Journal of Psychosomatic Research 132 (2020) 109968

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Polygenic risk score for schizophrenia was not associated with glycemic level (HbA1c) in patients with non-affective psychosis: Genetic Risk and Outcome of Psychosis (GROUP) cohort study

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ARTICLE INFO

Keywords:
Diabetes
Schizophrenia
Psychosis
Polygenic risk score
Antipsychotics

ABSTRACT

Introduction: Type 2 diabetes (T2D) is a common comorbidity in patients with schizophrenia (SCZ). The underlying pathophysiologic mechanisms are yet to be fully elucidated, although it can be argued that shared genes, environmental factors or their interaction effect are involved. This study investigated the association between polygenic risk score of SCZ (PRS_{SCZ}) and glycated haemoglobin (HbA1c) while adjusting for polygenic risk score of T2D (PRS_{T2D}), and clinical and demographic covariables.

Methods: Genotype, clinical and demographic data of 1129 patients with non-affective psychosis were extracted from Genetic Risk and Outcome of Psychosis (GROUP) cohort study. The glycated haemoglobin (HbA1c) was the outcome. PRS was calculated using standard methods. Univariable and multivariable linear regression analyses were applied to estimate associations. Additionally, sensitivity analysis based on multiple imputation was done. After correction for multiple testing, a two-sided *p*-value $\leq .003$ was considered to discover evidence for an association.

Results: Of 1129 patients, 75.8% were male with median age of 29 years. The mean (standard deviation) HbA1c level was 35.1 (5.9) mmol/mol. There was no evidence for an association between high HbA1c level and increased PRS_{SCZ} (adjusted regression coefficient (aβ) = 0.69, standard error (SE) = 0.77, *p*-value = .37). On the other hand, there was evidence for an association between high HbA1c level and increased PRS_{T2D} (aβ = 0.93, SE = 0.32, p-value = .004), body mass index (aβ = 0.20, SE = 0.08, p-value = .01), diastolic blood pressure (aβ = 0.08, SE = 0.04, p-value = .03), late age of first psychosis onset (aβ = 0.19, SE = 0.05, p-value = .0004) and male gender (aβ = 1.58, SE = 0.81, p-value = .05). After multiple testing correction, there was evidence for an association between high HbA1c level and late age of first psychosis onset. Evidence for interaction effect

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https://doi.org/10.1016/j.jpsychores.2020.109968
Received 11 October 2019; Received in revised form 13 February 2020; Accepted 13 February 2020
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between PRS_{scz} and antipsychotics was not observed. The multiple imputation-based sensitivity analysis provided consistent results with complete case analysis.

Conclusions: Glycemic dysregulation in patients with SCZ was not associated with PRS_{SCZ}. This suggests that the mechanisms of hyperglycemia or diabetes are at least partly independent from genetic predisposition to SCZ. Our findings show that the change in HbA1c level can be caused by at least in part due to PRS_{T2D}, late age of illness onset, male gender, and increased body mass index and diastolic blood pressure.

1. Introduction

Schizophrenia (SCZ) is a heterogeneous psychiatric disorder manifested by positive (i.e., delusions and hallucinations) and negative (i.e., impaired motivation, social withdrawal and reduction in spontaneous speech) symptoms [1]. SCZ shortens life expectancy by 15–30 years compared to the general population [2,3], of which approximately 60% is caused by co-occurring somatic diseases, such as type 2 diabetes (T2D) [4]. Metabolic disorders, including T2D, have been common long-term complications in patients with SCZ [5]. The worldwide prevalence of T2D among patients with SCZ is 10.8% [6] and the prevalence in Dutch patients with SCZ is 15.3% [7]. Besides, increased level of glycated haemoglobin (HbA1c) is observed in 14.4% [8], impaired fasting blood glucose in 15.0% [9] and impaired glucose tolerance in 14.0% [10] of patients with SCZ. Further evidence shows an increase in blood glucose and hepatic insulin resistance in patients with first-episode psychosis or antipsychotic naïve patients [11,12].

Epidemiologic evidence suggests a shared (pleiotropic) genetic aetiology between T2D and SCZ that explains part of the aforementioned comorbidity [13]. First, individuals born from a mother with gestational diabetes have a seven-fold increased risk of SCZ later in life [14]. Second, family history of SCZ is significantly associated with a family history of T2D and vice versa [15–18]. Third, the co-occurrence of T2D and SCZ has been reported before the discovery of antipsychotics, leaving T2D more likely to be associated with genetic aetiology of SCZ [19]. Furthermore, a recent genome-wide association study (GWAS) and polygenic risk score analysis identified 29 shared genes and significant association between polygenic risk scores of the two diseases [20]. An advanced network and pathway-based analysis also depicted shared pathogenetic association between SCZ and T2D [21–23].

Beyond the possibility of shared genetic susceptibility, several longitudinal, randomized controlled trial and meta-analysis studies [24–28] show that the use of antipsychotic drugs has also been independently associated with metabolic disturbances in SCZ. For example, use of olanzapine substantially increases blood glucose level and the risk of T2D up to 59% among patients with SCZ [29–31] even though individual differences of susceptibility to antipsychotics-induced cardiometabolic impairment is observed [32–36]. Similar to the general population, glycaemic dysregulation among people with SCZ can also be associated with demographic and clinical diabetogenic risk factors [5,13,37,38].

In spite of these broad ranges of evidence, variation in diagnostic criteria or use of phenotype for T2D, study population, sample size and number of single nucleotide polymorphisms (SNPs) used to construct polygenic risk score (PRS) has been observed between studies. Moreover, comorbidity studies to explore the genetic bases of these two diseases are scarce due to the complex nature of the diseases and underdiagnosis of T2D patients. So, the findings have been inconsistent, and it is not yet fully elucidated who of SCZ patients may develop glucose dysregulation and T2D. In this study, we aimed to investigate the association between polygenic risk score of SCZ (PRS_{SCZ}) and glycated haemoglobin level (HbA1c) while adjusting for polygenic risk score of T2D (PRS_{T2D}), and clinical and demographic covariables. We hypothesized that PRS_{SCZ} significantly associated with high glycated haemoglobin level HbA1c.

2. Methods

2.1. Study population

Data release 7.00 of Genetic Risk and Outcome of Psychosis (GROUP) cohort study was used for this study. GROUP is a multi-centre longitudinal cohort study in the Netherlands, which constituted of patients, parents, siblings and controls [39]. Details of the original cohort were explained elsewhere [39]. Patients with non-affective psychotic disorders, age between 16 and 50 years and good command of the Dutch language were included. In GROUP cohort study, data were collected at baseline, and after three years and six years. In the present study, 1129 eligible patients who had cardiometabolic data that have been collected only on the second wave of assessment at the third year of follow-up were included. Genotype, clinical and demographic data were collected from patients after obtaining verbal and written informed consent.

2.2. Genotyping and quality control (QC)

Genotyping of samples performed using Illumina and Affymetrix platforms. The DNA data of 1434 individuals (758 patients and 676 controls) were genotyped for 547,383 single nucleotide polymorphisms (SNPs) using Illumina HumanHap 550 k version 3.0 beadchip (https://www.illumina.com). Besides, the DNA data of 1968 individuals (393 patients, 154 controls and 1421 healthy relatives) were genotyped for 929,556 SNPs using Affymetrix genome-wide Human SNP Array version 6.0 (http://www.affymetrix.com/estore/index.jsp). Thirty-six participants were excluded because of sex mismatch (i.e. discrepancy between the recorded and genetically determined sex) and five participants due to genotype missing rate > 10%. SNPs were excluded if haploid, a missing rate per SNP was >0.10, a minor allele frequency < 0.01 and a Hardy–Weinberg equilibrium (HWE) p-value $< 1 \times 10^{-6}$. Moreover, pruning was done using a window/step size of 50 kb/5 and $r^2 > 0.2$ [40]. As a result, 515,286 SNPs and 1393 individuals (737 cases and 656 controls) passed QC for further analysis. Similarly, 729,597 SNPs and 1968 individuals genotyped using Affymetrix passed QC. The genomic coordinate of all sample SNPs (except for 57 from Illumina and 86 from Affymetrix) was converted from Human NCBI36/hg18 to Human GRCh37/hg19 using liftover [41]. As implemented in the Haplotype Reference Consortium (HRC) [42], both platform samples were imputed on the backbone of 1000G Phase-3 reference haploblocks by using Michigan Imputation Server and option of SHAPEIT for phasing. This yielded 46,178,415 imputed SNPs, which was down to 16,353,433 SNPs after selecting SNPs with a quality score (info score) threshold of >0.30. Of these, 9,067,392 SNPs and 1393 subjects passed the post-imputation QC. For Affymetrix genotyped SNPs, 1000G based imputation yielded 46,178,419 imputed SNPs, and 9,122,501 SNPs and 1968 individuals passed the post-imputation QC. Genotype QC was carried out using PLINK toolset version 1.9 [43].

2.3. Polygenic risk score calculation

The summary statistics of the 62 T2D risk SNPs ($p < 5 \times 10^{-8}$) were obtained from the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium, a meta-analysis of GWAS with more than 34,840 cases and 114,981 controls (Table S1) [44,45]. The summary

statistics of the SCZ risk SNPs were obtained from the phase 2 Psychiatric Genomics Consortium (PGC-2), a meta-GWAS of SCZ with 36,989 cases and 113,075 controls (Table S2) [46]. There was no sample overlap between the study sample and SCZ/T2D GWAS. Polygenic risk scores were calculated for each individual using PRSice software version 1.25 for Windows [47] as a sum of the number of risk alleles multiplied by their corresponding effect sizes (i.e. the logs of the OR) across genetic loci. It is well known that PRS_{SCZ} is more predictive when including a larger number of genetic markers [48], so that PRS was calculated using five *p*-value thresholds (i.e. 5×10^{-8}, 5×10^{-4}, 0.01, 0.05, 0.1). We used PRS, which is built of SNPs associated with SCZ at a p-value threshold (PT) of ≤ 0.05 given that this has been reported to be the most predictive threshold for SCZ [46]. However, for T2D, PRS was calculated based on p-value threshold $< 5 \times 10^{-8}$ given that evidence on the predictive power of genome-wide non-significant SNPs is lacking. To control for the population stratification effect, the PRS was adjusted for the first ten ancestry principal components estimated by EIGENSTRAT software version 3.2.4 [49]. Finally, we standardized the PRS to a standard normal distribution (mean of 0 and standard deviation of 1) for ease of interpretations [50].

2.4. Measurement variables

Glycated haemoglobin level (HbA1c) in mmol/mol, which is one of the phenotypes of T2D, was the outcome variable. The main exposure variable was PRS_{SCZ}. The covariables were PRS_{T2D}, clinical indicators (i.e., age of psychosis onset, duration of illness, episode of psychosis, presence of comorbid diseases, physical examination reports and laboratory test reports) and demographic characteristics (i.e., gender, age, ethnicity, marital status, cigarette smoking and alcohol drinking). Physical examination report includes body mass index (kg/m^2), umbilical waist circumference (cm), blood pressure (mmHg) and pulse rate (beats/min), whereas laboratory test report includes triglycerides (mmol/l), high-density lipoprotein (mmol/l), low-density lipoprotein (mmol/l). Reported comorbid diseases were hematologic, hormonal, metabolic, heart, vascular, liver-bilious-pancreas-spleen, abdominal/gastrointestinal and kidney disorders. Moreover, platform/batch effect indicating the variance in PRS due to use of different genotyping platforms (Illumina vs Affymetrix) was considered. Data were collected from patient themselves or their therapists. The Comprehensive Assessment of Symptoms and History (CASH) [51] and Schedules for Clinical Assessment for Neuropsychiatry (SCAN) [52] structured questionnaire were used to assess psychotic disorders. Diagnosis was made based on the fourth text-edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) axis one [53]. We classified antipsychotics as high metabolic risk (olanzapine and clozapine), moderate metabolic risk (risperidone, quetiapine, amisulpride, pipamperone, levomepromazine and sertindole), low metabolic risk (haloperidol, aripiprazole, bromperidol, flupentixol, pimozide, sulpiride and zuclopenthixol), and unknown metabolic risk (clotiapine and perphenazine) [25–27]. Antipsychotic drug dosage was calculated based on chlorpromazine equivalents (CPZE), which is defined as the dose of a drug that is equivalent to 100 mg of oral dose of chlorpromazine. Patients without prescription of antipsychotic drugs were classified as nonusers.

2.5. Statistical analyses

First, the predictors, which were identified through reading of previous literature [5] and available in GROUP cohort study were included in the univariable linear regression model. Those predictors with a *p*-value of ≤ 0.25 in univariable analyses were included in the multivariable linear regression model. Next, considering our hypothesis and the relatedness of variables to the outcome, we developed four hierarchical models to adjust confounders and identify relevant independent predictors of high HbA1c. Model 1 included only PRS_{SCZ}. Model 2 included Model 1 and PRS_{T2D}, type of genotyping platform and use of antipsychotics. Model 3 expanded Model 2 with cardiometabolic profiles that included body mass index, waist circumference, blood pressure, pulse, triglycerides, high-density lipoprotein and low-density lipoprotein. Finally, Model 4 was an extension of Model 3 by inclusion of age of onset of psychosis, duration of illness, gender, ethnicity, current age, alcohol drinking and interaction term between PRS_{SCZ} by high-risk antipsychotics for metabolic disturbance. The best-fitting model was selected using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Log-Likelihood (LL), and R^2. Multicollinearity in the best fitting model was investigated using the variance inflation factor (VIF) (1.0 to 10.0) and tolerance (> 0.20) statistics [54]. Since 18 variables were tested in model 4, to accommodate multiple hypothesis testing, the statistical significance two-sided *p*-value was set to be 0.05 divided by 18 reaching at 0.003. We reported evidence for an association using unstandardized coefficients (i.e., regression coefficient (β) and standard error (SE)) along with the p-value. The Statistical Package for the Social Sciences (SPSS) software version 23.0, R software version 3.3.2 and PLINK toolset version 1.90 were used for data analyses.

2.6. Sensitivity analysis

To explore the amount and likely mechanisms of missingness in our data, we analysed the patterns of data missingness. In addition, independent *t*-test for continuous variables and Chi-square test for categorical variables were performed to compare differences between complete and missing cases, and test missing completely at random (MCAR) or missing at random (MAR). Finally, missing data were handled by multiple imputation (i.e., data were imputed 20 times) using Markov chain Monte Carlo (MCMC) method assuming missing at random (MAR). Predictive mean matching (PMM) model was used for continuous variables and logistic regression model was used for categorical variables. A sensitivity analysis based on Model 4 was done using the imputed dataset. We also performed sensitivity analysis after excluding individuals with self-reported diabetes ($N = 10$), and hormonal and metabolic disorders other than diabetes ($N = 7$).

3. Results

3.1. Patient characteristics

Of 1129 patients, 75.8% were male and 79.2% were Caucasian. The median (interquartile range (IQR)) age and age of onset of first psychosis was 29 (10) years and 21 (9) years, respectively. The mean (standard deviation) HbA1c was 35.1(5.9) mmol/mol. More than three-quarters of patients (78.8%) have used antipsychotics. The median (IQR) antipsychotic dosage was 300 (330) mg/day. In addition, 13.4% of patients reported cardiometabolic diseases other than diabetes. Detailed patient characteristics have shown below in Table 1.

3.2. Risk factors of high HbA1c

In the univariable regression model, there was evidence for an association between high HbA1c level and PRS_{SCZ}, PRS_{T2D}, use of antipsychotics and most cardiometabolic profiles (Table 2).

In the multivariable regression analysis, we built four models and selected model 4 as the best-fitting model (BIC = 2304.82, AIC = 2227.77, LL = −1093.88, R^2 = 19.20%) (Table 3). Waist circumference was excluded from model 4 due to collinearity with body mass index, and current age was excluded due to collinearity with age of first psychosis onset and duration of psychosis illness. There was no evidence for an association between high HbA1c level and increased PRS_{SCZ} (adjusted regression coefficient (aβ) = 0.69, standard error (SE) = 0.77, *p*-value = .37). The patient glycated haemoglobin level, on average, was increased by 0.69 mmol/mol for every increase of one point (i.e., one standard deviation change) on the PRS_{SCZ}. On the other

Table 1
Background characteristics of patients (N = 1129).

Characteristics	N = 1129
Demographics and lifestyle	
Gender, male (%)	75.8
Marital status, not married (%)	85.0
Ethnicity, Caucasian (%)	79.2
Age, median (IQR) years	29.0 (10.0)
Alcohol drinking[a] (%)	74.3
Cigarette smoking[b] (%)	62.3
Disease diagnosis and treatment	
Diagnosis, psychotic disorder (Schizophrenia) (%)	96.6
Age of onset of first psychosis, median (IQR) years	21.0 (9.0)
Duration of psychotic illness, median (IQR) years	7.3 (5.2)
First psychotic episode (%)	32.1
Total transition (sibling and controls) to psychosis (%)	0.9
Current use of antipsychotics (any type) (%)	78.8
High metabolic risk antipsychotics[c] (%)	25.0
Medium metabolic risk antipsychotics[d] (%)	14.9
Low metabolic risk antipsychotics[e] (%)	11.2
Antipsychotic daily dosage (CPZE), median (IQR) mg/day	300 0.0 (330.0)
Cardiometabolic profile	
Glycated haemoglobin (HbA1c), mean (SD) mmol/mol	35.1 (5.9)
Body mass index, mean (SD) kg/m^2	26.1 (4.9)
Umbilical waist circumference, mean (SD) cm	95.0 (14.4)
Systolic blood pressure, mean (SD) mmHg	127.2 (15.4)
Diastolic blood pressure, mean (SD) mmHg	79.4 (11.1)
Pulse rate, mean (SD) beat/min	75.6 (15.4)
Triglycerides, median (IQR) mmol/l	1.4 (1.2)
High-density lipoprotein, mean (SD) mmol/l	1.2 (0.6)
Low-density lipoprotein, mean (SD) mmol/l	3.1 (0.9)
Diabetes, Type 2[f] (%)	2.5
Comorbid diseases[g] (%)	13.4
Genotyping platform, Affymetrix	57.1%

CPZE = Chlorpromazine equivalent; SD = Standard deviation; IQR = Interquartile range; [a] = Greater than 12 units during the last 12 months; [b] = Daily use of cigarettes during the last 12 months; [c]Includes olanzapine and clozapine; [d]Includes risperidone, quetiapine, amisulpiride, pipamperone, levomepromazine and sertindole; [e]Includes haloperidol, aripiprazole, bromperidol, flupentixol, pimozide, sulpiride and zuclopenthixol; [f] = Self-reported; [g] = Self-reported hematologic, hormonal, metabolic, heart, vascular, liver-bilious-pancreas-spleen, abdominal/gastrointestinal, and kidney disorders.

hand, there was evidence for nominal association between high HbA1c level and increased PRS_{T2D} (aβ = 0.93, SE = 0.32, p-value = .004), body mass index (aβ = 0.20, SE = 0.08, p-value = .01), diastolic blood pressure (aβ = 0.08, SE = 0.04, p-value = .03) and male gender (aβ = 1.58, SE = 0.81, p-value = .05). After multiple testing correction, there was evidence for an association between high HbA1c level and late age of first psychosis onset (aβ = 0.19, SE = 0.05, p-value = .0004). Despite the adjustment for several covariables (models 2 to 4), the association between high HbA1c level and PRS_{SCZ} was attenuated solely due to platform effect. In a follow-up stratified analysis by the genotyping platform, based on model 4, there was no evidence of an association between high HbA1c level and PRS_{SCZ} in both platforms. In addition, the association between high HbA1c level and high metabolic risk antipsychotics was attenuated only due to the interaction term (model 4).

3.3. Missing data and sensitivity analysis

Data missingness pattern analysis showed that 16 out of 19 variables had at least one missing value and 781 patients had at least one missing value on a variable (Fig. S1, Table S4). Overall, 28.13% of the total sample data were missing (Fig. S1). As illustrated in Fig. S2, the pattern of missing values seems random. Little's test was significant (X^2 = 596.33, df = 339, $p < .001$), which indicate a lack of evidence that support missingness completely at random (MCAR). The independent t-test (Table S5) and Chi-square test (Table S6) results showed significant difference between complete and missing cases on many variables, and missing values can be predicted based on other variables, which support evidence of missing at random (MAR) and assumption of multiple imputation. Finally, sensitivity analysis based on multiple imputation provided consistent results with complete case analysis.

4. Discussion

Whether shared genetic susceptibility to SCZ and T2D is predisposing to a high glycaemic level among patients with non-affective psychosis has been an ongoing debate and yet to be investigated. Though, the general body of current evidence suggests that antipsychotics play an important role in hyperglycaemia. One may suggest that antipsychotics may not be significantly associated with high glycemia level in the absence or low level of genetic susceptibility to SCZ and/or T2D. To clarify this ambiguity, we investigated the association between polygenic risk score of SCZ (PRS_{SCZ}) and glycated haemoglobin level (HbA1c) while adjusting for polygenic risk score of T2D (PRS_{T2D}), and clinical and demographic covariables in a relatively large sample of patients with non-affective psychotic disorder that follows the same diagnostic criteria and treatment guideline. In this study, there was no evidence for an association between high HbA1c level and increased PRS_{SCZ}, whereas late age onset of psychosis found to be a strong predictor associated with high HbA1c.

Our finding was in line with previous studies [55–59] that showed weak or absence of association between PRS_{SCZ} and high glycaemia level or T2D. On the other hand, one study reported a positive association between high glycemia level and PRS_{SCZ} while adjusting for the use of antipsychotic medications [60] and another study [61] found a negative association between PRS_{SCZ} and high HbA1c level in patients with SCZ. This discrepancy might be due to constructing PRS using different version of the GWAS summary statistics [56–58,60], use of different measurement of glycaemic state (e.g. self-reported diabetes or laboratory reports) or different phenotype of T2D with different sensitivity (e.g. fasting or random blood sugar) [60], lack of adjustment to various important variables and inclusion of patients from different ethnicities [55,58]. The use of more than one different genotyping tool may also be a reason whereby Illumina and Affymetrix were used in our study. Our analysis showed that, despite the adjustment for multiple covariables, the association between high HbA1c level and PRS_{SCZ} was attenuated only due to platform effect. This can be due to the significant difference in mean PRS_{SCZ} between platforms (i.e., -1.01 for Illumina and 0.75 for Affymetrix) though the stratified analysis did not show evidence of an association. In addition, more samples were genotyped by Affymetrix platform (i.e. 441 vs 331). Of interest, there was a nominal positive association between PRS_{T2D} and high glycaemic level, in which previous studies [55,58] with comparable study design and setting also found similar results in patients with psychosis while others [56,60] failed to confirm the association.

In agreement with Cohen et al. [62], Mookhoek et al. [10] and Padmanabhan et al. [60], we found no significant association between use of antipsychotic drugs and high glycaemic level. Our study indicated that antipsychotics can be associated with high glycemia level only when genetic susceptibility to SCZ is high given that the association was attenuated when we adjusted our model for the interaction term (i.e., PRS_{SCZ} by high metabolic risk antipsychotics). In contrast, several longitudinal, randomized control trial and meta-analysis studies [24-28] found a significant positive association between the use of antipsychotic drugs particularly olanzapine and clozapine and high glycaemic level. One possible explanation for this discrepancy may be that psychiatrists are more aware of the risk and may switch sooner to low metabolic risk antipsychotic medication, once metabolic disturbances have occurred in daily practice. In addition, the difference in the age of patients may explain this variation at least in part. In this study, the mean age was 30 years suggesting they are physically active

Table 2
Univariable regression analyses on the association between HbA1c and polygenic risk scores, clinical and demographic predictors.

Risk factors	Unstandardized Coefficients	p-value	Explained variance (R^2) (%)
	β(SE)		
PRS_{SCZ}	0.69 (0.29)	0.02	1.33
PRS_{T2D}	1.03 (0.30)	0.001	2.80
Platform, Affymetrix	1.00 (0.58)	0.09	0.70
Current use of antipsychotics (any type)	1.39 (0.65)	0.03	0.80
High metabolic risk antipsychotics[a]	1.04 (0.50)	0.04	0.70
Medium metabolic risk antipsychotics[b]	0.73 (0.60)	0.23	0.30
Low metabolic risk antipsychotics[c]	−0.59 (0.65)	0.36	0.10
Antipsychotic daily dosage (CPZE) mg/day	0.001 (0.001)	0.43	0.10
Interaction term[d]	1.94 (1.07)	0.07	0.80
Body mass index (kg/m^2)	0.28 (0.05)	<0.001	5.10
Waist circumference (cm)	0.09 (0.02)	<0.001	4.60
Systolic blood pressure (mmHg)	0.05 (0.02)	0.003	1.60
Diastolic blood pressure (mmHg)	0.09 (0.02)	0.0002	2.50
Pulse rate (beat/min)	0.03 (0.02)	0.04	0.80
Triglycerides (mmol/l)	0.55 (0.17)	0.001	1.80
High-density lipoprotein (mmol/l)	−0.59 (0.39)	0.13	0.40
Low-density lipoprotein (mmol/l)	1.05 (0.26)	0.0001	2.70
Age of first psychosis onset (years)	0.19 (0.04)	<0.0001	4.30
Duration of psychotic illness (years)	0.11 (0.06)	0.07	0.60
≥ one psychotic episode	0.20 (0.49)	0.69	0.001
Gender, male	1.30 (0.58)	0.03	0.80
Ethnicity, non-Caucasian	1.52(0.66)	0.02	0.90
Current age (years)	0.20 (0.03)	0.001	5.40
Alcohol drinking[e]	−1.12 (0.58)	0.05	0.60
Cigarette smoking[f]	0.52 (0.51)	0.31	0.20

PRS_{SCZ} = Polygenic risk score for schizophrenia (p-value threshold 0.05 and standardized to a standard normal distribution with mean of 0 and standard deviation of 1), see also Table S3 for the association based on other p-value thresholds; PRS_{T2D} = Polygenic risk score for type 2 diabetes (p-value threshold 5×10^{-8} and standardized to a standard normal distribution with mean of 0 and standard deviation of 1); CPZE = Chlorpromazine equivalent; [a]Includes olanzapine and clozapine; [b]Includes risperidone, quetiapine, amisulpiride, pipamperone, levomepromazine and sertindole; [c]Includes haloperidol, aripiprazole, bromperidol, flupentixol, pimozide, sulpiride and zuclopenthixol; [d] = PRS_{SCZ} X High metabolic risk antipsychotics; [e] = Greater than 12 units during the last 12 months; [f] = Daily use of cigarettes during the last 12 months.

and perform regular exercise. The design of the study, degree of glycaemic dysregulation and difference in duration of treatment may also explain this incongruity [10,24,63]. Our study is cross-sectional in which the mean HbA1c was 35.1 mmol/mol and duration of antipsychotics treatment was not clearly known.

In this study, late age of psychosis onset was the strongest predictor that independently associated with high HbA1c, which is in line with previous studies that report diabetes and related comorbidities are more common in older people with SCZ [64,65]. Despite this, it is not yet clear whether medical comorbidities are more prevalent among older persons with SCZ or whether these disorders have an earlier age of onset [64]. It is known that the typical age of SCZ onset is late adolescence [66] and a recent meta-analysis also concluded that glucose dysregulation occurs starting from the onset of SCZ [12]. In addition, we found evidence of a nominal association between high HbA1c and increased body mass index and diastolic blood pressure. Glycaemic dysregulation among people with SCZ has been attributed to common diabetogenic factors, such as high body mass index or obesity, high blood pressure or hypertension, and dyslipidaemia [13,38]. A large cohort study and meta-analysis of 30 studies conducted in the general population also concluded that people with elevated blood pressure are at increased risk of diabetes [67].

In general, the mechanisms of cardiometabolic risk factors and/or disorders in patients with SCZ are complex and multidimensional that include polygenic and polyenviromic risk factors, such as the use of antipsychotic drugs, poor nutrition, smoking, and physical inactivity. Current studies show that antipsychotic drugs might affect glucose and lipid metabolisms leading to an increased risk of hyperglycaemia, insulin resistance, type 2 diabetes, dyslipidaemia, and metabolic syndrome, and cardiovascular morbidity and mortality, as a result. In addition, various genes and neurotransmitter receptors, such as dopamine D2R, histamine H1R, serotonin 5-HT2R, and muscarinic M3R might also play a significant part in the risk and differential cardiometabolic effects of antipsychotic drugs. For example, patients with SCZ who are carriers of risk genetic variants in *HTR2C, AMPK, LEP, BDNF, MC4R, HRH1, NDUFS1, GHRL, LEPR, NPY, MTHFR, FTO, OGFRL1, CNR1, and CNR1* genes are more prone to weight gain and metabolic syndrome and eventually T2D [32-36], whereas patients who are carriers of endocannabinoid receptor type 1 gene polymorphisms have a lower risk of antipsychotics induced cardiometabolic dysregulation [68]. Through extensive characterization of these risk factors and disentangling underlying pathophysiology, it is can be possible to improve the effectiveness of interventions for prevention and treatment [5,37].

The public health burden of the comorbidity between SCZ and T2D is high and two-thirds of T2D cases in patients with SCZ were undiagnosed. In our study, the prevalence rate of self-reported T2D (2.5%) was lower than the prevalence reports in the Netherlands [7,63,69] and in other parts of the world [70]. This might be due to under-diagnosis as reported by Ward and colleagues [70] that up to 70% of T2D among patients with SCZ were undiagnosed compared to 25–30% in the general population. The comorbidity leads to poor functioning, quality of life, cognitive performance and prognosis of both diseases, and premature death due to complications [71,72]. Evidence for intervention strategies to reduce the burden of physical co-morbidity, improve health outcomes and reduce the mortality gap in patients with psychosis and other severe mental illness are still in their infancy [73]. Therefore, evidence-based care directed at patients with high polygenic load, body mass index and blood pressure, and who use high metabolic risk antipsychotics is required to tackle this problem and make sustained progress [73].

Our study has several strengths. First, the glycaemic level was ascertained based on the laboratory report of HbA1c, which has a high specificity [6]. In this study, using HbA1c as a biomarker of T2D can also be validated by the presence of a relatively high level of HbA1c in

Table 3
Multivariable regression analysis on association between HbA1c and polygenic risk scores, and clinical and demographic predictors.

Models	Included risk factors	Unstandardized Coefficients	p-value*	Model fit criteria			
		β (SE)		BIC	AIC	LL	R^2 (%)
1	PRS_{SCZ}	0.69 (0.29)	0.02	2693.13	2681.03	−1337.51	1.33
2	PRS_{SCZ}	0.86 (0.62)	0.17	2699.56	2671.31	1328.66	5.42
	PRS_{T2D}	1.01 (0.29)	0.001				
	Platform effect, Affymetrix	−0.51 (1.24)	0.68				
	High metabolic risk[a]	1.65 (0.64)	0.01				
	Medium metabolic risk[b]	0.97 (0.79)	0.22				
3	PRS_{SCZ}	1.13 (0.65)	0.08	2419.79	2365.00	−1168.50	13.74
	PRS_{T2D}	0.95 (0.31)	0.003				
	Platform effect, Affymetrix	−0.62 (1.30)	0.64				
	High metabolic risk[a]	1.51 (0.75)	0.05				
	Medium metabolic risk[b]	0.56 (0.84)	0.50				
	Body mass index (kg/m^2)	0.15 (0.07)	0.04				
	Systolic blood pressure (mmHg)	−0.005(0.03)	0.99				
	Diastolic blood pressure (mmHg)	0.09 (0.04)	0.01				
	Pulse blood pressure (beat/min)	−0.03 (0.02)	0.26				
	Triglycerides (mmol/l)	0.33 (0.31)	0.28				
	High-density lipoprotein (mmol/l)	0.03 (0.53)	0.96				
	Low-density lipoprotein (mmol/l)	0.83 (0.35)	0.02				
4	PRS_{SCZ}	0.69 (0.77)	0.37	2304.82	2227.77	−1093.88	19.20
	PRS_{T2D}	0.93 (0.32)	0.004				
	Platform effect, Affymetrix	0.18 (1.43)	0.90				
	High metabolic risk[a]	1.46 (1.51)	0.33				
	Medium metabolic risk[b]	0.75 (0.88)	0.39				
	Body Mass Index (kg/m^2)	0.20 (0.08)	0.01				
	Systolic blood pressure (mmHg)	−0.01 (0.03)	0.75				
	Diastolic blood pressure (mmHg)	0.08 (0.04)	0.03				
	Pulse blood pressure (beat/min)	−0.02 (0.02)	0.43				
	Triglycerides (mmol/l)	0.25 (0.35)	0.47				
	High-density lipoprotein (mmol/l)	0.56 (0.59)	0.34				
	Low-density lipoprotein (mmol/l)	0.60 (0.37)	0.10				
	Duration of psychosis illness (years)	0.07 (0.07)	0.37				
	Age of first psychosis onset (years)	0.19 (0.05)	0.0004				
	Gender, male	1.58 (0.81)	0.05				
	Ethnicity, non-Caucasian	0.38(1.07)	0.72				
	Alcohol drinking[c]	−1.13 (0.78)	0.15				
	Interaction term [d]	0.41(2.63)	0.88				

PRS_{SCZ} = Polygenic risk score for schizophrenia(p-value threshold 0.05 and standardized to a standard normal distribution with mean of 0 and standard deviation of 1); PRS_{T2D} = Polygenic risk score for type 2 diabetes (p-value threshold 5×10^{-8} and standardized to a standard normal distribution with mean of 0 and standard deviation of 1); BIC = Bayesian Information Criterion; AIC = Akaike Information Criterion; LL = Log-Likelihood; [a]Includes olanzapine and clozapine; [b]Includes risperidone, quetiapine, amisulpiride, pipamperone, levomepromazine and sertindole; [c] = Greater than 12 units during the last 12 months; [d] = PRS_{SCZ} X High metabolic risk antipsychotics; * = P < .05/18 was used to discover the evidence of an association.

individuals with self-reported T2D (i.e., 45.1 mmol/mol). Second, the PRS was constructed using many SNPs discovered from large training samples. Third, genetic and non-genetic risk factors were studied in a relatively large number of patients with SCZ, which can offer a less biased estimate of the association with glycaemic level. This study has also limitations. First, a single measurement of the HbA1c level was used to reveal hyperglycaemia and HbA1c is not the most sensitive measure of glucose-insulin homeostasis. In addition, the genetic architecture of the HbA1c and T2D might not necessarily the same. Even though we have evidence that supported missing at random (MAR), in general, it is difficult to test or prove the mechanism of data missingness and multiple imputation (MI) is not usually recommended for data missing not at random (MNAR). However, in this study, MI performed on MNAR data is unlikely to bias estimates to a greater extent than complete case analysis [74]. Another limitation was that the associated risk factors were determined only based on the availability of data in the GROUP cohort study; as a result, important risk factors, such as physical inactivity, inflammatory biomarkers, and poor diet, were not included in the analyses. It was also impossible to infer causality due to the cross-sectional nature of the study, but to strengthen the estimation of true effect and overcome this limitation, we used the sum effect of genetic variants, which is considered as a permanent marker of diseases/symptoms. Furthermore, our effect estimates may suffer from collider bias due to the use of PRS [75].

5. Conclusions

Glycemic dysregulation in patients with SCZ was not associated with PRS_{SCZ}. This suggests that the mechanisms of hyperglycemia or diabetes are at least partly independent from genetic predisposition to SCZ. Our findings show that the change in HbA1c level can be caused by at least in part due to PRS_{T2D}, late age of illness onset, male gender, and increased body mass index and diastolic blood pressure. Therefore, the PRS_{SCZ} may not be an exclusively informative predictor of T2D in patients with SCZ, rather clinical and demographic diabetogenic predictors remain still useful in clinical practice. Future studies with more sensitive measures of T2D, such as HOMA, HOMA2, fasting insulin or fasting plasma glucose, and PRS based on recently identified genetic variants are needed. In addition, it is also relevant to investigate glycaemic dysregulation among unaffected siblings of patients and other relevant diabetogenic risk factors, such as inflammation, poor diet, and physical inactivity. Finally, Linkage Disequilibrium score regression and common heritability study in a large sample is recommended to obtain strong evidence of association.

Funding statement

This work was supported by Geestkracht programme of the Dutch Health Research Council (Zon-Mw) (10-000-1001), and matching funds

from participating pharmaceutical companies (Lundbeck; AstraZeneca; Eli Lilly and Janssen Cilag) and, Universities and Mental Health Care organizations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Center and the mental health institutions: GGZ Ingeest; Arkin, Dijk en Duin; GGZ Rivierduinen; Erasmus Medical Centre and GGZ Noord Holland Noord. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland; GGZ Drenthe; Dimence; Mediant; GGNet Warnsveld; Yulius Dordrecht and Parnassia psycho-medical center The Hague. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven en De Kempen; GGZ Breburg; GGZ Oost-Brabant; Vincent van Gogh voor Geestelijke Gezondheid; Mondriaan; Virenze riagg; Zuyderland GGZ; MET ggz; Universitair Centrum Sint-Jozef Kortenberg; CAPRI University of Antwerp; PC Ziekeren Sint-Truiden; PZ Sancta Maria Sint-Truiden; GGZ Overpelt and OPZ Rekem. Utrecht: University Medical Center Utrecht and the mental health institutions: Altrecht; GGZ Centraal and Delta). The sponsors have no role in designing the study, in the collection, analysis, and interpretation of data, in the writing of the report and in the decision to submit the paper for publication.

Tesfa Dejenie Habtewold is supported by the University Medical Center Groningen (UMCG) scholarship, Graduate School of Medical Science, University of Groningen, the Netherlands.

Declaration of Competing Interest

There are no conflicts of interest from any of the authors to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2020.109968.

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