PRIME

Prevention and Remediation of Insulin Multimorbidity in Europe

H2020 – 847879

D1.4.– Report on familial co-aggregation of insulin-related morbidities and compulsivity disorders in a multi-generational nationwide cohort-study

Dissemination level	Public
Contractual date of delivery	31. March 2022
Actual date of delivery	30. March 2022
Type	Report
Version	1
Filename	PRIME_Deliverable Report_D1.4.
Workpackage	1
Workpackage leader	Søren Dalsgaard (AU)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847879. This report reflects only the author's views and the Commission is not responsible for any use that may be made of the information it contains.

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Abbreviations

PRIME	Prevention and Remediation of Insulin Multimorbidity in Europe
WP1	Work Package 1
T2DM	Type 2 diabetes mellitus
OCD	Obsessive-compulsive disorder
ASD	Autism spectrum disorder
ODD/CD	Oppositional defiant disorder / conduct disorder
ADHD	Attention deficit / hyperactivity disorder
N	Number
ATC	Anatomical Therapeutic Chemical Classification
IQR	Inter-quartile-range
95% CI	95% confidence interval
ICD	International Classification of Diseases
HR	Hazard ratio

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1. Executive Summary

In this population-based epidemiological study (Task 2 in PRIME WP1), we used nationwide register-data to estimate familial co-aggregation of diagnosis of a range of psychiatric disorders (in 662,490 probands) and T2DM (in 2,243,150 relatives of different genetic relatedness). For our analyses, we included of a large number of child-relative pairs in the analyses (N = 5,235,460 pairs in total).

We found that the relatives of children and adolescents diagnosed with a psychiatric disorder were at increased risk of T2DM. The association was strongest in 1st degree relatives (mothers: HR=1.5 (95% CI = 1.5-1.6), and fathers: 1.3 (1.2-1.3)), and lower in 2nd degree relatives (grandparents: HR=1.1 (1.1-1.2), and aunts/uncles: HR=1.2 (1.2-1.2)).

For most of the individual psychiatric disorders, we observed a similar pattern. However, for OCD, other (non-anoretic) eating disorders, and tic disorder we did not find clear associations with T2DM in relatives. For anorexia nervosa, we found inverse associations with T2DM in relatives, with HR=0.7 for both mothers and fathers.

Overall, we found that the estimates for the association between psychiatric disorders in probands and T2DM in relatives were attenuated with decreasing degree of genetic relatedness (higher estimates in 1st than in 2nd degree relatives). This suggest that psychiatric disorders and T2DM share some common genetic risk factors, and that the association is not merely explained by other common familial risks.

2. Deliverable report

As part of Task 2 in PRIME WP1, we aimed to perform epidemiological investigations to estimate familial co-aggregation of somatic and brain-related insulinopathies at population level. Type 2 diabetes mellitus (T2DM) often co-occur with psychiatric and neurological disorders and these associations are often bi-directional, as we have shown in Task 1 in WP1 in PRIME. Still, the underlying mechanisms for these associations are largely unknown. The bidirectionality we found previously suggests that the associations may not be due to a causal relationship, but likely is explained by other factors, including shared familial risks (environmental or genetic).

In a multigenerational study we have estimated the familial co-aggregation of psychiatric disorders (in probands) and T2DM (in parents, grandparents, and aunts/uncles), applying methods from genetic epidemiology. If the strength of an association correlates with the degree of relatedness (i.e. strongest associations in 1st degree relatives and lowest in 2nd degree relatives), this suggests that shared genetic risks explain part of the association.

Data sources

We accessed and merged data from the following registries, covering the entire population of Denmark: The Danish Civil Registration System (basic individual-level information, since 1968), the Danish National Patient Register (inpatient contacts since 1977, outpatient contacts since 1995), the Danish Psychiatric Central Research Register (inpatient contacts since 1969, outpatient contacts since 1995), and the Danish National Prescription Register (prescriptions from all Danish pharmacies since 1995). Links to relatives were obtained through the Danish Civil Registration System. Clinical diagnoses in Denmark were made according to the International Classification of Diseases, version 8 (ICD-8) until 1993, and version 10 (ICD-10) since 1994. We identified the first diagnosis of any psychiatric disorder as well as of specific psychiatric diagnoses (in probands) listed in Table 2. ICD-codes are presented in Table S1. T2DM (in relatives) was defined as a clinical diagnosis of T2DM, diabetic complications, (ICD-10: E11, O24.1, ICD-8: 250), or filling a prescription of an oral antidiabetic drug (ATC code A10B), after age 30.

Statistical analysis

We calculated HRs for the association between the disorder of interest in probands (observed until their 18th birthday) and T2DM in relatives. All relatives (parents, grandparents and aunts/uncles) were followed from their 30th birthday or 1977 (which ever comes last) until T2DM, death, emigration, or end of follow-up, December 31, 2018. Cox regression analysis with T2DM in relatives as the time-to-event outcome and using age of the relative as the underlying time scale, was chosen to account for the varying length of follow-up. Estimates were accompanied by 95% CIs based on a cluster-robust (sandwich) estimator to account for the repetition of individuals and non-independence within family clusters.

Results

Please note, that results have not yet been published. We plan to submit a paper entitled 'Familial co-aggregation of type 2 diabetes and psychiatric disorders – a multigenerational nationwide register-based study' to an international peer-reviewed psychiatric journal. Hence, the present report only describes our main findings and with a limited level of details. For example, numbers are rounded to nearest 10, to comply with regulations at Statistics Denmark.

We identified all children born in Denmark between January 1, 1990, and December 31, 2000 (N=736,340). For this study, we only included children who were singletons, had identifiable parents, were not adopted, did not emigrate from Denmark before age 18, and who were alive at age 18 years (N = 662,490). We included these children's parents, grandparents, and uncles and aunts (N = 2,243,150 relatives in total). This resulted in the inclusion of a large number of child-relative pairs in the analyses (N = 5,235,460 pairs in total).

For the number of relatives of different degree of relatedness and the number of specific child-relative pairs, please see Table 1. For the characteristics of probands and relatives, see Table 2.

Table 1: Number of relatives, number of probands with a relative, and number of pairs

Cohort	**Number of (unique) individuals**	**Number of probands with at least one relative**	**Number of proband-relative pairs**
Any relative	2,243,150	659,910	5,235,460
Parents	845,000	658,880	1,298,750
Grandparents	1,006,560	624,210	2,263,980
Uncles/aunts	790,230	587,670	1,672,730

Table 2: Characteristics of probands and relatives

Cohort		**All**
Probands	N	659,910
	Birth year, median (IQR)	1995 (1992-1998)
	Any psychiatric disorder	63,620
	OCD	3,960
	ASD	13,010
	Anorexia nervosa	3,050
	Other eating disorder	3,070
	Substance use disorder	12,610
	Schizophrenia spectrum disorder	3,510
	Major depressive disorder	10,710
	Anxiety disorder	10,710
	ADHD	20,090
	ODD/CD	4,410
	Tic disorder	4,000
Parents	N*	845,000
	T2DM, N	47,800
	Birth year, median (IQR)	1965 (1960-1969)
	Age at end of follow-up, median (IQR)	53 (49-58)
	Age at T2DM, median (IQR)	48 (42-54)
Grandparents	N*	1,006,560
	T2DM, N	147460
	Birth year, median (IQR)	1938 (1930-1944)
	Age at end of follow-up, median (IQR)	75 (68-81)
	Age at T2DM, median (IQR)	67 (59-73)
Uncles/aunts	N*	790,230

	T2DM, N	42320
	Birth year, median (IQR)	1965 (1960-1970)
	Age at end of follow-up, median (IQR)	53 (47-58)
	Age at T2DM, median (IQR)	48 (42-54)

*) Some relatives are included repeatedly for proband siblings and cousins. This is taken into account in the analyses. In this table, the unique number of relatives are included.

Familial co-aggregation and degree of relatedness

The relatives of children and adolescents diagnosed with a psychiatric disorder were all at increased risk of T2DM. We found an association for all the included degrees of relatedness and associations were strongest in mothers and attenuated with decreasing degree of genetic relatedness: Mothers: HR=1.5 (95% CI = 1.5-1.6), Fathers: 1.3 (1.2-1.3), Grandparents: 1.1 (1.1-1.2), Aunts/uncles: 1.2 (1.2-1.2). For most of the individual psychiatric disorders, a similar pattern was found. This includes the following disorders: ASD, SUD, Schizophrenia, Major depressive disorder, Anxiety, ADHD and ODD/CD, with largest effect sizes for T2DM in mothers ranging from HR=1.2 (SUD) to HR=1.8 (ODD/CD). No clear associations with T2DM in relatives were found for OCD, other (non-anoretic) eating disorders and tic disorder, and inverse associations were found for anorexia nervosa, HR=0.7 for both mothers and fathers.

3. Conclusion

Our findings indicate that psychiatric disorders and T2DM run in the same families, and that the two disorders share common familial risk factors. This may support the previously suggested concept of 'insulinopathies of the brain'. Overall, we found that the estimates for the association between psychiatric disorders in probands and T2DM in relatives were attenuated with decreasing degree of genetic relatedness (higher estimates in 1st than in 2nd degree relatives). This suggest that psychiatric disorders and T2DM share some common genetic risk factors, and that the association is not merely explained by other common familial (environmental) risk factors.

4. Supplementary material

Table S1: Diagnostic classification of T2DM and psychiatric disorders

	ICD-10	**ICD-8**
Any psychiatric disorder	F00-F99	295-315
OCD	F42	300.39
ASD	F84 (excl. F84.2-4)	299.00-299.03
Anorexia nervosa	F50.0, F50.1	306.50
Other eating disorder	F50 (excl. F50.0 and F50.1)	306.58, 306.59
Substance use disorder	F10-F19, F10 (alcohol), F12 (cannabis), F11, F13-16, F18-19 (other illicit drugs)	291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90, 304.x9
Early-onset schizophrenia spectrum disorder	F20-F29	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83
Major depressive disorder	F32-F33	296.09, 296.29, 298.09, 300.49
Anxiety disorder	F40.00-F41.19, F4200-F43.10, F93	300.09, 300.29, 300.39
ADHD	F90, F98.8	308.1
ODD/CD	F90.1, F91	308.03-06
Tic disorder	F95	306.29