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Supplementary Table 1: Diagnostic classification of psychiatric disorders and T2DM

	ICD-10	ICD-8	Data sources
Psychiatric disorders ^a			
Any psychiatric disorders	F00-F99	295-315	DPCRR
OCD	F42	300.39	DPCRR
ASD	F84.0, F84.1, F84.5, F84.8, F84.9	299.00-299.03	DPCRR, DNPR, spec. 20, 80
AN	F50.0, F50.1	306.50	DPCRR, DNPR
OED	F50 (excl. F50.0, F50.1, F50.4, and F50.5)	306.58, 306.59	DPCRR, DNPR
Substance use disorders	F10-F19	291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90, 304.x9	DPCRR, DNPR
Schizophrenia spectrum disorders	F20-F29	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83	DPCRR
MDD ^b	F32-F33 (original iPSYCH cases F30-39 Affective disorders)	296.09, 296.29, 298.09, 300.49	DPCRR
Anxiety disorders	F40.00-F41.19, F4200-F43.10, F93	300.09, 300.29, 300.39	DPCRR
ADHD ^b	F90, F98.8 (original iPSYCH cases F90.0)	308.01	DPCRR, DNPR, spec. 20, 80
ODD/CD	F90.1, F91	308.03-06	DPCRR
Tic disorders	F95	306.29	DPCRR, DNPR, spec. 20, 80
T2DM	E11, O24.1	250	DNPR
Diabetes complications	H28.0, H334B, H36.0, I79.2, G59.0, G63.2, G99.0, M14.2, M14.6, N08.3	250.01-05	DNPR
Oral antidiabetic medication	ATC codes A10B		DNPreR

a) All psychiatric disorders were identified if diagnoses were registered in DPCRR by age 18 years. Some disorders were also identified at hospital specialties 20 (neurology) and 80 (pediatrics) in the DNPR.

b) Some codes differ slightly from those originally used to extract iPSYCH cases, e.g. we used a broader definition of ADHD in the current study (ICD-10 code: F90.x F98.8) than the original iPSYCH ADHD-case definition (ICD-10 code F90.0) and thus included additional individuals with ADHD identified from the entire iPSYCH2015 case-cohort sample.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ATC: Anatomical Therapeutic Chemical Classification System, ASD: Autism spectrum disorder, DPCRR: Danish National Psychiatric Central Research Register, DNPR: Danish National Patient Register, DNPreR: Danish National Prescription Register, ICD: International Classification of Diseases, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OED: Other eating disorders, T2DM: Type 2 diabetes mellitus.

Supplementary Table 2: Characteristics of probands and relatives, stratified by sex

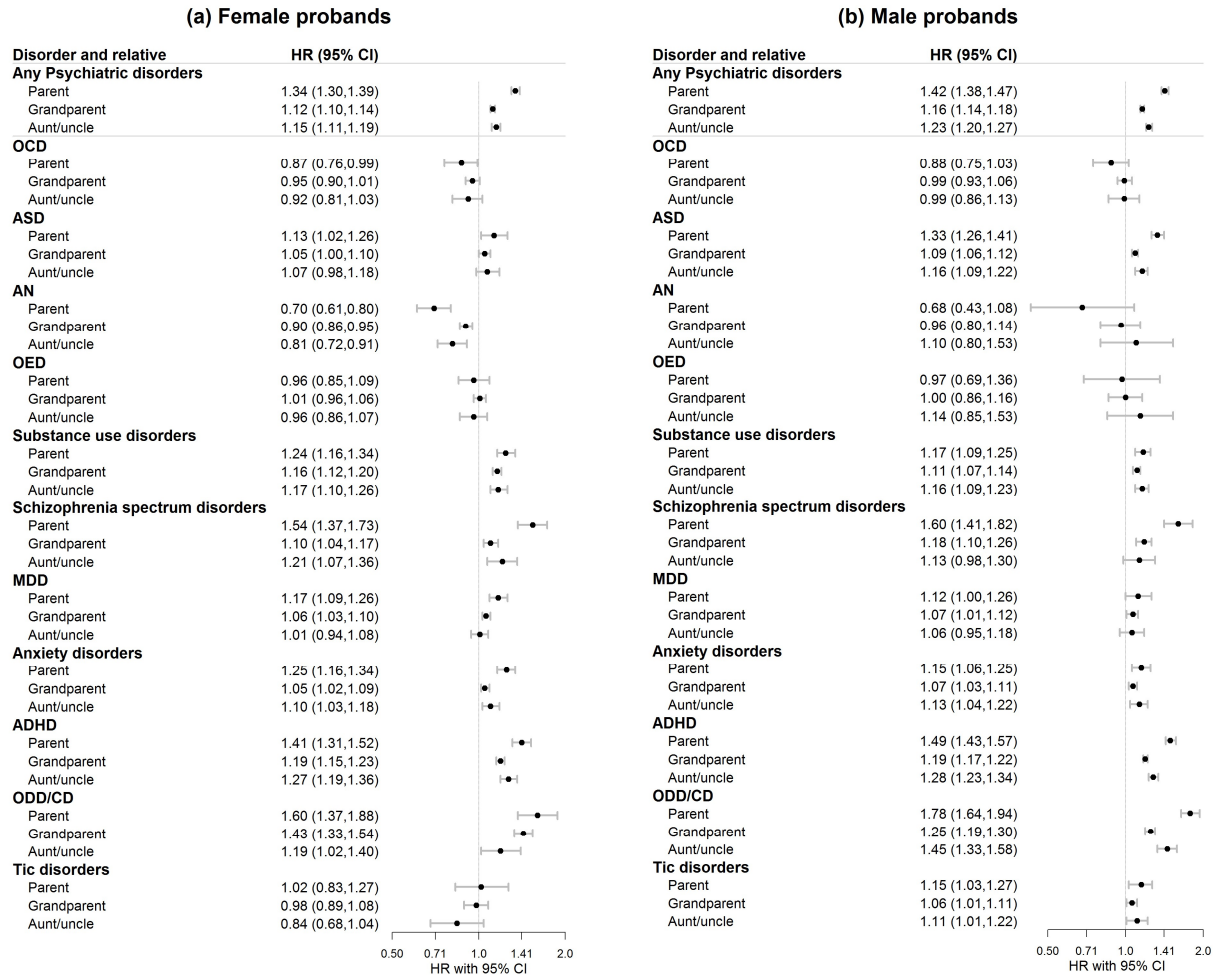
Cohort		All	Females	Males
Probands	N	659906 (100.0)	320689 (48.6)	339217 (51.4)
	Birth year, median (IQR)	1995 (1992-1998)	1995 (1992-1998)	1995 (1992-1998)
	Psychiatric disorders ^a			
	Any psychiatric disorders	63615 (9.6)	30785 (9.6)	32830 (9.7)
	OCD	3957 (0.6)	2273 (0.7)	1684 (0.5)
	ASD	13011 (2.0)	3456 (1.1)	9555 (2.8)
	AN	3046 (0.5)	2805 (0.9)	241 (0.1)
	OED	3069 (0.5)	2741 (0.9)	328 (0.1)
	Substance use disorders	12612 (1.9)	5910 (1.8)	6702 (2.0)
	Schizophrenia spectrum disorders	3510 (0.5)	2002 (0.6)	1508 (0.4)
	MDD	9129 (1.4)	6478 (2.0)	2651 (0.8)
	Anxiety disorders	10714 (1.6)	6227 (1.9)	4487 (1.3)
	ADHD	20093 (3.0)	6284 (2.0)	13809 (4.1)
	ODD/CD	4408 (0.7)	1057 (0.3)	3351 (1.0)
	Tic disorders	4000 (0.6)	831 (0.3)	3169 (0.9)
Parents ^b	N	844928 (100.0)	423830 (50.2)	421098 (49.8)
	T2DM, N (%)	47793 (5.7)	18835 (4.4)	28958 (6.9)
	Birth year, median (IQR)	1965 (1960-1969)	1966 (1962-1970)	1964 (1959-1968)
	Age at EOF, median (IQR)	53 (49-58)	53 (48-57)	54 (50-59)
	Age at T2DM, median (IQR)	48 (42-54)	46 (41-52)	50 (44-55)
Grandparents ^b	N	1006534 (100.0)	511844 (50.9)	494690 (49.1)
	T2DM, N (%)	147452 (14.6)	67176 (13.1)	80276 (16.2)
	Birth year, median (IQR)	1938 (1930-1944)	1939 (1932-1945)	1936 (1929-1943)
	Age at EOF, median (IQR)	75 (68-81)	75 (69-81)	75 (67-81)
	Age at T2DM, median (IQR)	67 (60-73)	67 (60-73)	66 (59-73)
Uncles/aunts ^b	N	790229 (100.0)	375353 (47.5)	414876 (52.5)
	T2DM, N(%)	42312 (5.4)	16712 (4.5)	25600 (6.2)
	Birth year, median (IQR)	1965 (1960-1970)	1965 (1961-1970)	1965 (1960-1970)
	Age at EOF, median (IQR)	53 (47-58)	53 (47-57)	53 (47-58)
	Age at T2DM, median (IQR)	48 (42-54)	47 (41-53)	49 (43-54)

^a All psychiatric disorders were identified if hospital diagnoses were registered by age 18 years.

^b Some relatives are included repeatedly for probands, their siblings and cousins and there is clear differences in length of follow-up indicated by distributions of birth year and age at end of follow-up. This is taken into account in the analyses. In this table, the unique number of relatives are included.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ASD: Autism spectrum disorder, EOF: end of follow-up, IQR: inter-quartile range, N: number, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OED: Other eating disorders, T2DM: Type 2 diabetes mellitus.

Proband psychiatric disorder and T2DM in relatives

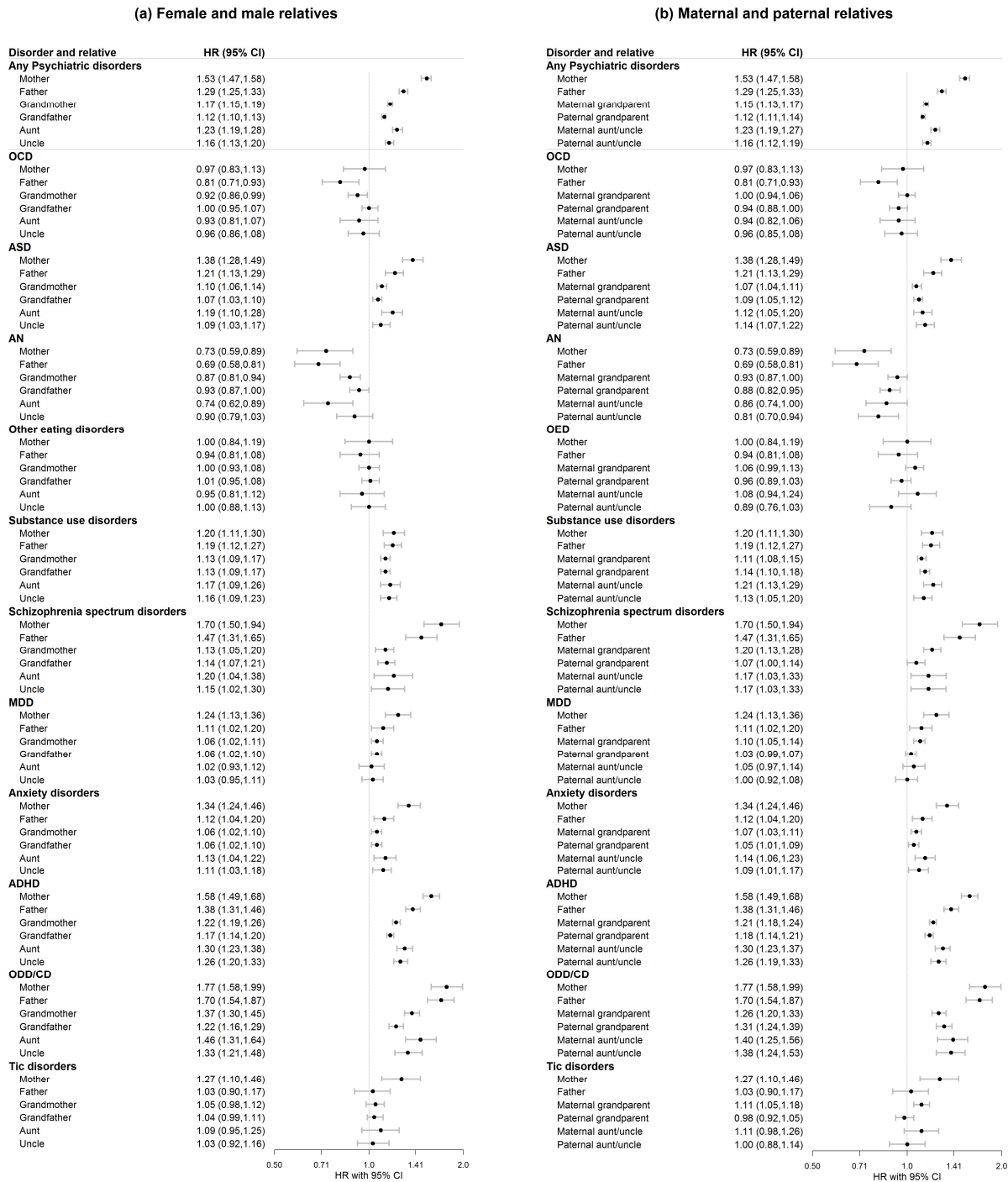


Supplementary Figure 1: Psychiatric disorder in child and T2DM in relatives for females and males, separately.

HRs were adjusted for birth year of the probands, sex of relatives, calendar year and age of the relatives as the underlying time scale.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ASD: Autism spectrum disorder, CI: Confidence interval, HR: Hazard ratio, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OED: Other eating disorders, T2DM: Type 2 diabetes mellitus.

Proband psychiatric disorder and T2DM in relatives



Supplementary Figure 2: Psychiatric disorder in proband and T2DM in relatives by (a) relative's sex and (b) parental relation. HRs were adjusted for birth year of the probands, sex of probands (and relatives), calendar year, and age of the relatives as the underlying time scale.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ASD: Autism spectrum disorder, CI: Confidence interval, HR: Hazard ratio, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OED: Other eating disorders, T2DM: Type 2 diabetes mellitus.

Supplementary Table 3: Tetrachoric correlations with 95% confidence intervals estimating correlations between the underlying liabilities of psychiatric disorders (in probands) and T2DM (in relatives).

Disorder	Relative type	Tetrachoric correlation ^a (95% CI) ^b
Any psychiatric disorders	Parent	0.08 (0.07, 0.08)
	Grandparent	0.02 (0.02, 0.03)
	Aunt/uncle	0.04 (0.04, 0.05)
OCD	Parent	-0.02 (-0.04, -0.01)
	Grandparent	-0.01 (-0.02, 0.00)
	Aunt/uncle	-0.01 (-0.02, 0.01)
ASD	Parent	0.05 (0.04, 0.06)
	Grandparent	0.01 (0.01, 0.02)
	Aunt/uncle	0.02 (0.01, 0.03)
AN	Parent	-0.06 (-0.08, -0.04)
	Grandparent	-0.02 (-0.03, -0.01)
	Aunt/uncle	-0.03 (-0.05, -0.01)
OED	Parent	-0.01 (-0.03, 0.01)
	Grandparent	0.00 (-0.01, 0.01)
	Aunt/uncle	-0.01 (-0.02, 0.01)
Substance use disorders	Parent	0.03 (0.02, 0.04)
	Grandparent	0.01 (0.01, 0.02)
	Aunt/uncle	0.03 (0.02, 0.04)
Schizophrenia spectrum disorders	Parent	0.07 (0.06, 0.09)
	Grandparent	0.01 (0.00, 0.02)
	Aunt/uncle	0.02 (0.01, 0.04)
MDD	Parent	0.02 (0.01, 0.04)
	Grandparent	0.01 (0.00, 0.01)
	Aunt/uncle	0.00 (-0.01, 0.01)
Anxiety disorders	Parent	0.03 (0.02, 0.04)
	Grandparent	0.01 (0.00, 0.01)
	Aunt/uncle	0.02 (0.01, 0.03)
ADHD	Parent	0.08 (0.07, 0.09)
	Grandparent	0.03 (0.02, 0.03)
	Aunt/uncle	0.05 (0.04, 0.06)
ODD/CD	Parent	0.09 (0.08, 0.11)
	Grandparent	0.03 (0.03, 0.04)
	Aunt/uncle	0.05 (0.04, 0.07)
Tic disorders	Parent	0.02 (0.00, 0.04)
	Grandparent	0.00 (-0.01, 0.01)
	Aunt/uncle	0.01 (-0.01, 0.02)

^a Tetrachoric correlations were estimated using a structural equation modeling approach in which models were adjusted for birth year and sex of probands and relatives.

^b The 95% CIs were normal-based and family clusters were not taken into account due to time constraints, however, a 95% confidence interval based on only 20 bootstrap resamples, accounting for family clusters, resulted in virtually equivalent confidence limits. The proband-relative samples were the same as those used for the main Cox regression models including all possible proband-relative pairs.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ASD: Autism spectrum disorder, CI: Confidence interval, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OED: Other eating disorders, T2DM: Type 2 diabetes mellitus.

Supplementary Table 4: Sex-specific ORs and 95% CIs for associations between the T2DM-PRS and psychiatric disorders

Disorder	Females		Males	
	N	OR (95% CI)	N	OR (95% CI)
Any psychiatric disorders	45364	1.08 (1.04,1.12)	48972	1.15 (1.10,1.19)
OCD	3347	0.99 (0.89,1.10)	2047	1.05 (0.88,1.26)
ASD	6147	1.07 (0.99,1.16)	18162	1.13 (1.07,1.18)
AN	6690	0.89 (0.85,0.94)	512	0.73 (0.56,0.96)
OED	5137	0.92 (0.84,1.00)	426	0.98 (0.75,1.30)
Substance use disorders	8187	1.12 (1.04,1.20)	10312	1.06 (0.99,1.13)
Schizophrenia spectrum disorders	7411	1.15 (1.07,1.23)	8518	1.07 (1.02,1.13)
MDD	23499	1.09 (1.04,1.14)	11568	1.10 (1.04,1.17)
Anxiety disorders	11263	1.05 (0.98,1.11)	7182	1.05 (0.97,1.14)
ADHD	10517	1.25 (1.16,1.34)	22661	1.24 (1.18,1.31)
ODD/CD	1072	1.40 (1.12,1.75)	3426	1.27 (1.11,1.44)
Tic disorders	639	0.97 (0.76,1.24)	2886	0.96 (0.83,1.12)

Analyses were adjusted for calendar year of birth, the first five principal components, and observation time, and weighted by the inverse selection probabilities to account for the oversampling of iPSYCH cases.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ASD: Autism spectrum disorder, CI: Confidence interval, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OR: Odds Ratio, PRS: Polygenic risk score, OED: Other eating disorders, T2DM: Type 2 diabetes mellitus.

Supplementary Table 5: Sub-analyses of the association between T2DM-PRS and psychiatric disorders

Disorder	All		Individuals followed until age 18		Individuals of European ancestry	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Any psychiatric disorders	94336	1.11 (1.08,1.14)	42288	1.09 (1.05,1.13)	86535	1.12 (1.09,1.15)
OCD	5394	1.01 (0.92,1.11)	2056	0.96 (0.83,1.11)	4979	1.04 (0.95,1.15)
ASD	24309	1.11 (1.07,1.16)	12890	1.07 (1.03,1.12)	21997	1.11 (1.06,1.16)
AN	7202	0.88 (0.83,0.93)	3846	0.91 (0.87,0.95)	6774	0.87 (0.82,0.92)
OED	5563	0.92 (0.85,1.01)	2208	0.88 (0.78,1.01)	5172	0.92 (0.84,1.01)
Substance use disorders	18499	1.08 (1.03,1.14)	4924	1.08 (0.99,1.18)	16872	1.09 (1.04,1.14)
Schizophrenia spectrum disorders	15929	1.11 (1.06,1.16)	4005	1.15 (1.05,1.26)	14154	1.10 (1.05,1.15)
MDD	35067	1.09 (1.06,1.13)	9843	1.08 (1.03,1.13)	32779	1.09 (1.05,1.13)
Anxiety disorders	18445	1.05 (1.00,1.10)	5685	0.97 (0.89,1.06)	17042	1.04 (0.99,1.09)
ADHD	33178	1.24 (1.19,1.29)	14742	1.24 (1.17,1.31)	30458	1.25 (1.19,1.30)
ODD/CD	4498	1.29 (1.16,1.45)	2732	1.22 (1.08,1.39)	4079	1.31 (1.16,1.48)
Tic disorders	3525	0.96 (0.85,1.10)	1929	0.85 (0.74,0.99)	3216	1.01 (0.88,1.15)

Analyses were restricted to 1) individuals with complete follow-up until age 18 (to mimic the observation period in the multigenerational approach), and 2) individuals of European ancestry (because the T2DM-PRS were based on European samples).

Analyses were adjusted for sex, calendar year of birth, the first five principal components, genotyping chip, and observation time, and weighted by the inverse selection probabilities to account for the oversampling of iPSYCH cases.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ASD: Autism spectrum disorder, CI: Confidence interval, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OR: Odds ratio, PRS: Polygenic risk score, OED: Other eating disorders, T2DM: Type 2 diabetes mellitus.

Supplementary Table 6: ORs for the association between T2DM-PRS and psychiatric disorders in three adjusted models

Disorder		Main model	Main + BMI polygenic score	Main + educational attainment polygenic score
	N	OR (95% CI)	OR (95% CI)	OR (95% CI)
Any psychiatric disorders	94336	1.11 (1.08,1.14)	1.07 (1.04,1.10)	1.08 (1.05,1.10)
OCD	5394	1.01 (0.92,1.11)	1.04 (0.94,1.15)	1.01 (0.91,1.11)
ASD	24309	1.11 (1.07,1.16)	1.09 (1.05,1.14)	1.13 (1.08,1.17)
AN	7202	0.88 (0.83,0.93)	0.94 (0.88,1.00)	0.90 (0.85,0.96)
OED	5563	0.92 (0.85,1.01)	0.92 (0.84,1.01)	0.93 (0.86,1.02)
Substance use disorders	18499	1.08 (1.03,1.14)	1.03 (0.98,1.08)	1.03 (0.98,1.08)
Schizophrenia spectrum disorders	15929	1.11 (1.06,1.16)	1.08 (1.03,1.13)	1.09 (1.05,1.14)
MDD	35067	1.09 (1.06,1.13)	1.08 (1.04,1.11)	1.07 (1.03,1.11)
Anxiety disorders	18445	1.05 (1.00,1.10)	1.03 (0.98,1.08)	1.02 (0.97,1.07)
ADHD	33178	1.24 (1.19,1.29)	1.15 (1.10,1.20)	1.16 (1.11,1.21)
ODD/CD	4498	1.29 (1.16,1.45)	1.16 (1.03,1.30)	1.15 (1.03,1.28)
Tic disorders	3525	0.96 (0.85,1.10)	0.95 (0.83,1.09)	0.93 (0.82,1.07)

1) Main model: adjusted for sex, calendar year of birth, the first five principal components, genotyping chip, and observation time; 2) Main model additionally including BMI polygenic score; 3) Main model additionally including educational attainment polygenic score..

All analyses were weighted by the inverse selection probabilities to account for the oversampling of iPSYCH cases.

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, AN: Anorexia nervosa, ASD: Autism spectrum disorder, BMI: Body mass index, CI: Confidence interval, MDD: Major depressive disorder, OCD: Obsessive-compulsive disorder, ODD/CD: Oppositional-defiant disorder/Conduct disorder, OR: Odds ratio, OED: Other eating disorders, T2DM-PRS: Polygenic risk score for type 2 diabetes mellitus.