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Polygenic risk for type 2 diabetes mellitus among individuals with psychosis and their relatives

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ABSTRACT

Background: An elevated prevalence of Type 2 diabetes (T2D) has been observed in people with psychotic disorders and their relatives compared to the general population. It is not known whether this population also has increased genetic risk for T2D.
Methods: Subjects included probands with schizophrenia, schizoaffective disorder, or psychotic bipolar I disorder, their first-degree relatives without psychotic disorders, and healthy controls, who participated in the Bipolar Schizophrenia Network for Intermediate Phenotypes study. We constructed sets of polygenic risk scores for T2D ($PGRS_{T2D}$) and schizophrenia ($PGRS_{SCHIZ}$) using publicly available data from genome-wide association studies. We then explored the correlation of $PGRS_{T2D}$ with psychiatric proband or relative status, and with self-reported diabetes. Caucasians and African–Americans were analyzed separately. We also evaluated correlations between $PGRS_{SCHIZ}$ and diabetes mellitus among Caucasian probands and their relatives.
Results: In Caucasians, $PGRS_{T2D}$ was correlated with self-reported diabetes mellitus within probands, but was not correlated with proband or relative status in the whole sample. In African–Americans, a $PGRS_{T2D}$ based on selected risk alleles for T2D in this population did not correlate with proband or relative status. $PGRS_{SCHIZ}$ was not correlated with self-reported diabetes within Caucasian probands.
Conclusion: Differences in polygenic risk for T2D do not explain the increased prevalence of diabetes mellitus observed in psychosis probands and their relatives.

1. Introduction

An elevated prevalence of diabetes mellitus among individuals with psychosis has been noted long before the invention of atypical antipsychotic medication. In *The Pathology of Mind*, published in

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1897, Sir Henry Maudsley observed that "diabetes often shows itself in families in which insanity prevails". In 1991, before common use of atypical antipsychotics, the Schizophrenia Patient Outcomes Research Team (PORT) found that the rate of diabetes mellitus among people with schizophrenia was 15%, exceeding the general population (Dixon et al., 2000). In the post-antipsychotic era, the prevalence of Type 2 diabetes mellitus (T2D) is reportedly in the range of 11–15% in individuals with schizophrenia and is around 12% in those with bipolar disorder (Regenold et al., 2002; Ruzickova et al., 2003).

Many possible reasons have been proposed for this elevated prevalence, including lifestyle choices, poor compliance with or access to medical care, and most notably, the effects of antipsychotic medication. However, an increased genetic risk of T2D among those with schizophrenia or bipolar disorder is an underexplored possibility (Holt and Mitchell, 2015). Studies of antipsychotic naïve individuals with schizophrenia have observed elevated plasma insulin levels (Chen et al., 2013; Ryan et al., 2003; Venkatasubramanian et al., 2007), lower insulin growth factor (IGF-1) levels (Venkatasubramanian et al., 2007), impaired glucose tolerance (Fernandez-Egea et al., 2008; Spelman et al., 2007) and elevated fasting glucose, even when health habits are accounted for (Kirkpatrick et al., 2012; Ryan et al., 2003). However, other studies have not confirmed these findings (Sengupta et al., 2008). In addition, some studies have noted increased rates of T2D among relatives of people with schizophrenia (Fernandez-Egea et al., 2008; Mothi et al., 2015; Mukherjee et al., 1989), and a clustering of diabetes mellitus and psychosis in family histories of people with psychosis (Foley et al., 2015). These family data raise the possibility of shared genetic and environmental risk factors between T2D and psychosis.

Some studies have explicitly explored whether specific genes are shared between these two disorders. Several association studies have reported significant correlations between schizophrenia and well-replicated candidate genes for T2D, including *ARHGEF11* (Mizuki et al., 2014), *IGF2BP2* (Zhang et al., 2013), and *TCF7L2* (Hansen et al., 2011; Irvin et al., 2009), among others (Lin and Shuldiner, 2010). In a cross-disorder analysis, Stringer et al. (2014) found that a polygenic risk score for schizophrenia was correlated with T2D in a case-control sample of individuals with and without T2D (Stringer et al., 2014). However, no study has examined whether polygenic risk for T2D is associated with psychosis. Also, while several studies have reported increased prevalence of diabetes mellitus among relatives of people with psychosis, it is not known whether increased genetic risk for T2D accounts for this finding.

The primary aim of this study was to evaluate whether polygenic loading for T2D correlates with psychotic disorder proband status, or with first-degree relative status. Our additional goals were to determine (1) whether polygenic loading for T2D correlates with self-reported diabetes mellitus among probands and their relatives; and (2) whether polygenic loading for schizophrenia correlates with diabetes mellitus among probands or their relatives.

2. Materials and methods

2.1. Study design and measures

Analysis was conducted on data from the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study, a multi-site investigation of psychosis biomarkers. This investigation was approved by the Institutional Review Boards for each site and was conducted in accordance with the Declaration of Helsinki. Subjects included individuals with schizophrenia, schizoaffective disorder, or bipolar I with psychosis, their first-degree relatives, and healthy controls. Relatives with Axis I or II psychotic disorders (e.g. schizoid, schizotypal, or paranoid personality disorders), or who reported taking antipsychotics, were excluded so that the remaining sample consisted of subjects with familial risk of psychosis but without the experience of having a chronic psychotic disorder. Demographic data are presented in Table 1. The Structured Clinical Interview for DSM-IV (First et al., 2002) was performed on all subjects and diagnosis was determined using a consensus process, led by a senior clinician, which involved review of the structured diagnostic interview, medical and psychiatric records. Subjects were asked to self-report current co-morbid medical diagnoses, including any type of diabetes mellitus. The data collection process did not distinguish between Type 1 and Type 2 diabetes mellitus. Subjects also reported whether or not they were taking medication to treat diabetes. Those who either reported a diagnosis of diabetes or being on medication to treat diabetes were classified as having diabetes mellitus.

2.2. Collection and quality control of genetic data

Genomic data were collected using the Illumina Infinium PsychArray BeadChip™ platform. Genotype calling was performed at the Broad Institute using methods detailed online (Broad Institute, 2015), and genotypes underwent quality control using PLINK 1.9 (Chang et al., 2015; Purcell et al., 2007), based on a standardized protocol (Anderson et al., 2010). Details have been described in earlier work (Meda et al., 2014; Narayanan et al., 2015). To summarize, markers were removed if they had a missing rate greater than 5%, deviated from Hardy–Weinberg equilibrium ($p < 0.000001$), had a very low minor allele frequency (<0.01), or demonstrated a significantly different call rate between psychiatric probands and controls ($p < 0.00001$). Subjects were removed for discordant sex information, outlying heterozygosity (>3 standard deviations above the mean), or excessive proportion of missing genotype data (>0.05).

2.3. Imputation

Imputation of genetic data was performed using ShapeIt for prephasing (Delaneau et al., 2012, 2013; Howie et al., 2012) and Impute2 for imputation (Howie et al., 2009, 2012), using the multiethnic 1000 Genomes phase 3 data as a reference panel (Howie et al., 2011). Chromosomes were phased, then divided into 5 million base pair chunks for imputation. Imputed SNPs were removed for poor quality (information score less than 0.5) (Marchini and Howie, 2010) or a minor allele frequency < 0.01. For polygenic risk score analyses, linkage disequilibrium pruning was performed in PLINK 1.9 based on a pairwise R^2 of 0.5 and a window of 50 SNPs, shifting 5 SNPs at a time. 390 SNPs that approached genome-wide significance (p-value under 5×10^{-6}) in a multiethnic T2D study (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014) were also retained.

2.4. Population stratification and treatment of ethnicity effects

Principal component analysis was performed in the pre-imputed whole sample (Caucasians and African–Americans) using the "—pca" function in PLINK 1.9, and the first five components were retained as covariates to control for population stratification in subsequent analyses.

Due to potential confounding effects of race, Caucasians and African–American were subsequently analyzed separately. This decision was made because the odds ratios used to construct polygenic risk scores for schizophrenia ($PGRS_{SCHIZ}$) and diabetes

($PGRS_{T2D}$) originated from meta-analyses of genome-wide association studies that did not include African populations (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014; Morris et al., 2012; Schizophrenia Working Group of the Psychiatric Genomics, 2014), and thus the accuracy of these odds ratios is unclear in populations of African descent. Whole-genome odds ratios are not publicly available for African–Americans, but some work indicates that the directionality of effect of at least some T2D risk alleles is similar across populations (Haiman et al., 2012). As exploratory analyses, we constructed unweighted $PGRS_{T2D}$ (using the same markers but weighting risk alleles equally) for African–Americans using markers studied in non-African populations (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014). In addition, as described below, we used published data on selected T2D risk alleles from a meta-analysis of African–American samples (Ng et al., 2014) to construct an additional weighted $PGRS_{T2D}$ specific for African–Americans, though this score only included a small number of markers.

2.5. Construction of PGRS

For Caucasians, a first set of polygenic risk scores for T2D ($PGRS_{T2D}$) was constructed using odds ratio data from a meta-analysis of T2D genome-wide association studies performed largely in Caucasians (Morris et al., 2012). This set of $PGRS_{T2D}$ consisted of scores constructed at 500-SNP increments using the following process: SNPs were ordered from lowest to highest p value according to their association with T2D in the meta-analysis. The first $PGRS_{T2D}$ was comprised of the top 500 SNPs most associated with T2D (in the meta-analysis) that were also available in our imputed sample, the second $PGRS_{T2D}$ was comprised of the top 1000 SNPs, and each subsequent $PGRS_{T2D}$ was formed by incorporating an additional 500 SNPs in the PGRS. Polygenic risk scores were constructed with the "score" function in PLINK 1.9. This function multiplies the log of the odds ratio for a risk allele (per meta-analytic data) by the number of risk alleles carried by that individual subject (either 0, 1, or 2), performs and sums this across all SNPs, and divides by the total number of SNPs to generate a polygenic risk score (Purcell et al., 2009).

A second set of $PGRS_{T2D}$ for the Caucasian sample was constructed using a similar process, with odds ratio data from a trans-ethnic meta-analysis of Caucasians, East Asians, Mexicans, and South Asians (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014). A similar process was used to calculate a set of $PGRS_{SCHIZ}$ for Caucasians at increments of 500 SNPs, using PGC2 Consortium data (Schizophrenia Working Group of the Psychiatric Genomics, 2014). For construction of unweighted $PGRS_{T2D}$ in African–Americans, risk alleles (with odds ratio > 1 for association with T2D per trans-ethnic meta-analytic data) were weighted equally (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014).

2.6. Statistical analyses

2.6.1. Analyses with $PGRS_{T2D}$

In Caucasians, two sets of $PGRS_{T2D}$ were analyzed, using Caucasian meta-analysis data (Morris et al., 2012), and trans-ethnic meta-analysis data (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014). In African–Americans, unweighted scores were analyzed (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014).

We considered $PGRS_{T2D\text{-}DIAB\text{-}PRO}$, $PGRS_{T2D\text{-}DIAB\text{-}REL}$, and $PGRS_{T2D\text{-}DIAB\text{-}PRO/REL}$ to quantify polygenic risk for T2D that are maximally associated with self-reported diabetes status within probands, within relatives, and within probands and relatives combined, respectively. We considered $PGRS_{T2D\text{-}PRO}$, $PGRS_{T2D\text{-}REL}$, and $PGRS_{T2D\text{-}PRO/REL}$ to quantify polygenic risk for T2D that are maximally associated with proband status, relative status, or proband/relative status (i.e., being either a proband or relative), respectively. To identify $PGRS_{T2D\text{-}DIAB\text{-}PRO}$, each $PGRS_{T2D}$ was correlated with self-reported diabetes mellitus among probands, with age, sex, and scores on the first five principal components as covariates in a logistic regression model. The $PGRS_{T2D}$ with the highest Nagelkerke R^2 for its associated model was selected and reported as the $PGRS_{T2D\text{-}DIAB\text{-}PRO}$. This analysis was repeated within relatives alone to identify $PGRS_{T2D\text{-}DIAB\text{-}REL}$, and within relatives and probands combined to identify $PGRS_{T2D\text{-}DIAB\text{-}PRO/REL}$.

Next, to identify $PGRS_{T2D\text{-}PRO}$, each $PGRS_{T2D}$ was correlated with psychiatric proband versus control status using logistic regression, with covariates of age, sex, and five principal components of population stratification. The $PGRS_{T2D}$ with the highest Nagelkerke R^2 for its associated model was selected and reported as the $PGRS_{T2D\text{-}PRO}$. This analysis was repeated with relatives and controls to identify $PGRS_{T2D\text{-}REL}$, and with probands, relatives, and controls to identify $PGRS_{T2D\text{-}PRO/REL}$.

Finally, as an exploratory analysis, the selected $PGRS_{T2D\text{-}DIAB\text{-}PRO}$ and $PGRS_{T2D\text{-}PRO}$ were assessed for correlations with self-reported diabetes or proband status, within each proband diagnostic group (i.e., schizophrenia, schizoaffective, and bipolar disorder), for each race.

2.6.2. Analysis with $PGRS_{SCHIZ}$ in Caucasians

We considered $PGRS_{SCHIZ\text{-}DIAB\text{-}PRO}$, $PGRS_{SCHIZ\text{-}DIAB\text{-}REL}$, and $PGRS_{SCHIZ\text{-}DIAB\text{-}PRO/REL}$ to quantify the polygenic risk for schizophrenia that is maximally associated with self-reported diabetes mellitus among probands, relatives, and probands and relatives together, respectively. Because use of antipsychotic medication may confound this association, antipsychotic medication status was first correlated with self-reported diabetes mellitus status in probands via logistic regression. Antipsychotic medication status was a binary variable representing whether or not the subject was taking antipsychotics at time of evaluation. Each $PGRS_{SCHIZ}$ was correlated with diabetes mellitus status among probands to identify $PGRS_{SCHIZ\text{-}DIAB\text{-}PRO}$, with covariates of age, sex, five principal components, and antipsychotic medication status. This analysis was repeated in relatives alone and probands and relatives together to identify $PGRS_{SCHIZ\text{-}DIAB\text{-}REL}$ and $PGRS_{SCHIZ\text{-}DIAB\text{-}PRO/REL}$, respectively.

2.6.3. Post-hoc analyses within African–Americans

We performed an association analysis within our African–American sample using 68 risk alleles from a meta-analysis of association studies of T2D in African–Americans (Ng et al., 2014). These risk alleles had been significant at $p = 1 \times 10^{-5}$ at Stage 1 of this meta-analysis, or they had been selected *a priori* from the literature for replication (Tables S4 and S5 from the cited study). The logistic regression function in PLINK 1.9 was used to correlate the risk alleles with proband/relative status, then with self-reported diabetes, with covariates of age, sex, and five principal components of population stratification, using an additive model. Proband/relative status was a covariate in the association with self-reported diabetes, and self-reported diabetes was a covariate in the association with proband/relative status. Next, we created a polygenic risk score from 62 of these 68 selected SNPs, using odds ratios from the Ng et al. meta-analysis, and correlated this score with control versus proband/relative status, and with self-reported diabetes. Finally, to assess for ancestry differences between African–American probands, relatives, and controls, the five principal components of population stratification were correlated with control versus proband/relative status using logistic regression.

Table 1
Subject demographics.

Caucasians	Healthy controls	Psychiatric probands					Relatives		
		All probands	Schizophrenia	Schizoaffective	Psychotic bipolar I	All relatives	Schizophrenia	Schizoaffective	Psychotic bipolar I
N	218	384	129	85	170	413	134	100	179
Mean Age (SD)[a]	38.1 (13.1)	34.7 (12.8)	34.6 (12.8)	35.5 (12.6)	34.5 (13.0)	44.6 (15.2)	45.9 (14.5)	47.0 (14.6)	42.3 (15.8)
Sex (% M)[b]	48%	55%	80%	51%	39%	30%	25%	28%	35%
% Taking Antipsychotics	0%	82.8%	93.8%	91.8%	70.0%	0%	0%	0%	0%
% T2D[b]	2.3%	10.4%	12.4%	10.6%	8.8%	5.8%	4.5%	6.0%	6.7%
African–Americans									
N	104	257	140	72	45	173	99	46	28
Mean Age (SD)[c]	38.0 (11.9)	39.9 (12.1)	39.3 (12.7)	39.7 (11.6)	41.9 (10.7)	39.8 (15.3)	42.9 (14.3)	34.5 (15.7)	37.3 (15.9)
Sex (%M)[b]	43.3%	45.9%	55.7%	37.5%	28.9%	27.7%	26.2%	23.9%	39.3%
% Taking Antipsychotics	0%	84.4%	88.6%	80.6%	77.8%	0%	0%	0%	0%
% T2D[b]	1.9%	16.8%	15.0%	18.1%	20.0%	10.4%	12.1%	10.9%	3.6%

[a] Significantly different across probands, relatives, and controls per χ^2 test ($p < 0.0001$).
[b] Significantly different across probands, relatives, and controls per analysis of variance ($p < 0.001$).
[c] No significant group difference.

2.6.4. Analyses with antipsychotic medication status

Antipsychotic medication status (defined earlier as a binary variable) was evaluated for correlation with self-reported diabetes mellitus among probands using a regression model and covariates of age, sex, and the five principal components of population stratification. This analysis was repeated instead using current antipsychotic dose in chlorpromazine equivalents (CPZ dose), which was available for some psychiatric probands (N = 247 in Caucasians, N = 165 in African–Americans).

3. Results

3.1. Demographics

Within each race, prevalence of self-reported diabetes mellitus was significantly different across healthy controls, probands, and relatives, with probands demonstrating the highest prevalence (Table 1, Fig. 1). Prevalence of diabetes did not differ between African–American and Caucasian controls, but was higher in African–American probands and relatives than in Caucasian probands and relatives.

3.2. Analyses with $PGRS_{T2D}$

Among Caucasians, $PGRS_{T2D\text{-}DIAB\text{-}PRO}$ and $PGRS_{T2D\text{-}DIAB\text{-}PRO/REL}$ were correlated with self-reported diabetes status whether constructed with Caucasian-only meta-analysis data or trans-ethnic meta-analysis data. Among Caucasian relatives, $PGRS_{T2D\text{-}DIAB\text{-}REL}$ did not correlate with self-reported diabetes mellitus (Table 2, Supplementary Fig. 1). $PGRS_{T2D\text{-}PRO}$, $PGRS_{T2D\text{-}REL}$, and $PGRS_{T2D\text{-}PRO/REL}$ were not significantly correlated with psychiatric proband, relative, or proband/relative status (Table 2).

Among African–Americans, $PGRS_{T2D\text{-}DIAB\text{-}REL}$ was significantly correlated with self-reported diabetes within relatives (Table 3, Supplementary Fig. 2). $PGRS_{T2D\text{-}PRO}$, $PGRS_{T2D\text{-}REL}$, and $PGRS_{T2D\text{-}PRO/REL}$ were correlated with proband, relative, and proband/relative status, respectively (Table 3).

Within diagnostic categories, several correlations remained significant, though these would not have survived correction for multiple comparisons (Supplementary Table 1).

3.3. Analyses with $PGRS_{SCHIZ}$ in Caucasians

$PGRS_{SCHIZ}$ score was not correlated with diabetes mellitus in probands or relatives (Table 2).

3.4. Post-hoc analyses within African–Americans

Three out of 68 alleles were nominally associated with proband/relative status, and eight alleles were associated with self-reported diabetes mellitus, but these results did not survive multiple comparison correction (Supplementary Table 2). A weighted polygenic risk score constructed from 62 SNPs was not significantly correlated with either self-reported diabetes or proband/relative status. One of five principal components of population stratification was associated with proband/relative status ($p = 0.04$).

3.5. Analyses with antipsychotic medication

Antipsychotic medication status and CPZ dose did not correlate with diabetes mellitus among probands in either race.

4. Discussion

In this study, we found an elevated prevalence of self-reported diabetes in probands with psychotic disorders and their relatives compared to controls, in concordance with

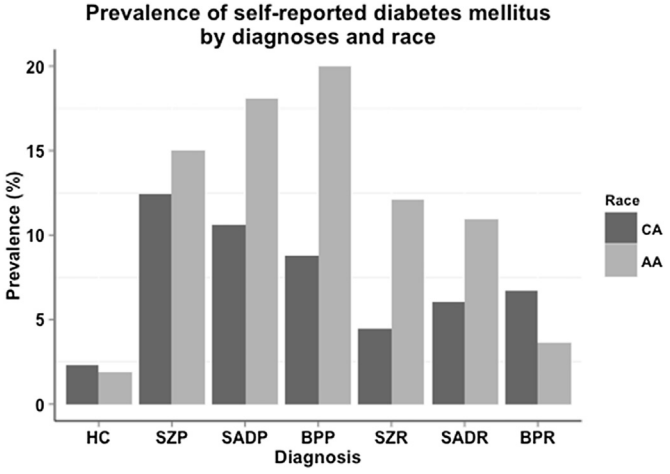

Fig. 1. Prevalence of self-reported diabetes mellitus by race and diagnostic group. Prevalence is depicted as a percentage in our sample. HC = healthy controls. SZP, SADP, and BPP = probands with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder, respectively. SZR, SADR, and BPR = relatives of probands with schizophrenia, schizoaffective disorder, and bipolar disorder, respectively.

Table 2
Logistic regression correlation of optimal PGRS with proband or self-reported diabetes mellitus in Caucasians.

Score	Sample	Outcome variable	p-value cut-off (from GWAS)	Number of SNPs in score	Odds ratio[a]	Nag R^2	p-value (Logistic regression)
Scores constructed using odds ratios from largely Caucasian meta-analysis (Morris et al., 2012)							
$PGRS_{T2D\text{-}DIAB\text{-}PRO}$	Probands	Diabetes	0.904	10,000	1.74	0.218	**0.0082**
$PGRS_{T2D\text{-}DIAB\text{-}REL}$	Relatives	Diabetes	0.064	1500	1.32	0.110	0.19
$PGRS_{T2D\text{-}DIAB\text{-}PRO/REL}$	Pro and Rel[b]	Diabetes	0.904	10,000	1.45	0.117	**0.0071**
$PGRS_{T2D\text{-}PRO}$	Pro and Controls	Proband status	0.543	6500	1.06	0.065	0.51
$PGRS_{T2D\text{-}REL}$	Rel and Controls	Relative status	0.029	1000	1.05	0.120	0.58
$PGRS_{T2D\text{-}PRO/REL}$	All	Pro/rel status	0.294	4000	1.05	0.034	0.58
Scores constructed using odds ratios from trans-ethnic meta-analysis (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014)							
$PGRS_{T2D\text{-}DIAB\text{-}PRO}$	Probands	Diabetes	0.039	8500	1.78	0.224	**0.0038**
$PGRS_{T2D\text{-}DIAB\text{-}REL}$	Relatives	Diabetes	0.39	78,000	1.40	0.111	0.17
$PGRS_{T2D\text{-}DIAB\text{-}PRO/REL}$	Pro and Rel	Diabetes	0.33	64,500	1.38	0.111	**0.029**
$PGRS_{T2D\text{-}PRO}$	Pro and controls	Proband status	0.12	24,000	0.94	0.065	0.53
$PGRS_{T2D\text{-}REL}$	Rel and controls	Relative status	0.36	71,000	1.07	0.121	0.47
$PGRS_{T2D\text{-}PRO/REL}$	All	Pro/rel status	0.12	24,000	0.92	0.035	0.35
Scores constructed using odds ratios from Psychiatric Genomics Consortium data (Schizophrenia Working Group of the Psychiatric Genomics, 2014)							
$PGRS_{SCHIZ\text{-}DIAB\text{-}PRO}$	Probands	Diabetes	0.015	27,000	1.41	0.20	0.087
$PGRS_{SCHIZ\text{-}DIAB\text{-}REL}$	Relatives	Diabetes	0.369	256,000	1.30	0.104	0.39
$PGRS_{SCHIZ\text{-}DIAB\text{-}PRO/REL}$	Pro and Rel	Diabetes	0.00092	6000	1.22	0.135	0.18

[a] Predictors were standardized; thus, odds ratios reflect the increase in the odds ratio of the outcome for a one standard deviation increase in the PGRS score.
[b] Pro = Probands, Rel = Relatives.

Table 3
Logistic regression correlation of optimal PGRS with proband or self-reported diabetes mellitus in African–Americans.

Score	Sample	Outcome variable	p-value cut-off (from GWAS)	Number of SNPs in score	Odds ratio[a]	Nag R^2	p-value (Logistic regression)
Unweighted scores constructed from trans-ethnic meta-analysis (DIAbetes Genetics Replication Meta-analysis Consortium et al., 2014)							
$PGRS_{T2D\text{-}DIAB\text{-}PRO}$	Probands	Diabetes	0.039	8500	1.17	0.23	0.43
$PGRS_{T2D\text{-}DIAB\text{-}REL}$	Relatives	Diabetes	0.0085	2500	2.59	0.41	**0.0051**
$PGRS_{T2D\text{-}DIAB\text{-}PRO/REL}$	Probands and relatives	Diabetes	0.013	3500	1.31	0.23	0.076
$PGRS_{T2D\text{-}PRO}$	Probands and controls	Proband status	0.12	24,000	1.50	0.078	**0.0036**
$PGRS_{T2D\text{-}REL}$	Relatives and controls	Relative status	0.22	44,500	1.61	0.13	**0.0053**
$PGRS_{T2D\text{-}PRO/REL}$	All	Proband/relative status	0.22	44,500	1.54	0.068	**0.0019**

[a] Predictors were standardized; thus, odds ratios reflect the increase in the odds ratio of the outcome for a one standard deviation increase in the PGRS score.

previously published data (Bushe and Holt, 2004; Dixon et al., 2000; Fernandez-Egea et al., 2008; Mothi et al., 2015; Mukherjee et al., 1989). Prevalence of self-reported diabetes was also elevated in African–American probands in comparison with Caucasian probands, corroborating findings in the general population, in which incidence (Brancati et al., 2000) and prevalence of T2D (Carter et al., 1996) are also higher in African–Americans. Modifiable risk factors such as adiposity (body-mass index and waist-hip ratio) partly, but not fully, explain increased risk for development of T2D in African–Americans (Brancati et al., 2000; Marshall, 2005). Socioeconomic status also does not fully account for this increased prevalence (Robbins et al., 2000); liability to some aspects of T2D pathophysiology, such as insulin resistance, may differ as well (Marshall, 2005). Finally, genetic liability for T2D may be increased among those of African descent (Cheng et al., 2012).

Polygenic analyses in our sample did not demonstrate an association of polygenic risk scores for T2D with psychosis proband or relative status among Caucasians. One interpretation of the findings is that among Caucasians with chronic psychotic disorders, lifestyle risk factors and antipsychotic medication use primarily account for their higher prevalence of diabetes, rather than any difference in genetic liability. These lifestyle factors include diminished physical activity, poor diet, and smoking (Bly et al., 2014). Antipsychotic medication is associated with T2D (Cross-Disorder Group of the Psychiatric Genomics et al., 2013; Nielsen et al., 2010) perhaps because of the effect of these medications on weight gain (Bak et al., 2014), insulin release (Teff et al., 2013), glucose transport (Dwyer et al., 1999), and muscarinic receptor signaling (Weston-Green et al., 2012). Additionally, prolonged stress and autonomic activity may contribute to findings of glucose dysregulation among antipsychotic-naïve individuals with psychosis (Shiloah et al., 2003). The higher prevalence of diabetes in relatives may potentially reflect environmental risk factors shared with probands, such as poor diet and physical inactivity. In addition, relatives of people with psychotic disorders have a higher prevalence of non-psychotic mental illness compared to the general population (Maier et al., 1994), such as depression, and these disorders have themselves been associated with T2D (Roy and Lloyd, 2012).

In the African–American sample, an unweighted $PGRS_{T2D}$ was associated with proband status. However, even after co-varying for population stratification, subtle ancestry differences between the African–American probands and African–American controls remain a likely explanation of this finding, given that one of five principal components of population stratification was significantly associated with proband/relative status among African–Americans. An unweighted $PGRS_{T2D\text{-}DIAB}$ was correlated significantly but weakly with self-reported diabetes in African–American relatives, but not in probands. Thus, the validity of these scores in African–Americans is unclear. A weighted $PGRS_{T2D}$ using a small number of markers did not significantly correlate with proband/relative status. These findings suggest that, as with Caucasians, polygenic loading for T2D does not account for the higher prevalence of diabetes among African–American probands compared to controls.

$PGRS_{SCHIZ}$ was not correlated with self-reported diabetes mellitus among Caucasian probands or relatives. This finding

corroborates two other studies that correlated $PGRS_{SCHIZ}$ with T2D in case/control samples of T2D and found either no correlation (Purcell et al., 2009), or a small correlation (Stringer et al., 2014). We found no correlation of current antipsychotic medication use or dosage with diabetes, in contrast to the substantial evidence in the literature for such a correlation (Sernyak et al., 2002; Smith et al., 2008), which suggests that the cross-sectional medication data in our sample was not an adequate proxy for longitudinal antipsychotic exposure.

Of potential clinical interest is the strong correlation between self-reported diabetes and $PGRS_{T2D}$ among Caucasian probands. While this correlation was expected, it raises the question of whether $PGRS_{T2D}$ may have value in predicting the development of T2D and other metabolic co-morbidities in this population. Vassy et al. recently reported that $PGRS_{T2D}$ was significantly correlated with incident T2D in the general population, but did not add value to existing clinical and demographic predictive models (Vassy et al., 2014). However, this study also found that $PGRS_{T2D}$ had greater predictive value among younger individuals without overt clinical risk factors. Young individuals with psychotic disorders are particularly vulnerable to development of T2D due to environmental and iatrogenic risk factors but may lack traditional laboratory predictors of T2D; thus, $PGRS_{T2D}$ may have greater predictive value in this population. The precise relation between $PGRS_{T2D}$ and diabetes risk could not be evaluated in this study, but deserves further investigation.

There are a number of limitations with this study. One significant limitation was that the diagnosis of diabetes status was determined by self-report rather than laboratory measures; however, this limitation did not affect our primary research question, which was to examine whether polygenic loading for T2D is associated with psychotic disorder proband or relative status. Additionally, we found that $PGRS_{T2D}$ was significantly correlated with self-reported diabetes, supporting reasonable validity of this measure. Studies indicate that self-reported medical histories, including histories of T2D, can be reasonably accurate (Pastorino et al., 2014; Selim et al., 2004). A second limitation was that these self-reported data did not distinguish between Type 1 and Type 2 diabetes mellitus, which have significantly different etiologies, demographic and clinical features. While this does not affect our primary research aim, the correlation between $PGRS_{T2D}$ and self-reported diabetes may have been diluted if some of these individuals actually had T1D. However, only an estimated 6% of diabetes mellitus cases are T1D in the United States (Menke et al., 2013), so T1D likely constituted only a small proportion of cases of diabetes in our sample. Finally, as noted earlier, medication information was cross-sectional, and thus it was not possible to control for lifetime antipsychotic exposure, or exposure to specific antipsychotics.

Given that individuals with psychosis are at increased risk of T2D, it is important to determine whether genetic markers, including polygenic markers, can help predict emergent metabolic disorders in this high-risk population, particularly in those exposed to antipsychotics. Future investigations could prospectively study associations between glucose dysregulation and genetic risk for T2D while collecting information on longitudinal medication exposure. Models such as homeostatic model assessment (HOMA) (Matthews et al., 1985) and laboratory biomarkers of T2D may be more sensitive correlates of genetic risk, and would be important to measure in future studies. If the predictive value of polygenic risk scores can be further validated, they could eventually help guide clinicians in monitoring and mitigating risk of metabolic disorders and in choosing appropriate pharmacotherapy for patients with psychotic disorders.

Conflicts of interest

There are no conflicts of interest. However, we would like to report the following disclosures: Dr. Padmanabhan has received support from the Janssen Academic Research Mentorship program. Dr. Keshavan has received research support from Sunovion and GlaxoSmithKline. Dr. Pearlson has served on an advisory panel for Bristol-Myers Squibb. Dr. Sweeney has been on advisory boards for Bristol-Myers Squibb, Eli Lilly, Pfizer, Roche, and Takeda and has received grant support from Janssen. Dr. Tamminga has the following disclosures to make: Intracellular Therapies (ITI, Inc)—Advisory Board, drug development; PureTech Ventures—Ad Hoc Consultant; Eli Lilly Pharmaceuticals—Ad Hoc Consultant; Sunovion—Ad Hoc Consultant; Astellas—Ad Hoc Consultant; Cypress Bioscience—Ad Hoc Consultant; Merck—Ad Hoc Consultant; International Congress on Schizophrenia Research—Organizer, unpaid volunteer; National Alliance on Mental Illness—Council Member, unpaid volunteer; American Psychiatric Association—Deputy Editor. The other authors report no disclosures.

Contributors

J.L.P. conceived of the project idea, conducted the analysis and wrote the manuscript. P.N. helped design the analysis. N.T. and J.L.P. conducted the quality control and imputation of the genetic data. All authors contributed to the interpretation of the data or suggested additional analyses, and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2016.02.015.

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