ABSTRACTS

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(1) HORMONAL IMBALANCE AND RISK OF MULTIPLE SCLEROSIS IN WOMEN: FINDINGS FROM A NATIONWIDE COHORT STUDY AND GENOME-WIDE CROSS-TRAIT ANALYSIS

Yuan Jiang [1], Carolyn Cest [2], Qianwen Liu MD [1], Sara Oberg [3], Elaine Kingwell [4,5], Pernilla Strid [1], Klementy Shchetynsky [1], Tomas Olsson [1], Ingrid Kockum [1], Xia Jiang [1], Ali Manouchehrinia [1]

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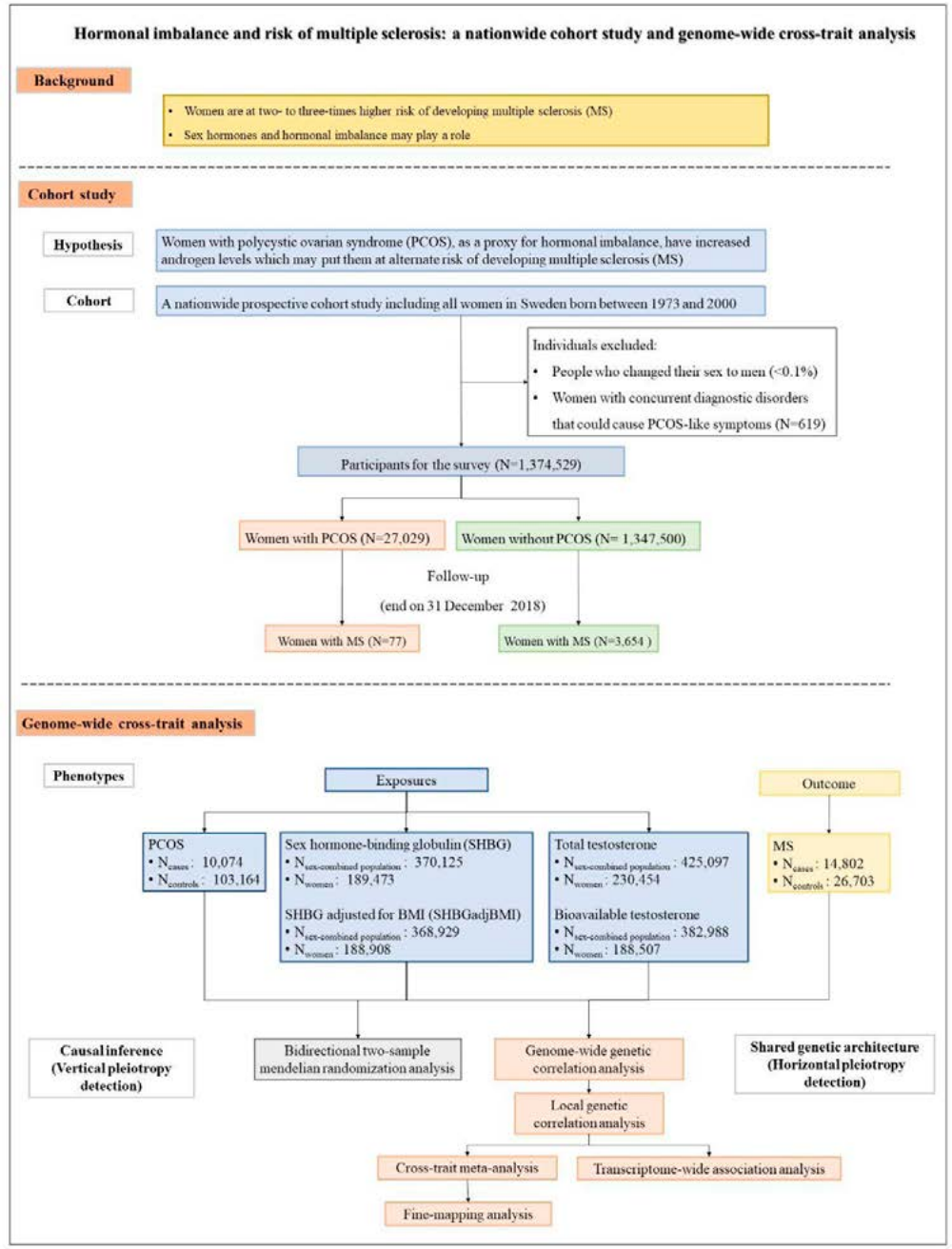
Background Multiple sclerosis (MS) disproportionately affects women, for which sex hormones are the presumed cause. Here we hypothesize that hormonal imbalance, proxied by polycystic ovary syndrome (PCOS), will be associated with the risk of MS.

Methods Using data from a prospective cohort including all women in Sweden born in 1973-2000, we analyzed the effect of PCOS on MS onset with Cox regressions. Leveraging GWAS(s) summary statistics of PCOS (Ncases = 10,074; Ncontrols = 103,164), sex hormone-binding globulin (SHBG, N = 189,473-188,908), testosterone (N = 188,507-230,454), and MS (Ncases = 14,802; Ncontrols = 26,703), we further performed a genome-wide cross-trait analysis to infer causal relationships and to investigate the shared genetic architecture.

Results We included 1,374,529 women, of whom 27,029 (2.0%) had been diagnosed with PCOS. During the follow-up period, 77 (0.3%) with PCOS and 3,654 (0.3%) without PCOS were diagnosed with MS. After adjusting for calendar year of birth and body mass index, we found no association between PCOS and MS development (HR = 0.92, 95%CI = 0.74-1.16). The absence of phenotypic correlation was confirmed by Mendelian randomization analysis, where genetically predisposed PCOS or genetically predicted level of sex hormones did not confer a causal effect on MS (all P-values > 0.05). When exploring horizontal pleiotropy, we identified several genetic regions that play a role in the risk of both traits. Furthermore, we identified 19 independent pleiotropic SNPs for SHBG (crude or BMI-adjusted) with MS, and 11 for testosterone (total or bioavailable) with MS, of which 50% were supported by fine-mapping analysis or replicated by transcriptome-wide association study.

Conclusion We did not find a causal role of hormonal imbalance in MS development. Nonetheless, the shared genetic loci between sex hormones and MS provided biological insights.



(2) SHARED GENETIC ARCHITECTURE BETWEEN SCHIZOPHRENIA AND ANOREXIA NERVOSA: A CROSS-TRAIT GENOME-WIDE ANALYSIS

Zheng-An Lu[1], Alexander Ploner[1], Andreas Birgegård[1], Cynthia M. Bulik[1,2,3], Sarah E. Bergen[1]

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Schizophrenia (SCZ) and anorexia nervosa (AN) are two severe and highly heterogeneous disorders showing substantial familial co-aggregation. Genetic factors play a role in both, and a significant SCZ-AN single nucleotide polymorphism-based genetic correlation has been observed (rg=0.19-0.29). However, little is known about the shared genetic etiology between SCZ and AN. Using summary statistics from recent large genome-wide association studies on SCZ (Ncases = 53,386) and AN (Ncases = 16,992), MiXeR was employed to quantify the polygenic overlap between SCZ and AN. A conditional/conjunctional false discovery rate (FDR) framework was adopted to boost genomic loci discovery for these disorders individually and identify loci jointly associated with both disorders. Furthermore, a bidirectional two-sample Mendelian randomization (MR) analysis was performed to estimate the causal bidirectional relationship between SCZ and AN. We observed a cross-trait pleiotropic enrichment and considerable polygenic overlap (Dice Coefficient = 62.2%) between SCZ and AN. The proportion of variants with concordant effect directions among all variants influencing SCZ and AN was estimated to be 69.9%. Leveraging the overlapping genetic associations , we identified 7 novel loci for AN and 70 novel loci for SCZ at conditional FDR < 0.01. At conjunctional FDR < 0.05, we identified 12 loci jointly associated with two disorders, implicating several genes, such as: CELSR3, RELN, CYP7B1, TSNARE1, NCAM1 and SOX5. The genes are particularly expressed in the cerebellum and pituitary, and GO enrichment analysis implicated synapse organization, protein kinase inhibitor activity, hexosaminidase activity, and kinase inhibitor activity. The MR analysis suggested a two-way causal relationship (SCZ on AN: odds ratio = 1.13, 95%CI: 1.06-1.19, P < 0.001; AN on SCZ: odds ratio = 1.15, 95% confidence interval: 1.05-1.27, P = 0.003) between the two disorders. This study provides novel insights into the relationship between SCZ and AN by revealing their shared genomic loci and offers a window into the biological mechanisms underlying the two disorders.

(3) USING COMMON GENETIC VARIANCE TO STUDY COPY NUMBER VARIATIONS (CNVS) ROLE IN COMPLEX HUMAN TRAITS

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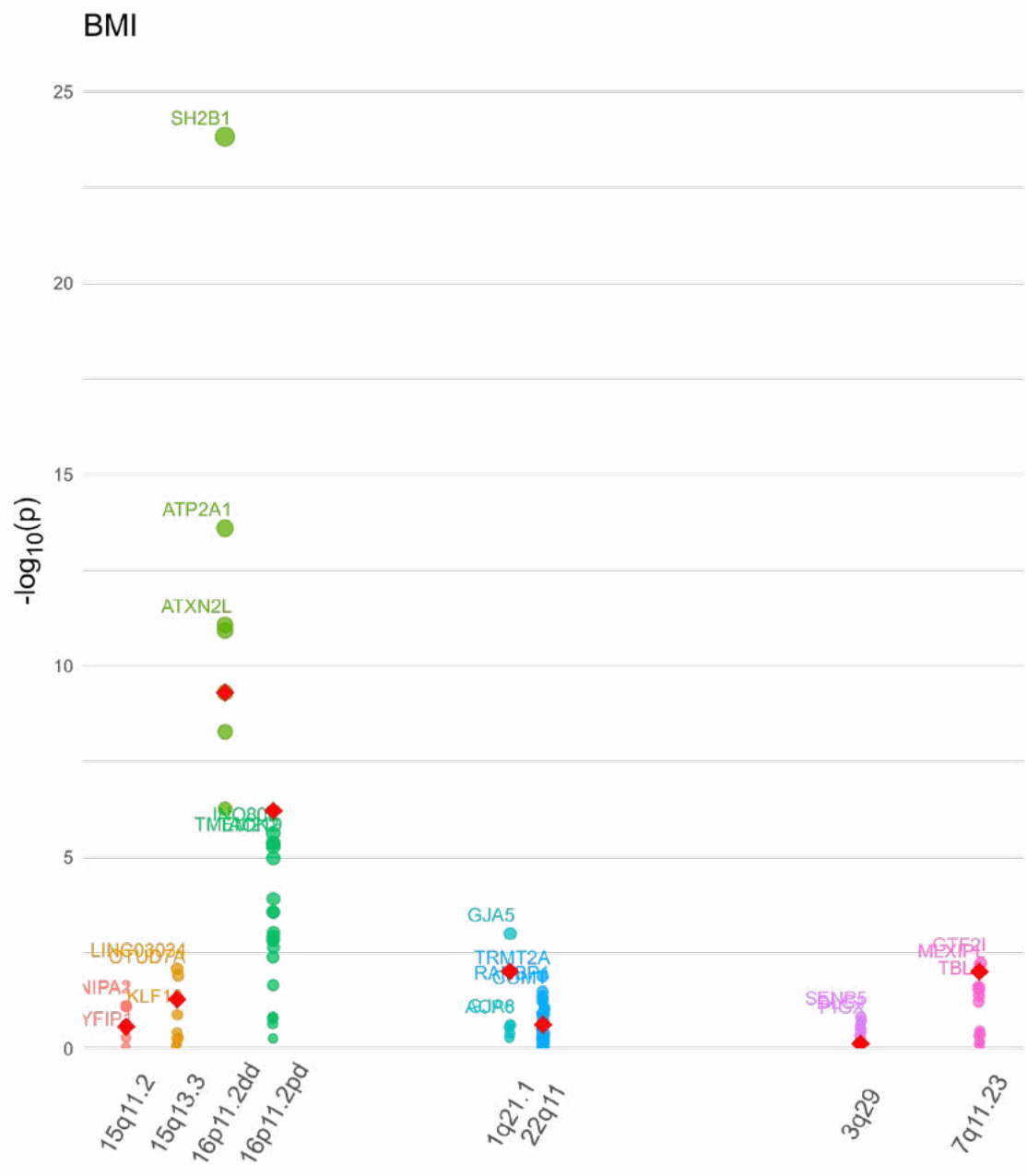
Purpose Copy Number Variations (CNVs) are variations in the number of copies of a genomic region, often covering multiple genes. CNVs play a significant role in population diversity and are associated with human complex traits and diseases, influencing different functional body systems. Individual pathogenic CNVs are rare, impeding research through the low availability of data from carriers. To better understand the mechanisms through which CNVs impact human health, common variations in the genomic region of the CNV, available from large samples, could be used as a proxy.

Methods We used common genetic variants to study CNVs' influence on complex traits. We aggregated the effects of variants in genomic regions with known pathogenic CNVs (1q21.1, 3q29, 7q11.23, 15q11.2, 15q13.3, 16p11.2 distal deletion (16p11.2dd), 16p11.2 proximal deletion (16p11.2pd), 22q11), using MAGMA software applied to GWAS summary statistics of mental disorders, somatic disorders, anthropomorphic measures, and cognition. Then we compared the obtained test statistics from the CNV region analyses with those obtained from 10000 random genomic regions of the same size. We further performed gene-based analysis for individual genes in the abovementioned CNV regions.

Results We demonstrated a link between complex human traits and common genetic variation in genomic regions containing known pathogenic CNVs. After comparing the regions with the random regions of the same size across the genome, five of the CNV regions had significant associations at least with one trait. Two CNV regions showed widespread effects on the traits under investigation: 16p11.2dd CNV was associated with body mass index (BMI), alcohol use disorder, cannabis use, educational attainment and intelligence; 16p11.2pd CNV was associated with BMI, Alzheimer's disease, autism spectrum disorder (ASD), bipolar disorder, and schizophrenia.
Upon comparison of the significance of the whole CNV region with the significance of the specific genes in that region, two distinct patterns were observed: 1) cumulative value of separate genes, resulting in the higher significance of the whole region than of the particular genes (16p11.2pd and BMI on Figure 1) or 2) higher significance of the specific genes that account for the association of the whole region (16p11.2dd and BMI on Figure 1). These patterns should be investigated separately to unravel the biological mechanisms of their association with complex traits.
The gene-based analysis for individual genes resulted in 1) there are genes in the region that were significant for multiple traits; 2) there were genes that were significant only for one of the traits, for example, the SPN gene for Alzheimer's disease and C16orf54 gene for ASD in 16p11.2pd. The genes that had a significant association with more than one trait participate in crucial cell functions, such as ion binding, autophagy, cell homeostasis or calcium transfer. However, it is the genes that had a significant association with only one of the traits that should be studied in detail due to the specificity of this association for a particular trait.

Conclusion We showed that a novel approach to studying CNVs, by aggregating over common genetic variation in the corresponding genomic regions independent of carrier status, enables biological insight. Making a bridge from the whole CNV region to the genes inside it to the biological mechanisms involved in complex traits can contribute to a better understanding of the CNV-related syndromes and, in the future, to new effective therapeutic interventions.



(4) RARE COPY NUMBER VARIATION IN ADDISON'S DISEASE

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Autoimmune Addison's disease (AAD), or primary adrenocortical insufficiency, is a rare but

Table 1. Rare CNVs frequency distribution by interval size in cases vs. controls

				Frequency		Association	
CN	CNVs length	CNVs Cases [1182]	CNVs Controls [3810]	Cases	Controls	OR (95% CI)	*P*
DELs	50KB_100KB	435	1298	0.37	0.34	1.13 (0.98-1.29)	0.09
	100KB_200KB	260	919	0.22	0.24	0.89 (0.76-1.04)	0.13
	200KB_500KB	102	323	0.09	0.09	1.02 (0.81-1.29)	0.87
	500KB_1000KB	17	65	0.01	0.02	0.84 (0.49-1.44)	0.53
	> 1000KB	**13**	**10**	**0.011**	**0.003**	**4.23 (1.85-9.66)**	0.0002
DUPs	50KB_100KB	297	1050	0.25	0.28	0.88 (0.76-1.02)	0.01
	100KB_200KB	204	614	0.17	0.16	1.09 (0.91-1.29)	0.35
	200KB_500KB	157	488	0.13	0.13	1.04 (0.86-1.26)	0.67
	500KB_1000KB	48	150	0.04	0.04	1.03 (0.74-1.44)	0.85
	> 1000KB	15	65	0.013	0.017	0.74 (0.42-1.30)	0.30

(5) GENOME-WIDE ASSOCIATION STUDY REVEALS A LOCUS IN ADARB2 GENE FOR COMPLETE FREEDOM FROM HEADACHE

Isa Amalie Olofsson [1,2], Ragnar P. Kristjansson [2], Ida Callesen [2], Olafur Davidsson [3], Bendik Winsvold [4,5,6], Henrik Hjalgrim [3], Sisse R. Ostrowski [7,8], Christian Erikstrup [9], Mie Topholm Bruun [10], Ole Birger Pedersen [11], Kristoffer S. Burgdorf [12], Karina Banasik [12], Erik Sørensen [7], Christina Mikkelsen [7], Maria Didriksen [7], Khoa Manh Dinh [9], Susan Mikkelsen [9], International Headache Genetic Consortium, DBDS Genomic Consortium, Søren Brunak [12], Henrik Ullum [13], Mona Ameri Chalmer [2], Jes Olesen [2], Lisette J. A. Kogelman [2] & Thomas Folkmann Hansen [2]

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Purpose Headache disorders are the most common disorders of the nervous system. Yet, 4% of the Danish population have never experienced headache. The etiology of complete freedom from headache is not known. To assess genetic variants associated with complete freedom from headache, we performed the first genome-wide association study of individuals who have never experienced a headache.

Methods The discovery cohort included 63,992 Danish adults (2,998 individuals with complete freedom from headache and 60,994 controls) of Northern European ancestry originating from the Danish Blood Donor Study Genomic Cohort. Complete freedom from headache was defined based on the question “Do you believe that you never ever in your whole life have had a headache?”. The question had a “Yes/No” answer. All who answered “Yes” were classified as individuals with complete freedom from headache and all who answered “No” were classified as controls. The replication cohort included 3,395 Danish adults (175 individuals with complete freedom from headache and 3,220 controls) from the Danish Blood Donor Study Genomic Cohort. There was no overlap between the discovery and replication cohort.
Genome-wide association analysis was performed using a generalized linear mixed model. Annotation of genome-wide significant loci, tissue expression analysis and MAGMA gene-set enrichment analysis were performed using FUMA. Phenome-wide association analyses were conducted on genome-wide significant loci using >5000 human traits from the GWAS Catalog.
SNP heritability was estimated using restricted maximum likelihood analysis. We estimated genetic correlation between complete freedom from headache and migraine using LD Score Regression with the summary statistics from the most recent migraine meta-GWAS.
The polygenic risk score for migraine was calculated for the entire discovery cohort using LDpred2 based on summary statistics from the most recent migraine meta-GWAS. A logistic regression model was used to predict complete freedom from headache.

Results We discovered a genome-wide significant association of the intronic variant rs7904615[G] in ADARB2 (OR=1.20 [1.13–1.27], p=3.92x10-9). In the replication the lead SNP did not reach statistical significance (p=0.157), however, the direction of its effect was replicated (OR=1.21 [0.93–1.59]). Six out of seven genome-wide significant SNPs in the risk locus in LD (r2>0.6) with the lead SNP (rs7904615), were replicated. SNP heritability for complete freedom from headache was 3.71% (SE=3.05, p=0.11) on the liability scale.
All genome-wide significant SNPs mapped to the ADARB2 gene, both based on positional and eQTL mapping. None of the ADARB2 SNPs were previously associated with any of the >5,000 human traits in the GWAS Catalog. ADARB2 is preferentially expressed in the brain.
Participants with CFH had a lower polygenic burden of migraine than controls (OR=0.76 [0.75–0.80], p=3.67×10-42). Genetic correlation showed a negative genetic correlation with migraine (rg=-0.73, p=4.65x10-5).

Conclusions In conclusion, we show that complete freedom from headache has a genetic component, and we suggest that ADARB2 is involved in complete freedom from headache. The gene encodes an RNA-editing enzyme expressed in the brain, primarily in inhibitory neurons. The genomic locus was not associated with any headache disorders. The low PRS for migraine, together with the negative genetic correlation with migraine, might suggest a shared biology or indicate the existence of a biological continuum of susceptibility to headache. Further studies are needed before ADARB2 can be proven a gene contributing to protection from headache.

(6) POLYGENIC RISK SCORES ENHANCE ONSET PREDICTION FOR 7/18 DISEASES WHEN ADDED TO MODELS WITH ENVIRONMENTAL AND CLINICAL RISK FACTORS

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Background/Objectives Polygenic Risk Scores (PRSs) have emerged as a promising tool to guide the screening and treatment of complex diseases. However, systematic comparisons with non-genetic risk factors are lacking. In this work, we studied the ability of PRSs to predict the onset of 18 diseases in FinnGen R8 (N=342,499). We compared PRSs with the phenotypic predictors age, sex, education, region of birth, general morbidity risk (Charlson index, CCI) and Phenotype Risk Scores (PheRSs), capturing disease risk from electronic health records (EHR). Additionally, we replicated the comparison for 5/18 diseases in the UK Biobank (UKBB).

Methods We set up individual studies for the 18 diseases. A single study consisted of an exposure (1999-2009), a washout (2009-2011), and an observation period (2011-2019). Eligible individuals cannot have the selected disease of interest inside a disease-free period, which ranges from birth until the beginning of the observation period. We then defined the case and control status based on the diagnoses in the observation period and calculated the phenotypic scores on the exposure period. We trained disease-specific PheRSs on a training set, using elastic net models, incorporating up to 287 diagnoses from EHR between the years 1999 to 2009 as predictors. The PRSs were calculated using MegaPRS and the latest publicly available genome-wide association study summary statistics. We then fitted separate Cox proportional hazards models for each disease on a test set to predict disease onset during the observation period.

Results In FinnGen, the model's predictive ability (c-index) with all predictors ranges from 0.57 for Acute Appendicitis to 0.83 for Atrial Fibrillation. For 12/18 diseases in FinnGen and 4/5 diseases in the UKBB, integrating the PRSs significantly increases our ability to predict disease onset compared to a baseline model with age and sex. For 7/12 of these diseases in FinnGen and 4/5 in the UKBB, the PRSs still add information on top of the non-genetic predictors education, region of birth, CCI, and PheRS. Adding the PRSs and non-genetic data to the baseline model significantly increases the c-index for 17/18 diseases in FinnGen and 4/5 diseases in the UKBB. In FinnGen, we achieve the greatest c-index increase for Rheumatoid Arthritis, Breast Cancer, and Type 2 Diabetes, with increases of 0.09 (0.07-0.11 95% CI), 0.08 (0.07-0.1 95% CI), and 0.08 (0.07-0.09 95% CI), respectively. In the UKBB, we gain the greatest increase for Prostate and Breast Cancer, with increases of 0.12 (0.11- 1.15 95% CI) and 0.08 (0.07-0.09 95% CI), respectively.

Conclusion Overall, both PRSs and PheRSs add predictive power over commonly used predictors - such as age, sex, CCI, and education. However, whether the PRSs or the phenotypic predictors perform better depends on the disease of interest. Overall, the PRSs outperform the PheRSs for most of the 18 diseases and enhance onset prediction for many diseases when added to a model with non-genetic environmental and clinical risk factors. Because of a training set overlap for the PRSs of many endpoints in the UKBB, we currently lack the power to compare the c-index estimates in the two biobanks. However, we aim to replicate these findings in more biobanks as part of the INTERVENE project.

Grant References: ERC Horizon 2020 grant No. 101016775.

(7) A MAP OF GENETIC AND PHENOTYPIC ASSOCIATIONS ACROSS MALE REPRODUCTIVE PHENOTYPES

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Male infertility is a common, complex disease, affecting ~7-10% of men, and manifesting in diverse phenotypes ranging from morphological and functional abnormalities in sperm to severe spermatogenic impairment, in which few or no sperm are produced by the testis. Epidemiological data indicates that male infertility is often not an isolated condition, and it is not only a concern related to failed fatherhood. The accumulated evidence shows clearly that male infertility and overall health are interconnected. Recent research has revealed that many of the molecular pathways and mechanisms involved in male reproductive traits are shared with chronic diseases such as diabetes, heart disease, and cancer. Therefore, understanding the underlying causes of male infertility and finding ways to improve overall male reproductive health can advance reproductive health outcomes and help identify and prevent other health issues. Here, we carry out the most extensive effort to map the genetic background of phenotypes related to male reproductive health and provide an atlas of genetic and phenotypic correlations.

In a joint analysis of three large population-based biobanks (EstBB, FinnGen and UKBB) we perform a genome-wide association study (GWAS) meta-analysis of up to 532,376 men across 53 phenotypes defined using International Classification of Disease 10 (ICD-10) classification and encompassing diagnoses related to cancers of the reproductive tract and diseases of the genitourinary system. In addition to ICD-10 codes, 12 EstBB lab measurements were used in the analyses. Besides annotating the GWAS findings from individual phenotypes, we estimated the heritability of analysed phenotypes. Altogether, our analyses identify 143 genome-wide significant ($p<5 \times 10^{-8}$) variants, including numerous novel findings, many of which tag coding variants. We explored the genetic correlations across phenotypes using the LDScore framework and thus provide the first large-scale map of shared genetic architecture for male reproductive health phenotypes with several estimated pairwise genetic correlations. To compare genetic and phenotypic associations, we also analysed associations amongst the studies reproductive diagnoses using a logistic regression framework adjusted for year of birth and 10 genetic principal components. Overall, we found the genetic and phenotypic correlations to be quite similar and reflecting shared biological background.

In conclusion, our work represents the largest effort to comprehensively characterize and map the genetic determinants of different male reproductive health-associated diagnoses.

(8) A DNA METHYLATION STUDY OF COMMON AND SPECIFIC TREATMENT EFFECTS OF THREE ANTIPSYCHOTICS IN THE TREATMENT OF PSYCHOSIS

Jonelle D. Villar [1,2], Anne-Kristin Stavrum [1,2], Letícia Spíndola [1,2], Tetyana Zayats [3,4,5], Ingrid Melle [6], Ole A. Andreassen [6], Stéphanie Le Hellard [1,2]

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Background Antipsychotic (AP) medication is prescribed to alleviate symptoms of psychosis in schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD). Epigenetic studies have previously revealed altered DNA methylation (DNAm) patterns associated with APs. Many of these studies, however, fail to distinguish treatment effects of polypharmacy from specific effects of monotherapy [1]. Furthermore, the specific DNAm patterns associated with these disorders are not separated from the general treatment effects of these medications. Developing models that differentiate the DNAm patterns associated with psychosis from pharmacological treatment effects are lacking. In Norway, quetiapine, olanzapine, and risperidone are among the top 5 prescribed APs. We aim to identify DNAm signatures that are specific to each of the three medications or common among them.

Method Patients were recruited through the TOP Study (Thematically Organised Psychosis, Oslo, Norway). European patients diagnosed with SCZ, BPD, and MDD adhering to antipsychotic monotherapy (serum values > 0) or medication-free patients were selected. Methylation data derived from peripheral blood samples were assessed genome-wide using the Illumina 850K EPIC array. Differentially methylated positions (DMPs) were identified using limma [2]. For the common effects, the serum values from medicated patients (n=131) were regressed against methylation values (beta-values). For the specific effects, methylation values from patients on monotherapy were compared with medication-free patients (MF): quetiapine vs. MF (n=155), olanzapine vs. MF (n=217), and risperidone vs. MF (n=153). The statistical model was corrected for age, sex, smoking score, estimated cell-type composition, diagnosis, and technical batch effects. All analyses were performed using R Statistical Software (v4.2.2; R Core Team, 2021).

Results For the common effects, two DMPs were identified: cg23075732 (p-value=2.57e-08, q-value=0.02, annotated to ACVR1) and cg12129848 (p-value=6.38e-08, q-value=0.02, unannotated). No significant DMPs were identified for the specific effects. Additional analyses are ongoing to identify differentially methylated regions (DMRs), Gene Ontology (GO) terms, and pathway analysis. Results will be presented at NSHG-PM workshop in June 2023.

Discussion The quantitative analysis of serum values in the common effects model adjusted for patient-specific factors known to influence peripheral AP concentration. One DMP (cg23075732) was associated with Activin A receptor, type I (ACVR1), shown to be enriched in neurogenesis-related pathways and significantly associated with hippocampal volume [3]. Furthermore, an association is reported between alterations in neurogenic cells in the hippocampus and psychiatric disorders [4]. As shown in Figure 1, DNAm levels for cases are significantly lower compared to controls. The difference between the lowest levels, MF vs. controls, may suggest an association with psychosis at this DMP, while the DNAm levels of the 3 APs are marginally higher, suggestive of an AP effect. For the specific effects, we expect to see DNAm patterns associated with AP when medicated patients are compared to MF patients.

Conclusion Identification of the common and specific DNAm patterns of APs may distinguish AP effects from psychosis. Effective pharmacological treatment for psychosis, and eventually precision medicine in psychiatry, will require this knowledge.

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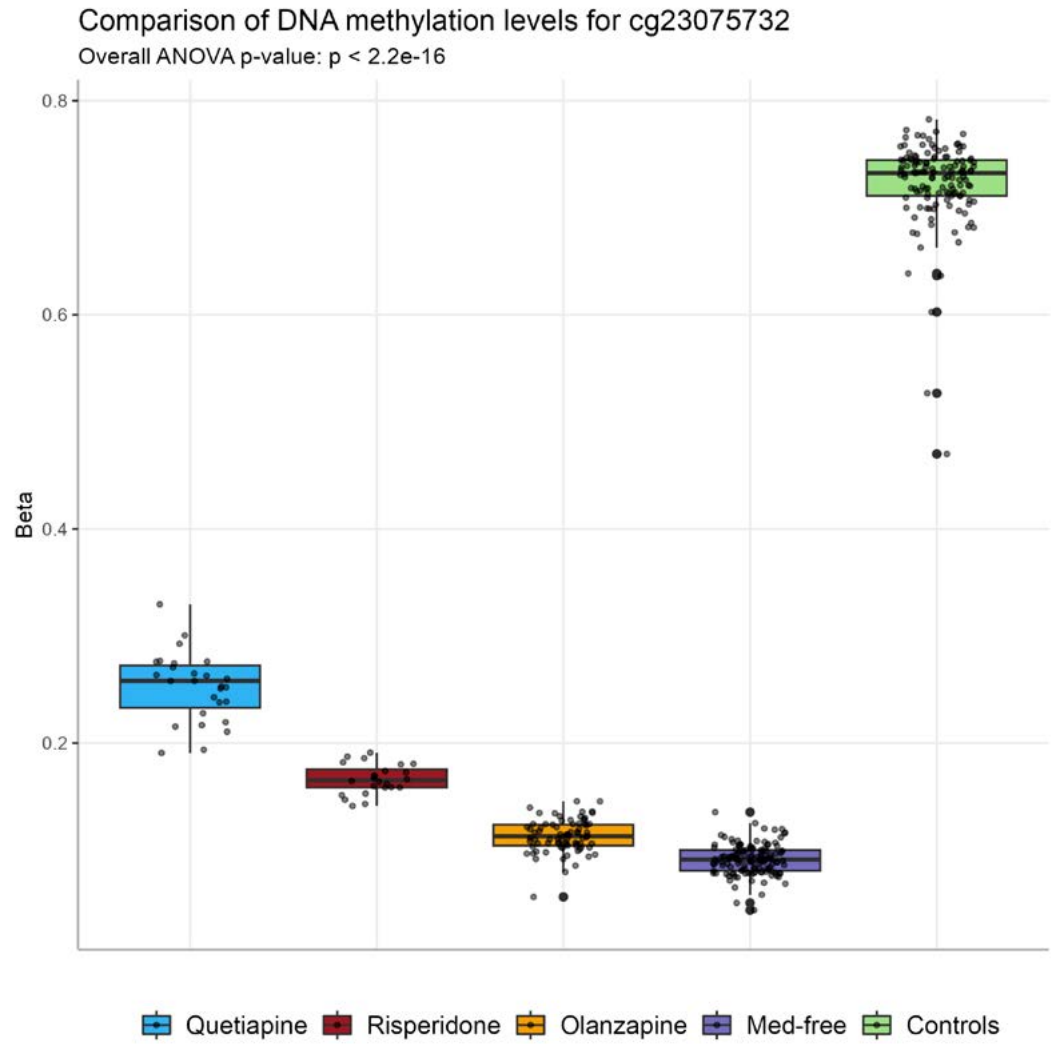

(9) INTEGRATING A CHAT-BASED DOCTOR'S APPOINTMENT TO KARDIOKOMPASSI ENCOURAGES PREVENTIVE ACTION IN INDIVIDUALS WITH ELEVATED RISK OF CORONARY ARTERY DISEASE

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Purpose There is a growing interest in translating polygenic risk scores to clinical practice. Previous studies have shown that communicating genetic risk information for coronary artery disease (CAD) promotes positive health behaviour including motivating people to contact medical doctor. We studied how returning CAD risk information based on both traditional and genetic risk factors through a simple smartphone application and allowing for an app-based consultation of clinician motivates for preventive actions.

Methods The Genna study included 1,060 middle-aged individuals (59.2 % women, age 40–60) who were customers of Mehiläinen Oy, a private provider of health care in Finland. Eligible individuals had at least one of the following self-reported risk factor for CAD: body mass index > 27, being a smoker or hypertension (systolic blood pressure > 150 mg). A CAD risk analysis incorporating polygenic and clinical risk factors was returned to the participants through a smartphone application with the opportunity to discuss their results with a doctor through a chat-based interactive interface. We compared the likelihood of seeking care in the current study to that in a similar study, (the GeneRISK study, N = 5,330, 62 % women, mean age 56) in which the participants had no opportunity for a chat-based consultation.

Results Of the 1060 participants, 147 persons (13.8 %) contacted a medical doctor after having received their personal risk report, 121 of which did so through the digital clinic interface. Participants at high CVD-risk were more likely to seek care than those at low risk (OR 2.13; 95 % CI 1.02 - 4.48 p = 0.045). Compared to the GeneRISK study, the mobile application platform increased the odds of contacting doctor (OR 2.85; 95 % CI 2.20 - 3.69 p = 1.7e-15, adjusted for age, sex, reported risk and smoking status). A similar effect was observed when restricting the analysis to people at high risk (OR of Genna 2.67, 95 % CI 1.41 - 5.06 p = 0.0027, adjusted for age and sex). All participants believed that both genetic and lifestyle factors affect the risk of CAD. 91 % believed that clinical doctors and 52 % that health care professionals other than doctors know how to utilize genetic risk information in their care.

Conclusions We used a simple, mobile framework for communicating a personalized CAD risk analysis and contacting medical doctor in one app to motivate preventive actions. Our findings support the clinical utility of the combined polygenic risk score and traditional risk factor model for CAD to be used for screening in middle-aged people.

(10) COVID-19 AND RISK OF MENTAL HEALTH PROBLEMS: A MENDELIAN RANDOMIZATION STUDY USING DATA FROM THE NORWEGIAN MOTHER, FATHER AND CHILD COHORT STUDY

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Purpose Following an acute COVID-19 infection, a significant number of patients experience persisting symptoms for months, which is referred to as Long COVID. Fatigue, depression, anxiety, stress, memory problems and brain fog are among the most common mental and cognitive symptoms of Long COVID. The severity of COVID may increase the likelihood and severity of Long COVID symptoms.
Studies have reported factors associated with Long COVID, including biographical factors (Caucasian, Middle age and Female) and preexisting diseases (Poor mental health, diabetes mellitus, hypertension and obesity).
As most previous studies were conventional observational studies, the causal effects of the COVID-19 infection and its severity on Long COVID symptoms have not yet been demonstrated, for the highly heterogeneous findings. We performed a one-sample Mendelian randomization (MR) to study the causal effects of COVID-19 on Long COVID.

Methods This study used data of 128,550 adults with known COVID-19 infection status (2536 infected; 957 had severe illness) from the Norwegian Mother, Father and Child Cohort Study (MoBa) with questionnaire data available. From March 2020 to September 2021, MoBa participants were invited to complete a series of COVID questionnaires bi-weekly. Exposure: The self-reported SARS-CoV-2 infection and severe illness (indicated by bedridden defined as more than 6 days confined to bed or admitted to hospital) collected before February 2021. Outcomes: At separate time points these questionnaires included measures of fatigue (The Chalder fatigue scale CFQ-11), perception of stress (the Perceived Stress Scale-4, PSS-4), COVID-19-related distress (the Primary Care PTSD Screen for the Diagnostic and Statistical Manual of Mental Disorders-5, PC-PTSD-5) and single items for memory problems and brain fog. A measure of mental distress (the five-item Hopkins Symptom Checklist, SCL-5) was included three times after February 2021. Instrumental variable (IV): Polygenic risk scores were created based on GWAS summary statistics (release 7) of the susceptibility and severity of COVID-19 from the COVID-19 Host Genetics Initiative. Only independent genetic variants (LD r2 < 0.01 and 1000 kb; MAF>0.01) were included. 73,257 unrelated participants were available with genetic data for MR analysis.

Analyses Firstly, we conducted multivariable regression of the two exposures on Long COVID outcomes, adjusting for age, sex, education level, body mass index, history of psychiatric disorder, chronic medical condition and smoking status. Linear regression and robust Poisson regression were used for analysis on scores of CFQ-11, PSS-4, PC-PTSD-5, and single questions about memory problems and brain fog, respectively. Generalized estimating equation was used for repeated measures of SCL-5. Secondly, we conducted one-sample MR using the two-stage least-square method to explore possible causal effects of COVID-19 exposures on Long COVID symptoms.

Results The multivariable regression showed that COVID-19 infection and severity of the disease were significantly associated with all the Long COVID outcomes, except for the COVID-19 distress measure (PC-PTSD-5). The significant associations were moved forward to MR analyses step. There was limited evidence of a causal relationship between COVID-19 infection and the Long COVID outcomes. Genetically predicted severe COVID-19 was associated with higher risk of mental distress. However, the IV was weak.

Conclusion Our results do not support causal effects of COVID-19 infection on Long COVID symptoms of mental distress, memory problems and brain fog. For the weakness of IV, our study cannot conclude that severe COVID illness may increase the risk of such Long COVID symptoms. Further analysis with larger sample size is recommended to understand the associations between COVID-19 and Long COVID symptoms. We are preparing stronger IVs for MR, the results of which could be presented at the conference in June.

(11) RISPERIDONE TREATMENT REVERTS DIFFERENCES IN ESTIMATED BLOOD CELL PROPORTIONS AND DNA METHYLATION IN ANTIPSYCHOTIC-FREE FIRST EPISODE OF PSYCHOSIS

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The efficient selection of antipsychotic therapy for schizophrenia currently relies on a time-consuming trial-and-error approach, as there are no markers available to guide clinicians and patients in their choice of antipsychotics. This lack of markers can be attributed, in part, to the difficulty of obtaining biological samples from patients at the precise time when they begin their first monotherapy treatment with antipsychotics. Typically, biological samples are collected from patients who have already undergone prolonged medication and have been exposed to multiple antipsychotics, making it challenging to isolate the effects of a single antipsychotic from other factors such as polypharmacy and exposure to schizophrenia symptoms. Biological samples derived from individuals at their first-episode psychosis (FEP) are crucial for searching for biomarkers for treatment and response to antipsychotics, as the confounding effects of disease progression and polypharmacy are minimized at this stage.

In this study, our aim was to identify biological markers associated with the treatment and response to risperidone in a cohort of antipsychotic-naïve FEP. We chose to investigate DNA methylation (DNAm) and estimated white blood cell (eWBC) proportions as biological markers. Blood were collected from 125 antipsychotic-naïve FEP (anFEP) individuals in a psychiatric emergency unit in Sao Paulo, Brazil. Risperidone was prescribed, and after 2 months of risperidone treatment, blood samples were collected again from 123 individuals (FEP-2M). Additionally, 126 healthy controls (HC) were included in the study. DNAm was measured using DNAm microarray, and the data were analyzed to identify DNAm sites and regions associated with treatment and response to risperidone. Treatment response was assessed using the total Positive and Negative Syndrome Scale (PANSS) and its domains (positive, negative, or general psychopathology). Moreover, DNAm was used to estimate the proportions of six subtypes of white blood cells, and the eWBC proportions were compared between the groups (anFEP, FEP-2M, and HC).

We identified 4 DNAm sites and 1 region that were associated with risperidone treatment. Three of these sites showed differential methylation in the opposite direction when comparing anFEP and HC, indicating that DNAm was abnormal in anFEP individuals and returned to control levels after risperidone treatment. In terms of treatment response, we identified 100 DNAm sites and 291 regions associated with PANSS domains. These findings were enriched for pathways relevant to neuronal function, such as "cell adhesion" and "calcium ion binding".

Regarding eWBC, we observed differences in eWBC proportions when comparing anFEP with both HC and FEP-2M. anFEP individuals had significantly decreased estimated proportions of T CD8+ (CD8T) / CD4+ (CD4T) lymphocytes, and natural killer (NK) cells, whereas neutrophils

was increased when compared to controls. After treatment, the estimated proportions of lymphocytes and NK cells increased in FEP individuals, and these proportions were no longer different between FEP-2M and HC groups. Conversely, the neutrophils decreased after 2 months of treatment, and was no longer different between FEP-2M and HC.

Several studies have reported association between blood cell proportions and schizophrenia. However, it is unclear whether these changes were induced by antipsychotic treatment or were related to schizophrenia etiology. In our study, we demonstrated that eWBC were altered in FEP individuals compared to controls, and these alterations were reversed after 2 months of treatment, suggesting that the changes in cell proportions may be caused by the etiology of schizophrenia rather than antipsychotic treatment. Furthermore, our study identified DNAm markers associated with risperidone treatment and clinical response, which may serve as potential biomarkers to guide clinicians and patients in their choice of antipsychotics.

(12) QUANTIFYING THE ASSORTATIVE MATING OF PSYCHIATRIC DISORDERS AND ITS CONSEQUENCES IN DANISH POPULATION

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Introduction Phenotypic similarity between partners defines as assortative mating(AM) which is quite widespread in psychiatric disorders. As psychiatric disorders are highly heritable, AM implies genetic and environmental implications in the succeeding generations which has been barely explored in the literature. Here we aim to quantify AM in psychiatric disorders and its consequences in terms of prevalence, heritability, and fecundity in Danish register data.

Methods The study was conducted on two generations of Danish residents born between January 1969 and December 2015. Odds ratio on 5:1 case-control and tetrachoric correlation on the population scale were used to quantify AM within several psychiatric diagnosis, including Substance Abuse, Schizophrenia, Major Depressive Disorder, Obsessive-Compulsive Disorder, Generalized Anxiety Disorders, Phobia, Autism Spectrum, Attention-Deficit/Hyperactivity Disorder, Anorexia, and Bipolar. We have evaluated the consequences of non-random mating on prevalence, heritability, and fecundity by randomizing the pattern of mating in the population.

Results In 571534 unique couples residing in Denmark, substantial similarities between partners' diagnostic statuses for psychiatric disorders were observed. The odds of psychiatric cases, males and females probands on average having an affected partner were substantially higher than matched controls ranging from 2.52 for Major Depressive Disorder to 14.97 for Schizophrenia which is in accordance with diagnostic status correlations of partners in the whole population, 0.20 and 0.39 respectively.

We have evaluated the consequences of AM for the phenotype 'any mental disorder' on 822209 offspring of those couples. Randomizing partners suggests that on average (with 1000 replication in each gender) population prevalence of any mental disorder would be 2.25 % less if couples had mated randomly. Moreover, the elimination of spousal phenotypic resemblance in the population results in a 20 % decrease in the heritability of offspring generation. Finally, the predictive model for fecundity calculation made by randomized partners reveals that the effect of AM of psychiatric disorders on fecundity is small though significant (a decrease of 7 for every 10000 births).

Discussion Assortative Mating is substantially high in psychiatric disorders in Danish population. This increases heritability and population prevalence significantly in the succeeding generation. Also, it decreases the average number of children per family.

(13) GENETIC ASSOCIATIONS WITH AGE OF RHEUMATOID ARTHRITIS

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Background To date over 120 genetic loci have been reported as associated with rheumatoid arthritis (RA). Although, early age of RA is associated with more severe disease, currently no GWAS on age of RA onset have been published. The aim of this study was to assess genetic associations with age at diagnosis of RA.

Methods Study sample included 3,397 patients with RA from Swedish the Epidemiological Investigation of RA cohort (1). RA case was defined as a first diagnosis of RA made by rheumatologist and fulfilling 1987 American College of Rheumatology (ACR) criteria. Approximately, 65% (2,335) were positive for ACPA auto-antibodies. The study participants were predominantly women (66%) and of European ancestry.
Genotyping was performed using Illumina 300K chip containing a variety of genetic markers of specific immunologic importance, based on previous observations. Markers with minor allele frequency <1 % and Hardy- Weinberg disequilibrium p-value <0.05 as well as samples with genomic missingness exceeding 5% were excluded. After quality control procedures, 4,374786 SNPs and 3,591 samples were advanced for analyses.
Genetic associations with age of RA diagnosis, which was transformed using RNOmni (2), were assessed using mixed linear models in SAIGE (3). The model was adjusted for sex and first three principal components.

Results The strongest genetic association was seen with a variant located within classic HLA locus (rs111394249, p=6.43x10-11 Figure 1). Moreover, we identified thirteen additional suggestive associations (p-value<5x10-06) all of which were novel. Borderline genome-wide association among novel signals was observed with rs10489318 (p-value=8.19x10-08) in TNR gene. Tenascin-R was previously implicated in acute myeloid leukemia (4).In ACPA+ group, in addition to HLA locus (rs1779657819, p-value=2.57x10-08), six genomic regions showed suggestive associations with age of RA diagnosis. In the ACPA- group, markers within two regions demonstrated associations with age of RA at suggestive levels of genome-wide significance. Specifically, genetic variant rs2252377 (p-value= 2.54x10-06) was located within novel FLVCR1 gene which was previously linked to autoimmunity (5) but not RA. Another, independently-associated variant, rs141039439 (p-value= 3.21x10-06), was mapped to novel ZBTB20 gene which was implicated in innate immune response (6).

Conclusions Our study found several novel loci associated with age of RA diagnosis.

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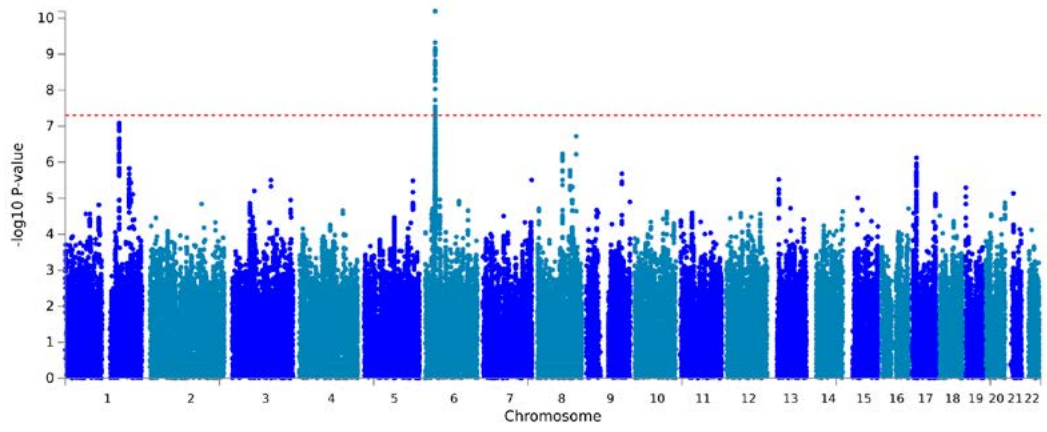

(14) QUANTIFYING THE RELATIVE IMPORTANCE OF GENETICS AND THE ENVIRONMENT ON THE COMORBIDITY BETWEEN MENTAL AND CARDIOVASCULAR DISORDERS USING REGISTER DATA

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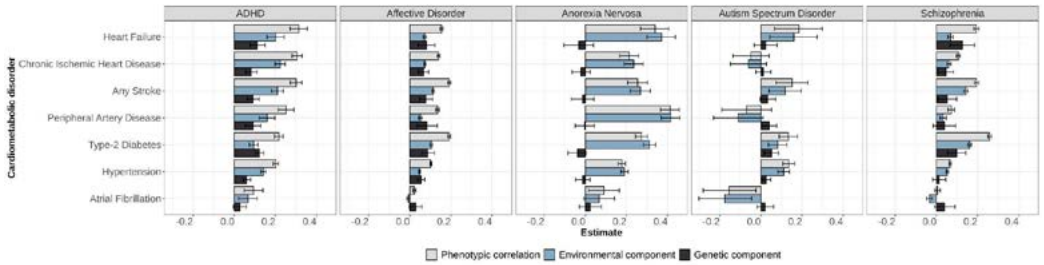
Epidemiological studies have investigated the association between mental (MD) and cardiovascular (CVD) disorders by using national data such as the Danish and Swedish registers comprising millions of individuals and generally observed a positive bidirectional association. Risk estimates derived from the same nationwide registers observed a substantial comorbidity and absolute lifetime risk; with mental disorders to be associated with a 40% higher risk of CVD. However, specific risk varies from disorder to disorder.

While there is large epidemiological evidence for the comorbidity between MD and CVD, there is very little research on the underlying causes of this comorbidity. Plausible causes could be biological and environmental. Studies have identified a substantial genetic overlap between some CVD and some MD suggesting genetics as a putative cause of the MD- CVD comorbidity. However, these studies have three main limitations: 1) most cover a specific MD–CVD combination or use heterogeneous broad diagnostics categories; 2) sole use of methods based on GWAS summary statistics that are susceptible to incorporate different kinds of biases that can compromise the results; and 3) no quantification of the relative importance of genetics and environment on the observe comorbidity was estimated. Here we address these limitations and examine the genetic relationship between mental disorders and CVD by combining two complementary large datasets.

Using polygenic risk scores calculated in the uniquely designed IPSYCH study, we observed that individuals with an ADHD, affective disorder, and to a lesser extend schizophrenia diagnosis were more likely to have a higher CVD PRS compared to unaffected individuals. The inverse relationship was observed with anorexia. The same pattern of associations was observed using LDSC analysis. Estimates of genetic correlations using cumulative incidences derived from national registry data were mostly in line with LDSC estimates, yet often were smaller in magnitude. This high degree of concordances suggesting a clear shared genetic contribution to both disorder groups.

The Scandinavian countries share many similarities such as history, (genetic) ancestry, cultural characteristics and all operate a government funded and run health care system. These similarities would suggest a high degree of transferability of register-based estimates, yet this is often not the case. Replication analysis of heritability estimates derived using the much larger Swedish registers correlated well with the Danish estimates (mental disorders=0.99, p-value=8.37e-05; CVD=0.83, p-value=1.95e-4). Register based genetic correlations correlated substantially less between the two countries however near all presented overlapping confidence intervals. The high degree of transferability suggests that our approach produces reliable estimates of heritability and genetic correlations that account for clinical and social differences over time associated in seeming comparable national register data.

Understanding the balance between genetic and environmental factors driving the comorbidity between disorders is clinically important. Here we quantified these contributions using risk estimates previously reported by Moment et al 2020, and observed that for, for instance, anorexia nervosa near all risk is derived from environmental factors, even in the presence of a small, seemingly, protective genetic contribution. Disorders such as ADHD, affective disorders, and to a lesser extend schizophrenia have a roughly equal genetic to environmental risk component ratio. These results are clinically crucial as medical staff can inform patients and start treatment (e.g., changes in medication prescription and lifestyle) whiles knowing the underlying balance between the biological and environmental risk components.



(15) REPEATS R/T RATIO IS ASSOCIATED WITH HUMAN Y CHROMOSOME HAPLOGROUPS

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SNP based Y chromosome haplogroup determination for ancestry and relatedness analyses is challenging because of the ultra-low coverage (<0.1x) sequence data that is often achievable from poorly preserved human remains. These challenges are due to low probability of critical clade-defining markers that are covered by data. While most previous research on genetic ancestry in the last two decades has focused on single nucleotide variants, the completion of human genome sequencing is opening new avenues for the use of structural variation for the analysis of genetic ancestry. More than one half of the human genome contains repeated sequences and the completed sequence of human Y chromosome (CHM13v2.0) includes extensive heterochromatin regions. Here we aim to show how specific k-mers can be used to predict Y chromosome haplogroups and to assess variation in tandemly repeated and single copy regions for the assessment of genetic ancestry as well as, potentially genetic relatedness. Random repeat (Line) k-mer frequency/tandem repeat k-mer frequency ratios (R/T ratios) of 198 Estonian males are graphically 3D visualized http://bioinfo.ut.ee/randomtandem/EGV.html. We show that the clustering of the male samples by the R/T ratios of the three Y chromosome-specific tandem repeats (VNTR, CEN, HET) clearly separates the main haplogroups (N3a, I, R1a, R1b, E). We have explored the potential for R/T ratio-based method for assessing specific tandem repeat length ratios in Y chromosome and using these ratios as predictors of Y chromosome haplogroups. We have tested the approach on three Y chromosome-specific k-mers using high coverage (~20x Y chromosome) Illumina WGS reads as a proof of principle. The method can be improved by using more and shorter k-mers for low coverage short read sequencing applications like in NIPT, forensic and ancient DNA studies. Variation inside haplogroups shows potential for ancestry detection from non-imputed data for individual identification, assessment of relatedness and for the basic understanding of the rate of structural variation in human genome.

(16) INVESTIGATING THE CAUSAL EFFECTS OF CHILDHOOD AND ADULTHOOD ADIPOSITY ON LATER LIFE MENTAL HEALTH OUTCOME: A MENDELIAN RANDOMISATION STUDY

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Background Obesity particularly during childhood is considered a global public health crisis and has been linked with different later life health consequences including mental health. However, there is lack of causal understanding if childhood adiposity has a direct effect on mental health or has a indirect effect after accounting for adulthood body size.

Objective To investigate the total and direct effect of childhood adiposity on later life anxiety and depression.

Method Two-sample univariable and multivariable Mendelian randomization (MR) was performed to estimate the total effect and direct effect (i.e. after accounting for adulthood body size) of childhood body size on anxiety and depression. Genetic instruments for childhood (10 years of age, 313 SNPs) and adulthood body size (mean age 56.5 years, 580 SNPs) were retrieved from the genome-wide association study (GWAS) performed in UK Biobank (n=453,169). GWAS summary statistics of the outcomes were retrieved from large GWAS consortia (sample size: n=175,163 for anxiety and n=173,005 for depression).

Result Univariable MR did not indicate genetically predicted effects of childhood body size with later life anxiety (beta=-0.05 per change in body size, 95% CI=-0.13 to 0.02, p value=0.171), and depression (OR=1.06 per change in body size, 95% CI=0.94 to 1.20, p value=0.345). However, using multivariable MR, we observed that the higher body size in childhood reduced the risk of later life anxiety (beta=-0.19 per change in body size, 95% CI=-0.29 to -0.08, p value<0.001) and depression (OR=0.83 per change in body size, 95% CI=0.71 to 0.97, p value=0.019). Both univariable and multivariable MR indicated that the higher body size in adulthood increased the risk of later life anxiety (beta=0.24 per change in body size, 95% CI=0.15 to 0.33, p value<0.001) and depression (OR=1.45 per change in body size, 95% CI=1.27 to 1.68, p value<0.001).

Conclusion These findings suggest that the higher body size in childhood has a protective effect on later life anxiety and depression, provided that the obesity is not present into adulthood. However, higher body size in adulthood was a risk factor for later life anxiety and depression.

(17) POLYGENIC SCORES FOR PSYCHIATRIC DISORDERS ASSOCIATE WITH YEAR OF FIRST BIPOLAR DISORDER DIAGNOSIS: A REGISTER-BASED STUDY BETWEEN 1972 AND 2016

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The formal diagnostic criteria of bipolar disorder (BD), and how these have been implemented in clinical practice, have changed over the years. If and how these changes are reflected in patient's polygenic liabilities for psychiatric disorders are not known. We tested if year of first bipolar diagnosis in the Swedish National Patient Register associate with changes in polygenic scores (PGS) for psychiatric disorders between 1972-2016. We included 3,277 participants in the Swedish Bipolar Collection (SWEBIC) study who had a diagnosis in the patient register and genotype information. We found that PGS for BD (β = -0.0081, P = 1.0 x 10-7), and BD type I specifically (β = -0.010, P = 2.4 x 10-11), decreased over time, while PGS for depression (β = 0.0052, P = 0.0013) and attention deficit hyperactivity disorder (β = 0.0044, P = 0.0064) increased over time. In analyses stratified by BD subtypes, we found that PGS were stable over time in BD type 1, and that the secular changes mainly were driven by changes within the BD type 2 group. Our results indicate that while the polygenic constitution of people with BD type 1 has remained stable over the study period, BD type 2 and has undergone significant changes. Specifically, people with polygenetic liability for other psychiatric disorders than BD has increased within the BD type 2 and NOS groups. This information has bearing on genetic studies of BD where the results could be affected by when the BD diagnosis was made.

(18) MUTATIONAL ANALYSIS PROFILE IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS IN RELATION TO HEMOSTATIC COMPLICATIONS – A RETROSPECTIVE STUDY

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Introduction Myeloproliferative neoplasms (MN) patients have the complication in both side of hemostasis - related to bleeding and thrombosis. The major goal of therapy is to reduce thrombosis risk, which impacts MN morbidity and mortality. However, bleedings have equally important role on the quality of life. Acquired von Willebrand disease (AvWD) may result from increased proteolysis together with platelet activation, which leads to reduced von Willebrand factor activity (vWFact). Approximately 60% of patients with MN carry a genetic mutation.
Aims: We analyzed our MN patient cohort to lab analysis related to hemostasis in order to better understand the patients genetic profile.

Methods Chart review of Pärnu Hospital case records with diagnosis of D47.3, D45 and D47.1 between years 2016-2021.

Results During 2016-2022 in total 102 patients with MN where in regular follow-up in Pärnu Hospital. Patients with essential thrombocythemia (ET) consisted of 31.37%, with polycythemia vera (PV) of 31,37% and with primary myelofibrosis (PMF) of 37,25%. There where Janus kinase 2 (JAK2), calreticulin (CALR), and ASXL1 mutations with frequencies of these mutations 78,12%, 0%, and 0% in PV; 58%, 9,67% and 0% in ET, and 51,28%, 7,69%, and 5,13% in PMF detected. In 48 patients the analysis of von Willebrand factor antigen (vWFAg),von Willebrand factor activity (vWFact), Factor 8 were measured in case of bleeding tendency or before operation and invasive procedures. In addition, semiautomated von Willebrand factor multimer assay was performed and according the test results (loss of high weight multimers) 18 patients had AvWD diagnosis: 10 from 20 patients with ET, in 5 from 14 patients with PMF and in 3 from 12 patients with PV. In all patients except two the vWFact/vWFAg ratio was below 0.7 and the multimeric assay shows decreased high molecular weight of multimers. In two cases the ratio was normal but with decreased high molecular weight multimers at the same time. In patients with AvWD diagnosis 4 where CALR pos and 12 patients had JAK2 positivity. 7 patients died during the observation period- four of them from hemostasis related complications- 3 from arterial thrombosis and one from bleeding.

Conclusion AvWD can be a severe complication in patients with ET, PV and PMF. JAK2 and CALR mutations can play a role in disease cause and can cause hemostasis complications. Based our analysis, we recommend in CALR and JAK2 mutation positive MN patients VWF Ag and vWFact testing during the disease cause and also before planned surgical intervention or invasive procedures, with the aim to prevent coagulation system complication and to reduce fatality.

(19) PRELIMINARY GENOME-WIDE ANALYSIS OF SELF-REPORTED PSYCHOTIC EXPERIENCES IN THE NORWEGIAN MOTHER, FATHER, AND CHILD STUDY

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Purpose Psychotic experiences (PEs) are relatively common in the general population but are also linked to risk of transition to frank psychosis. There is evidence of associations between genetic risk factors of PEs and risk of schizophrenia and major depressive disorder. Still, much about the genetic underpinnings of PEs is yet be discovered. Critically, a well-defined measure of the phenomenon in a large sample is necessary, prior to these discoveries. Hence, reliability and validity of the measurements are key. In this study, we used a large sample of fathers and children from the Norwegian Mother, Father, and Child cohort study to perform a genome-wide association (GWA) study of psychotic experiences.

Method Our sample consisted of fathers (N=29,021) and adolescents (N=21,647) from the MoBa cohort who responded to the Community Assessment of Psychic Experiences (CAPE-9) questionnaire, a short self-report measure of PEs. The CAPE-9 is a 9-item questionnaire comprising two scales: frequency of experiences and subjective distress. We performed psychometric assessment consisting of explorative and confirmative factor analyses, in addition to testing measure invariance. Next, we conducted a GWA analysis using the Regenie software version 3.2.5 on the summary score of the two CAPE subscales.

Results CAPE-9 shows good psychometric properties and fits the previously hypothesized three-factor PE dimensions both in fathers and adolescents. We observed notable differences in response patterns between fathers and adolescents with adolescents reporting substantially higher positive scores. In our preliminary GWA results, we found substantial heritability (h2 = 0.0981 (±0.0355) for distress and 0.1072 (±0.0354) for frequency sub-scales but no genome-wide significant hits overall.

Conclusion CAPE-9 is a reliable and effective measure of PEs in this population sample. Differences in positive response rate between fathers and children may suggest important generational variations in responses – an important consideration in the use of such instruments across generations and time. We found high heritability of PEs and identified a few promising sub-threshold genetic associations, which will be pursued through meta-analysis with other cohorts.

(20) PERSONALITY TRAITS PREDICT VACCINATION AGAINST COVID-19 BETTER THAN A POLYGENIC SCORE AND DEMOGRAPHICS

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Purpose As COVID-19 vaccines' accessibility has grown, so has the role of personal choice in vaccination, and not everybody has been willing to get vaccinated. If personality traits predict vaccination over and above other variables such as genetic variants or demographic characteristics, personality data could provide unique information in understanding and predicting vaccination decisions. Personality traits' associations with vaccination could additionally highlight some person-level drivers of, and barriers to, vaccination.

Methods Using an Estonian Biobank subsample who had responded to a 198-item personality item pool (100 Nuances of Personality; N = 56,575) approximately at the time of vaccination, we tested if (a) the broad Big Five personality domains or their narrower subtraits, represented by questionnaire items, could predict vaccination against COVID-19, and (b) whether personality data could provide additional predictive accuracy over and above five demographic variables (age, sex, education, urban or rural residency, and blue-collar or white-collar occupation) and a polygenic score for vaccination (PGS; Hartonen et al., 2023). Self-rated as well as informant-rated personality traits (available for a subset of the participants) were used to predict vaccination status (binary variable).

Results Out of the Big Five personality domains, people who had received at least one dose of a COVID-19 vaccine scored slightly higher on Neuroticism and Agreeableness and lower on Openness to Experience, whereas no association was found with Extraversion or Conscientiousness. Item-level analyses revealed vaccinated people to be, on average, more science-minded, politically liberal, respectful of rules and authority, and anxious, but less spiritual, religious, and self-assured. Prediction of vaccination by different variable types was tested using elastic net models trained and tested in independent partitions of a subsample of 11,244 people, 50% of whom had received at least one dose of a COVID-19 vaccine. Vaccination was predicted most accurately by the 198 personality items (70% accuracy), followed by the five demographic variables (61%) and the PGS along with 10 principal components of ancestry (52%), whereas the Big Five domains provided no predictive accuracy above the 50% random-guess baseline (49%; Figure 1). Together, the 198 personality items, five demographic characteristics, and polygenic scores along with principal components predicted vaccination at 72%, suggesting that personality items provided substantial incremental accuracy over the demographic characteristics and the PGS, but the demographic and genetic data provided little incremental prediction over and above personality data. The results were broadly similar in informant-reported personality data available for a subset of the participants (n = 2,506).

Conclusions Altogether, vaccination was related to many narrow personality traits, which together had more utility in predicting vaccination than either demographic or genetic data. The personality–vaccination associations also suggest some potential areas for action in future vaccination campaigns.

(21) EATING PROBLEMS AMONG ADOLESCENTS BEFORE AND DURING THE COVID-19 PANDEMIC

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Purpose It is not yet understood why some adolescents, particularly girls, experience eating problems and eating disorders. Several studies have also found an increase in self-reported eating problems and prevalence of diagnosed eating disorders among adolescents during the pandemic. We will use genetic and questionnaire data collected from adolescents before and during the pandemic to increase our understanding of the development of eating problems.

Methods Based on a preregistered analysis plan, we will use data from the population-based Norwegian Mother, Father and Child Cohort Study (MoBa) that recruited pregnant women between 1999-2009. When the children were 14 years old, they were invited to answer a questionnaire, including 8 selected items from the Eating Disorder Examination Questionnaire (EDE-Q) in addition to one item concerning how the adolescent considers their own weight. Of a total of 22,098 adolescents (53% females), 9,584 reported their symptom level before and 12,514 reported their symptom level during the pandemic (i.e. after March 12th, 2020).
To identify the underlying structure of the measured eating problems, we will perform exploratory and confirmatory factor analyses (CFA). We will then investigate to what extent adolescents reported a higher level of eating problems (overall and symptom-specific) during the pandemic compared to before using multigroup CFA from the previously established model. Next, we will use multigroup SEM models to examine how eating problems among adolescents are associated with 1) genetic scores for anxiety, depression, neuroticism, obsessive-compulsive disorder and eating disorder, and 2) environmental factors (e.g., level of exercise, screen time, social media usage, parent-child-conflict). Finally, we will investigate if the associations found vary according to whether they were assessed before or during the pandemic.

Results Results will be presented at the meeting.

Conclusions These results will provide important knowledge for our understanding of the development of eating disorders among adolescents in general, and how a societal crisis might affect such problems.

(22) PRENATAL MATERNAL STRESS: TRIANGULATING EVIDENCE FOR INTRAUTERINE EXPOSURE EFFECTS ON BIRTH AND EARLY CHILDHOOD OUTCOMES ACROSS MULTIPLE APPROACHES

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Purpose Maternal stress during pregnancy has been linked to a range of negative developmental outcomes in offspring. Causal effects, mediated via changes to the intrauterine environment, have been posited as one possible explanation for these links. However, maternal exposure to and reporting of stress during pregnancy may be influenced by genetic and environmental factors that are also shared with children, confounding this pathway. Genes also influence maternal sensitivity to stress (GxE) and so may moderate any causal effects of maternal stress on fetal and child development. In the current study, we measure prenatal maternal stress and estimate associations with offspring birthweight, gestational age, emotional and behavioral problems, and triangulate across methods that variously account for potential confounding and test for GxE to evaluate the plausibility of an underlying causal mechanism.

Methods We use data from the Norwegian Mother, Father, and Child Cohort Study (MoBa), comprising mothers' self-reported exposure to stress – pre- and post-natally – in the workplace, at home, and via stressful life events, maternal reports of offspring emotional and behavioral problems in early childhood, and maternal genotype data. Additionally, we use the information on offspring birthweight and gestational age from linked birth registry data as anthropometric outcomes. We then interrogate associations between stress exposures and offspring outcomes with a series of approaches designed to assess their compatibility with a causal model: i) sibling control analyses; ii) GxE analyses; iii) intergenerational Mendelian Randomization (MR) analyses; and iv) negative control analyses.

Results Maternal prenatal stress was observationally associated with lower birthweight (e.g., work = -0.02 [95%CI: -0.03,-0.01]), earlier birth (e.g., work = -0.05 [-0.05,-0.04]), and more emotional (e.g., events = 0.09 [0.08,0.10]) and behavioral problems (e.g., relationship = 0.15 [95%CI: 0.14,0.16]) in the full sample (N=112,896). In sibling control analyses (N=36,585), all associations were attenuated to the null after accounting for unmeasured familial confounding. In GxE analyses (N=76,288) we found no evidence of the associations between measures of maternal prenatal stress being moderated by polygenic scores for traits linked to stress sensitivity – and, therefore, no indirect evidence for a causal exposure effect. Intergenerational MR analyses (N=30,263) showed no evidence of causal effects on any offspring outcomes of maternal prenatal stress as instrumented by maternal genetic variants linked to plasma cortisol. Negative control analyses revealed effect size estimates of comparable magnitude whether exposures were measured pre- or post-natally.

Discussion The results of four sets of analyses, with different assumptions and limitations, provided a consistent account of the nature of associations between measures of maternal prenatal stress and offspring birthweight, gestational age, behavioral problems, and emotional problems. We found no evidence supporting a causal link between intrauterine exposure to stress and variation in any offspring outcomes. The absence of evidence for a causal effect is not evidence of absence of such an effect. Moreover, conclusions drawn based on these results should be cautious and not extended to sources or levels of prenatal stress beyond the relatively normative exposures (stressful life events, work stress, and relationship stress) included in this study, and some limitations remain despite the strengths of the triangulation approach applied. Nonetheless, we present a robust collection of findings from a large, population-based cohort study that implicates confounding – rather than causality – in observational links between prenatal stressors and offspring outcomes.

(23) INCORPORATING FAMILY HISTORY IN GWAS OF MAJOR DEPRESSIVE DISORDER IMPROVES DETECTION OF POLYGENIC SIGNAL.

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Purpose Major Depressive Disorder (MDD) is a leading cause of disability with a complex, polygenic etiology marked by modest heritability. This combination of polygenicity and modest heritability makes GWAS for MDD among the least powered in psychiatry. The recent advent of large-scale biobanks can advance our understanding of complex disorders by providing multiple sources of complementary information, including comprehensive family history assessments. Several recent approaches have incorporated family history into genetic association tests, including GWAX, LT-FH, and LT-FH++, but none currently accommodate both extended pedigrees and partially observed relatives. We apply our recently developed method for estimating liability from pedigree data, PA-FGRS, to perform family-history-informed GWAS for MDD.

Methods We recently developed a Pearson-Aitken framework for Family Genetic Risk Scores (PA-FGRS) that estimates an individual's liability for a disease using their family's genetic history, even if some relatives are only partially observed. This framework uses a liability threshold model for the disease and treats partially observed relatives as mixtures of cases and controls. PA-FGRS extends previous methods by accounting for censoring, leveraging distant relatives, and utilizing a flexible, model-based approach for analysis. Liabilities were estimated using phenotypic records of ~2.5 million partially observed relatives. We perform GWAS on estimated liabilities for MDD in two cohorts of 17,501 cases and 23,962 controls and 8,372 cases and 15,547 controls from the iPSYCH 2012 and 2015i case-cohorts, respectively. We compare the empirical power of case-control logistic regression to linear regression on estimated liabilities in five ways: counting significant and suggestive loci, comparing association tests at known loci identified by Howard et al., comparing the performance of PGS from each GWAS, comparing the SNP heritability from each approach, and comparing genetic correlation with external studies.

Results Case-control logistic regression identified 3 significant (p<5e-8) and 18 suggestive loci (FDR < 0.05), while linear regression on estimated liabilities identified 2 significant (p<5e-8) and 20 suggestive loci (FDR < 0.05). We observed a significant improvement in the strength of association at the 29 loci previously discovered (p = 0.018) when using estimated liabilities versus case-control data in association tests. PGS predicting across the two independent iPSYCH subcohorts based on estimated liability GWAS significantly improved classification, in both directions (iPSYCH 2012, case-control vs. liability, 0.534 vs. 0.540; iPSYCH 2015i, case-control vs. liability, 0.547 vs. 0.550). SNP heritability estimated from liability GWAS explained 2% more variability (n.s.) in MDD liability (Case-control SNP h2=8% and liability SNP h2=10%). GWAS based on estimated liability showed larger genetic correlations with all considered external studies (Dahl et al, 0.927 vs 0.990; Cai et al 0.875 vs. 0.933 and 0.887 vs. 0.935, Howard et al, 0.870 vs 0.887, Kurki et al, 0.777 vs 0.810), although no single difference was significant.

Conclusions Our study provides further evidence that incorporating family history in GWAS can improve power in otherwise underpowered polygenic traits, however, in highly ascertained data the gain is quantitative and most significant when considering improving PGS performance.

(24) A NOVEL LOCUS ASSOCIATED WITH MULTIPLE SCLEROSIS SEVERITY IMPLICATES CNS RESILIENCE IN DISEASE OUTCOME

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) and a common cause of chronic neurological disability in young adults. The disease is characterized by episodes of temporary neurological dysfunction (relapses) together with persistent disability accumulation (progression). The impact of relapses and progression varies over time and differs greatly between people with MS. Genome-wide association studies (GWAS) have identified over 230 genetic variants associated with susceptibility to develop MS, with the vast majority involving immune functions. Risk variants have little influence on the severity of MS, and previously published efforts to systematically examine severity have not identified any convincingly associated genetic variants.

To provide insight into the genetic architecture determining progression, we conducted a GWAS of the age-related MS severity score (ARMSS) in 12,584 MS cases of European ancestry genotyped on Illumina Global Screening Array. Imputation to the Haplotype Reference Consortium generated 7.8 million autosomal single nucleotide variants (SNV) with a minor allele frequency (MAF) > 0.01 for analysis. The findings were replicated in 9,805 persons with MS assembled through 9 European centers and genotyped on various Illumina arrays.

The SNV-based heritability estimate for ARMSS was 0.13. We identified and replicated a significant association with rs10191329 in the DYSF-ZNF638 locus (fixed-effects meta-analysis p=3.6×10-9). The effect on disability outcomes was investigated in 8,325 individuals with longitudinal assessments from >54,000 study visits spanning up to 13.9 years. DYSF–ZNF638 risk allele carriers displayed faster disability progression (p = 0.002) and 24-week confirmed disability worsening (p = 7.9×10-3). In homozygous carriers, rs10191329A also conferred a 3.7-year shorter median time to using a walking aid (p = 9.3×10-4), a clinically relevant MS disability milestone. Eleven additional loci showed suggestive association with ARMSS in discovery (p < 5×10-6), and rs149097173 in the DNM3-PIGC locus replicated but did not reach genome-wide significance in the combined analysis (p = 2.3×10-7). Carriage of the low frequency (MAF = 0.01) risk allele rs149097173T was only nominally associated with faster disability accrual.

We further explored the impact of rs10191329 on disease-relevant tissue injury in an independent MS autopsy cohort comprising 4,652 tissue blocks from 290 individuals. Homozygous DYSF-ZNF638 risk allele carriers had more brainstem and cortical lesions (p = 0.023 and p = 0.001, respectively), confirming that rs10191329A is associated with worse target organ injury at key locations.

Intriguingly, although MS is primarily driven by immune mechanisms, heritability enrichment analysis of 205 tissues and cell types revealed significant enrichment exclusively in CNS tissues across multiple brain regions and the C1 segment of the cervical spinal cord. Furthermore, we found evidence of inverse genetic correlations between MS severity and cognitive and aging traits, while a range of neurological, psychiatric, and autoimmune disorders did not display a shared genetic contribution with MS severity. Mendelian randomization analyses indicated a protective role for higher educational attainment (p = 0.005) and detrimental effect of smoking (p = 0.005), which remained significant after adjustment for socioeconomic status in two

independent population-based MS cohorts with recorded educational attainment, smoking status, and income (GEMS N=5228 and EIMS N=2878).

Notably, in contrast to immune-driven susceptibility, this study indicates a key role for CNS resilience and neurocognitive reserve in determining outcome of MS, and provides the first candidate genes for severity. Our work has the potential to inform the development of safe, effective, rationally based treatments capable of controlling progression, the greatest currently unmet clinical need facing people with MS.

(25) EXPLAINING FAMILIAL RISK OF DISEASES WITH INTERPRETABLE UNSUPERVISED LATENT REPRESENTATIONS FROM COMPREHENSIVE NATIONWIDE FINNISH DATA

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Purpose The emerging large-scale datasets containing electronic health record (EHR), sociodemographic and genetic information offer unprecedented opportunities to harness the power of machine learning (ML) methods to benefit public health strategies. While increasing the size and diversity of health-related data available for training ML models arguably leads to more accurate predictions, training models with thousands of variables is not without challenges. These datasets typically consist of clusters of highly correlated features that partly measure the same information making interpretation of predictions difficult.

Methods Here, we train unsupervised latent representations with health- and sociodemographic data of parents of all children born in Finland between 1987-1992 (Nparents=628,980, Nchildren=335,330) from the nationwide FinRegistry study. The aim is to compress the information contained in 692 variables, of which 198 are continuous and the rest binary, into a smaller number of interpretable latent variables (LV). We then use the LVs to predict the onset of life events, such as diseases or purchases of certain medications, in the children of these individuals using survival analysis. We create 10 LVs both using a linear model (factor analysis, FA), as well as with a non-linear, recently published sparse variational autoencoder (sparse VAE).

Results FA explained 13.2% of the variance in the dataset. Sparse VAE reconstructed binary variables relatively well, with mean Matthews correlation coefficient, MCC=0.26 (on a test set). The best-reconstructed disease diagnoses were cardiovascular disease (MCC=0.89), type 2 diabetes with complications (MCC=0.87) and any arthropathies (MCC=0.86). Notably, sex was the most accurately reconstructed binary variable (MCC=0.98). Numbers of different types of medication purchases were modeled as continuous variables, and were generally not reconstructed as well as the binary variables. The best-reconstructed medication was Selective beta-2-adrenoreceptor agonists (coefficient of determination, r2=0.22). Some of the LVs seem to capture similar themes, such as mental health or cardiovascular disease, regardless of which method is used to train them, but there are also differences. We used the LVs separately from FA and from sparse VAE to predict the onset of four life events of children: type 1 diabetes, type 2 diabetes, pain and use of antidepressants. We did not find a significant difference in discrimination between models trained with LVs from sparse VAE and from FA. We aim at expanding these preliminary analyses by demonstrating the performance of the LV models on a more extensive selection of life events of children as well as by comparing the prediction performance to state-of-the-art survival models that directly incorporate nonlinearities, but at the cost of interpretability.

Conclusions This study presents a latent variable-based alternative for training prediction models on complex health data that can be easier to interpret than existing approaches. We show that the LVs can be interpreted by examining the loadings of the original features. Further exploration of the VAE model architectures is needed in order to understand if that approach can generate better LVs than FA. More interpretable ML models will help tease out explanations for public health issues from biobank and large-scale registry data.

(26) THE GENETIC BASIS OF EATING BEHAVIORS

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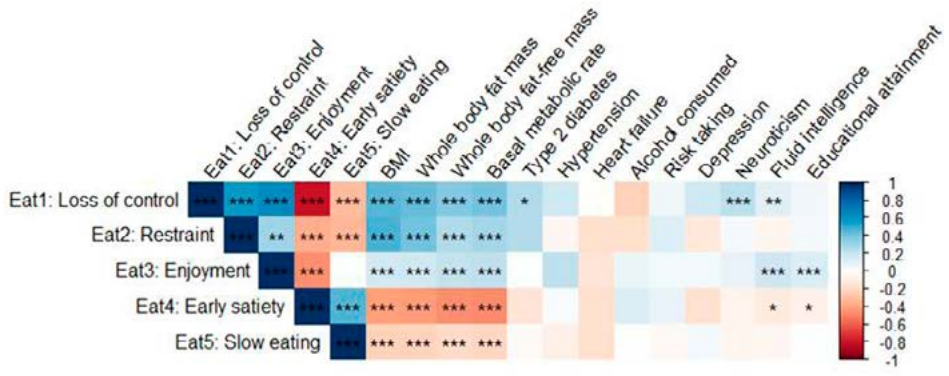
Purpose Obesity increases the risk of several diseases and is associated with premature death. Bodyweight depends on both genetic and environmental factors. Genetic factors can affect bodyweight through eating behaviors. The purpose of the study was to find the genetic basis of selected eating behaviors and their genetic correlations with body mass index (BMI) and other traits.

Methods We used Estonian Biobank (EstBB) data of 77,400 participants who filled out a personality questionnaire between November 2021 and April 2022. The questionnaire collected information about personality, attitudes, life events, socioeconomic status and eating behavior. Eating behavior was assessed with five questions measuring loss of control (Reward-Based Eating Drive Scale), restriction in order to prevent weight gain (Three-Factor Eating Questionnaire), enjoyment of eating, early satiety and speed of eating (Adult Eating Behavior Questionnaire). Genome-wide association studies (GWAS) were performed using the statistical program Regenie and genetic correlations calculated using a web-based platform Complex-Traits Genetics Virtual Lab. Final GWAS sample consisted of 75,561 individuals of whom 30% were men.

Results Loss of control over eating was statistically significantly associated with 11 genome-wide loci: NEGR1, AMPD2, TMEM18, ZNF385D, ROBO2, CADM2, TFAP2B, FTO, ARL4D,L3MBTL4, MC4R. Nine of them (FTO, NEGR1, TMEM18, ZNF385D, ROBO2, CADM2,TFAP2B, MC4R, AMPD2) have been associated with BMI or obesity in previous GWAS'. ARL4D and L3MBTL4 may indirectly be related to BMI because they have previously been associated with type II diabetes and sugar consumption respectively. All following statistically significant loci have previously been associated with BMI. Restriction to prevent weight gain was associated with three genes: FAM150B, FTO and PMAIP1. Enjoyment of eating was associated only with the FTO loci. PRKD1 and FTO were associated with early satiety. Slow eating was associated with SLC25A12, PLCL1 and ZCCHC7 genes. There were statistically significant positive genetic correlations between loss of control, restriction, enjoyment of eating and BMI (rg = .16-.63). Loss of control and early satiety were positively genetically correlated with fluid intelligence (rg = .11-.18).

Conclusions Loss of control over eating was associated with two loci previously not associated with BMI but which may indirectly affect BMI. The results suggest a shared genetic basis between eating behaviors and BMI which should be investigated in further analyses. The found genetic markers enable follow-up polygenic prediction of eating
behaviours as well as causal modelling between health and eating behaviours.



(27) PHENOME-WIDE ASSOCIATION STUDY OF ADHD GENETIC LIABILITY AND ICD-10 MEDICAL CONDITIONS IN THE ESTONIAN BIOBANK

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Purpose Attention-deficit hyperactivity disorder (ADHD) is typically a childhood onset disorder which often persists into adulthood, but is extremely underdiagnosed in adults. Moreover, little is known about the medical comorbidities in undiagnosed adult individuals with high ADHD liability. In this study we investigated associations between ADHD genetic liability and electronic health record (EHR)-based ICD-10 diagnoses across all diagnostic categories, in individuals without ADHD diagnosis history.

Methods We used data from the Estonian Biobank cohort (N=111,261) and generated polygenic risk scores (PRS) for ADHD (PRSADHD) based on the ADHD genome-wide association study. We performed a phenome-wide association study (PheWAS) to test for associations between standardized PRSADHD and 1,515 EHR-based ICD-10 diagnoses in the full and sex-stratified sample. We compared the observed significant ICD-10 associations to associations with: 1) ADHD diagnosis and 2) questionnaire-based high ADHD risk analyses. Additionally, we ran a causal mediation analysis to explore the effect of depression on the identified phenotypes.

Results After Bonferroni correction (p=3.3x10-5) we identified 80 medical conditions associated with PRSADHD. The strongest evidence was seen with obesity (OR=1.13, CI=1.11-1.15), type 2 diabetes (OR=1.11, CI=1.09-1.14), mental disorders due to alcohol use (OR=1.13, CI=1.09-1.16) and depressive episode (OR=1.06, CI=1.05-1.08). Sex-stratified analysis generally showed similar associations in males and females. Out of all identified associations, 40% and 78% were also observed using ADHD diagnosis or questionnaire-based ADHD, respectively, as the predictor. The results from causal mediation analysis indicated that depression was a significant mediator for all medical conditions (except depression diagnosis).

Conclusions Overall, our findings indicate that ADHD genetic liability is associated with an increased risk of a substantial number of medical conditions in undiagnosed individuals. These results highlight the need for timely detection and improved management of ADHD symptoms to reduce the health risks in adulthood.

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