Diabetologia (2022) 65:800–810
https://doi.org/10.1007/s00125-022-05665-x

ARTICLE

Familial aggregation and shared genetic loading for major psychiatric disorders and type 2 diabetes

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Received: 5 July 2021 / Accepted: 13 December 2021 / Published online: 23 February 2022

Abstract

Aims/hypothesis Psychiatric disorders, such as schizophrenia (SCZ), major depressive disorder (MDD) and bipolar disorder (BPD), are highly comorbid with type 2 diabetes. However, the mechanisms underlying such comorbidity are understudied. This study explored the familial aggregation of common psychiatric disorders and type 2 diabetes by testing family history association, and investigated the shared genetic loading between them by testing the polygenic risk score (PRS) association.

Methods A total of 105,184 participants were recruited from the Taiwan Biobank, and genome-wide genotyping data were available for 95,238 participants. The Psychiatric Genomics Consortium-derived PRS for SCZ, MDD and BPD was calculated. Logistic regression was used to estimate the OR with CIs between a family history of SCZ/MDD/BPD and a family history of type 2 diabetes, and between the PRS and the risk of type 2 diabetes.

Results A family history of type 2 diabetes was associated with a family history of SCZ (OR 1.23, 95% CI 1.08, 1.40), MDD (OR 1.19, 95% CI 1.13, 1.26) and BPD (OR 1.26, 95% CI 1.15, 1.39). Compared with paternal type 2 diabetes, maternal type 2 diabetes was associated with a higher risk of a family history of SCZ. SCZ PRS was negatively associated with type 2 diabetes in women (OR 0.92, 95% CI 0.88, 0.97), but not in men; the effect of SCZ PRS reduced after adjusting for BMI. MDD PRS was positively associated with type 2 diabetes (OR 1.04, 95% CI 1.00, 1.07); the effect of MDD PRS reduced after adjusting for BMI or smoking. BPD PRS was not associated with type 2 diabetes.

Conclusions/interpretation The comorbidity of type 2 diabetes with psychiatric disorders may be explained by shared familial factors. The shared polygenic loading between MDD and type 2 diabetes implies not only pleiotropy but also a shared genetic aetiology for the mechanism behind the comorbidity. The negative correlation between polygenic loading for SCZ and type 2 diabetes implies the role of environmental factors.

Keywords Bipolar disorder · Comorbidity · Depression · Diabetes · Familial aggregation · Polygenic risk score · Schizophrenia

Abbreviations

aOR	Adjusted odds ratio
BPD	Bipolar disorder
EAS	East Asian population
EUR	European population
GWAS	Genome-wide association study
LD	Linkage disequilibrium
MDD	Major depressive disorder

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Research in context

What is already known about this subject?

- Type 2 diabetes is comorbid with common psychiatric disorders
- The comorbidities may be partly due to a bi-directional effect

What is the key question?

- Are there shared familial factors or shared genetic loading between type 2 diabetes and common psychiatric disorders?

What are the new findings?

- Among a large Taiwanese cohort, family aggregations were found between type 2 diabetes and schizophrenia, major depressive disorder and bipolar disorder. Maternal type 2 diabetes demonstrated a stronger association with schizophrenia family history than paternal type 2 diabetes
- Higher genetic loading for major depressive disorder was associated with increased risk of type 2 diabetes
- Higher genetic loading for schizophrenia was associated with decreased risk of type 2 diabetes in women but not in men

How might this impact on clinical practice in the foreseeable future?

- Early detection or intervention for type 2 diabetes should target high-risk populations such as individuals with higher genetic risk and a family history of psychiatric disorders

PC	Principal component
PGC	Psychiatric Genomics Consortium
PRS	Polygenic risk score
SCZ	Schizophrenia
TWB	Taiwan Biobank

Introduction

Psychiatric disorders have been found to be comorbid with type 2 diabetes [1, 2], and such comorbidities affect disability [3, 4] and increase all-cause mortality [5, 6]. Hence, detecting possible underlying mechanisms contributing to such comorbidities is a crucial issue. Beyond the bi-directional effect, the comorbidity between psychiatric disorders and type 2 diabetes suggests a shared pathophysiological mechanism.

Familial aggregation of type 2 diabetes and common psychiatric disorders has been observed. The risk of type 2 diabetes is higher in relatives of those with schizophrenia (SCZ) than in relatives of healthy participants [7]. In addition, first-degree relatives of patients with SCZ or bipolar disorder (BPD) have an increased risk of metabolic dysfunction compared with healthy control participants [8]. Population-based data from sibling registries also revealed that unaffected siblings of patients with SCZ are more likely to develop type 2 diabetes later in life than control participants [9]. Evidence for familial aggregation implies an influence of shared environmental factors or genetic background.

To clarify the effect of environmental and genetic effects on familial aggregation, a structural equation model using twin registration data indicated that the association between type 2 diabetes and psychiatric disorders was primarily attributable to genetic background, especially in female participants [10]. A genome-wide association study (GWAS) for BPD further identified a susceptibility SNP rs12772424, in an intron of *TCF7L2*, one of the strongest genetic risk variants for type 2 diabetes, and the BPD susceptibility risk of this SNP is dependent on BMI [11]. Several pleiotropic variants in the *IGF2BP2*, *CDKAL1*, *CDKN2B-AS1* and *PLEKHA1* genes were identified between type 2 diabetes and major depressive disorder (MDD) based on a bivariate GWAS approach [12]. However, the identified susceptibility variants from the GWAS account for little of the heritability of diseases; applying polygenic architecture profiling [13] by calculating the polygenic risk score (PRS), which refers to the cumulative additive effect of disease-associated variants across the genome, would improve the prediction and may then be used to explore the polygenic overlap between traits.

Previous PRS analyses showed no association between MDD PRS and type 2 diabetes (n = 19,858) [14], and between SCZ PRS and type 2 diabetes in both people of European origin (n = 1812) and African-Americans (n = 964) [15]; this may have resulted from the relatively small target sample sizes and

the PRS being derived from a GWAS with insufficient discovery sample sizes. Furthermore, sex differences in PRS analyses were not considered. Sex differences have been found in the association of family history of psychiatric disorders and family history of diabetes [16], and the prevalence of type 2 diabetes in the mothers and fathers of those with psychosis is different [17]. Paternal and maternal history should be considered separately while investigating familial aggregation, and sex differences in genetic overlap should be considered in molecular studies.

Using a large collection of community samples (~100,000) from the Taiwan Biobank (TWB), this study aimed to investigate the association between a family history of common psychiatric disorders (SCZ, MDD and BPD) and a family history of type 2 diabetes, and a stratification analysis for maternal/paternal type 2 diabetes was performed. We further applied polygenic profiling to calculate PRS, examined the association of PRS for common psychiatric disorders with type 2 diabetes, explored the possible modified effect of sex on the PRS association, and explored the possible mediating effect of environmental factors on the PRS influence.

Methods

Study participants and measurements The study participants were recruited from the TWB, which collects information on lifestyle, health survey information, biochemical tests, physical examinations and genomic data. More details about sample recruitment have been described elsewhere [18, 19]. This study was approved by the Central Regional Research Ethics Committee of China Medical University, Taichung, Taiwan (CRREC-108-30).

Participants were interviewed face-to-face to obtain demographic information and self-reported disease diagnoses, including physical illness and diabetes (type 1 diabetes, type 2 diabetes or gestational diabetes). Family history of first-degree relatives, including biological parents and full siblings, was also collected. A total of 105,385 participants were recruited. After removing participants with insufficient information and those with self-reported type 1 diabetes and gestational diabetes, 105,184 individuals remained.

Genotyping and quality control Genotyping in 95,238 participants were performed using custom TWB chips, and processed on the Axiom genome-wide array plate system (Affymetrix, Santa Clara, CA, USA); 26,274 participants were genotyped using the TWBv1 chip, and 68,964 participants were genotyped using the TWBv2 chip. We refer to samples genotyped using the TWBv1 chip as 'batch 1' and those genotyped using the TWBv2 chip as 'batch 2.' We performed quality control for the two batches separately before imputation. Quality control processes included the exclusion of variants with a call rate <5%, minor allele frequency <0.001, and deviation from Hardy–Weinberg equilibrium with $p<1 \times 10^{-6}$. Participants with a missing rate of more than 5% were also removed. We used the 504 EAS panel from the 1000 Genomes Project [20] and the 973 TWB panel from whole-genome sequencing in TWB participants as the reference panels to impute genotypes using IMPUTE2 for the two batches separately (16,537,709 variants for batch 1 and 16,222,535 variants for batch 2), and then retained variants with imputation info score >0.7 (13,803,712 variants for batch 1 and 13,586,691 variants for batch 2). A total of 12,605,051 variants were available in both batches and kept for subsequent PRS calculation. The batch version was adjusted for in the PRS association analyses.

We analysed population stratification using principal components (PCs) analysis. No population structure outliers or heterozygosity outliers were found. To remove cryptic relatedness, we estimated the identity using descent sharing coefficients (PI-HAT) between any two participants. For pairwise participants with PI-HAT >0.1875, one of the study participants was removed [21]. In total, 80,161 unrelated participants were included in the subsequent PRS analysis. In the PRS analyses, we excluded participants with the corresponding diagnosis while calculating SCZ, MDD, and BPD PRS.

PRS calculation Data from the Psychiatric Genomics Consortium (PGC) meta-analysis were used as discovery samples to calculate PRS for SCZ, MDD and BPD. The SCZ PRS was derived from the Asia PGC of East Asian descent, which included 22,778 cases and 35,362 control participants [22]. The MDD PRS was derived from MDD GWAS of European ancestry (EUR), a meta-analysis of 246,363 cases and 561,190 control participants of European descent [23], and MDD GWAS of East Asia population (EAS), a meta-analysis of 13,042 cases and 88,467 control participants of East Asian descent [24], separately. Summary statistics for BPD were obtained from a meta-analysis of 20,352 cases and 31,358 control participants of mostly European descent [25]. For the supplementary analysis, we calculated PRS for type 2 diabetes based on a GWAS of East Asian descent, which comprised 77,418 cases and 356,122 control participants [26].

To exclude variants in linkage disequilibrium (LD), all SNPs (the intersection of kept post-imputation variants and summary from discovery samples) were subjected to LD clumping with a pairwise R^2 threshold of 0.5, and a sliding window size of 250 kb. The extracted independent variants were the same between the two batches. Different p value thresholds for retrieving variants into sets were defined at 1, 0.5, 0.1, 0.05 and 0.005, which are the thresholds that maximally capture the heritability of diseases [22, 23, 25]. The PRS

at non-conservative thresholds have been suggested enriched to capture the variance of a disease. The PRS was calculated using PLINK version 1.90 (https://www.cog-genomics.org/plink2) [27] and normalised to the *Z* score. The PRS for SCZ, MDD (EUR), MDD (EAS), BPD and type 2 diabetes explained 1.0–1.7%, 0.2–0.4%, 0.0%, 0.1–0.2% and 1.5–2.3%, respectively, of the corresponding disease status in the TWB (electronic supplementary material [ESM] Table 1). The PRS derived from MDD (EUR) explained more variance for MDD in the TWB than that from MDD (EAS), thus it was used in the subsequent PRS association analysis.

Genetic correlation LD score regression [28] was used to quantify the separated contributions of polygenic influence and other factors, and to estimate genetic correlation between type 2 diabetes and psychiatric disorders within the matched ancestry. In the European population, genetic correlations between type 2 diabetes [29] and SCZ (PGC2) [30], MDD (EUR) [23] and BPD [25] were calculated. As the available large-scale GWAS summary in the Asian population is limited, we only estimated the genetic correlation between type 2 diabetes [26] and SCZ (Asia PGC) [22] and MDD (EAS) [24].

Statistical analysis The distribution of demographic and clinical characteristics of participants with and without type 2 diabetes is described using numbers and percentages. The χ^2 test and unpaired Student's *t* test were used to compare the difference in the distribution between type 2 diabetes and non-type 2 diabetes patients based on data properties. The temporal relationship between the initial development of each psychiatric disorder and type 2 diabetes among those who had both disorders was tested.

To investigate the familial aggregation between type 2 diabetes and three common psychiatric disorders, we first examined the distribution of family history of SCZ, MDD and BPD by family history of type 2 diabetes. Logistic regression models adjusted for age, sex, the number of first-degree relatives, educational attainment, marital status, and self-reported psychiatric disorders were then used to estimate the strength of association between the two family histories. For family history of type 2 diabetes, paternal type 2 diabetes and maternal type 2 diabetes were also analysed separately to explore differential parental influence, and the *Z* test was used to compare the difference in parental influence. For sensitivity analyses, familial aggregation analyses were limited to patients without self-reported type 2 diabetes and without psychiatric disorders (n = 95,894).

To explore the polygenic overlap between type 2 diabetes and three common psychiatric disorders, a logistic regression model with adjustment for age, sex, batch effect and 20 PCs was used to estimate the association of the PRS for a psychiatric disorder with the risk of type 2 diabetes. To detect whether sex is a moderator, we tested the interaction term between sex and PRS. When a significant interaction effect was detected, we reported the strength of the association between PRS and type 2 diabetes in men and women separately. To explore the potential mediating effect of obesity, drinking and smoking on the association of PRS, we further included BMI, regular alcohol use (>150 ml weekly for >6 months), and regular tobacco use (>6 months), respectively, in the model to evaluate the corresponding change in the estimates of the PRS.

For the supplementary analysis for polygenic overlap between type 2 diabetes and common psychiatric disorders, we tested the association of PRS for type 2 diabetes with the risk of three psychiatric disorders.

We set the overall significance level at 0.05. Because the comparisons were carried out between type 2 diabetes and three psychiatric disorders, the Bonferroni-corrected significance level was set at 0.05/3 = 0.017. All statistical analyses were performed using the SAS statistical package (version 9.4 for Windows; SAS Institute, Cary, NC, USA).

Results

Of the 105,184 participants, 5251 (4.99%) reported that they had type 2 diabetes. The distribution of demographic and clinical characteristics of participants with type 2 diabetes and without type 2 diabetes is shown in Table 1. Compared with those without type 2 diabetes, patients with type 2 diabetes had a higher mean age (58.35 vs 49.53), a higher proportion of men (48.70% vs 35.26%), MDD (5.39% vs 3.47%), BPD (1.20% vs 0.64%), regular alcohol use (6.76% vs 5.77%) and tobacco use (29.12% vs 19.21%), and higher mean BMI (26.20 vs 24.10). In terms of the temporal relationship, the onset of type 2 diabetes was more frequent after the three psychiatric disorders, but significance was only found in BPD (ESM Table 2).

The distribution of family history of SCZ, MDD and BPD by family history of type 2 diabetes, and the adjusted odds ratios (aORs), adjusted for age, sex, the number of first-degree relatives, educational attainment, marital status, and self-reported SCZ, MDD and BPD, and 95% CIs are shown in Table 2. A family history of type 2 diabetes was associated with a family history of SCZ (aOR 1.23, 95% CI 1.08, 1.40), MDD (aOR 1.19, 95% CI 1.13, 1.26) and BPD (aOR 1.26, 95% CI 1.15, 1.39). Compared with paternal type 2 diabetes, maternal type 2 diabetes was associated with a higher risk for a family history of SCZ (aOR 1.27, 95% CI 1.11, 1.46 vs aOR 1.04, 95% CI 0.90, 1.22), but the parental difference did not reach significance (p=0.06). After limiting the study samples to participants without self-reported type 2 diabetes and psychiatric disorders, the results of the sensitivity analyses remained similar (ESM Table 3).

The distribution of demographic and clinical characteristics of 80,161 unrelated participants with GWAS data is shown in ESM Table 4. The results of the logistic regression analyses of

Table 1 Distribution of demographic and clinical characteristics according to presence of type 2 diabetes in 105,184 participants from the TWB

Characteristic	No T2D (n=99,933) n (%)	Self-reported T2D (n=5251) n (%)	p value
Age (years)	49.53 (10.87)	58.35 (7.90)	<0.0001
Age			<0.0001
<40	23,302 (23.32)	157 (2.99)	
40–50	24,415 (24.43)	546 (10.40)	
50–60	30,092 (30.11)	1862 (35.46)	
≥60	22,124 (22.14)	2686 (51.15)	
Male	35,236 (35.26)	2557 (48.70)	<0.0001
Self-reported psychiatric disorder			
SCZ	190 (0.19)	14 (0.27)	0.2195
MDD	3463 (3.47)	283 (5.39)	<0.0001
BPD	635 (0.64)	63 (1.20)	<0.0001
Education			<0.0001
College or above	56,978 (57.02)	2140 (40.75)	
Below college	42,955 (42.98)	3111 (59.25)	
Marital status[a]			<0.0001
Unmarried	13,395 (13.41)	306 (5.83)	
Married	73,857 (73.95)	4012 (76.46)	
Divorced/separated	8255 (8.27)	465 (8.86)	
Death of spouse	4370 (4.38)	464 (8.84)	
Regular alcohol use	5769 (5.77)	355 (6.76)	0.0029
Regular tobacco use	19,200 (19.21)	1529 (29.12)	<0.0001
BMI (kg/m^2)	24.10 (3.72)	26.20 (4.19)	<0.0001

Values for age and BMI are means (SD)

[a] There are 60 missing marital status where 56 are no T2D and four are self-reported T2D

T2D, type 2 diabetes

PRS for a psychiatric disorder on type 2 diabetes are shown in Table 3. A higher PRS for SCZ was associated with a lower risk of type 2 diabetes, and the signal was most enriched (explaining the most variance) at a threshold of 0.005 (aOR 0.96, 95% CI 0.93, 0.99, variance explained = 0.03%, p=0.01). A higher PRS for MDD was associated with a higher risk of type 2 diabetes at a threshold of 0.005 (aOR 1.04, 95% CI 1.00, 1.07, variance explained = 0.02%, p=0.04), although it did not reach Bonferroni-corrected significance. PRS for BPD was not associated with type 2 diabetes.

Among the three psychiatric disorders, a modified effect by sex was only detected for PRS for SCZ. The sex-stratified results are presented in Table 4. The interaction between sex and PRS was most enriched at a threshold of 0.05 (p=0.008 for the interaction term); a higher PRS for SCZ was associated with a lower risk of type 2 diabetes in women (aOR 0.92, 95% CI 0.88, 0.97, variance explained = 0.08%, p=0.0008) but not in men (aOR 1.01, 95% CI 0.96, 1.06, variance explained = 0.00%, p=0.75).

After adjusting for BMI (but neither smoking nor drinking), the strength of association of PRS for SCZ with type 2 diabetes reduced toward the null in the total sample and female sample (ESM Table 5); the results indicate the potential mediation role of obesity. After adjusting for BMI or smoking, the strength of association of PRS for MDD with type 2 diabetes was reduced (ESM Table 6).

For the supplementary analysis, the PRS for type 2 diabetes was not associated with any psychiatric disorder (ESM Table 7). There was a positive genetic correlation between MDD and type 2 diabetes in the European population (r_g = 0.13, p=0.00002) and the Asian population (r_g = 0.14, p=0.048) (ESM Table 8). There was a negative genetic correlation between BPD and type 2 diabetes (r_g = −0.07, p=0.01) in the European population. There were small negative genetic correlations between SCZ and type 2 diabetes in the Asian and European populations (r_g = −0.04 and −0.06, respectively) but these were not significant (p=0.08 and 0.06, respectively).

Discussion

Using a large collection of community samples from the TWB, this study explored the underlying mechanisms of the comorbidity between psychiatric disorders and type 2 diabetes by investigating familial aggregation and testing for polygenic overlap using a molecular approach. To the best of our knowledge, this is the first study using PRS for common psychiatric disorders to predict type 2 diabetes in Asia, and with the largest sample size among community samples to date. We found that a family history of type 2 diabetes is associated with family history of all three common psychiatric disorders, and maternal type 2 diabetes demonstrated a higher strength of association with SCZ family history than paternal type 2 diabetes did. PRS analyses provided evidence for a significantly negative polygenic overlap between SCZ and type 2 diabetes, a suggestive positive polygenic overlap between MDD and type 2 diabetes, and no polygenic overlap between BPD and type 2 diabetes. We also provided evidence for the sex differences in polygenic overlap, with SCZ PRS being negatively associated with type 2 diabetes in women but not in men. The mediation analyses showed that the polygenic effect of SCZ on type 2 diabetes may be partly mediated by obesity, and the polygenic effect of MDD on type 2 diabetes may be partly mediated by obesity or smoking.

Our findings of familial aggregation between type 2 diabetes and common psychiatric disorders are consistent with those of previous studies [7, 9]. We further showed a stronger maternal influence in the association of family history of type 2 diabetes with SCZ, in line with previous research, suggesting that women demonstrate a more predominant effect of family history of type

Table 2 Association of family history of type 2 diabetes and family history of common psychiatric disorders

Family history of common psychiatric disorders	Family history of T2D			Father with T2D			Mother with T2D			*p* value for the differences in aOR between parental T2D
	Yes (*n*=37,080)	No (*n*=68,104)	aOR (95% CI)	Yes (*n*=15,753)	No (*n*=89,431)	aOR (95% CI)	Yes (*n*=20,006)	No (*n*=85,178)	aOR (95% CI)	
SCZ	543 (1.46)	708 (1.04)	1.23 (1.08, 1.40)†	202 (1.28)	1049 (1.17)	1.04 (0.90, 1.22)	303 (1.51)	948 (1.11)	1.27 (1.11, 1.46)†	0.0554
MDD	2661 (7.18)	4035 (5.92)	1.19 (1.13, 1.26)†	1141 (7.24)	5555 (6.21)	1.13 (1.06, 1.21)†	1424 (7.12)	5272 (6.19)	1.18 (1.11, 1.25)†	0.3926
BPD	942 (2.54)	1331 (1.95)	1.26 (1.15, 1.39)†	402 (2.55)	1871 (2.09)	1.17 (1.05, 1.31)†	531 (2.65)	1742 (2.05)	1.31 (1.19, 1.45)†	0.1422

Values for yes/no columns are number (%)

Family history indicates the diseases among first-degree relatives, which includes biological parents and full siblings

† *p* value <0.017 (Bonferroni-corrected significance level, 0.05/3)

T2D, type 2 diabetes

Table 3 Association of PRS for common psychiatric disorders with type 2 diabetes

Threshold	SCZ PRS[a]			MDD PRS[b]			BPD PRS[c]		
	aOR (95% CI)[d]	Increased R^2 (%)[e]	*p* value	aOR (95% CI)[d]	Increased R^2 (%)[e]	*p* value	aOR (95% CI)[d]	Increased R^2 (%)[e]	*p* value
p=1	0.98 (0.95, 1.02)	0.01	0.3192	1.03 (1.00, 1.07)	0.01	0.0899	0.99 (0.95, 1.02)	0.01	0.4195
p=0.5	0.98 (0.95, 1.01)	0.01	0.2656	1.03 (1.00, 1.07)	0.01	0.0853	0.99 (0.95, 1.02)	0.01	0.4133
p=0.1	0.97 (0.94, 1.01)	0.02	0.0940	1.03 (1.00, 1.07)	0.01	0.0786	0.99 (0.96, 1.02)	0.01	0.4892
p=0.05	0.96 (0.93, 1.00)	0.02	0.0287*	1.03 (1.00, 1.07)	0.01	0.0871	0.99 (0.96, 1.02)	0.01	0.5836
p=0.005	0.96 (0.93, 0.99)	0.03	0.0121†	1.04 (1.00, 1.07)	0.02	0.0439*	0.98 (0.95, 1.01)	0.01	0.2113

[a] Sample size = 80,020

[b] Sample size = 77,291

[c] Sample size = 79,652

[d] Estimated from logistic regression model with adjustment for age, sex, batch effect and 20 PCs

[e] Increase in Nagelkerke pseudo R^2 when adding the PRS into the model including age, sex, batch effect and 20 PCs

* *p* value <0.05; † *p* value <0.017 (Bonferroni-corrected significance level, 0.05/3)

2 diabetes on SCZ and non-affective psychosis than men [16]. The larger maternal influence may represent the role of mutations in mitochondrial DNA, which were inherited from the mothers. Mitochondrial DNA mutations were identified as high penetrance risk for type 2 diabetes and were maternally inherited [31, 32]. In addition, mitochondrial DNA mutations also contributed to psychiatric disorders [33], which have been linked to maternal inheritance [34].

To examine PRS association, some previous studies tested the association of PRS for type 2 diabetes with psychiatric disorders [35, 36], while our main analyses tested the association of PRS for psychiatric disorders with type 2 diabetes, and supplementary analyses tested the association of PRS for type 2 diabetes with psychiatric disorders. As the prevalence of type 2 diabetes is higher than that of psychiatric disorders in the TWB, we analysed type 2 diabetes as the outcome to achieve a better power for PRS association.

This study showed that higher genetic loading for SCZ was associated with a lower risk of type 2 diabetes, in line with a previous study using transcriptome-wide expression data and a machine learning approach to derive SCZ PRS, which found a negative correlation with HbA_{1c}, an index for diabetes [37]. However, a study with approximately 3000 samples found no association between SCZ PRS and type 2 diabetes [15], and another study found that type 2 diabetes PRS was positively associated with psychotic experiences, including positive psychotic symptoms and symptoms of thought interference and psychotic disorder [35].

We observed positive familial aggregation between type 2 diabetes and SCZ, but, in contrast, a negative polygenic overlap and negative genetic correlation between them. This discordant finding implies the importance of environmental factors in the mechanisms underlying the comorbidity of type 2 diabetes and SCZ. Antipsychotic medication has been shown to increase the risk of type 2 diabetes [38, 39], hence

Table 4 Sex differences in the association of PRS for schizophrenia with type 2 diabetes

Threshold	Male			Female			*p* value for sex×PRS for SCZ
	aOR (95% CI)[a]	Increased R^2 (%)[b]	*p* value	aOR (95% CI)[a]	Increased R^2 (%)[b]	*p* value	
p=1	1.03 (0.98, 1.08)	0.01	0.2981	0.95 (0.90, 0.99)	0.04	0.0169	0.0127
p=0.5	1.02 (0.98, 1.07)	0.00	0.3266	0.94 (0.90, 0.99)	0.05	0.0126	0.0115
p=0.1	1.02 (0.97, 1.07)	0.00	0.4897	0.93 (0.89, 0.98)	0.06	0.0028	0.0078
p=0.05	1.01 (0.96, 1.06)	0.00	0.7533	0.92 (0.88, 0.97)	0.08	0.0008	0.0077
p=0.005	0.97 (0.93, 1.02)	0.01	0.2320	0.95 (0.90, 0.99)	0.04	0.0199	0.3866

[a] Estimated from logistic regression model with adjustment for age, batch effect and 20 PCs

[b] Increase in Nagelkerke pseudo R^2 when adding the PRS into the model including age, sex, batch effect and 20 PCs

the association of co-occurrence of SCZ and type 2 diabetes may be stronger than the genetic correlation between them.

The findings indicate familial aggregation between type 2 diabetes and BPD, but the lack of a polygenic association between them implies a role of environmental factors in the mechanisms underlying the comorbidity between type 2 diabetes and BPD. Previous studies have shown that BPD patients are less active and more sedentary than healthy participants [40], which may subsequently increase the risk of diabetes [41, 42], However, the lack of association for BPD PRS may be due to the relatively limited statistical power for analyses of BPD PRS, which was derived from a GWAS with an insufficient discovery sample size of unmatched ancestry.

In addition to familial aggregation between type 2 diabetes and MDD, this study provides further evidence for polygenic overlap and genetic correlation between them. In a recent study using the UK Biobank, PRS for cardiometabolic traits, including type 2 diabetes, BMI, coronary artery disease, ischaemic and small vessel disease, was associated with an increased risk of MDD [36]. Twin studies also support the genetic correlation between MDD and type 2 diabetes [10, 43]. Taken together, these findings suggest a shared genetic aetiology for the mechanism underlying comorbidity between type 2 diabetes and MDD. Depressive symptoms have been shown to have a low fractional anisotropy [44], which is also linked to more negative self-referential thinking [45]. A brain imaging study showed that type 2 diabetes PRS was associated with low fractional anisotropy, which mediates the association of type 2 diabetes PRS with cognitive impairments [46].

Sex differences in genetic influence are an important issue. The genetic correlation between type 2 diabetes and depression was observed only in women in twin studies [10, 43]. A Mendelian randomisation study identified sex-specific genetic variants as instrumental variables for testosterone, and found that female-specific testosterone levels showed a positive causal relationship with BMI and waist circumference, whereas male-specific testosterone level showed positive causality with hip circumference but negative causality with type 2 diabetes [47]. The present study added evidence for sex differences in PRS association, with the SCZ PRS being negatively associated with type 2 diabetes in women only. These findings suggest that the genetic effect on human diseases, especially metabolic-related traits, may be modified by sex. A recent population-based health outcome study showed that SCZ was associated with mortality risk in patients with type 2 diabetes, particularly in men, and an adverse effect of SCZ on post-complication mortality risk was observed in men only [48].

Evidence has shown that obesity, smoking and alcohol consumption are risk factors for type 2 diabetes [49], and the present study further suggests that the polygenic effect of psychiatric disorders on type 2 diabetes may be partly mediated by these risk factors, e.g. the polygenic effect of SCZ is mediated by obesity, and the polygenic effect of MDD is mediated by obesity or smoking. This implied that prevention in terms of these modifiable risk factors is crucial for intervention for type 2 diabetes.

This study has some limitations. First, the phenotypes of type 2 diabetes and common psychiatric disorders were obtained by retrospective self-reporting, which may have led to recall bias and resulted in misclassification and underestimation of the prevalence of diseases. We evaluated the accuracy of the self-reported disease status with the ICD diagnosis, including ICD-9 (http://www.icd9data.com/2007/Volume1/default.htm) and ICD-10 (http://apps.who.int/classifications/icd10/browse/2016/en), in the Taiwan National Health Insurance Research Database, and the tetrachoric correlations for SCZ, MDD, BPD and type 2 diabetes were 0.95, 0.82, 0.72 and 0.91, respectively. We assume that this misclassification did not vary among individuals with different genetic loadings. Hence, the reported strength of association for PRS would be underestimated given non-differential misclassification. Second, our measures of covariates were limited by the cross-sectional nature of the study. Longitudinal measures for BMI, smoking and alcohol consumption were lacking, and there was not enough information for these covariates before and after type 2 diabetes onset. Although we attempted to explore the possible mediating effect of these environmental covariates on the polygenic influence on type 2 diabetes, the causative pathway could not be clearly distinguished. Also, the psychiatric medications used were unknown, and their role in the aetiology of type 2 diabetes warrants further investigations. Third, in the analysis of family history association, we did not control for the condition that one of the parents has type 2 diabetes and the other has any psychiatric disorder. Assortative mating, e.g., paternal type 2 diabetes with maternal psychiatric disorders or vice versa, may contribute to observed familial aggregation; however, spousal correlation between type 2 diabetes and psychiatric disorders has been shown to be limited [50]. Fourth, our study participants were limited to individuals of Taiwanese ancestry, and our results may not be generalisable to other ancestries. Fifth, the SNP-based PRS did not capture the total heritability from the family studies. Using cross-ancestry GWAS results to derive PRS may lead to a low prediction [51] as genetic architecture may differ across populations. When using European ancestry as discovery samples, the prediction performance in target samples of Asian or African ancestry was reduced by 37–78% compared with that in target samples of European ancestry [52]. In this study, the PRS for MDD (EUR), in which the variance of MDD explained by the PRS was 3.2% [23], explained only 0.4% of MDD in the TWB samples; the BPD PRS derived from European ancestry, in which the variance of BPD explained by the PRS was 8% [25], explained only 0.2% of BPD in the TWB samples. For comparison, the SCZ PRS derived from matched ancestry (Asia PGC), in which the variance of SCZ

explained by the PRS was approximately 3% [22], explained approximately 2% of SCZ in the TWB samples. Hence, the power of the PRS analysis is higher for SCZ in this study. Most large-scale GWAS have been performed in individuals of European ancestry, with only a few reported in individuals of Asian ancestry (such as SCZ). Some modest-scale GWAS of BPD have been performed in Asian populations, e.g. a study with a sample size of 1822 cases and 4650 control participants among a Han Chinese population [53] and a study with 2964 cases and 61,887 control participants among a Japanese population [54]. A moderate-scale GWAS of MDD (EAS) in an Asian population has recently been published [24]; however, the PRS derived from matched ancestry (EAS) did not lead to a better prediction of MDD in the TWB samples than the PRS derived from non-matched ancestry (EUR) with a much larger sample size. In addition to the issue of cross-ancestry prediction, the sample size for the discovery sample is crucial for PRS prediction. Further large-scale genetic research in individuals of diverse ancestries is needed to mitigate the health disparities that exist across the populations [55].

Conclusion These findings of familial aggregation between type 2 diabetes and common psychiatric disorders indicate that the comorbidity of type 2 diabetes with psychiatric disorders may be explained by shared familial factors, including not only shared environmental factors but also genetic background. The findings of shared polygenic loading between type 2 diabetes and MDD implies not only pleiotropy but also a shared genetic aetiology for the mechanism behind the comorbidity. The negative correlation between polygenic loading for SCZ and type 2 diabetes implies a role for environmental factors, such as a mediating effect of obesity. Further studies are necessary to develop suitable preventive interventions and treatment plans in the initial development of type 2 diabetes and its comorbidity with psychiatric disorders.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-022-05665-x.

Authors' relationships and activities CYC is an employee of Biogen. The remaining authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement SHW conceptualised and designed the study. MHS and YHS drafted the manuscript and performed the data analysis. YFL, PCC, CYC, PCH, YJP, YLL, SJT, PHK, CSW and YTH interpreted the results and critically revised the draft. All authors reviewed and approved the final manuscript. SHW is responsible for the integrity of the work as a whole.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-022-05665-x.

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