
Typical (number)	15	7	34	7			
Atypical (number)	52	27	91	30			
Antipsychotic dose (CPZ equivalents) (mg)	410.8±188.8	438.2±270.0	445.1±348.2	556.8±666.9	2.0 (0.157)	1.7 (0.198)	0.6 (0.434)
Fasting glucose (mmol/L)	6.4±1.9 ⁺⁺⁺	6.1±1.2 ⁺⁺⁺	5.2±0.6	5.2±0.5	41.1(0.000)	0.5 (0.480)	0.5 (0.490)
Hemoglobin A1c (%)	6.9±1.4 ⁺⁺⁺	6.2±0.8 ⁺⁺⁺	6.0±0.7	5.8±0.6	25.8(0.000)	9.2(0.003)	4.3(0.039)
Cholesterol (mmol/L)	4.5±0.7	4.6±0.9	4.5±0.9	4.8±0.7	0.7 (0.402)	2.6 (0.111)	0.5 (0.473)
Triglyceride (mmol/L)	2.1±1.2	2.0±1.3	1.8±1.0	1.7±0.9	3.4 (0.066)	0.4 (0.554)	0.0 (0.948)
High-density lipoprotein (mmol/L)	1.3±0.3 ^{**}	1.5±0.3	1.3±0.6	1.4±0.2	0.0 (0.834)	4.8 (0.029)	0.3 (0.558)
Low-density lipoprotein (mmol/L)	2.7±0.6	2.8±0.6	2.7±0.6	3.0±0.6	2.8 (0.094)	3.4 (0.068)	0.6 (0.440)

^a shows no significant differences in antipsychotic types used in the schizophrenia with and without diabetes. The asterisk symbol (*) indicates the comparison between males and females with schizophrenia with and without diabetes: *p<0.05, **p<0.01. The plus sign (+) indicates the comparison between schizophrenia with and without diabetes in males and females: ⁺⁺⁺p<0.001. CPZ: chlorpromazine.

Table 2

Cognitive function in schizophrenia with and without diabetes.

	Schizophrenia with diabetes		Schizophrenia without diabetes		Diagnosis F (p value)	Gender F (p value)	Diagnosis × Gender F (p value)
	Male (n=67)	Female (n=34)	Male (n=125)	Female (n=37)			
Immediate memory	59.6±14.8**+	68.8±19.0	65.5±18.4*	73.6±20.4	4.6 (0.033)	11.7 (0.001)	0.1 (0.821)
Visuospatial/constructional	79.3±22.7**+	92.0±13.2	85.6±18.7	90.5±17.9	0.8 (0.369)	10.7 (0.001)	2.1 (0.150)
Language	83.2±15.5*++	90.4±11.6	88.5±11.5	89.5±15.2	1.4 (0.232)	5.0 (0.026)	2.8 (0.097)
Attention	70.0±18.0**+++	80.9±14.4	83.8±14.7	85.4±17.0	16.8 (0.000)	7.7 (0.006)	4.4 (0.038)
Delayed memory	71.4±16.3**	82.9±18.4	72.4±19.1**	82.8±19.2	0.0 (0.863)	17.8 (0.000)	0.0 (0.825)
Total RBANS scores	66.8±13.3***++	77.9±13.8	73.6±14.5*	79.9±16.8	4.7 (0.031)	18.3 (0.000)	1.4 (0.245)

The asterisk symbol (*) indicates the comparison between males and females with schizophrenia with or without diabetes: *p<0.05, **p<0.01, ***p<0.001. The plus sign (+) indicates the comparison between schizophrenia with and without diabetes in males and females: +p<0.05, ++p<0.01, +++p<0.001. RBANS: repeatable battery for the assessment of neuropsychological status.

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Table 3

Correlations between HbA1c and cognitive performance measures in schizophrenia with diabetes ^a.

	HbA1c	
	Male (n=67)	Female (n=34)
Immediate memory	-0.22(0.07)	-0.11(0.56)
Visuospatial/constructional	-0.16(0.21)	-0.35(0.06)
Language	-0.11(0.39)	0.05(0.81)
Attention	-0.31(<0.05)	-0.35(0.06)
Delayed memory	-0.21(0.09)	-0.03(0.88)
Total RBANS score	-0.31(<0.05)	-0.23(0.21)

^a Values are shown as $r(p)$, control value: age and education. RBANS: repeatable battery for the assessment of neuropsychological status. HbA1c= hemoglobin A1c.

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