Shared familial risk for type 2 diabetes mellitus and psychiatric disorders: a nationwide multigenerational genetics study

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Abstract

Background. Psychiatric disorders and type 2 diabetes mellitus (T2DM) are heritable, polygenic, and often comorbid conditions, yet knowledge about their potential shared familial risk is lacking. We used family designs and T2DM polygenic risk score (T2DM-PRS) to investigate the genetic associations between psychiatric disorders and T2DM.

Methods. We linked 659 906 individuals born in Denmark 1990–2000 to their parents, grandparents, and aunts/uncles using population-based registers. We compared rates of T2DM in relatives of children with and without a diagnosis of any or one of 11 specific psychiatric disorders, including neuropsychiatric and neurodevelopmental disorders, using Cox regression. In a genotyped sample (iPSYCH2015) of individuals born 1981–2008 ($n = 134\ 403$), we used logistic regression to estimate associations between a T2DM-PRS and these psychiatric disorders.

Results. Among 5 235 300 relative pairs, relatives of individuals with a psychiatric disorder had an increased risk for T2DM with stronger associations for closer relatives (parents: hazard ratio = 1.38, 95% confidence interval 1.35–1.42; grandparents: 1.14, 1.13–1.15; and aunts/uncles: 1.19, 1.16–1.22). In the genetic sample, one standard deviation increase in T2DM-PRS was associated with an increased risk for any psychiatric disorder (odds ratio = 1.11, 1.08–1.14). Both familial T2DM and T2DM-PRS were significantly associated with seven of 11 psychiatric disorders, most strongly with attention-deficit/hyperactivity disorder and conduct disorder, and inversely with anorexia nervosa.

Conclusions. Our findings of familial co-aggregation and higher T2DM polygenic liability associated with psychiatric disorders point toward shared familial risk. This suggests that part of the comorbidity is explained by shared familial risks. The underlying mechanisms still remain largely unknown and the contributions of genetics and environment need further investigation.

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease that affects 4–7% of the population, with increasing prevalence over the past decades (Carstensen, Ronn, & Jorgensen, 2020; Khan et al., 2020). Several psychiatric disorders are associated with increased risk of developing T2DM, with evidence of a bidirectional association (Lindekilde et al., 2022; Wimberley et al., 2022). With increasing rates of diagnosed and medically treated T2DM and several psychiatric conditions (Carstensen et al., 2020; Dalsgaard et al., 2019), the elevated risk for T2DM in psychiatric populations, and vice versa, is a growing public health concern.

Yet, the exact mechanisms underlying their association remain unclear, but are likely to include both environmental and genetic risk factors. First, physical inactivity, sedentary behaviors, poor dietary habits, and obesity are known to be associated with both T2DM and psychiatric disorders (Borovcanin, Vesic, Petrovic, Jovanovic, & Mijailovic, 2023). Second, several biological mechanisms have been suggested to link T2DM and psychiatric disorders, such as alterations in brain insulin signaling, inflammatory and immune disturbances, oxidative stress, and hypothalamic-pituitary–adrenal axis dysregulation (Borovcanin et al., 2023; Fanelli et al., 2022; PRIME, 2020–2024). From an epidemiological perspective, the bi-directional associations between the conditions suggest that these conditions may to a substantial degree share familial risk factors (referring to any genetic and environmental factors shared among family

members). T2DM and psychiatric disorders are heritable conditions, which aggregate in families; results of epidemiological studies document familial aggregation, with higher risk in first- than in second-degree relatives of affected probands, both for T2DM (Hemminki, Li, Sundquist, & Sundquist, 2010; Liao et al., 2022) and for many psychiatric disorders, including obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), anorexia nervosa (AN), schizophrenia, and attention-deficit/hyperactivity disorder (ADHD) (Chen et al., 2017; Chou et al., 2017; Hansen et al., 2019; Pardue et al., 2014; Steinhausen, Jakobsen, Helenius, Munk-Jorgensen, & Strober, 2015). Genome-wide association studies (GWAS) have confirmed the polygenic nature of each of these conditions (Demontis et al., 2023; Grove et al., 2019; Strom et al., 2021; Trubetskoy et al., 2022; Watson et al., 2019; Xue et al., 2018), and studies using GWAS summary statistics have also demonstrated genetic overlap between T2DM and several psychiatric disorders; this includes genetic correlations of T2DM with ADHD and major depressive disorder (MDD) in the positive direction, and with OCD, AN, and to some extent also schizophrenia in the negative direction (Fanelli et al., 2022; Zammarchi, Conversano, & Pisanu, 2022). Since GWAS-based genetic correlations do not always reflect phenotypic association patterns, using other genetically informative study designs, such as family designs, can help triangulate evidence of how genetic as well as environmental factors contribute to the associations between T2DM and psychiatric disorders. One recently published study showed an association between early-onset T2DM and mood, anxiety, and stress-related disorders within individuals and by investigating pairs of siblings and cousins (Liu et al., 2022). In addition to GWAS correlation and epidemiological familial risk studies, genetic cross-disorder association can be studied using polygenic risk scores (PRSs), which capture an individual's genetic risk for a specific condition by summarizing the effect of risk variants across the genome. PRSs have been found to predict disease status in independent samples and to be associated with related phenotypes and comorbidities (Lewis & Vassos, 2020).

For T2DM, there is currently a lack of epidemiological studies investigating shared familial risk with the full spectrum of psychiatric disorders. We are also not aware of any studies using PRS to explore the genetic link between T2DM and a broad range of psychiatric disorders, particularly not in population-representative samples. To address these knowledge gaps, we used two complementary genetically informative methods to evaluate the familial and genetic contribution to the association between T2DM and psychiatric disorders: First, we used nationwide register data in a multigenerational family design, allowing examination of disorders developing at different ages and the influence of different degrees of relatedness, to estimate multigenerational familial associations between psychiatric disorders and T2DM. Second, we used genomic-level data from the Integrative Psychiatric Research (iPSYCH) sample, a nationally representative case-cohort sample and the world's largest single-site genetic study of psychiatric disorders (Bybjerg-Grauholm, Pedersen, Bækvad-Hansen, & Pedersen, 2020; Pedersen et al., 2018), to investigate to what extent a PRS for T2DM (T2DM-PRS) is associated with psychiatric disorders.

Methods

Data sources

We used Danish population-based registers containing continuously updated information on all Danish citizens in the Danish Civil Registration System, including sex, date of birth, death, place of living, and link to relatives (Schmidt, Pedersen, & Sorensen, 2014). Clinical hospital diagnoses (International Classification of Diseases (ICD) versions 8 and 10) were registered for inpatient contacts in the Danish National Patient Register since 1977 (Schmidt et al., 2015), and in the Danish Psychiatric Central Research Register since 1969 (Mors, Perto, & Mortensen, 2011), and for outpatient and emergency room contacts since 1995. The Danish National Prescription Registry includes all prescriptions redeemed from Danish pharmacies since 1995 (Pottegard et al., 2016).

Through iPSYCH, the above-mentioned registers were further enriched with genetic information on genotyped dried blood spots since 1981 from the Danish Neonatal Screening Biobank (Norgaard-Pedersen & Hougaard, 2007). All registers were accessed and linked on the individual level through servers at Statistics Denmark.

The project was approved and access was governed by the Danish Data Protection Agency, the Danish Health Data Authority, and Statistics Denmark. The iPSYCH study was additionally approved by the Danish Newborn Screening Biobank Steering Committee and the Danish Scientific Ethical Committee, which in accordance with Danish legislation, has, for this study, waived the need for informed consent in biomedical research based on existing biobanks (Mortensen, 2019).

Study populations

We defined two population-based study cohorts using different approaches (Fig. 1). First, the familial co-aggregation of T2DM and psychiatric disorders was investigated in Danish multigenerational data. We identified index individuals from the general population – hereafter referred to as probands – as all individuals born in Denmark 1990–2000, who fulfilled the following criteria: singleton birth, identifiable parents, not included in the adoption registry (Petersen & Sorensen, 2011), and ≥18 years of follow-up. For all eligible probands, we identified their first-degree relatives (parents, who share 50% of their segregating genes with the proband) and second-degree relatives (grandparents and aunts/uncles, who share 25% of their segregating genes with the proband). Relatives were eligible if they were alive and resided in Denmark by age 30 years or in 1977, whichever came last (index date), for register coverage to identify T2DM in older generations. All relatives were followed from the index date until T2DM or end of follow-up (death, emigration from Denmark, or end of 2018). This multigenerational approach is in line with previous multigenerational register-based studies (Zhang et al., 2022).

Second, we used genetic data from the iPSYCH2015 sample to investigate associations between T2DM-PRS and psychiatric disorders. The iPSYCH2015 sample includes all cases with specific psychiatric disorders (ASD, ADHD, bipolar disorder, affective disorder, schizophrenia spectrum disorder, or postpartum depression) by the end of 2015 identified in a source population of all Danish-born singletons (1981–2008) with known mothers and residing in Denmark at their one-year birthday. Additionally, it includes a 3.1% population-representative subcohort formed by two randomly selected subcohorts from the same source population: (1) 2.0% selected in connection with iPSYCH2012 (birth cohort 1981–2005) and (2) 1.3% selected in connection with iPSYCH2015 (extended birth cohort 1981–2008) (Bybjerg-Grauholm et al., 2020). AN cases were identified from diagnoses by the end of 2016, as part of the Anorexia Nervosa Genetics
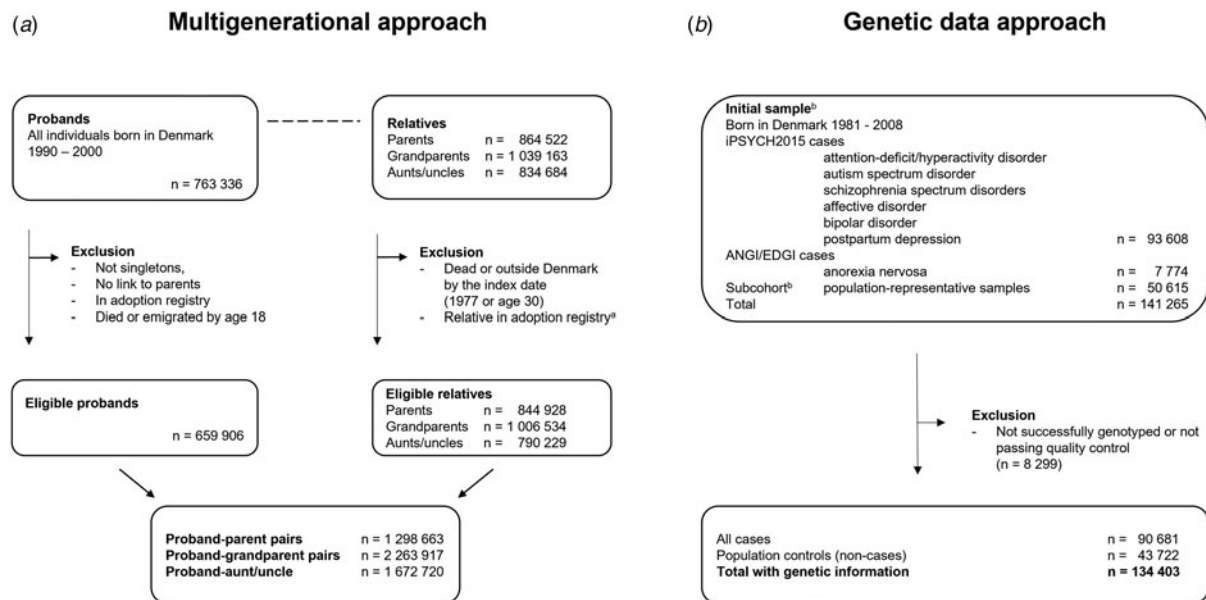
Figure 1. Flow charts of the study population included for analyses. (a) Multigenerational approach based on the entire Danish population. [a]Grandparents and aunts/uncles were excluded if parents of the proband was included in the adoption register, to minimize the potential inclusion of non-biological relatives. Similarly, aunts/uncles in the adoption register were not included. (b) Study population for the genetic approach based on data from the iPSYCH2015 case-cohort sample. [b]Groups are not mutually exclusive. Abbreviations: ANGI, Anorexia Nervosa Genetics Initiative; EDGI, The Eating Disorders Genetics Initiative; iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research.

Initiative (ANGI) and the Eating Disorder Genetics Initiative (EDGI) (Bulik et al., 2021; Thornton et al., 2018). The final study population included all successfully genotyped individuals from the iPSYCH2015 sample and AN cases and controls. Procedures for sampling, genotyping, and quality control are described elsewhere (Bybjerg-Grauholm et al., 2020; Pedersen et al., 2018).

Psychiatric disorders

For both study populations, we identified the following psychiatric disorders if they were registered as a primary or secondary diagnosis in the Danish Psychiatric Central Research Register: Any psychiatric disorders (ICD-10: F00-F99, ICD-8: 295–315), OCD, ASD, AN, other eating disorders (OED) including bulimia nervosa and eating disorders not otherwise specified, substance use disorders, schizophrenia spectrum disorders, MDD, anxiety disorders, ADHD, oppositional defiant disorder/conduct disorder (ODD/CD), and tic disorders (online Supplementary Table 1). These disorders were chosen according to our young proband cohorts (born 1990–2000 in multigenerational cohort and 1981–2008 in iPSYCH sample) thus targeting early-onset type of these disorders, e.g. early-onset schizophrenia. For the same reason, we did not include other typical adult-onset disorders such as personality disorder and bipolar disorder, which have a very low incidence before age 18 (Dalsgaard et al., 2019).

T2DM in relatives

Date of T2DM was defined as either a diagnosis of T2DM, a diabetic complication (ICD codes in online Supplementary Table 1) or having filled at least one prescription of an oral antidiabetic drug (Anatomical Therapeutic Chemical Classification code A10B), whichever appeared first in the registers. T2DM often develops in middle-aged and elderly individuals, and was here

identified in older relatives (parents, grandparents, and aunts/uncles) after age 30. This choice of age cut-off has shown an adequate discrimination between type 1 diabetes and T2DM (Shields et al., 2015), and the true incidence of T2DM before age 30 is known to be very low (Carstensen et al., 2020), Redemptions of metformin by women before age 40 were excluded, as the indication for antidiabetics in this group may have been other than T2DM (e.g. polycystic ovary syndrome).

Polygenic risk score for T2DM

A PRS for T2DM was generated using LDpred2-auto (Prive, Arbel, & Vilhjalmsson, 2020a) on GWAS summary statistics from a meta-analysis including ~16 million common genetic variants of 62 892 T2DM cases and 596 424 controls of European ancestry (Xue et al., 2018). SNPs were restricted to HapMap3 variants overlapping with the iPSYCH sample, resulting in 1 118 443 SNPs. LDpred2-auto is a Bayesian PRS method that does not require a validation dataset as it infers the PRS weights directly from the GWAS summary statistics. The calculated T2DM-PRS weights were then projected into the imputed genotypes of the iPSYCH data.

The Illumina PsychChip v1.0 Array was used for genotyping the iPSYCH2012 case-cohort sampled in 2012 and AN cases up to 2013, whereas the Illumina Global Screening Array was used for additional iPSYCH cases and controls sampled in 2015 and AN cases up to 2016. The T2DM-PRS was standardized based on weighted mean and standard deviation in the entire sample, with weights corresponding to the inverse of the selection probabilities (Bybjerg-Grauholm et al., 2020; Pedersen et al., 2018).

Statistical analysis

In the familial co-aggregation analyses, we performed Cox regression analysis to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between psychiatric disorders

(probands) and T2DM (relatives) among all possible proband-relative pairs for parent, grandparent, and uncle/aunt, respectively. This approach enabled us to account for the varying follow-up times of the relatives, while all probands were observed for a fixed time period until 18 years of age to study psychiatric disorders during childhood and adolescence and to keep a fixed exposure observation window for all probands. All analyses were adjusted for sex, age of the relative (as underlying time scale), and birth year of proband (continuous) and relative (given by calendar time and age). Calendar time (total period of 1977–2018) was split into five time periods at years 1995, 2005, 2012, 2016 with broader intervals for earlier calendar years due to lower incidence of psychiatric disorders and T2DM in relatives. In analyses of proband-grandparent pairs, the first period was further split into two periods at calendar year 1985. In all analyses, a cluster-robust (sandwich) estimator was used to calculate standard errors, to account for dependency between relatives.

Associations between T2DM-PRS (continuous and categorical in quintiles based on weighted iPSYCH sample) and psychiatric disorders were estimated as odds ratios (ORs) with 95% CI using logistic regression. For the categorical T2DM-PRS a test for linear trend was conducted. Analyses were adjusted for sex, birth year, observation time, and the first five principal components to account for population stratification, and genotyping chip to account for differences related to the genotyping. Analyses were weighted by the inverse selection probability (inverse of 3.3% and 1.3% for individuals born 1981–2005 and 2006–2008, respectively) to account for the oversampling of iPSYCH cases and retrieve estimates representative of associations in the general population.

Main analyses were conducted in Stata version 16 (StataCorp, College Station, Tex.) and figures generated using R, version 4.1.1. The software for inferring PRS and principal components were available in the R package bigsnpr (Prive, Luu, Blum, McGrath, & Vilhjalmsson, 2020b).

Secondary analyses

We conducted sex-specific analyses to explore potential sex differences in the observed associations. In the multigenerational cohort, analyses were stratified on (1) sex of the probands, (2) sex of the relatives, and (3) maternal/paternal relatives (grandparents and aunts/uncles on mother's and father's side, respectively). As a different measure of association (in addition to the HRs), we calculated tetrachoric correlations adjusted for sex and birth year of proband and relatives. This was done by an extended structural equation modeling approach using OpenMx package in R as used in a previous register-based family study (Du Rietz et al., 2021). Tetrachoric correlations should be interpreted as the correlation between the underlying liabilities, assumed normally distributed under the liability-threshold model (Neale & Cardon, 1992).

In the iPSYCH sample, we repeated the main PRS analyses for males and females and also restricted follow-up until age 18 to mimic the observation period for psychiatric disorders in the multigenerational approach. Further, we conducted a sensitivity analysis restricting the sample to individuals of European ancestry, to evaluate the robustness of results. This restriction was based on robust Mahalanobis distances of the principal components using the dist_ogk function of the R package bigutilsr (Prive et al., 2020b). Finally, as studies have demonstrated that both T2DM and psychiatric disorders, particularly ADHD, genetically correlate with body mass index (BMI) (Fanelli et al., 2022; Zammarchi, Conversano, & Pisanu, 2022), we assessed the potential confounding or mediating role of BMI genetic liability by repeating the main PRS analyses including as a covariate a polygenic score for BMI based on a GWAS on 700 000 individuals (Yengo et al., 2018). Similarly, as a proxy of genetic susceptibility to low socioeconomic status, we included as a covariate a polygenic score for educational attainment based on a GWAS conducted in 766 345 European-descent individuals (Lee et al., 2018).

Results

Multigenerational familial co-aggregation

We identified 1 298 663 proband–parent pairs, 2 263 917 proband–grandparent pairs, and 1 672 720 proband–aunt/uncle pairs, which were included for analysis. In total, 659 906 unique probands were included in the study (Fig. 1). Among these, 63 615 (9.6%) were diagnosed with at least one psychiatric disorder before age 18 years, where the most common psychiatric disorders in females were MDD, ADHD, and anxiety disorders, and in males ADHD, ASD, and substance use disorders. Among the included relatives, the proportion with T2DM increased with higher age; 47 793 (5.7%) of the parents, 147 452 (14.6%) of grandparents, and 42 312 (5.4%) of aunts/uncles had T2DM (online Supplementary Table 2). Having at least one psychiatric diagnosis before age 18 years was associated with an increased rate of T2DM in relatives, with a stronger association in parents (HR = 1.38, 1.35–1.42), than in grandparents (HR = 1.14, 1.13–1.15) and aunts/uncles (HR = 1.19, 1.16–1.22). A similar pattern of results was seen for several disorders including ASD, schizophrenia spectrum disorder, MDD, anxiety disorders, and ADHD, and associations for ODD/CD were particularly strong (parents: HR = 1.74, 1.62–1.88, grandparents: HR = 1.29, 1.24–1.34, aunts/uncles: HR = 1.39, 1.29–1.50) (Fig. 2). Evidence of higher rates in first-degree compared to second-degree relatives was less clear for substance use disorders and tic disorders. An inverse association with T2DM in relatives was observed for AN (parents: HR = 0.70, 0.62–0.80, grandparents: HR = 0.91, 0.86–0.95, aunts/uncles: HR = 0.83, 0.75–0.93). Parental T2DM also was significantly less frequent in individuals with OCD, whereas no significant associations were observed for OED (Fig. 2).

Secondary analyses stratified on sex of the proband showed overall similar patterns for females and males, though with stronger links to parental T2DM for any psychiatric disorders and for ASD in males. For remaining disorders, no clear proband sex-differences were seen (online Supplementary Figure 1). For analyses stratified by relatives' sex and by maternal/paternal relatives (online Supplementary figure 2a and 2b, respectively), stronger associations were seen for female relatives (particularly mothers v. fathers) and for maternal relatives. These patterns were clear for the overall category of any psychiatric disorders, but not consistent across all specific disorders. Tetrachoric correlations mimicked patterns of main results, with nominally largest correlation estimates among proband-parent pairs (−0.06 for AN and 0.09 for ODD/CD, online Supplementary Table 3).

Genetic liability to T2DM

For the PRS analyses, a total of 134 403 individuals with genetic information were included. In this case-cohort sample, 94 336 have had at least one psychiatric diagnosis (Fig. 3).

One standard deviation increase in T2DM-PRS was associated with an increased risk for any psychiatric disorder (OR = 1.11,

Proband psychiatric disorder and T2DM in relatives

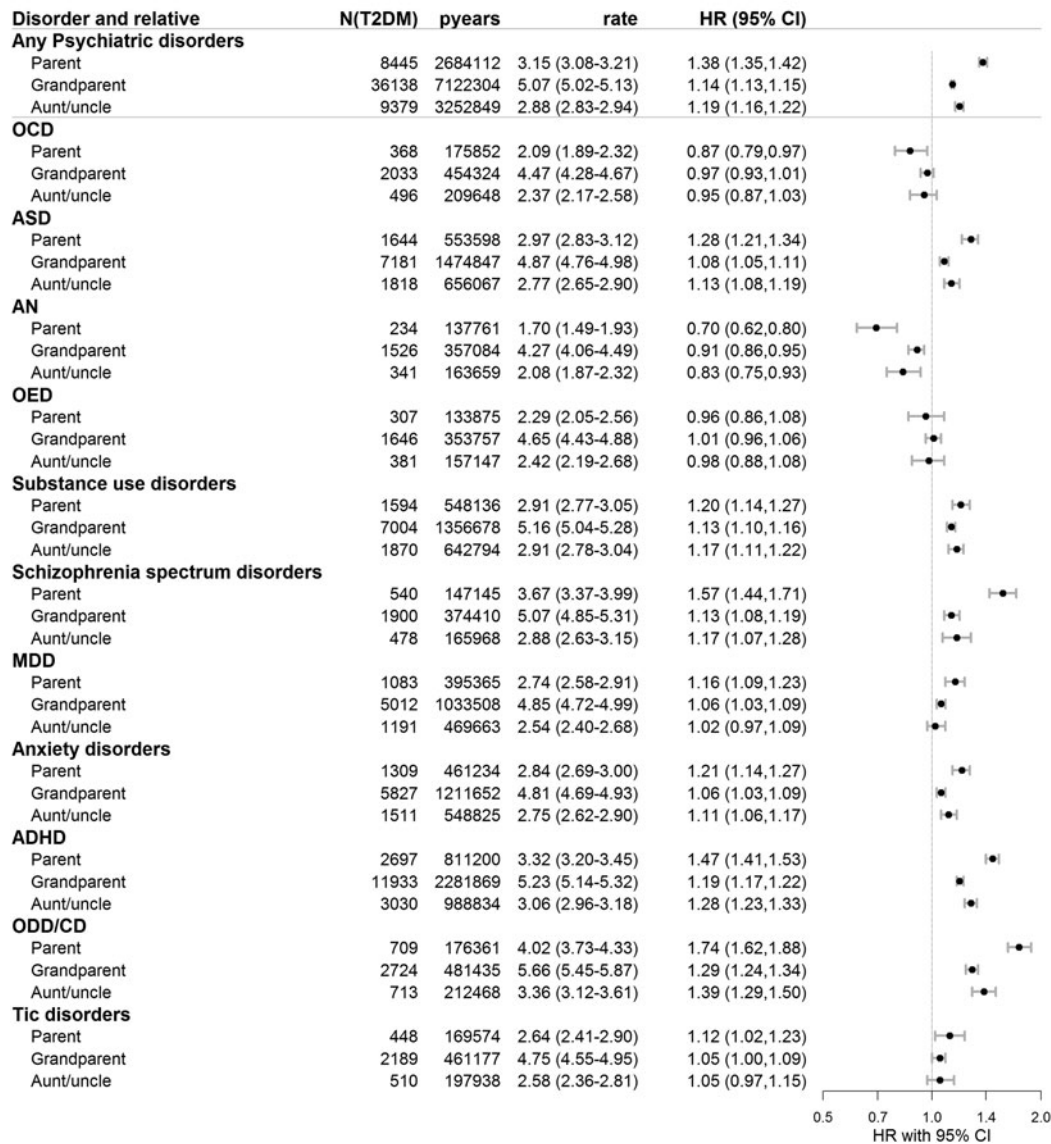| Disorder and relative	N(T2DM)	pyears	rate	HR (95% CI)
Any Psychiatric disorders				
Parent	8445	2684112	3.15 (3.08-3.21)	1.38 (1.35,1.42)
Grandparent	36138	7122304	5.07 (5.02-5.13)	1.14 (1.13,1.15)
Aunt/uncle	9379	3252849	2.88 (2.83-2.94)	1.19 (1.16,1.22)
OCD				
Parent	368	175852	2.09 (1.89-2.32)	0.87 (0.79,0.97)
Grandparent	2033	454324	4.47 (4.28-4.67)	0.97 (0.93,1.01)
Aunt/uncle	496	209648	2.37 (2.17-2.58)	0.95 (0.87,1.03)
ASD				
Parent	1644	553598	2.97 (2.83-3.12)	1.28 (1.21,1.34)
Grandparent	7181	1474847	4.87 (4.76-4.98)	1.08 (1.05,1.11)
Aunt/uncle	1818	656067	2.77 (2.65-2.90)	1.13 (1.08,1.19)
AN				
Parent	234	137761	1.70 (1.49-1.93)	0.70 (0.62,0.80)
Grandparent	1526	357084	4.27 (4.06-4.49)	0.91 (0.86,0.95)
Aunt/uncle	341	163659	2.08 (1.87-2.32)	0.83 (0.75,0.93)
OED				
Parent	307	133875	2.29 (2.05-2.56)	0.96 (0.86,1.08)
Grandparent	1646	353757	4.65 (4.43-4.88)	1.01 (0.96,1.06)
Aunt/uncle	381	157147	2.42 (2.19-2.68)	0.98 (0.88,1.08)
Substance use disorders				
Parent	1594	548136	2.91 (2.77-3.05)	1.20 (1.14,1.27)
Grandparent	7004	1356678	5.16 (5.04-5.28)	1.13 (1.10,1.16)
Aunt/uncle	1870	642794	2.91 (2.78-3.04)	1.17 (1.11,1.22)
Schizophrenia spectrum disorders				
Parent	540	147145	3.67 (3.37-3.99)	1.57 (1.44,1.71)
Grandparent	1900	374410	5.07 (4.85-5.31)	1.13 (1.08,1.19)
Aunt/uncle	478	165968	2.88 (2.63-3.15)	1.17 (1.07,1.28)
MDD				
Parent	1083	395365	2.74 (2.58-2.91)	1.16 (1.09,1.23)
Grandparent	5012	1033508	4.85 (4.72-4.99)	1.06 (1.03,1.09)
Aunt/uncle	1191	469663	2.54 (2.40-2.68)	1.02 (0.97,1.09)
Anxiety disorders				
Parent	1309	461234	2.84 (2.69-3.00)	1.21 (1.14,1.27)
Grandparent	5827	1211652	4.81 (4.69-4.93)	1.06 (1.03,1.09)
Aunt/uncle	1511	548825	2.75 (2.62-2.90)	1.11 (1.06,1.17)
ADHD				
Parent	2697	811200	3.32 (3.20-3.45)	1.47 (1.41,1.53)
Grandparent	11933	2281869	5.23 (5.14-5.32)	1.19 (1.17,1.22)
Aunt/uncle	3030	988834	3.06 (2.96-3.18)	1.28 (1.23,1.33)
ODD/CD				
Parent	709	176361	4.02 (3.73-4.33)	1.74 (1.62,1.88)
Grandparent	2724	481435	5.66 (5.45-5.87)	1.29 (1.24,1.34)
Aunt/uncle	713	212468	3.36 (3.12-3.61)	1.39 (1.29,1.50)
Tic disorders				
Parent	448	169574	2.64 (2.41-2.90)	1.12 (1.02,1.23)
Grandparent	2189	461177	4.75 (4.55-4.95)	1.05 (1.00,1.09)
Aunt/uncle	510	197938	2.58 (2.36-2.81)	1.05 (0.97,1.15)

Figure 2. HRs and 95% CIs for the association between psychiatric disorders in probands and T2DM in relatives. Estimates 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. Number of individuals with T2DM, person-years and rates (per 1000 person-years) are calculated among pairs, where the proband has the psychiatric disorder of interest. Note that all numbers correspond to number of proband-relative pairs included in the analyses (parent: 1 298 663; grandparent: 2 263 917; aunt/uncle: 1 672 720) and not unique individuals. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; CI, confidence interval; HR, hazard ratio; N, number; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; ODD/CD, oppositional-defiant disorder/conduct disorder; pyears, person years; OED, other eating disorders; T2DM, type 2 diabetes mellitus.

1.08–1.14). Strongest associations were seen for ODD/CD (1.29, 1.16–1.45) and ADHD (1.24, 1.19–1.29), and an inverse association was seen for AN (OR = 0.88, 0.83–0.93). Statistically significant associations were also found for ASD, substance use disorders, schizophrenia spectrum disorders, and MDD. Comparing quintiles of T2DM-PRS, the most clear statistically significant dose-response relationships ($p < 0.001$) were observed for AN (inverse), ADHD, ODD/CD, ASD, and MDD (Fig. 4). We found no clear evidence of an association between T2DM-PRS and OCD, OED, anxiety disorders, or tic disorders in any of the analyses.

Sex-specific associations were slightly stronger in males than in females for the overall category of any psychiatric disorder, but this pattern was not reflected across all disorders. The associations with T2DM-PRS remained significant for both males and females for the following disorders: AN, schizophrenia spectrum disorder, MDD, ADHD, and ODD/CD. The association in relation to ASD was only seen in males, whereas in case of substance use disorders an association was only seen in females (online Supplementary Table 4). PRS-analyses, restricted to individuals with 18 years of follow-up, did not alter the overall conclusion, and most estimates were only slightly attenuated. However, a marginally statistically significant *inverse* association was seen for tic disorders before age 18 years (OR = 0.85, 0.74–0.99). Restricting to individuals of European ancestry did not change the estimates remarkably (online Supplementary Table 5).

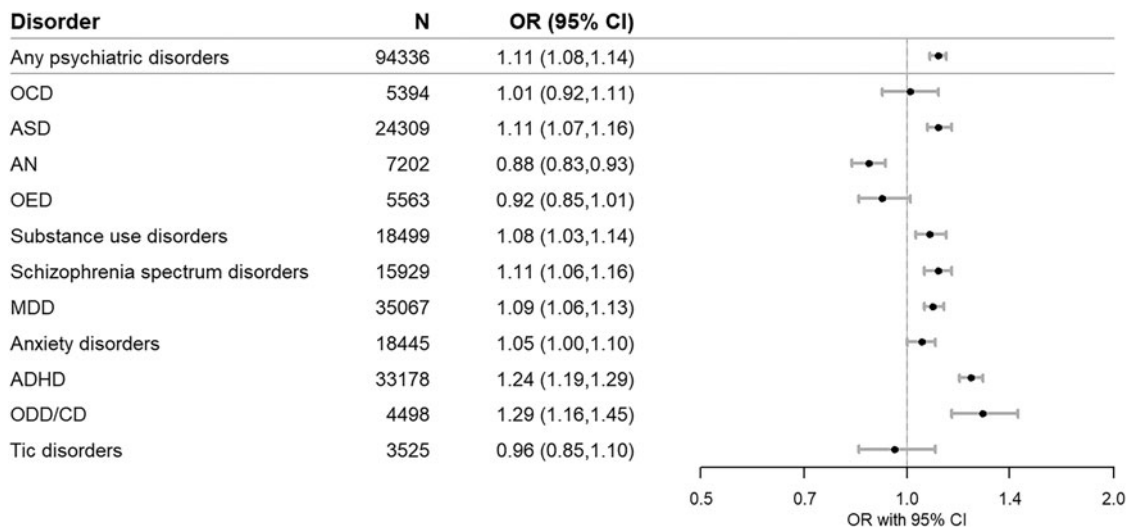## T2DM-PRS and psychiatric disorders

Disorder	N	OR (95% CI)
Any psychiatric disorders	94336	1.11 (1.08,1.14)
OCD	5394	1.01 (0.92,1.11)
ASD	24309	1.11 (1.07,1.16)
AN	7202	0.88 (0.83,0.93)
OED	5563	0.92 (0.85,1.01)
Substance use disorders	18499	1.08 (1.03,1.14)
Schizophrenia spectrum disorders	15929	1.11 (1.06,1.16)
MDD	35067	1.09 (1.06,1.13)
Anxiety disorders	18445	1.05 (1.00,1.10)
ADHD	33178	1.24 (1.19,1.29)
ODD/CD	4498	1.29 (1.16,1.45)
Tic disorders	3525	0.96 (0.85,1.10)

OR with 95% CI: 0.5 0.7 1.0 1.4 2.0

Figure 3. ORs and 95% CIs for associations between T2DM-PRS and the occurrence of a psychiatric disorder. 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. N = 134 403. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; CI, confidence interval; N, number; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; ODD/CD, oppositional-defiant disorder/conduct disorder; OR, odds ratio; OED, other eating disorders; T2DM, type 2 diabetes mellitus.

After adding a polygenic score for BMI to the main model, the OR for any psychiatric disorder was attenuated from 1.11 (1.08–1.14) to 1.07 (1.04–1.10) but remained statistically significant. Attenuation of the estimates was observed for ADHD (from 1.24 to 1.15) and for ODD/CD (from 1.29 to 1.15). For AN, the estimate also attenuated from 0.88 (0.83–0.93) to 0.94 (0.88–1.00), i.e. only marginally statistical significance. After including a polygenic score for educational attainment in the model, the overall estimate attenuated to 1.08 (1.05–1.10), again with the largest influence for ADHD and ODD/CD and the association between T2DM-PRS and AN remained statistically significant (see online Supplementary Table 6).

Discussion

Utilizing multigenerational epidemiological and genetic data, we found clear evidence of a shared familial risk between a broad range of psychiatric disorders and T2DM. We demonstrated familial co-aggregation with T2DM for nearly all psychiatric disorders, except for OCD and OED. Similarly, higher genetic liability to T2DM, as indexed by a T2DM-PRS, was significantly associated with most psychiatric disorders, except for OCD, OED, anxiety disorders, and tic disorders. In both analytical approaches, we found the strongest positive association for ADHD and ODD/CD and an inverse association of T2DM with AN.

The observed familial co-aggregation between T2DM and psychiatric disorders supports the hypothesis that shared familial risk factors contribute to the association between them. Cross-generational associations were stronger in first-degree relatives (parents) compared with second-degree relatives (grandparents and aunts/uncles); estimates clearly attenuated with decreased level of genetic relatedness for the following disorders: ASD, schizophrenia spectrum disorders, MDD, anxiety disorders, ADHD, ODD/CD, and inversely for AN. Shared familial risks include both genetic and environmental factors, which may affect both the risk for T2DM (in relatives) and risk for psychiatric disorders (in probands). Other mechanisms behind the observed familial co-aggregation of disorders have been suggested, including familial co-aggregation of psychiatric disorders and direct associations with T2DM, likely mediated through changes in socioeconomic and lifestyle factors (Zhang et al., 2022).

Our findings of stronger associations for first- than second-degree relatives for MDD and anxiety disorders are in line with the findings of a Swedish familial co-aggregation study of early-onset T2DM and these disorders, where they similarly found a stronger association in full-siblings (sharing 50% of their segregating genes) than in cousins (sharing 25% of their segregating genes), the latter not reaching statistical significance for MDD (Liu et al., 2022). A Taiwanese study found that a family history of T2DM was correlated with a family history of major psychiatric disorders with ORs around 1.2 for schizophrenia, MDD, and bipolar disorder, but found no evidence of association between T2DM-PRS and these disorders (Su et al., 2022). A study with data from the UK Biobank did not find T2DM-PRS to be associated with AN but found some evidence for inverse associations between PRSs for anthropometric measures (such as obesity and BMI) and AN. Furthermore, they found T2DM-PRS to be associated with binge-eating disorder but not bulimia nervosa. Another UK Biobank study found no statistically significant evidence for associations between a T2DM-PRS and self-reported mental health symptoms including psychosis, addiction, depression, and anxiety (Rodrigue et al., 2022).

The findings of the present study, based on both familial co-aggregation and PRS analyses, add new insights into the clustering of psychiatric disorders on the familial/genetic and genomic levels. Our findings support recent findings of a positive genetic correlation between T2DM and ADHD and negative genetic correlations with T2DM for both OCD and AN, which have also been demonstrated for other insulin- and metabolic-related traits (Fanelli et al., 2022; Watson et al., 2019). The lack of evidence for positive genetic associations between T2DM and OCD, AN and OED indicate that known within-individual,
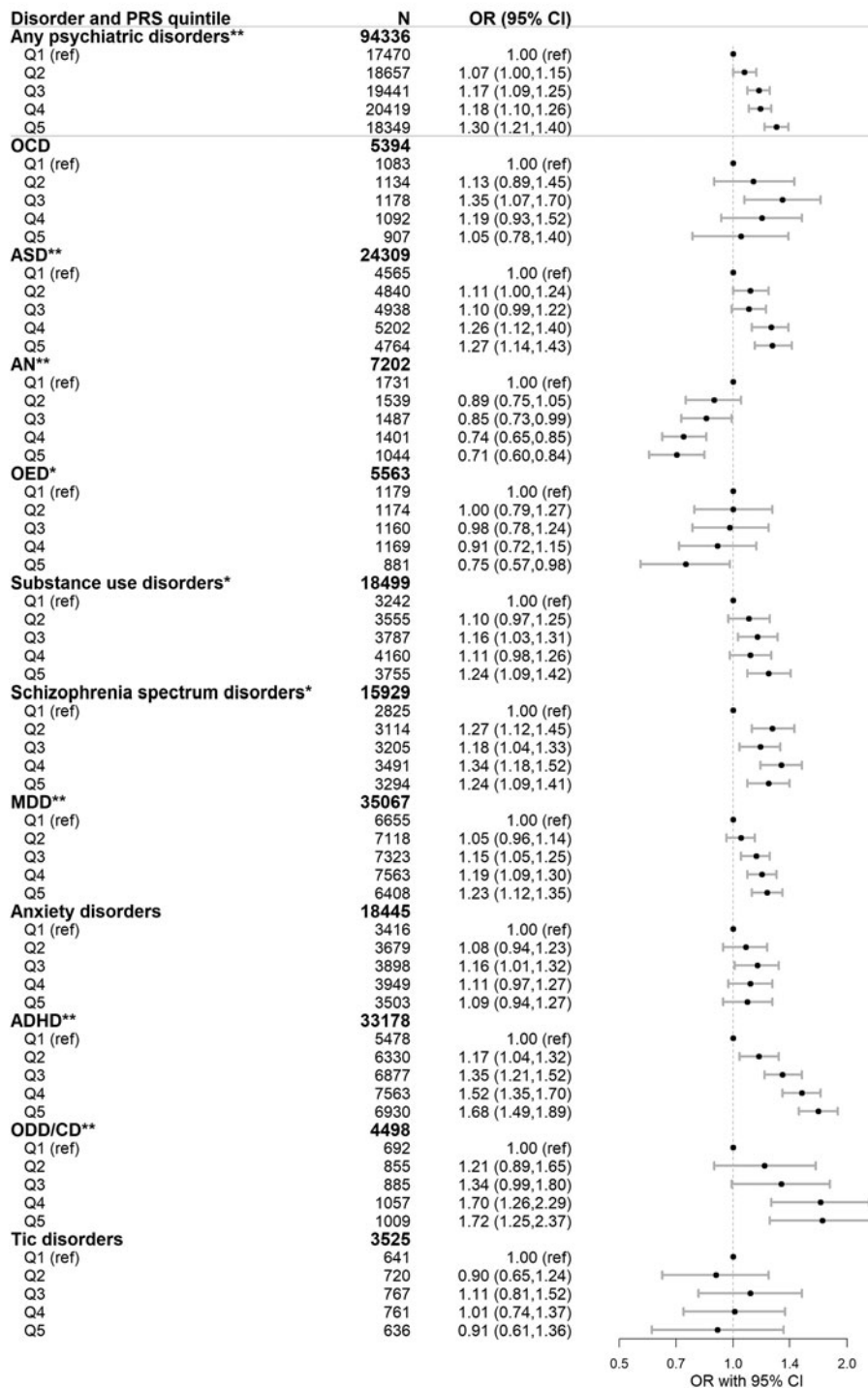
Figure 4. ORs and 95% CIs for associations between the T2DM-PRS divided into quintiles (Q1–Q5) and the occurrence of a psychiatric disorder. Analyses were adjusted for sex, calendar year of birth, the first five principal components, genotyping chip, and observation time, and weighted by the inverse selection probabilities to account for the oversampling of iPSYCH cases. N = 134 403. *$p < 0.05$, **$p < 0.001$, test for linear trend. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; CI, confidence interval; N, number; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; ODD/CD, oppositional-defiant disorder/conduct disorder; OR, odds ratio; PRS, polygenic risk score; T2DM, type 2 diabetes mellitus.

phenotypic associations may be explained by psychiatric comorbidities, shared environmental and lifestyle mediating or confounding factors rather than shared familial factors. In contrast, ADHD shows both genetic links to T2DM as well as clear within-individual associations (Garcia-Argibay et al., 2023). Less evidence exists for the link between T2DM and ODD/CD, but a Finnish study also found T2DM as well as other types of diabetes in mothers to be significantly associated with the combined group of offspring ADHD and conduct disorder (Kong, Nilsson, Brismar, Gissler, & Lavebratt, 2020). Nevertheless, the well-

established overlap of ODD/CD with ADHD on both the phenotypic and genetic level may partly explain our findings (Bachmann et al., 2024; Demontis et al., 2021).

In the present study, we did not observe clear sex differences in estimates for females and males for the specific psychiatric disorders. However, in the overall analyses, estimates indicated stronger familial co-aggregation of T2DM and psychiatric disorders for female and maternal relatives than for male and paternal relatives, suggesting that maternal-specific effects (e.g. in-utero and birth-related exposures) and greater sharing of environment between

children and mothers may contribute to the familial associations, beyond genetic factors. Other potential contributing explanations include mitrochondrial DNA transmission (Poulton et al., 2002), impaired reproductive health in males with T2DM (Ye et al., 2021), and misclassification of registration of the biological father (Schmidt et al., 2014).

Our findings of familial co-aggregation and associations between a T2DM-PRS and psychiatric disorders suggest that there is an important genetic component in the underlying biological mechanisms explaining the relationship between T2DM and most psychiatric disorders. Replication of both within-individual, cross-generational, and genetic analyses is needed particularly for disorders OCD, AN, and OED to further elucidate potential underlying mechanisms in the overlap with T2DM.

Strengths and limitations

This study has several strengths, including individual-level linkage of multigenerational families and other nationwide registry information and the genotyped iPSYCH sample. These unique data sources minimize the risk for selection bias both with respect to the multigenerational design where we use a population-based sample, in which T2DM was assessed in older generations with higher T2DM prevalence, and in the iPSYCH sample which includes all psychiatric cases diagnosed in specialist care in Denmark as well a representative subsample of the general population as compared to other large data sources such as the UK Biobank (Fry et al., 2017). The prevalences of T2DM and psychiatric disorders in the present study is similar to previously estimated age- and cohort-specific risks in the general Danish population (Carstensen et al., 2020; Dalsgaard et al., 2019). Our study also has some limitations. First, the observational study design was chosen to investigate shared familial risk, i.e. timing of disorders was not considered. This means that our findings should not be interpreted as causal, and different study designs should be applied to further establish causality. Importantly, we found a very similar pattern of association across relatives both when hazard ratios and tetrachoric correlations were used. Second, information on psychiatric disorders was obtained from clinical diagnoses given at hospitals. Thus, our findings may not generalize to individuals in the general population who do not seek help or who are treated only in primary care. On the other hand, these data allowed for identifying important patient groups who received specialist treatment, i.e. with high specificity. For T2DM, we included information on antidiabetic prescriptions and thereby captured individuals who had not (yet) received a hospital diagnosis. Third, we did not adjust for potential confounders including socioeconomic factors (e.g. income and education) due to poor data coverage in the registers for the grandparent generation; therefore we cannot disregard residual confounding when analyzing the associations. Similarly, we did not adjust for obesity due to poor coverage, or BMI, for which data was not available. Both variables can potentially mediate the associations with T2DM; we therefore performed supplementary analyses using polygenic scores for BMI and educational attainment. Those analyses showed that such variables only partly explained the association between T2DM-PRS and psychiatric disorders.

Conclusions

This study showed clear evidence of shared familial risks of psychiatric disorders and T2DM. Most psychiatric disorders were associated with increased familial risk for T2DM and increased genetic liability to T2DM. By different approaches, ODD/CD and ADHD showed the strongest positive associations with T2DM. In addition, our results reveal inverse associations for AN with familial T2DM and genetic liability to T2DM. Our study suggests that part of the comorbidity is explained by shared familial risks. The underlying mechanisms still remain largely unknown and future research should aim at further disentangling genetic and environmental contributions to this shared familial risk.

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