PRIME

Prevention and Remediation of Insulin Multimorbidity in Europe

H2020 – 847879

D4.1. – Report on the genetic overlap between somatic and neurodegenerative brain insulinopathies and related traits

Dissemination level	Public
Contractual date of delivery	30. June 21
Actual date of delivery	31. May 21
Type	Report
Version	1
Filename	PRIME_Deliverable Report_D4.1
Workpackage	4
Workpackage leader	Janita Bralten (RUMC)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847879.

Author list

Organisation	Name	Contact information
Radboud University	Janita Bralten	Janita.Bralten@radboudumc.nl
Radboud University	Giuseppe Fanelli	Giuseppe.Fanelli@radboudumc.nl
Radboud University	Barbara Franke	Barbara.Franke@radboudumc.nl
Radboud University	Ward De Witte	Ward.DeWitte@radboudumc.nl
Groningen University	Hyun Ruisch	i.h.ruisch@umcg.nl
University of Bergen	Jan Haavik	Jan.Haavik@uib.no
Maastricht University	Veerle van Gils	v.vangils@maastrichtuniversity.nl
Maastricht University	Willemijn Jansen	Willemijn.Jansen@maastrichtuniversity.nl
Maastricht University	Stephanie Vos	Stephanie.Vos@maastrichtuniversity.nl
Uppsala University	Lars Lind	Lars.Lind@medsci.uu.se
Radboud University	Jan Buitelaar	Jan.Buitelaar@radboudumc.nl
Heidelberg University	Tobias Banaschewski	tobias.banaschewski@zi-mannheim.de
Aarhus University	Soren Dalsgaard	sdalsgaard@econ.au.dk
University of Bologna	Alessandro Serretti	alessandro.serretti@unibo.it
Radboud University	Nina Roth Mota	Nina.RothMota@radboudumc.nl
Radboud University	Geert Poelmans	Geert.Poelmans@radboudumc.nl

Abbreviations

WP4	Work Package 4
AD	Alzheimer's disease
ASD	Autism Spectrum Disorder
OCD	Obsessive-Compulsive Disorder
MetS	Metabolic Syndrome
T2DM	Type 2 Diabetes Mellitus
GWAS	Genome-Wide Association Study
SNP	Single Nucleotide Polymorphism
INSR	INSulin Receptor
CNS	Central Nervous System
mTOR	Mammalian Target Of Rapamycin
Aβ	β-amyloid
PI3K	phosphatidylinositol-3-kinase
AKT	protein kinase B
2hGlu	glucose levels 2 hours after an oral glucose challenge
Fins	Fasting insulin
LDSC	Linkage Disequilibrium Score Regression
GNOVA	GeNetic cOVariance Analyzer
BMI	Body Mass Index
FGlu	Fasting Glucose
HbA1c	glycated haemoglobin
HOMA-IR	homeostatic model assessment for insulin resistance
ADHD	Attention-Deficit Hyperactivity Disorder
AN	Anorexia Nervosa
BIP	BIPolar disorder
MDD	Major Depressive Disorder
SCZ	SChiZophrenia
TS	Tourette's Syndrome
QC	Quality Control
MSigDB	Molecular Database v7.1
KEGG	Kyoto Encyclopedia of Genes and Genomes
STX1A	syntaxin-1A
VAMP2	vesicle-associated membrane protein 2
CSK2	proprotein convertase subtilisin/kexin type 2
APOE	APOlipoprotein-E
HDL	high-density lipoprotein

Table of Contents

1. Executive Summary

In PRIME we are interested to explore the hypothesis that dysregulation of insulin plays a role in multimorbidity of somatic and brain based disorders. The prevalence of Alzheimer's disease (AD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) is higher among patients with somatic disorders that are related to insulin, like metabolic syndrome (MetS), obesity, and type 2 diabetes mellitus (T2DM). Dysregulation of insulin signalling has been implicated in these neuropsychiatric disorders, and shared genetic factors might partly underlie these observed comorbidities. In WP4 we investigated genetic overlap between AD, ASD, and OCD with MetS, obesity, and T2DM by estimating pairwise genetic correlations using the summary statistics of the largest available genome-wide association studies for these diseases. Stratified covariance analyses were performed to investigate the contribution of insulin-related gene-sets. In addition, novel brain-based "insulinopathies" were explored by estimating the genetic relationship of six additional neuropsychiatric disorders with nine insulin-related diseases/traits. Significant genetic correlations were found between ASD and MetS (r_g=0.115, p=0.002), OCD and MetS (r_g=-0.315, p=3.9e-8), OCD and obesity (r_g=-0.379, p=3.4e-5), and OCD and T2DM (r_g=-0.172, p=3e-4). Stratified analyses showed negative genetic covariances between ASD and MetS/T2DM through gene-sets comprising insulin signalling and/or insulin processing genes, and between AD/OCD and MetS/T2DM through an insulin receptor recycling gene-set (p<6.17e-4). Significant genetic correlations with insulin-related phenotypes were also found for anorexia nervosa, attention-deficit/hyperactivity disorder, major depression, and schizophrenia (p<6.17e-4). Our findings highlight genetic overlap of somatic insulin-related phenotypes with multiple neuropsychiatric disorders, pointing to a shared aetiology. These results represent a starting point for a new research line on "insulinopathies" of the brain, which may support the development of more effective/tolerated treatment strategies for neuropsychiatric disorders.

2. Deliverable report

After running the analyses and interpreting our findings we wrote down our findings in an academic paper, which we submitted to the journal "American Journal of Psychiarty" on March 4 2021 and received back at April 26 2021 with feedback. We have incorporated this feedback and will now submit the paper to Molecular Psychiatry. **The paper is entitled "Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders."**

The results we found in this study are described below

Input datasets

A description of the samples (with sample sizes, number of cases and controls, and the derived effective sample size) included in the analyses is provided in the table below.

	Consortium	Author	Year	Sample size	Cases	Controls
AD		Jansen et al.	2019	455.258	71.880	383.378
ASD	PGC	Grove et al.	2019	46.350	18.381	27.969
OCD	OCGAS/IOCDF-GC	OCGAS/IOCDF-GC	2018	9.725	2.688	7.037
MetS		Lind	2019	291.107	59.677	231.430
Obesity		Watanabe et al.	2019	244.890	9.805	235.085
T2DM	DIAGRAM	Mahajan et al.	2018	898.130	74.124	824.006

Pairwise genome-wide genetic correlations between neuropsychiatric disorders characterised by cognitive inflexibility and insulin-related somatic diseases and traits

After running genetic correlation analyses using LD-score (LDSC) and correcting for multiple testing, our primary analyses highlighted a positive genetic correlation between ASD and MetS (r_g=0.115, p=0.002), as well as negative genetic correlations between OCD and MetS (r_g=-0.315, p=3.9e-8), OCD and obesity (r_g=-0.379, p=3.6e-5), and OCD and T2DM (r_g=-0.172, p=3e-4). Our analyses did not reveal a significant genetic correlation between any of the considered somatic phenotypes and AD after correction for multiple testing, strongest genetic correlations were with MetS and T2DM (r_g=0.166, p=0.018, and r_g=0.175, p=0.013, respectively).

Our secondary analyses for insulin-related somatic traits (i.e., 2hGlu, BMI, FGlu, FIns, HbA1c, HOMA-IR), found OCD to be significantly negatively genetically correlated with BMI (r_g=-0.284, p=2.57e-11), but neither AD nor ASD showed significant correlations with the traits.

Genetic covariance of AD, ASD, and OCD with MetS, obesity and T2DM stratified by insulin-related gene-sets

Stratified genetic covariance analyses were performed on selected insulin-related gene-sets to investigate if insulin gene-sets might show genetic correlations that would not be detected on a genome-wide scale. After Bonferroni correction, stratified GeNetic cOVariance Analyser (GNOVA) analyses highlighted significant negative genetic covariance between AD and MetS through the Reactome INSR recycling gene-set (ρ_g=-2e-4, p=1e-5), between ASD and T2DM through the Reactome insulin processing gene-set (ρ_g=-5e-4, p=2.8e-4), as well as between ASD and MetS through the Biocarta, KEGG, and PID insulin signalling pathways (ρ_g=-4.1e-4, p=2e-5; ρ_g=-0.002, p=3e-5; ρ_g=-8e-4, p=1e-5, respectively). OCD showed negative genetic covariance with MetS and T2DM through the Reactome INSR recycling gene-set (ρ_g=-0.001, p=1e-5, and ρ_g=-0.001, p=1.6e-4, respectively). No genetic covariance between AD, ASD, OCD and obesity was found at the gene-sets level.

In search of new brain "insulinopathies": LDSC-based genetic correlation analyses for additional neuropsychiatric disorders and insulin-related diseases and traits

Secondary analyses were also extended to other neuropsychiatric disorders (i.e., Attention Deficit Hyperactivity Disorder (ADHD), Anorexia Nervosa (AN), Bipolar Disorder (BIP), Major Depressive Disorder (MDD), Schizophrenia (SCZ), and Tourette's Syndrome (TS)). Significant genetic correlations between the aforementioned disorders and insulin-related diseases/traits were found for ADHD, AN, MDD, and SCZ.

3. Conclusion

The hypotheses in PRIME are partly confirmed by our first genetic analyses in PRIME. Indeed, there is a genetic correlation between autism and OCD with somatic disorders that are linked to insulin. Additionally, for AD we see a genetic correlation when we restrict our analyses specifically to insulin genes. Next to the confirmation of our hypotheses we used our analyses also to investigate if novel brain-based 'insulinopathies' exist. Our results highlight that a genetic link with somatic disorders is also present for the psychiatric disorders anorexia nervosa, attention-deficit/hyperactivity disorder, major depression, and schizophrenia.