

## A META-ANALYSIS OF ABNORMAL GLUCOSE METABOLISM IN FIRST-EPIISODE DRUG-NAIVE SCHIZOPHRENIA

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### SUMMARY

**Background:** Patients with schizophrenia exhibit a higher mortality rate compared with the general population. This mortality has been attributed predominantly by the high risk of type 2 diabetes mellitus in the patients. We aimed to assess the inherent risk of glucose metabolism abnormalities in first-episode drug-naïve schizophrenia.

**Subjects and methods:** We searched English database (PubMed, EMBASE, MEDLINE, Cochrane Library databases) and Chinese database (Wan Fang Data, CBM disc, VIP, and CNKI) from their inception until Jul 2018 for case-control studies examining glucose metabolism abnormalities. Measurements, such as fasting plasma glucose levels, fasting plasma insulin levels, insulin resistance and HbA1c levels in first-episode antipsychotic-naïve patients were used to test for prediabetes. Standardized/weighted mean differences and 95% confidence intervals were calculated and analyzed.

**Results:** 19 studies (13 in English and 6 in Chinese) consisting of 1065 patients and 873 controls were included. Fasting plasma glucose levels (95% CI; 0.02 to 0.29;  $P=0.03$ ), 2 h plasma glucose levels after an OGTT (95% CI; 0.63 to 1.2;  $P<0.00001$ ), fasting plasma insulin levels (95% CI; 0.33 to 0.73;  $P<0.00001$ ), insulin resistance (95% CI; 0.29 to 0.6;  $P<0.00001$ ) in patients with first-episode schizophrenia were significant elevated. There was no significant difference in HbA1c level (95% CI; -0.34 to 0.18;  $P=0.54$ ) in patients with first-episode schizophrenia compared with controls.

**Conclusions:** This meta-analysis showed that glucose metabolism was impaired in patients with first-episode schizophrenia. Higher quality studies with larger samples are warranted to confirm these findings.

**Key words:** First-episode schizophrenia - drug-naïve - glucose metabolism

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### INTRODUCTION

It is now widely acknowledged that schizophrenia characterized by emotional, cognitive, and behavioral dysfunctions, which is a severe neurodevelopmental disorder. About 1% of the population worldwide suffering from schizophrenia (Zheng et al. 2018). Study demonstrate that schizophrenia contributes 13.4 million years of life lived with disability (YLDs) to burden of disease globally, equivalent to 1.7% of total YLDs globally in 2016 (Charlson et al. 2018). Furthermore, schizophrenia is the most costly mental disorders of all mental illnesses, for instance, societal economic burden of schizophrenia in US was \$62.7 billion in 2002. Recently, prevalence-based approach estimated that the costs amounted to \$155.7 billion in 2013 (Cloutier et al. 2016, Wu et al. 2005).

Schizophrenia is associated with elevated suicide rates and premature death. Numerous studies have identified that patient with schizophrenia have two-fold to three-fold higher mortality rates compared with general population (Brown et al. 2010, Chesney et al. 2014, Reininghaus et al. 2015). This mortality gap which translates to a life expectancy is around 15 to 21 years shorter in patients with schizophrenia (Hjorthøj et al. 2017). The leading cause of premature death was not only somatic diseases but also cardiovascular diseases (CVD). Moreover, several recent lines of evidence demonstrate that

morbidity of CVD was increased among patients with schizophrenia (Capasso et al. 2008, Laursen 2011, Saha et al. 2007). As a major risk factor for CVD, type 2 diabetes mellitus (T2DM) confers an approximately two-fold excess risk (Vancampfort et al. 2016). Recent studies demonstrated that diabetes was the most commonly diagnosed specific chronic disease among patients with schizophrenia. They also showed that women with schizophrenia have higher risk than man (Crump et al. 2013). Numerous studies also revealed that antipsychotics used in clinic may contribute to diabetes (Cohen & Correll 2009, Henderson et al. 2006), especially olanzapine and clozapine (Cohen & Correll 2009) (Meyer & Stahl 2009, Yood et al. 2009). However, the latest epidemiological study revealed that diabetes risk in patients who exposed to first- and second-generation antipsychotic drugs were similar, ranging from 1.94 (olanzapine) and 2.19 (aripiprazole) to 3.25 (clozapine) (Rajkumar et al. 2017). Recent reviews identified that schizophrenia confers an endogenous risk for the development of T2DM. Studies have showed that patient with first-episode schizophrenia exhibit alterations in glucose homeostasis compared with matched control (Greenhalgh et al. 2017, Kucukgoncu et al. 2019, Perry et al. 2016, Pillinger et al. 2017).

However, previous meta-analyses did not include non-English databases. Thus, we performed a systematic review and a meta-analysis to assess glucose homeostasis in individuals with schizophrenia.

## SUBJECTS AND METHODS

### Search strategy

This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009). The studies in our review were searched from English database (PubMed, EMBASE, MEDLINE, Cochrane Library databases) and Chinese databases (Wan Fang Data, CBM disc, VIP, and CNKI) from their inception until 15 July 2018. The key words included “schizophrenia”, “psychotic disorders”, “Schizophrenic disorders”, “schizophrenia”, “psychosis”, “psychotic”, “schizoaffective” and “diabetes mellitus”, “diabetes”, “glucose”, “insulin resistance”, “fasting glucose”, “glycated hemoglobin”, “insulin”, “homeostatic model assessment index”, “oral glucose tolerance test”, “impaired glucose tolerance”, “prediabetes”, “type 2”, “postprandial 2 hour glucose” and “first episode”, “early onset”, “at risk”, “ultra-high risk”, “prodrome” and “drug-naïve”, “antipsychotic-naïve”, “medication”, “drug”, “antipsychotic”. There no language restrictions in search.

### Inclusion and Exclusion Criteria

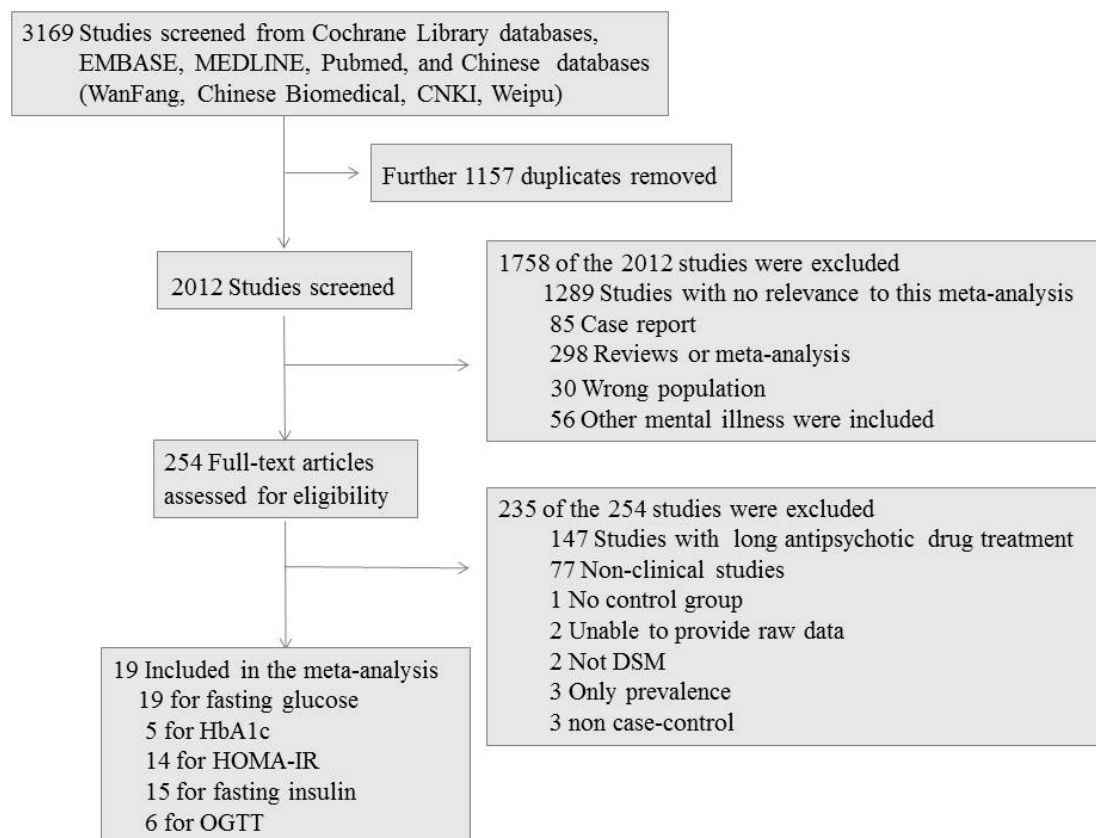
Inclusion criteria were (1) patients were diagnosed as schizophrenia according to the DSM-IV; (2) patients were  $\geq 16$  years of age; (3) patients were antipsychotic

naive or  $\leq 2$  weeks of antipsychotic treatment; (3) control group were healthy population; (4) fasting plasma glucose concentration (FG) or two hour values in the oral glucose tolerance test (OGTT) or hemoglobin A1c (HbA1c) or insulin resistance or fasting insulin (FI) were assessed.

Exclusion criteria were (1) patients were not diagnosed as schizophrenia; (2) antipsychotic exposure  $> 2$  weeks; (3) patients were children or elder or pregnant; (4) absence of measures in control group; (5) the review and conference report; (6) preclinical research; (6) study which unable to provide raw data; (7) only prevalence in study.

### Statistical Analysis

Quality appraisal was done using the Newcastle Ottawa Scale (NOS) for case-control studies. Continuous data were analyzed in our analysis. Standardized mean differences (SMDs) or mean difference (MD) and 95% CI between cases and controls were calculated and displayed in forest plots. Heterogeneity across studies was assessed with the  $I^2$  statistic. Publication bias was assessed using Egger test. All meta-analyzable data were analyzed with the RevMan (Version 5.3) software. A sensitivity analysis and publication bias was assessed using Stata SE 12.0.



Abbreviations: HbA1c - hemoglobin A1c; HOMA-IR - homeostatic model assessment–insulin resistance; OGTT - oral glucose tolerance test

**Figure 1.** Study selection for meta-analysis

## RESULT

### Search results and included participants

We screened 2012 potential, non-duplicate articles. The search process is demonstrated in Figure 1. 19 studies met the inclusion criteria and were included in the quantitative synthesis (Table 1). There were 19 studies with data on FG, 5 for HbA1c, 14 for HOMA-IR, 15 for FI and 6 for two-hour OGTT. Study qualities were rated based on Newcastle-Ottawa Scale (NOS) (Table 2).

### Fasting glucose concentration

19 studies involving 1065 patients and 873 controls were included in our analysis. Pooling this data showed that FG was significantly elevated in patients compared with controls (95% CI; 0.05 to 0.41;  $I^2=73\%$ ;  $P=0.01$ ). Findings of the Egger test ( $P=0.106$ ) suggested that publication bias was not significant. Sensitivity analyses revealed that estimate of one study was stray from the effect size (Quan 2015). After excluding the divergent

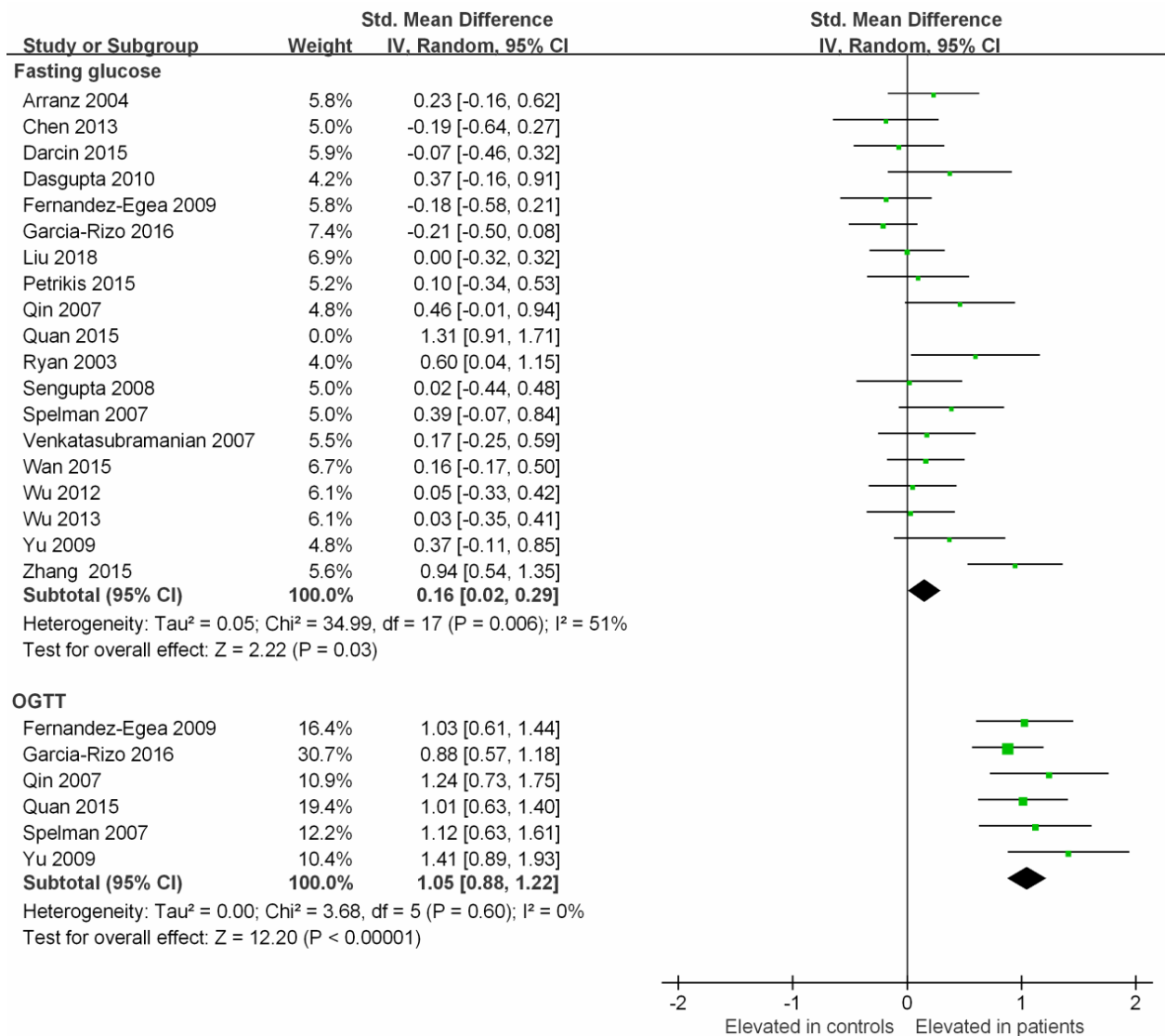
study, heterogeneity was decreased (95% CI; 0.02 to 0.29;  $I^2=51\%$ ;  $P=0.03$ ) (Figure 2).

### Two-hour glucose concentration after OGTT

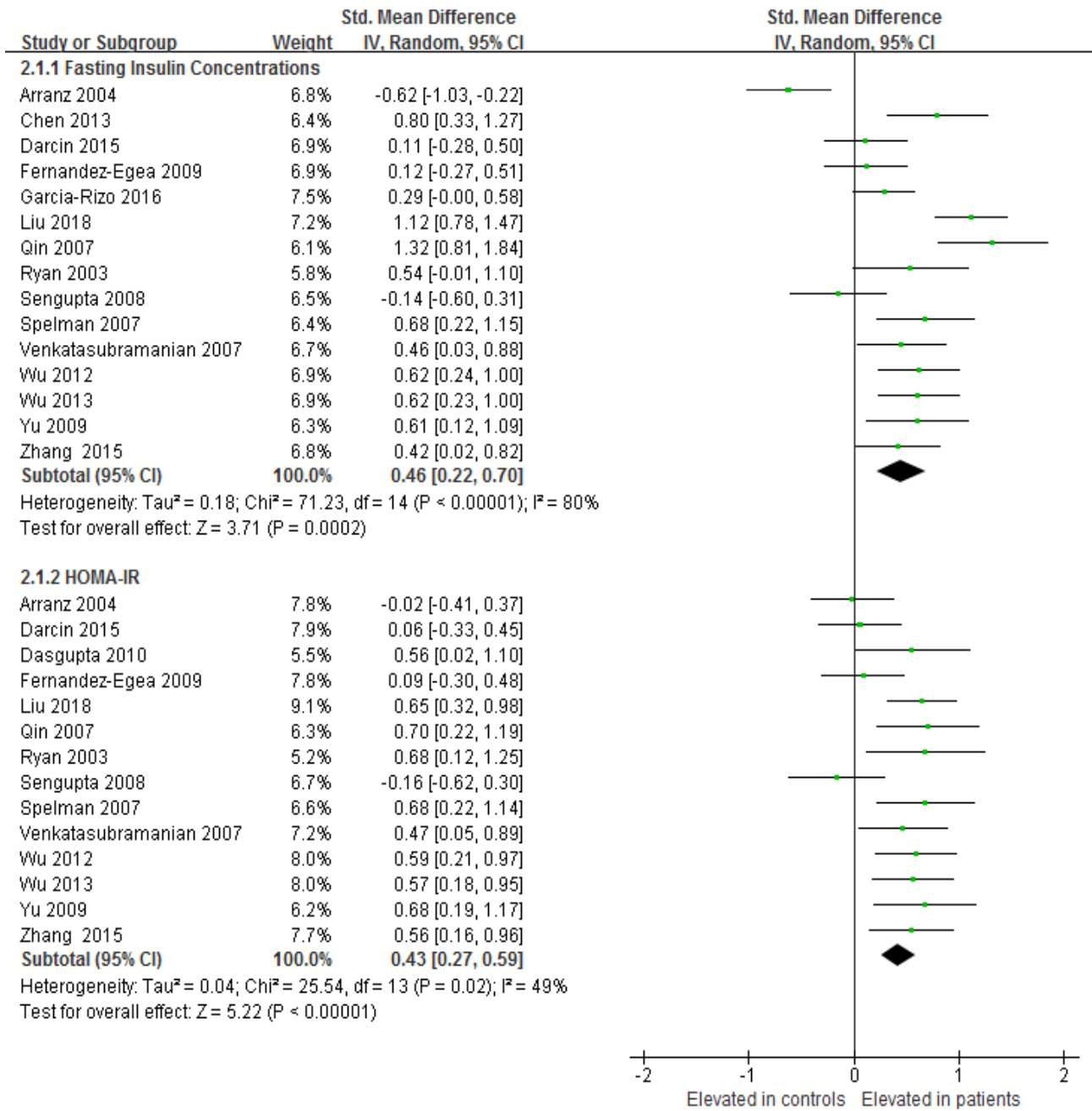
6 studies measured the level of two-hour OGTT. Compared to healthy controls, a significant elevation was observed in two-hour OGTT (95% CI; 0.63 to 1.2;  $I^2=0\%$ ;  $P<0.00001$ ) (Figure 2). In the context of low study numbers, publication bias was not performed.

### Fasting plasma level of insulin

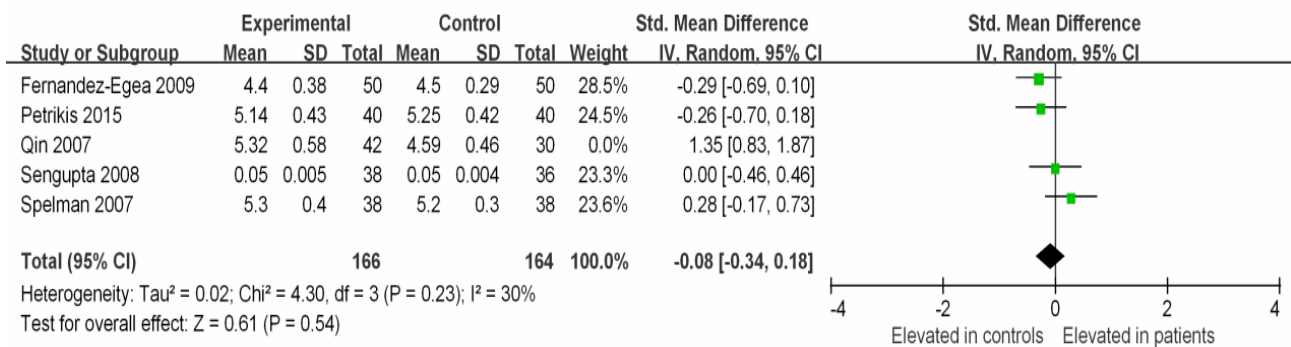
15 studies measured insulin concentration. Pooling the data suggested increased insulin concentration in patients (95% CI; 0.22 to 0.7;  $I^2=80\%$ ;  $P=0.0002$ ). Findings of the Egger test ( $P=0.583$ ) suggested that publication bias was not significant. There was a high level of heterogeneity in this analysis led by one outlier. Removing this study (Arranz 2004) in a sensitivity analysis reduced heterogeneity to 69% (95% CI; 0.33 to 0.73) (Figure 3).



**Figure 2.** Fasting Glucose Concentrations and 2h OGTT in Patients with First-Episode Schizophrenia and Control



**Figure 3.** Fasting Insulin Concentrations and HOMA-IR in Patients with First-Episode Schizophrenia and Control



**Figure 4.** HbA1c level in patients and control

**Table 1.** Studies meeting inclusion criteria

Source	Country	DSM Diagnoses	Diagnostic criteria	No. of Patients	Patient Age, Mean (SD)	Glucose Homeostasis Parameter	Antipsychotic Status	Quality score
Arranz et al. 2004	Spain	Schizophrenia	DSM-IV	50	25.2±0.6	FG,FI ,HOMA-IR	All drug naive	7
Chen et al. 2013	China	Schizophrenia	DSM-IV	49	26.8±8.1	FG, FI	All drug naive OR<2 wk	6
Darcin et al. 2015	Turkey	Schizophrenia	DSM-IV	40	34.6±1.1	FG, FI, HOMA-IR	All drug naive	6
Dasgupta et al. 2010	India	Schizophrenia	DSM-IV	30	32.53±10.53	FG, HOMA-IR	All drug naive	6
Fernandez-Egea et al. 2009	Spain	Schizophrenia,, brief psychotic disorder, delusional disorder, psychosis not otherwise specified	DSM-IV	50	28.8±7.7	FG, FI, OGTT, HbA1c, HOMA-IR	All drug naive OR<1 wk	7
Liu et al. 2018	China	Schizophrenia	DSM-IV	80	25.0±6.0	FG, FI, HOMA-IR	All drug naive	7
Garcia-Rizo et al. 2016	Spain	Schizophrenia, brief psychotic disorder, psychosis not otherwise specified	DSM-IV	84	27.28±5.5	FG, FI, OGTT	<1 wk of Total antipsychotic use	5
Petrikis et al. 2015	Greece	Schizophrenia, Schizophreniform disorder or Brief psychotic episode	DSM-IV	40	32.45±9.81	FG, HbA1c	All drug naive	6
Qin et al. 2007	China	Schizophrenia	DSM-IV	42	31.20±9.30	FG,FI, HbA1c, HOMA-IR, OGTT	All drug naive	6
Quan et al. 2015	China	Schizophrenia	DSM-IV	58	33.11±12.76	FG,OGTT	All drug naive	6
Ryan et al. 2003	Ireland	Schizophrenia	DSM-IV	26	33.6±13.5	FG,FI,HOMA-IR	All drug naive	7
Sengupta et al. 2008	Canada	Schizophrenia spectrum disorder	DSM-IV	38	25.4±5.6	FG,FI,HbA1c,HOMA-IR	<10 d of Total antipsychotic use	6
Spelman et al. 2007	Ireland	Schizophrenia	DSM-IV	38	25.20±5.64	FG, FI, OGTT, HbA1c, HOMA-IR	All drug naive	6
Venkatasubramanian 2008	India	Schizophrenia	DSM-IV	44	33.0±7.7	FG, FI, HOMA-IR	All drug naive	6
Wan 2015	China	Schizophrenia or schizophreniform disorder	DSM-IV	77	29.17±6.20	FG	All drug naive	6
Wu et al. 2012	China	Schizophrenia or schizophreniform disorder	DSM-IV	71	24.0±70.0	FG, FI, HOMA-IR	All drug naive OR ≤3d	5
Wu et al. 2013	China	Schizophrenia	DSM-IV	70	24.49±6.98	FG, FI, HOMA-IR	All drug naive	7
Zhang et al. 2015)	China	Schizophrenia	DSM-IV	120	26.5±6.30	FG, FI, HOMA-IR	All drug naive	7
Yu et al. 2009	China	Schizophrenia	DSM-IV	58	26.23±7.42	FG, FI, OGTT, HOMA-IR	All drug naive	7

Abbreviations: FG - fasting glucose; FI - fasting insulin; HbA1c - hemoglobin A1c; HOMA-IR - homeostatic model assessment-insulin resistance; OGTT - oral glucose tolerance test; Quality score using NOS: Newcastle - Ottawa Quality Assessment Scale

**Table 2.** Newcastle-Ottawa Scale for assessing the quality of studies in meta-analysis

Source	Selection			Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Exposure Same method of ascertainment for cases and controls	Non-Response rate	Quality score
	Adequate definition of cases	Representativeness of the cases	Selection of controls					
Arranz et al. 2004	1	1	1	1	0	1	1	7
Chen et al. 2013	1	1	no description	1	0	1	1	6
Darcin et al. 2015	1	1	no description	1	0	1	1	6
Dasgupta et al. 2010	1	1	no description	1	0	1	1	6
Fernandez-Egea et al. 2009	1	1	1	1	0	1	1	7
Liu et al. 2018	1	1	1	1	0	1	1	7
Garcia-Rizo et al. 2016	1	1	no description	no description	0	1	1	5
Petrikis et al. 2015	1	1	0	1	0	1	1	6
Qin et al. 2007	1	1	no description	1	0	1	1	6
Quan et al. 2015	1	1	1	no description	0	1	1	6
Ryan et al. 2003	1	1	1	1	0	1	1	7
Sengupta et al. 2008	1	1	no description	1	0	1	1	6
Spelman et al. 2007	1	1	no description	1	0	1	1	6
Venkatasubramanian et al. 2007	1	1	no description	1	0	1	1	6
Wan et al. 2015	1	1	1	no description	1	1	1	6
Wu et al. 2012	1	1	no description	no description	0	1	1	5
Wu et al. 2013	1	1	1	1	0	1	1	7
Zhang et al. 2015	1	1	1	1	0	1	1	7
Yu et al. 2009	1	1	1	1	0	1	1	7

Abbreviations: FG - fasting glucose; FI - fasting insulin; HbA1c - hemoglobin A1c; HOMA-IR - homeostatic model assessment-insulin resistance; OGTT - oral glucose tolerance test; Quality score using NOS: Newcastle - Ottawa Quality Assessment Scale

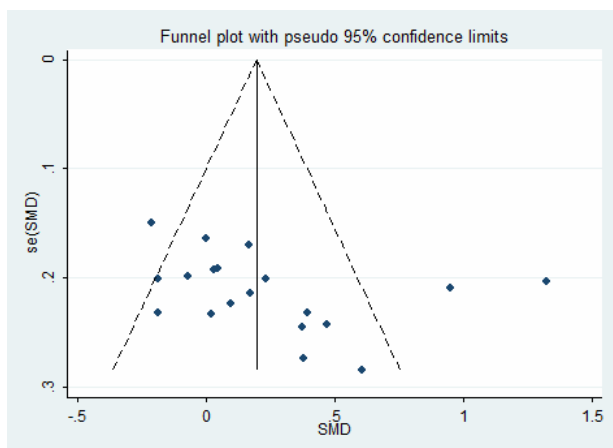
## Insulin resistance

HOMA-IR tool was used in patients and controls to analyze insulin resistance. 14 studies containing 757 patients and 582 controls were included in our analysis. Compared to healthy controls, HOMA-IR in patients was significant increased (95% CI; 0.29 to 0.6;  $I^2=49\%$ ;  $P<0.00001$ ) (Figure 3). Findings of the Egger test ( $P=0.599$ ) suggested that publication bias was not significant.

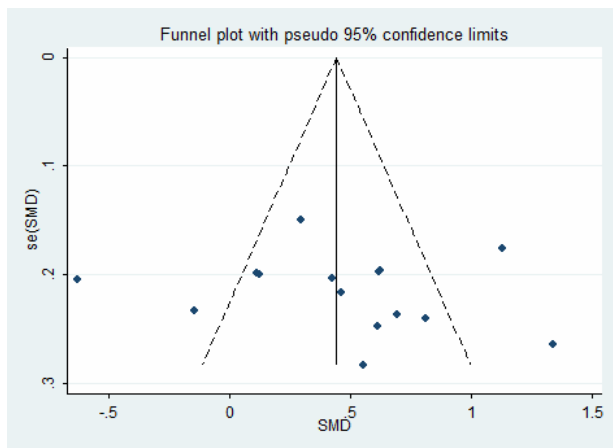
## HbA1c level

5 studies involving 208 patients and 194 controls were used for evaluate HbA1c level. Pooling this data showed that no significant difference in HbA1c level between patients and controls (95% CI; -0.34 to 0.75;  $I^2=86\%$ ;  $P=0.47$ ). Furthermore, sensitivity analysis showed that estimate of one studies were stray from the merger effect amount. After removal of the most divergent study (Qin 2007), heterogeneity was no longer significant (95% CI; -0.34 to 0.18;  $I^2=30\%$ ;  $P=0.54$ ) (Figure 4). In the context of low study numbers, publication bias was not performed.

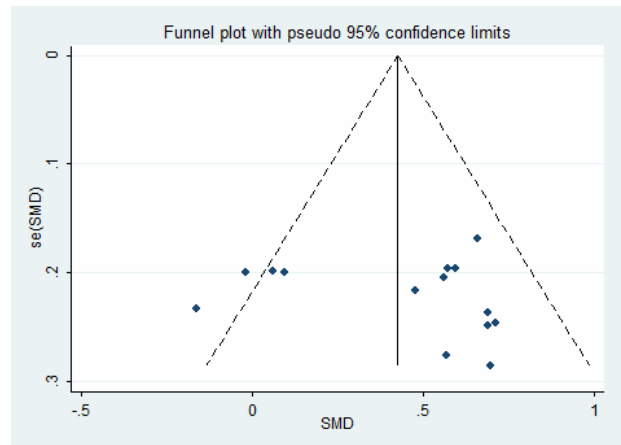
There did not appear to be a significant publication bias on funnel plots (Figure 5, 6 and 7).



**Figure 5.** Publication bias of studies about fasting glucose on funnel plots



**Figure 6.** Publication bias of studies about fasting insulin on funnel plots



**Figure 7.** Publication bias of studies about insulin resistance on funnel plots

## DISCUSSION

Our analysis revealed that patients with first-episode schizophrenia did significantly differ from healthy controls in their measurements of FG concentration, two-hour OGTT concentration, insulin concentration and insulin resistance. Compared with healthy controls, drug-naïve patients have higher FG, two-hour OGTT, and insulin levels. Insulin resistance results were also found to be higher. However, HbA1c levels were not significantly changed in patients when compared with controls. These data thus lend support to glycemic abnormality in patients with first-episode psychosis.

Our meta-analysis highlights the inherent risk of patients with first-episode schizophrenia for developing abnormal glucose metabolism. However, the exactly mechanisms of abnormal glucose metabolism in patients with first-episode psychosis are unknown. Studies suggested that inflammation, genetic polymorphisms, and chronic stress can lead to glucose metabolism abnormalities in patients with first episode psychosis (Amare et al. 2017, Belvederi Murri et al. 2016, Kucukgoncu et al. 2019). Recent study showed that familial abnormal glucose metabolism or primary insulin signaling pathway abnormality is related to risk for psychosis (Chouinard et al. 2018). Progression of insulin resistance can lead to metabolic syndrome and T2DM. Moreover, insulin resistance may precede the development of T2DM by 10 to 15 years (Freeman & Pennings 2018). 8 studies involving Chinese Han in our analysis, our pooled analysis indicated that insulin resistance is more common in patients with first-episode psychosis than in controls.

Several limitations arise from our analysis. Firstly, there was considerable heterogeneity ( $I^2=81\%$ ) in the result of the meta-analysis of fasting plasma glucose concentration. One study (Quan 2015) reported on results of the impaired fasting glucose (IFG). Heterogeneity was decreased from 81% to 48% after removing the study in a sensitivity analysis. 8 patients were reported with IFG in this study. IFG is defined by an elevated FG concentration ( $\geq 100$  and  $< 126$  mg/dl). It is

well known that IFG and IGT are intermediate states in glucose metabolism. Studies showed that up to 16% of patients with first-episode drug-naïve schizophrenia have IFG. Secondly, the number of studies for HbA1c and two-hour OGTT levels was small. After excluding one outlier (Qin 2007), the heterogeneity was decreased from 86% to 30%. Then, we found that the number of patients and controls were not matched in the study. Another limitation was that studies included in our analysis varied in their definition of antipsychotic naïve. 5 of 19 studies prescribed that cases could have taken antipsychotics in different period (maximum of 2 weeks). However, the results of FG and two-hour OGTT in these studies were in line with studies in which case are drug naïve. These findings support the assertion that exposure to antipsychotic medication in short term is unlikely to confound the results of this meta-analysis. Additionally, several studies have limited matching data. 5 of 19 studies have not matched with BMI. Several studies also have not matched with lifestyle, such as diet and smoking.

## CONCLUSION

Despite the limitations of our study, our results highlight the glycemic abnormalities in patients with first-episode drug-naïve schizophrenia. Thus, we should heighten the alteration of glycemic indices in patients with first-episode schizophrenia, which is essential to decrease the risk of 2TDM.

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**Conflict of interest:** None to declare.

### Contribution of individual authors:

Data from eligible studies were extracted by six independent reviewers: Lulu Zheng, Bei Zheng, Shen Zeng, Jingjing Li, Bingqing Liang & Jun Zhu.

Wenjuan Yang was responsible for the data collection and writing the manuscript.

Meiling Zhang was responsible for statistical analyses and took part in the writing of the manuscript.

All authors took part in reviewing draft versions of the manuscript and approved of the final version.

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